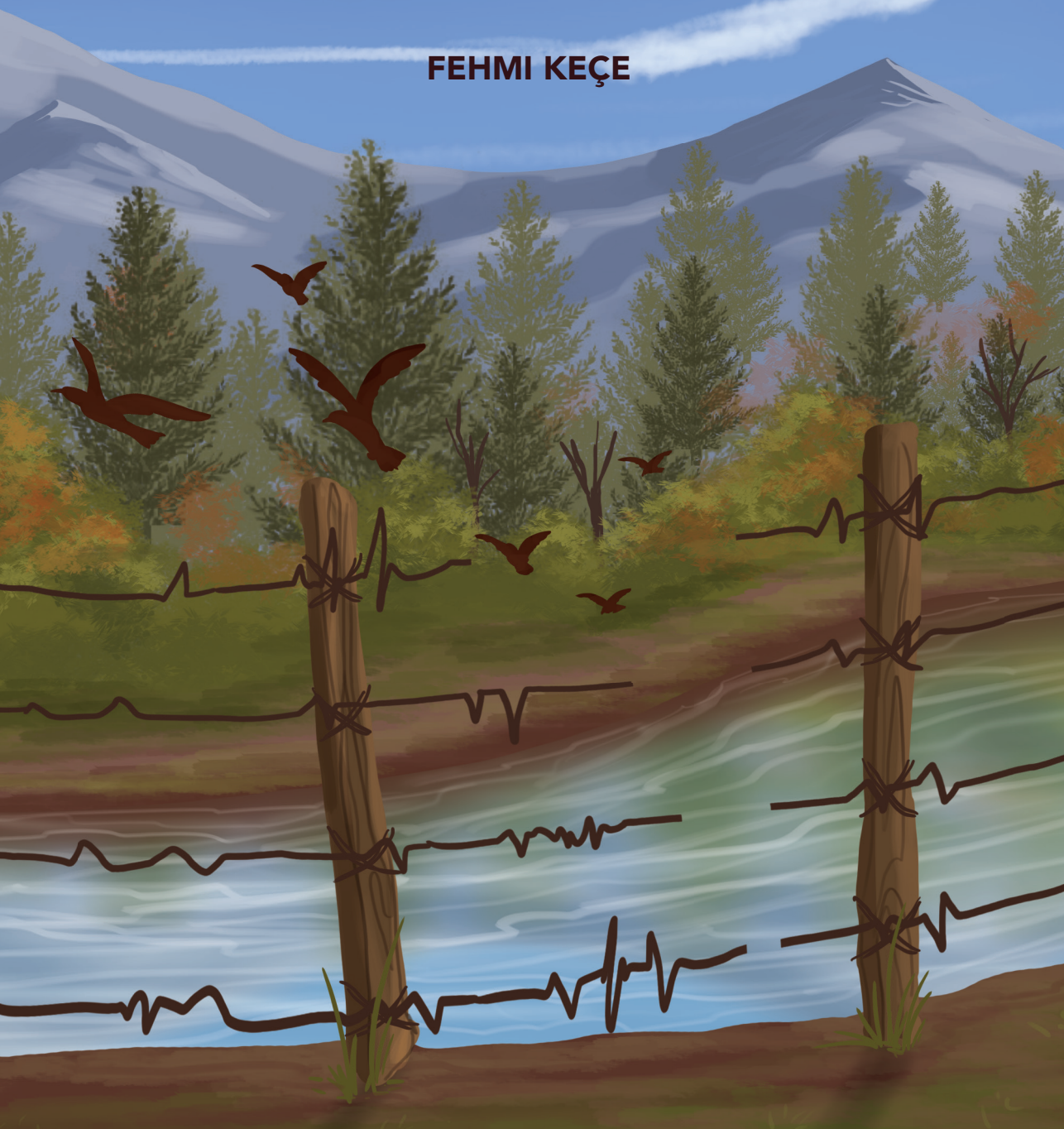
20/20: TWENTY YEARS AFTER THE FIRST CATHETER ABLATION OF ATRIAL FIBRILLATION

Towards freedom from procedure related complications and atrial fibrillation recurrence

FEHMI KEÇE



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Twenty years after the first catheter ablation of atrial fibrillation

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Fehmi Keçe

Colophon

The Studies in these thesis were conducted at the Department of Cardiology of the Leiden University Medical Center, Leiden. The Netherlands.

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Twenty years after the first catheter ablation of atrial fibrillation

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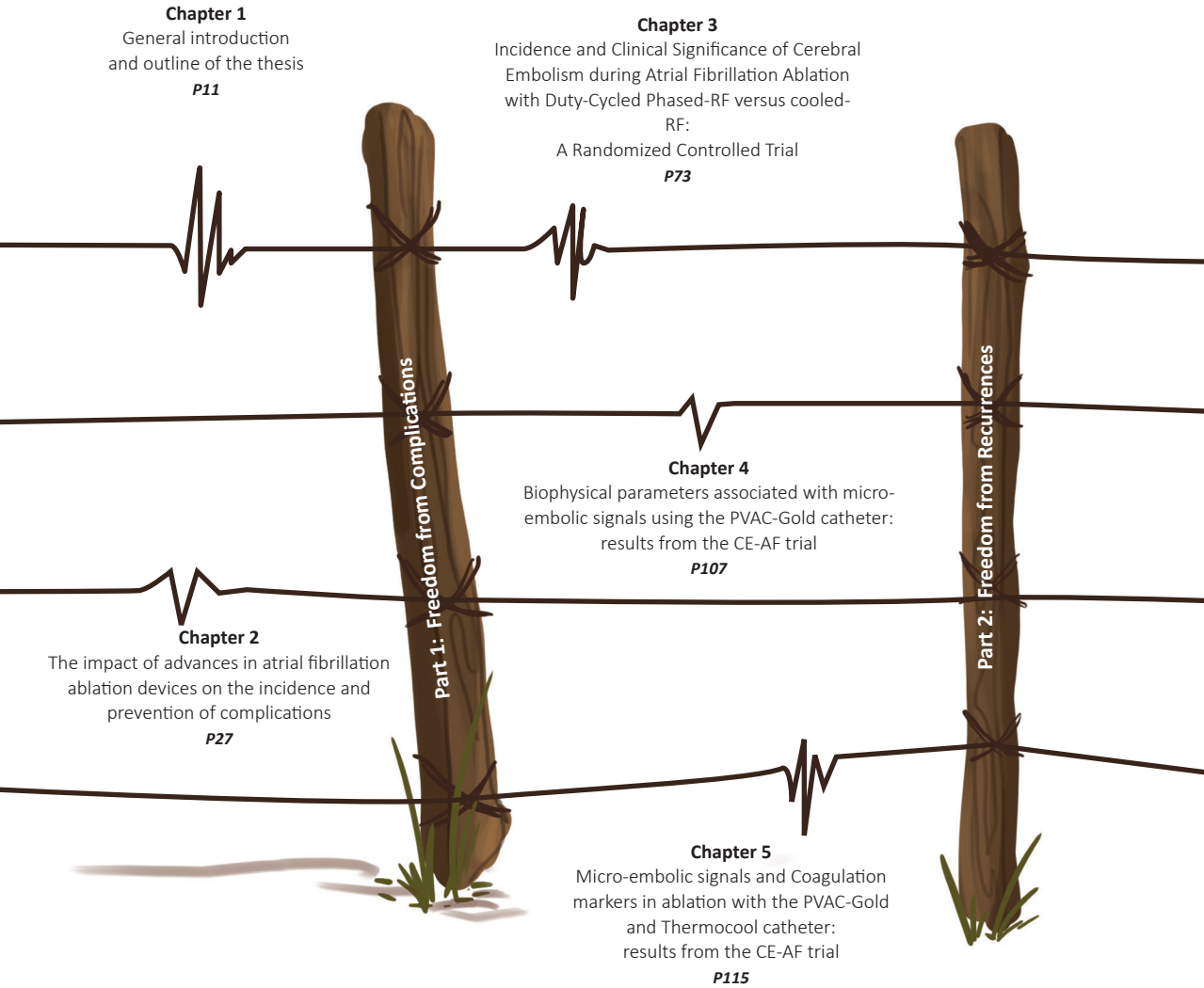
Dr. A.C.P. Wiesfeld (Universitair Medisch Centrum Groningen)

Freedom, in any case,
is only possible by
constantly struggling for it.

Albert Einstein (1879 – 1955)

Voor Özgür[1] en Arzu

1 Özgür means freedom or independency



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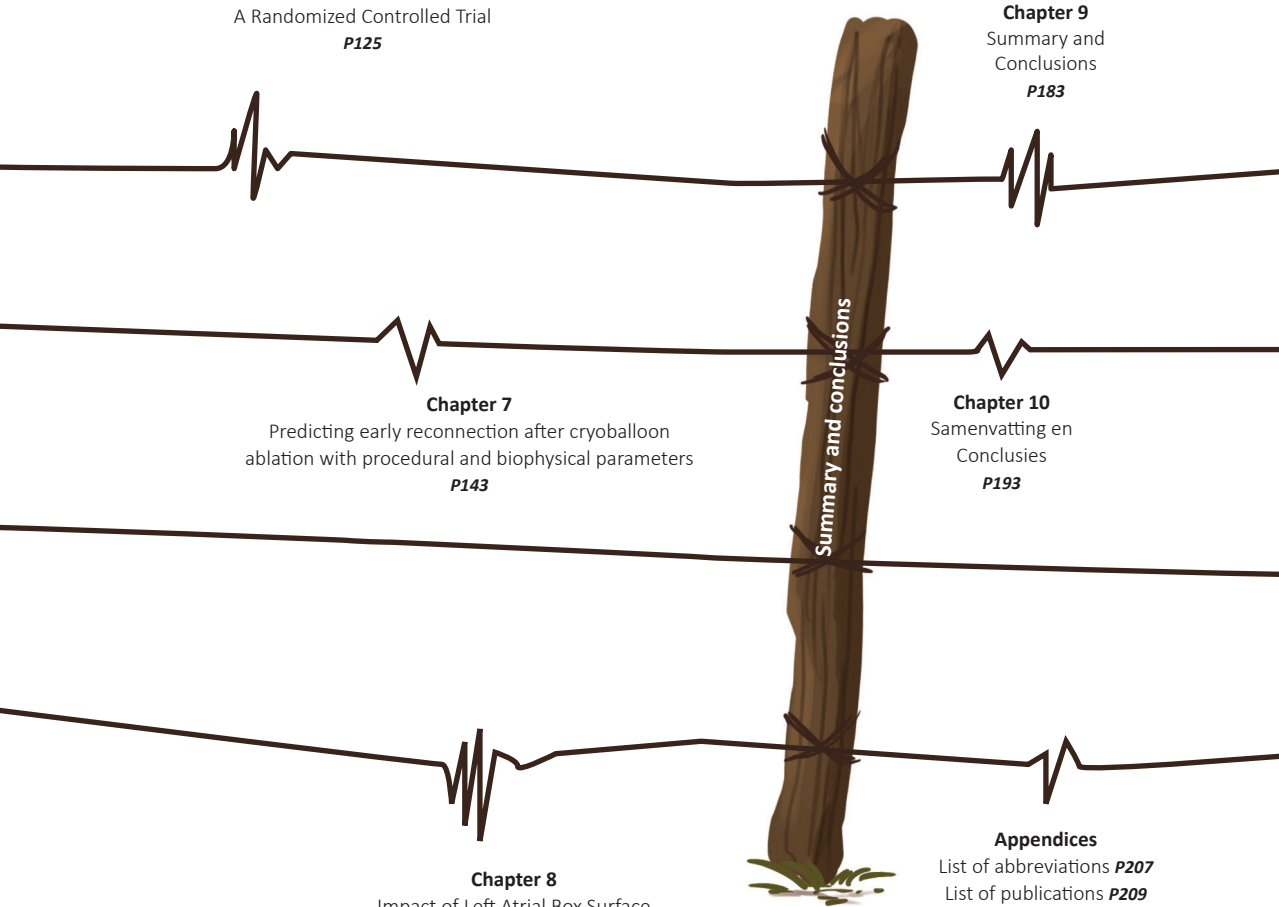
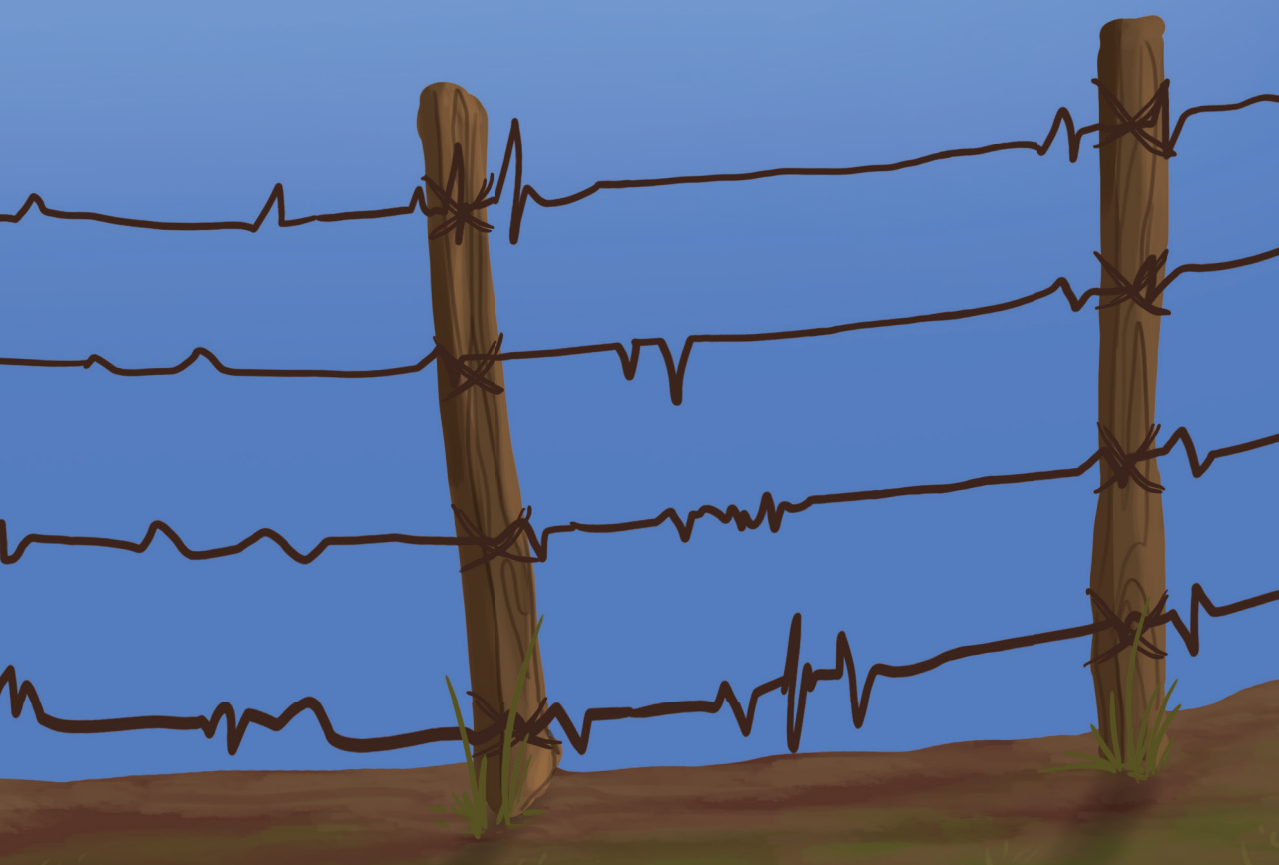
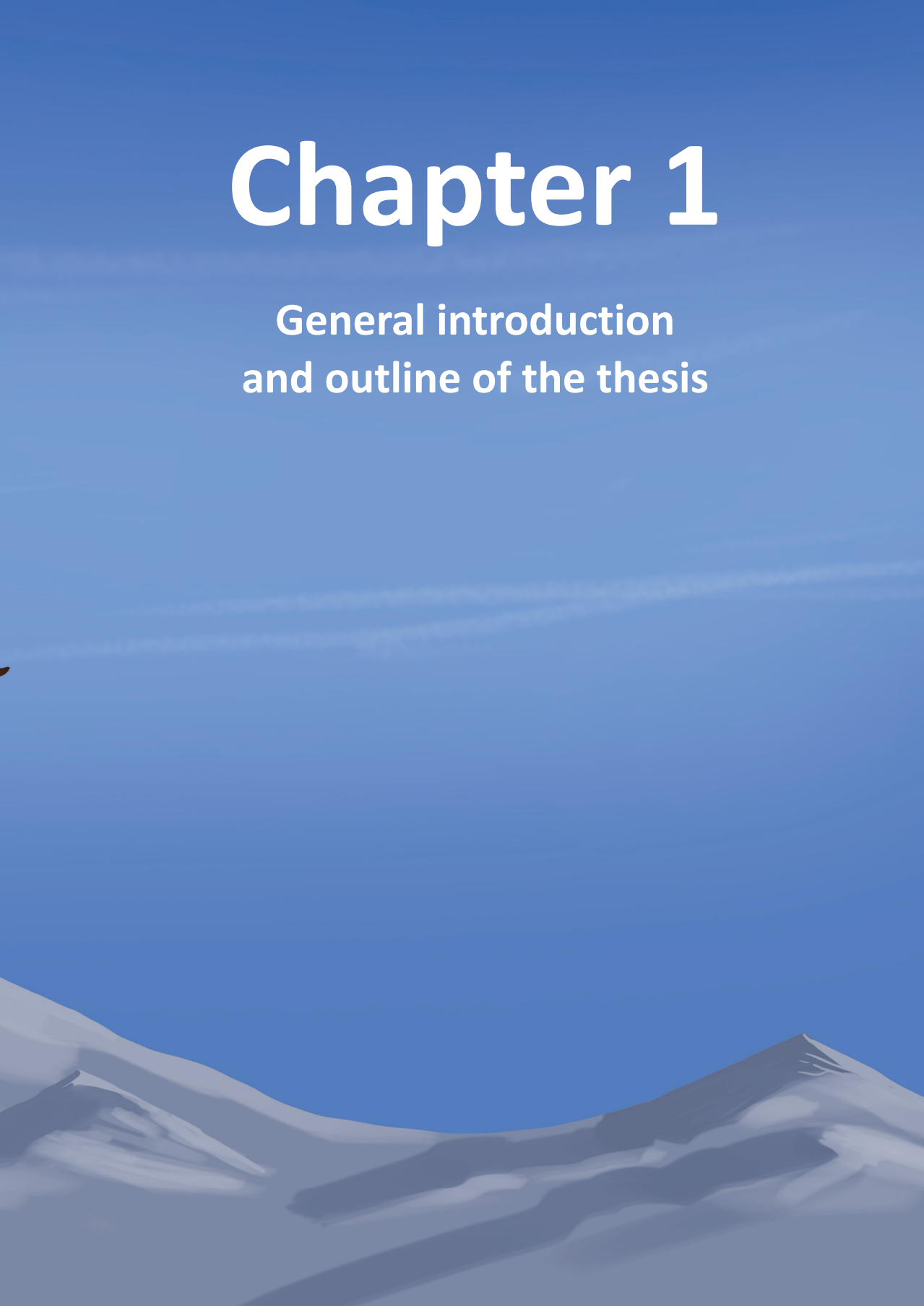


Introduction



Chapter 1

General introduction and outline of the thesis



1.1 The Era of Atrial Fibrillation Ablation

More than 33 million people worldwide have atrial fibrillation (AF), with a progressive increase in overall burden, incidence, prevalence and AF associated mortality (1). It is the most common tachycardia with reduction of quality of life necessitating frequent hospitalizations and high risk for complications, especially thrombo-embolic events (2).

AF occurs more frequently in patients with underlying heart disease, e.g. heart failure, ischemic cardiomyopathy and valvular heart disease but it can also occur in the absence of structural heart disease. Besides these specific causes for AF, also risk factors (obstructive sleep apnoea syndrome, metabolic syndrome and hypertension) contribute to the genesis of AF and are therefore significant treatment targets. The general classification of AF, described in the European society of Cardiology Guidelines is that of paroxysmal versus persistent AF (3), which is a rhythm-based classification. While this classification system is clinically useful, it does not reflect the underlying pathophysiology and substrate characteristics of the atria (4). To improve the treatment of AF however, understanding the pathophysiology of AF is of great importance.

The two main objectives in the treatment of symptomatic AF are stroke prevention and restoration and maintenance of sinus rhythm. While stroke prevention can be managed by oral-anticoagulation therapy, the pharmacological treatment to maintain sinus rhythm is limited by systemic toxicity, low efficacy and arrhythmogenicity (5). Therefore, interventional therapy of AF advanced to a serious alternative treatment strategy during the past decades (2).

The first surgical AF ablation in humans, the Maze procedure, was performed in seven patients concomitant to cardiac surgery in 1987 (6). The Cox-Maze procedure was effective with AF-free survival of 94% at 12 months (7), however it was also associated with significant chronotropic incompetence and the requirement of pacemaker implantation. In current practice the Cox-Maze-IV procedure is the gold-standard surgical treatment with high efficacy and safety. Cather ablation was performed for the first time around the year 2000 and has undergone impetuous advances over the last 20 years. In the Introduction section of this thesis, the pathophysiology of AF and the development of catheter ablation tools will be further discussed, with emphasis on the tools, techniques and safety.

1.2 Pathophysiology and ablation Techniques

The pathophysiology of AF is difficult and still not completely elucidated. The first theory is that of multiple wavelets, suggesting that AF results from multiple unstable re-entry circuits in the atria. The second theory in contrast, is of focal sources in the atria triggering and sustaining a chaotic rhythm. This theory gained support based on the role of the pulmonary veins showing short refractory periods and changes in myocyte fibre orientation as an ideal substrate for AF. Pulmonary vein isolation became therefore the cornerstone of AF ablation (8). However, in progressed AF also other sources outside the pulmonary veins sustaining AF have been identified. To define or improve a treatment strategy for AF, better understanding of the potential mechanisms of AF is of importance.

1.2.1 Pathophysiology

Mechanisms underlying AF can be divided in mechanisms responsible for its initiation (triggers) and in mechanisms responsible for its perpetuation. This is important to define ablation targets.

1.2.2 The role of the pulmonary vein electrophysiology

The role of the pulmonary veins with focal discharges initiating AF, firstly described by Haissaguerre in 1998 (9), is now the base of the ablation procedure. In histological studies muscle extensions, so called sleeves extending from the left atrium into the pulmonary veins with complex muscular architecture and fibre orientation producing great non-uniform anisotropic properties, act as an anatomical substrate for local re-entry (10). Also the presence of ectopic pacemaker tissue in the pulmonary vein myocardium, harbouring cells with pacemaker function (Cajal cells) may play a role in the arrhythmogenicity (11, 12). Pulmonary vein mediated arrhythmogenesis (PV-triggers) is based on re-entry, automaticity and triggered activity.

1.2.3 Functional re-entry

The functional re-entry as the ‘leading circle model’ was firstly described by Allessie *et al*. in 1976 (13). A circus movement of the impulse through a small area of atrial muscle results in a constant activation, making it continuously refractory. This area acts like a functional barrier, like a scar, which can sustain re-entry. A circus movement in one direction is initiated by an unidirectional block. The bordering myocardium and the center of the circuit become activated by the simultaneously spreading impulse. The number of reentrant circuits that can be sustained is dependent on wavelength and atrial size.

1.2.4 Rotors

Rotors or spiral waves describe a specific type of functional re-entry. The re-entry is in this case not circular, but curved or spiral. The wave front and wave tail meet at a focal point called a 'phase singularity'. The wave front is in contrast to the 'leading circle model' not constant but depends on the wave front curvature. The phase singularity region has the highest curvature and therefore the slowest wave front conduction velocity. The tissue core forms an area of functional block, similar to the centre of the leading circle model. The tissue core is not excitable, because the propagating wave front is unable to invade a core of tissue in the centre of the rotor, due the wave front curvature that is very high and the conduction velocity therefore very slow (14).

1.2.5 Endo-epicardial asynchrony

A relatively newly described mechanism is that of endo-epicardial asynchrony, characterized by dissociation of electrical activity not only within the epicardial layer but also between the epicardial layer and the endocardial bundle network. This concept may play a role in the maintenance of AF. During the first 6 months of AF, endo- and epicardial layers of the atrial wall become progressively dissociated. After that time, fibrillation waves in the endo- and epicardial layers often propagate at different speed and in different directions and endo-epicardial breakthroughs become more abundant (15). Dissociated layers of fibrillation waves will stabilize the fibrillatory process, because as soon as fibrillation waves die out, they can be replaced by breakthroughs from the opposite site. In this case, ectopic AF becomes 3-dimensional as a result of structural remodelling with a probably lower response to medication and ablation therapy, explaining why an early rhythm control strategy often has better results (16, 17).

1.2.6 Anatomical re-entry and remodelling of the atria

Re-entry occurs in the presence of unidirectional block and slow conduction making the wave length shorter than the length of the circuit. Anatomical re-entry occurs commonly in patients with atrial remodelling (18). Remodelling of the atria can be structural, electrical and autonomic.

1.2.7 Fibrosis (Structural Remodelling)

In patients with AF, structural remodelling of the atria occurs with activation of fibroblasts, enhanced connective tissue deposition and fibrosis (19, 20). In addition, inflammation, fatty infiltration, hypertrophy, necrosis and amyloidosis can be detected in patients with (a predisposition for) AF (21). Factors inducing structural remodelling are structural heart

disease, hypertension, obesity, sleep apnoea, diabetes, but also AF itself can result in fibrosis of the atria (19). The structural remodelling finally results in electrical dissociation of neighbouring atrial muscles bundles resulting in AF (19, 22).

1.2.8 Electrical Remodelling

During AF, auto-protective mechanisms become initiated by regulating the ion channel function in such a way that it promotes arrhythmias. As Ca^{2+} enters atrial cells with each action potential, rapid atrial rates increase Ca^{2+} loading initiating autoprotective mechanisms that reduce Ca^{2+} entry. Hereby the action potential duration decreases and atrial re-entry rotors stabilize. These mechanisms increase the atrial vulnerability to atrial arrhythmias leading to contractile dysfunction and tachycardia-induced atrial cardiomyopathy (18).

1.2.9 Autonomic and neural remodelling

Nerves and ganglionic neurons show great plasticity. Neural remodelling includes an increase in the atrial innervation (nerve sprouting), which results in initiation and maintenance of AF (18). Atrial fibrillation is associated with oxidative stress, which can cause neurodegeneration in the central nervous system. It is possible that oxidative stress causes cardiac nerve injury, which triggers the re-expression of nerve growth factor or other neurotrophic factor genes in the nonneural cells around the site of injury, leading to nerve regeneration through nerve sprouting. Moreover, the atrial rate is high during AF and the atria are deficient in coronary vessel distribution which makes the atrial myocardium prone to ischemic damage. Ischemic myocardial injury results in nerve degeneration followed by regeneration (23).

1.2.10 Genetics

AF has also an genetic component, which is independent of concomitant cardiovascular conditions. Especially early-onset AF is associated with heritability. Predominantly genes that encode cardiac ion channels with predicted mutation effects on the atrial action potential duration are thought to be responsible for AF. However, more recent studies have expanded the spectrum of disease-associated genes to myocardial structural components and cardiac transcription factors (24). More than 30 genes have been identified from studies of familial cases or individuals with lone atrial fibrillation. Genome-wide association studies (so called GWAS), test a large sample size comparing allele and genotype frequencies of single-nucleotide polymorphisms (SNPs) between individuals with atrial fibrillation and healthy controls. The power of any single SNP associated with atrial fibrillation is too weak to use as an informative marker to develop atrial fibrillation. However aggregating a set of SNPs associated with atrial fibrillation increases the risk for an individual to develop atrial fibrillation.

1.3 AF-Ablation and outcomes

Pulmonary vein isolation is the cornerstone of AF-ablation. Pulmonary vein isolation is associated with AF-Freedom between 60-79%. Late recurrences are in the most of the cases (98%) associated with electrical reconnection of the pulmonary veins, while this is 69-100% in very late recurrences of AF (25). In persistent AF electrical and structural remodelling of the left atrium occurs, requiring additional ablation strategies (14). The currently applied techniques in patients with persistent AF consist of pulmonary vein isolation and/or electrogram based ablation, linear lesions, targeting right atrial sites, autonomic ganglion ablation, rotor ablation, substrate ablation by voltage mapping and isolation of low voltages areas and posterior box lesion ablation (2, 8).

1.3.1 CFAE's

In CFAE ablation complex fractionated signals are targeted in patients with persistent AF. Although originally a high success rate was reported of 76% (Nademanee *et al*.)(26), this could not be reproduced (27, 28). In subsequent studies AF-freedom was not significantly different from PVI alone (28, 29).

1.3.2 Linear Lesions

In linear lesion ablation the goal is to place anatomical barriers to the wave front of the arrhythmia. In the STAR AF II study no benefit was shown of additional linear ablation in patients with persistent AF (29).

1.3.3 Right atrial ablation sites

The right atrium, inferior and superior vena cava, crista terminalis and the coronary sinus ostium are possible additional targets in right atrial ablation sites. These areas are borders between different embryonic tissues, capable of spontaneous depolarization (30). The diagnosis is made on the basis of a spontaneous onset of ectopic beats initiating AF during baseline or after provocative maneuvers with isoproterenol, adenosine and/or atrial pacing.

1.3.4 Autonomic Ganglion ablation

Ganglion ablation is shown to be beneficial when combined with pulmonary vein isolation in patients with paroxysmal AF. However in patients with persistent AF, large left atrium and previous catheter ablation it did not result in additional benefits at one year (31, 32).

1.3.5 Rotor ablation

With focal impulse and rotor modulation (FIRM) ablation, local sources and rotors are targeted. In the CONFIRM trial the success rate was 85% in a mixed AF-population, compared to only 20% with conventional ablation (33). Despite the promising results, poor long-term outcomes with FIRM-guided ablation are reported with randomized clinical trials (37% at 18±7 months)(34). It could be argued that in FIRM-ablations the favorable outcomes are attributed to adjunctive PVI, however this is difficult to conclude given these studies are non-randomized. PVI remains the foundation of all AF catheter ablation, and FIRM guided ablation alone, has not been shown to be efficacious (34, 35).

1.3.6 Substrate ablation

Substrate for AF may consist of fibrotic areas detected with MRI (DECAAF study)(36) or low voltage areas identified with voltage mapping. Yang *et al.* reported 70% AF-freedom after 30 months in patients who received additional substrate ablation compared to 51% who did not (37). Another novel ablation strategy is that of box isolation of fibrotic areas (BIFA) by Kottkamp *et al.* with success rate of 72% in patients with non-paroxysmal AF (38, 39). An interesting question is whether Delayed-Enhanced (DE)-MRI and voltage mapping both identify the same, potentially arrhythmogenic, atrial substrate. In a study of Chen *et al.* 61% of the low voltage areas co-located with DE-MRI and only 28% of the DE-MRI areas displayed low voltages (<0.5 mV). In this study the most arrhythmogenic sites co-located better with low voltage areas (78%) compared to DE on MRI (63%)(40). Arrhythmogenic sites were defined as spatio-temporal dispersion (potentially corresponding to rotational activity) or continuous activity. The authors suggest that further electrophysiological criteria should be used to guide ablation of arrhythmogenic substrate: late potentials, fractionated potentials, slow conduction areas, rapid/continuous activity or repetitive rotational activities with spatio-temporal dispersion during AF (40).

1.3.7 Posterior Box Isolation

Especially in persistent atrial fibrillation other left atrial structures proved to play a role in the maintenance of atrial fibrillation(2). Histological and electrophysiological determinants (fibrosis, drivers, rotors) are often found in the posterior wall of the left atrium. This may be explained by the common embryologic origin of the pulmonary veins (41-45). Several studies showed that posterior wall isolation in addition to pulmonary vein isolation improves ablation outcome (46, 47). The surgical treatment of persistent atrial fibrillation 'Cox Maze technique' emphasize the role of the posterior wall and also promotes the use of the Box Lesion approach.

1.4 Ablation Tools & Safety

For AF ablation many tools applying different energy sources have been developed and are still being amended. Point-by-point ablation of the ipsilateral pulmonary veins with radiofrequent energy with cooled single-tip catheters in combination with three-dimensional electro-anatomical mapping systems (Carto, Ensite, Rhythmia) is still a common approach in many electrophysiology laboratories.

The most frequently used single-shot device is the cryoballoon ablation system. Other single-shot devices are the laserballoon, hotballoon and the non-irrigated multi-electrode catheter (PVAC-Gold). Some ablation tools have been retracted from the market due to serious safety concerns (high-intensity-focused Ultrasound Balloon, Multi-electrode catheters (MASC, MAAC, nMARQ) (48), while new ones are still begin developed (multi-electrode radiofrequency balloons). The Kardium Globe contains 122 gold-plated mapping electrodes and 24 ablation electrodes (49) and the Multielektrode RF irrigated ablation catheter is a 28 mm diameter spherical compliant balloon with 10 gold surface electrodes to deliver radiofrequency energy, each with 4 holes for saline irrigation (50). Another new ablation concept is that pulsed field ablation (PFA), also known as electroporation, in which subsecond electric fields create microscopic pores in cell membranes (51).

All of the current devices are still being improved with new features (contact force), better cooling systems and optimization of the energy source delivery aiming at improvement of the efficacy and safety of the ablation procedure. During the last decade methods are developed e.g. oesophagus temperature monitoring, active cooling during ablation and power and energy limitations to prevent certain complications during AF ablation. In the next chapter, after the description of the outline of this thesis, different ablation devices and the incidence and prevention of complications are described.

1.5 Outline of this thesis

The purpose of this thesis is to investigate different ablation tools for efficacy and safety, with emphasis on two randomized controlled trials studying cerebral embolism with the PVAC-Gold catheter and investigating optimization of the cryoballoon ablation protocol.

In **chapter 2** as part of the **introduction** of this thesis, the reported incidence of complications is summarized, considering specific device-related aspects for point-by-point, multi-electrode and balloon-based devices. Secondly, the impact of technical advances on procedural outcome, length and radiation exposure is discussed. In **chapter 3** and **first part** of this thesis the first randomized clinical trial, studying the differences in incidence and clinical significance of asymptomatic cerebral embolism between the multi-electrode PVAC-Gold catheter and the Thermocool catheter, is presented. In **chapter 4** the biophysical data of the PVAC-Gold ablations from this trial are analysed to gain insight in the genesis of micro-emboli with this device. In **chapter 5** the origin of cerebral micro-emboli in this trial is studied from a haematological perspective by analysing different coagulation and haemostatic markers predicting these micro-emboli. In **chapter 6** and **second part** of this thesis, the second randomized controlled trial optimizing the cryoballoon ablation duration using dormant conduction to reveal incomplete pulmonary vein isolation is presented. In **chapter 7** the biophysical data of ablation with the second-generation cryoballoon is analysed to predict incomplete isolation. In **chapter 8** the impact of ablation surface area of the posterior box lesion on ablation outcome in persistent AF is studied. In **chapter 9 and chapter 10** conclusions of the chapters are summarized.

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Chapter 2

The impact of advances in atrial fibrillation ablation devices on the incidence and prevention of complications

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Abstract

The number of patients with atrial fibrillation currently referred for catheter ablation is increasing. However, the number of trained operators and the capacity of many EP labs are limited. Accordingly, a steeper learning curve and technical advances for efficient and safe ablation are desirable. During the last decades several catheter-based ablation devices have been developed and adapted to improve not only lesion durability, but also safety profiles, to shorten procedure time and to reduce radiation exposure. The goal of this review is to summarize the reported incidence of complications, considering device related specific aspects for point-by-point, multi-electrode and balloon-based devices for pulmonary vein isolation. Recent technical and procedural developments aiming at reducing procedural risks and complications rates will be reviewed. In addition, the impact of technical advances on procedural outcome, procedural length and radiation exposure will be discussed.

2.1 Introduction

Catheter ablation is an effective strategy to maintain sinus rhythm in patients with symptomatic atrial fibrillation (AF) which has evolved from a highly specialized technique to a first-line therapy (1-3). The cornerstone of ablation is pulmonary vein isolation (PVI) (4). Over the last decade, ablation devices have undergone technical improvements, aiming for better lesion durability and ablation outcomes. However, significant complications have been reported in survey studies and patient safety remains of concern (4-9). Although operators have become more experienced, technical advances with improved energy transfer may increase procedural risk. As a consequence, catheter design and ablation protocols have been adapted to prevent complications. For individualized patient care and device selection, knowledge of potential risks and benefits for the different available devices is important. The aim of this review is to provide an overview of type and incidence of complications and strategies for prevention for single-tip and multi-electrode radiofrequency catheter ablation (RFCA) and balloon-based ablation devices.

2.2 Point-by-Point radiofrequency ablation

After evidence that the pulmonary veins (PV) are the primary source of AF (10, 11), non-cooled radiofrequency ablation of ectopic beats from the PVs has been introduced (12, 13). Due to the high incidence of PV stenosis, (14) ablation has evolved from segmental ablation of the PVs guided by a circular mapping catheter (4, 15, 16) to wide-area circumferential PV isolation (17).

2.2.1 Historical overview

Catheter irrigation resulted in a lower risk for coagulum formation allowing for higher energy transfer with larger and deeper lesions (18, 19) and improved outcome (20), with a current AF free survival of 46-94% at one-year follow-up (table 1a/b). The introduction of three-dimensional electro-anatomical mapping systems (CARTO, Biosense Webster Inc. Diamond Bar, California, USA and Ensite, Abbott, St. Paul, Minnesota, USA) and image-integration tools has been associated with improved efficacy (21-25). Contact-force (CF) measurement during ablation has been developed to improve lesion formation (Thermocool Smarttouch, Biosense and Tacticath, Abbott; Figure 1) with a reported one-year AF free survival between 52-94% (table 1a/1b). There are conflicting reports whether CF improves ablation outcome (table 1b) (26, 27), suggesting that CF parameters need to be validated (26). Data from a recent meta-analysis suggest that ablation guided by CF is associated with improved median outcome at 12-months follow-up (28). Recent developments focus on improved near-field resolution by combining recordings from large-tip electrodes with recordings from micro-electrodes (QDOT-micro technology for Biosense Webster Inc.).

2.2.2 Procedure time

Procedural length has been associated with higher complication rates (29). Although radiation exposure can be reduced with 3D-mapping systems (24), point-by-point ablation often requires longer procedure times compared to single-shot techniques. Reported mean procedural time range between 101-284 minutes (table 1a/1b). Contact-force has been associated with reduced procedure, ablation and fluoroscopy times (28) and high-power-short-duration radiofrequency (RF) applications to further reduce procedure time are currently under investigation (30-32). Fluoroscopy time for RFCA, however approaches to zero under increasing experience of 3D-mappings systems and intracardiac electrocardiography (33, 34).

2.2.3 Complications

The use of image integration and electro-anatomical mapping has been associated with fewer complications (20-24, 35, 36). Whether CF-guided ablation improves safety requires additional investigation. In a recent meta-analysis, the overall complication and tamponade rates were 3.8% and 0.5% for CF and 3.9% and 0.9% for non-CF ablation (28). Irrigated catheters (Thermocool™, Biosense and Coolpath™, Abbot) have been introduced to prevent endothelial charring in particular at sites with low blood flow (19). Indeed, with irrigation, less micro-embolic signals have been detected with trans-cranial Doppler (37). Advanced irrigation technology (Thermocool Surround Flow and Abbot FlexAbility) reduces irrigation volume with maintenance of the safety profile (38). Thromboembolic event rates (stroke and transient ischemic attack) range between 0.2 and 1% for irrigated catheters. Phrenic nerve palsy (PNP) is rare (0.01-0.6%) and mainly transient. Similar, the reported incidence of oesophageal and vagal injury is low, ranging between 0.05-0.5% (table 1). However, a study focussing specifically on gastrointestinal complications reported an 11% incidence of thermal oesophageal lesions and a 17% incidence of gastroparesis (39). In the Manufacturer and User Facility Device Experience database of 2689 ablations the incidence of atrial-oesophageal fistula as a percentage of all reported complications for CF-catheters was higher (5.4% (65 of 1202 cases) compared to non-CF catheters (0.9% (13 of 1487 cases)(40). These numbers do not reflect the absolute incidence however. Pulmonary vein stenosis (PVS) after CF-guided ablation was only reported in one study with an incidence of 0.7% (41).

Table 1a. Overview of literature on radiofrequency ablation.

Author, year (study type)	Number of patients and type of ablation device	PAF (%)	Preventive techniques	AAD free survival (1 year) (%)	Procedural and ablation time (min)	Complications (%)
Aryana, 2015 (82) (retrospective)	N=423 RF	76	Power reduction (40W anterior, 30W posterior)	60 (P<0.001)	188 (p<0.001) 66 (p<0.001)	- Pericardial effusion/ Cardiac tamponade 1.7 - Transient ST elevation 0.2 - Vascular access 0.2 - Venous thromboembolism 0.2 - Other: pacemaker insertion 0.2
Chun, 2017 (122)(registry)	N=1559 RF N=556 RFA	43	Power reduction (40W anterior and 30 W posterior and inferior)	N.A.	101 (p=0.004) N.A.	- Cardiac tamponade 0.5 (p=0.024) - Stroke/TIA 0.2 - Atrial-oesophageal fistula 0.05 - Vascular access 2.6 - Other: Hemothorax 0.1
Khoueiry, 2016 (86) (observational)	N=376 RFA	100	Power reduction (30W anterior, 25W posterior). Temperature limitation 48°C	86	114 N.A	- Pericarditis/Cardiac tamponade 1.6 - Thromboembolic events 0.3 - Transient phrenic palsy 0.3 (p=0.016) - Upper digestive bleeding 0.3 - Vascular access /major bleeding 3.2 - Other 1.0 (haematuria, haemoptysis, and anaphylactic shock)
Kuck, 2016 (87) (multicenter RCT)	N=284 RF N= 93 RFA	100	Power reduction (40W anterior and inferior, 30W posterior)	64	124 (p<0.001) N.A.	- Pericardial effusion/Cardiac tamponade 1.3 - Transient neurologic complication 0.8 and Stroke/TIA 0.5 - Gastrointestinal complications 0.5 - Vascular access 4.3 - Other 2.7 (pulmonary or bronchial complication 1.1, dyspnea 0.5, contrast media reaction 0.3, contusion 0.3, hematuria 0.3 and local oedema 0.3)

Table 1a. Continued.

Author, year (study type)	Number of patients and type of ablation device	PAF (%)	Preventive techniques	AAD free survival (1 year) (%)	Procedural and ablation time (min)	Complications (%)
Luik, 2015 (161) (RCT)	N=159 RF	100	N.A	60	174 (IQR 147-218) N.A.	- Pericardial effusion 1.9 - Vascular access 3.1
Mugnai, 2014 (88) (retrospective)	N=260 RF	100	Power reduction (35W anterior and 25W posterior); Temperature limit 48˚C	63	192 (P<0.001) N.A. 36	- Pericardial effusion/Cardiac tamponade 10/1.5 - Vascular access 0.8 - Other: Third degree AV-block/Sinus arrest 0.8; Contrast reaction 0.4
Providencia, 2017 (162) (multicenter retrospective)	N=467 RF	100	Power reduction (30W anterior and 25W posterior)	46–79 at 18m	136 (p=0.001) N.A.	- Pericardial effusion 1.7 (p=0.036) - TIA 0.2 - Oesophageal bleeding 0.2 - Vascular access 1.9 - Other 0.9 (haemoptysis, haematuria, anaphylactic shock and temporary myocardial sideration)
Schmidt, 2014 (90) (multicenter retrospective)	N=2870 RF	100	Centers preference	N.A.	165 (IQR 120-210) 33 (IQR 21-50) (P<0.001)	- Cardiac tamponade 1.4 - Phrenic nerve palsy 0.0 (p=0.001) - Vascular access 1.1 and 1.1 - Other: pneumothorax 0.3, hemothorax 0.2 ; sepsis 0.0 and surgical accident 0.1
Squara, 2015 (91) (multicenter retrospective)	n=178 RFA	100	Power reduction (30-35W anterior and 20 W posterior) Oesophageal monitoring (discretion of the operator 38.5C cut-off)	83 DC testing	123 (p=0.003) N.A.	- Cardiac tamponade 1 - Embolic events 1 - Oesophageal complication 0.5 - Vascular access 4

Table 1a. Continued.

Author, year (study type)	Number of patients and type of ablation device	PAF (%)	Preventive techniques	AAD free survival (1 year) (%)	Procedural and ablation time (min)	Complications (%)
Straube, 2016 (92) (multicenter observational)	N=180 RF	100	N.A.	61	180 (p<0.001) 38 (P<0.001)	- Cardiac Tamponade 2.5 - Stroke 0.6 - Transient PNP 0.6 - Vascular access 7.5 and severe bleeding 0.6
Wasserlauf, 2015 (96) (retrospective)	N=100 RF	100	N.A.	61	284 (P<0.001) N.A.	- Cardiac tamponade 4 - Vascular access 1 - Other: respiratory arrest during extubation 1

Only observational/retrospective studies and randomized clinical trials with n > 100 are included. in patients with paroxysmal atrial fibrillation, showing the use of different ablation devices, outcomes, the use of preventive techniques and complication rates. AAD= anti-arrhythmic drugs, DC=dormant conduction, IQR=interquartile range, PAF=paroxysmal atrial fibrillation, PNP=phrenic nerve palsy, RF=radiofrequency ablation, RFA=radiofrequency advanced with CF technology and TIA=Transient ischemic attack. P-values indicated significant differences between catheters from the same technology (table 1) or between catheters from different technologies (table 1 vs. table 2).

Table 1b. Overview of literature on radiofrequency ablation with and without Contact-Force.

Author, year (study type)	Number of patients and type of ablation device	PAF (%)	Preventive techniques	AAD free survival (1 year) (%)	Procedural and ablation time (min)	Complications (%)
Itoh, 2016 (163) (prospective, non-randomized)	N=50 RF N=50 RFA	100	Power reduction (30W anterior, 25W posterior)	78 vs. 94	245 vs. 165 (p<0.001) N.A.	- No major complications in both groups
Jarman, 2015 (164) (multicenter, retrospective)	N=400 RF N=200 RFA	46	Power reduction (30-35W anterior, posterior 25W)	46 vs 59 (p=0.05)		- Pericardial effusion/Cardiac tamponade 1.2 RFA - Stroke 0.2 RF TIA 0.2 RFA - AE fistula 0.2 RF - Pulmonary vein stenosis 0.2 RF - Vascular access 1.8 (RF/RFA)
Lee, 2016 (165) (retrospective, observational, cohort)	N= 418 RF N=238 RFA	47 vs. 41	Power limitation (30W)	N.A.	200 vs. 240 (p<0.001) 43 vs. 35	- Pericardial effusion/Cardiac tamponade 0.8 vs. 1.0
Nair, 2017 (166) (observational cohort)	N=99 RF n=68 RFA	100	Power reduction (<40w anterior and <25w posterior)	51 vs. 66 (p=0.06) (3-year follow up)	347 vs. 257 (p<0.001) 57 vs. 43 (p<0.001)	- Cardiac tamponade 3 vs. 0 - Vascular access 1 RF - Other: Oesophageal tear during temperature probe insertion 1 RFA, Traumatic Foley catheter insertion 1 RF
Reddy, 2015(41) (multicenter RCT)	N=143 RF N=152 RFA	100	N.A.	68 vs. 69	N.A. 27vs.23. (p=0.044)	- Cardiac tamponade 2.7vs.2.1 and Pericarditis 1.3 RFA - Pulmonary vein stenosis 0.7 RF - Vascular access 2 vs. 2.1 - Other: Pulmonary oedema 1.3 vs. 1.4
Sigmund, 2015 (167) (prospective, case matched)	N=99 RF N=99 RFA	65 vs. 63	Power reduction (30-35 anterior, 25 posterior) Temperature limitation (43°C)	73 vs. 82	216 vs. 178 (p<0.001) 48 vs. 38 (p=0.001)	- Cardiac tamponade 3.0 vs. 2.0 - Vascular access 2 vs. 1

Table 1b. Continued.

Author, year (study type)	Number of patients and type of ablation device	PAF (%)	Preventive techniques	AAD free survival (1 year) (%)	Procedural and ablation time (min)	Complications (%)
Ullah, 2016 (27) (multicenter RCT)	N= 59 RF N= 59 RFA	100	Power limitation (30W) Temperature limitation (48°C)	49 vs. 52	39 [IQR 32-46] vs. 41 [IQR 34-50]	- Pericardial effusion/Cardiac tamponade 1.7 vs. 3.4 - Vascular access 6.8 vs. 3.9 - Other: pericarditis 3.4 RFA
Wutzler, 2014 (168) (prospective, non-randomized)	N=112 RF N=31 RFA	76 vs. 61	Power limitation (35W) Temperature limitation (43°C)	63 vs. 84 (p=0.031)	158 vs. 128	- Pericardial effusion/Cardiac tamponade 0.9 RF - Vascular access 2.7 vs. 3.2

Only observational/retrospective studies and randomized clinical trials with n>100 are included) in patients with paroxysmal atrial fibrillation, showing use of different RF ablation devices, outcomes, the use of preventive techniques and complications rates.AAD= anti-arrhythmic drugs, DC=dormant conduction, IQR=interquartile range, PAF=paroxysmal atrial fibrillation, PNP=phrenic nerve palsy, RF=radiofrequency ablation, , RFA=radiofrequency ablation advanced with CF technology and TIA=Transient ischemic attack. P-values indicated significant differences between catheters with and without contact-force (RF versus RFA).

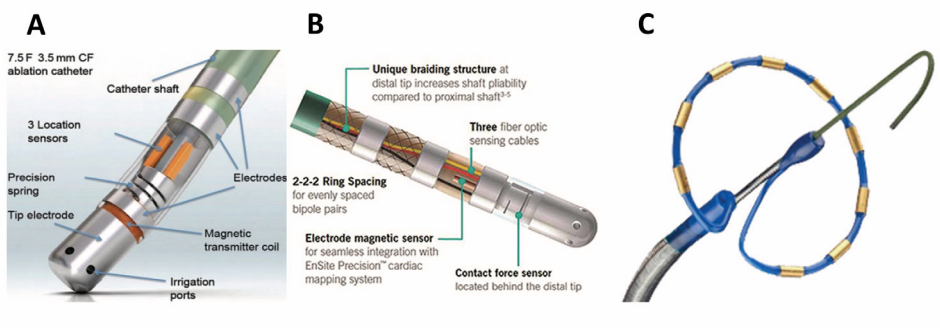

Figure 1. Radiofrequency Ablation Devices with CF and Multi-electrode Ablation Catheters. (A) The Thermocool Smarttouch from Lin *et al.* (170). (B) the Tacticath Catheter from Abott (sjmglobal.com). (C) PVAC-Gold – the non-irrigated multi-electrode catheter reproduced with the permission of Medtronic, Inc.

2.3 Multi-electrode catheters

2.3.1 Historical overview

Multi-electrode RF catheters have the potential to reduce ablation and procedural time. The pulmonary vein ablation catheter (PVAC, Medtronic, Minneapolis, MN, USA) can deliver RF energy in different duty-cycled unipolar/bipolar modes. One-year AF free survival off AAD with the first-generation device was 61% in patients with paroxysmal AF (42). To reduce the embolic risk potentially associated with non-irrigated RF catheters, submerging the catheter in saline before introduction and maintaining an activated-clotting time (ACT) above 350s have been recommended. As interaction of electrodes 1 and 10 was associated with occurrence of asymptomatic cerebral embolism (43), the current generation catheter (PVAC-Gold, Figure 2) has only 9 electrodes with a larger inter-electrode spacing and different electrode composition (from platinum to gold) for better heat conductivity. Reported one-year AF free survival with PVAC-Gold ranges from 60-71% (44-46). Studies comparing the efficacy of PVAC and PVAC-Gold found no significant difference at 1-year follow up (64-65% and 68-70%, respectively (45, 47)). Other (irrigated) multi-electrode catheters in the past were withdrawn because of safety concerns (e.g. new multipolar irrigated radiofrequency ablation catheter, Biosense Webster Inc., Multi-array septal catheter/Multi-array ablation catheter, Medtronic Inc. and High Density Mesh ablator, Bard Electrophysiology, Lowell, MA)(48).

2.3.2 Procedure time

Ablation with a smaller number of simultaneously activated electrodes to reduce thrombo-embolic risk has significantly prolonged procedure times (159±39 vs. 121±15 min) with the first generation PVAC (49). For the PVAC-Gold catheter shorter procedure times (94-117 min) have been reported (45, 47).

2.3.3 Complications

Asymptomatic cerebral embolisms were significantly higher with PVAC (incidence 38-39%) than with irrigated RFCA and cryoballoon ablation (50-53). The potentially high embolic risk is supported by studies on micro-embolic signals recorded with transcranial Doppler ultrasonography (54-56). However, after technical modifications to eliminate electrode 1-10 interaction, the duration of micro-embolic signals was reduced with only 33% (57, 58). The clinical relevance of asymptomatic cerebral embolism detected on MRI and trans-cranial Doppler remains, however, unclear (59, 60). Despite technical improvements, the second-generation PVAC-Gold catheter still showed a high incidence of asymptomatic

cerebral embolism (20% vs. none, p=0.011) and a higher amount and duration of micro-embolic signals compared to irrigated RFCA in a randomized clinical trial from our centre (58). PNP is uncommon after PVAC ablation. It was first reported in 2010 (61) and occurred in only 1/272 (0.4%) consecutive patients (62). PVAC ablation is usually performed at the ostium of the PVs and a detectable narrowing of the PV diameter has been reported in 23% of patients and 7% of veins (14, 63, 64).

2.4 Balloon-based devices

Several balloon-based devices have been developed for PVI (Figure 2), including the cryoballoon, the hotballoon, the endoscopic laserballoon and the high-intensity focused ultrasound balloon. The latter is no longer available (for safety reasons) and will not be discussed in this review. A potential limitation of these devices is the more distal PVI compared to point-by-point isolation (65). However, over the last decade, balloon-based devices have undergone important technical improvements.

2.4.1 Cryoballoon

2.4.1.1 Historical overview

First animal studies with cryoballoon ablation were published in 2005 (66, 67). A double-lumen balloon is cooled by expansion of NO_2 (66). The second-generation cryoballoon (Arctic Front Advance, Medtronic Inc., Minneapolis, MN, USA) have an increased gas flow, improved temperature uniformity and a more proximal cooling of the balloon with more internal injection ports compared to the first-generation (68). The broader cooling zone, together with easier positioning of the balloon with the second-generation steerable sheath (Flexcath Advance) and real-time assessment of PV isolation with the intraluminal spiral catheter (Achieve) has resulted in enhanced lesion durability and more antral ablation (69, 70). Recent studies reported success rates (off AAD) of 76-86% after 1-2 years for the first and second generation cryoballoon (71-78) (table 2). Freedom of AF off drugs was reported in 48-74% of patients for the first-generation cryoballoon and in 65-83% for the second-generation cryoballoon at 1 year follow-up. In a retrospective study, comparing the two balloons no significant differences in outcome was observed (78 vs. 83% at 1 year follow up) (79). The third-generation cryoballoon with a shorter tip to facilitate better PV-signal recordings is still being developed.

2.4.2 Procedure time

With the development of the second-generation cryoballoon, the ablation protocol has been adapted with reduced cryo-application times (180s instead of 2 times 300s) (79, 80). Recent studies evaluating shorter applications times based on the time-to-isolation showed a similar efficacy at 1 year follow-up (72-77, 81).

2.4.3 Complications

The reported incidence of complications is low and not significantly different between the first and second-generation cryoballoons (79, 82-96). Specifically, the reduction in ablation time was not associated with lower complication rates (table 2). Cardiac tamponade occurred in 0.7% (47 of 6672 procedures) and was similar for first and the second-generation balloons (table 2). The incidence of phrenic and vagal nerve damage is however, of concern. In a series of 66 patients, asymptomatic gastroparesis was reported in 9%, transient PNP in 8% and symptomatic inappropriate sinus tachycardia in 1% (97). The reported incidence of PNP ranged between 2-28% for the first-generation and between 1-16% for the second-generation cryoballoon (table 2). An association between cryoballoon use and any oesophageal injury has been reported in up to 17% (98, 99). However, atrial-oesophageal fistulae are rare and have only been case-reported (100-102). Stroke and transient ischemic attacks are reported in 0.3-0.5% of patients (table 2). Of importance, the risk for PVS is also low. In a recent study, 0.4% of the patients showed an only mild (25-50%) PVS (103).

Table 2. Overview of literature on ablation with the cryoballoon.

Author, year (study type)	Number of patients, ablation device and protocol*	PAF (%)	Preventive techniques	AAD free survival (1 year) (%)	Procedural, ablation time and fluoroscopy time (min)	Complications (%)
Aryana, 2014 (79) (retrospective)	N=140; CB 3x5	86	Temperature balloon (-60) Phrenic nerve pacing(20mA, 1500ms)	78 DC testing	209 (p<0.001) 61 (p<0.001) 42 (p<0.001)	- Transient PNP 12.1 and permanent PNP 0.7 - Vascular access 0.7 - Other: myocardial infarction 0.7 (after 8 weeks)
Aryana, 2014 (79) (retrospective)	N=200; CBA 2x3-4	72	Temperature balloon (-60) Phrenic nerve pacing(20mA, 1500ms)	83 DC testing	154 (p<0.001) 47 (p<0.001) 27 (p<0.001)	- Pericardial effusion/Cardiac tamponade 1.5 - Transient PNP 16 and permanent PNP 0.5 - Gastroparesis 0.5 (symptoms resolved after 2 months) - Vascular access 0.5 and haemorrhage requiring blood transfusion 0.5 Other: myocardial infarction 0.5
Aryana, 2015 (82) (retrospective)	N=773; CBA 1-3 x 2-4	77	Temperature balloon (-65) Phrenic nerve pacing (20-25mA, 800-1500ms)	77 (P<0.001)	145 (p<0.001) 40 (p<0.001) 29 (p<0.001)	- Pericardial effusion/Cardiac tamponade 0.6 - Transient ST-elevation 0.1 - Transient PNP 7.6 and permanent PNP 1.2 - Gastropareseis 0.1 - Vascular access 0.3 and venous thromboembolism 0.3
Aytemir, 2013 (83) (observational)	N=236; CBA 2x5	80	Phrenic nerve pacing	81 (18 months IQR 6-27)	72 Median 2 (IQR 2-5) 14	- Cardiac tamponade 0.8 - Transient PNP 1.2 - Vascular access 3.8
Chun, 2017 (122)(registry)	N=589 CB(A); N=286 Laserballoon CB 2x5; CBA 2x4	100	Oesophageal temperature monitoring	N.A.	106 (p=0.004) N.A. 13 (p<0.001)	- Cardiac tamponade 0.1 (p=0.024) - Stroke/TIA 0.4 - Permanent PNP 1.7 (p=0.001) - Vascular access 2.9 - Other: hemothorax 0.2

Table 2. Continued.

Author, year (study type)	Number of patients, ablation device and protocol*	PAF (%)	Preventive techniques	AAD free survival (1 year) (%)	Procedural, ablation time and fluoroscopy time (min)	Complications (%)
Ciconte, 2015 (84) (observational)	N=143; CBA 1x3	79	Phrenic nerve pacing	83	95 N.A. 14	- Transient PNP 6.3; permanent PNP 3.5(recovery <1 year) - Vascular access 1.4
Defaye, 2011 (85) (observational)	N=117; CB 2x4	79	Phrenic nerve pacing	69	155 N.A. 35	- Pericardial effusion 1.7 / Cardiac Tamponade 0.9 - Transient ST elevation 0.9 - Transient PNP 3.4 - Other: chest pain/haemoptysis 0.9
Khoueiry, 2016 (86) (observational)	N=208 CB; N=103 CBA; CB(A) 2x4 minutes	100	Phrenic nerve pacing	83	133 (p=0.001) N.A. 26 (p=0.005)	- Pericarditis/Cardiac tamponade 0.3 - Thromboembolic events 0.3 - Transient phrenic palsy 2.3 (p=0.016) - Gastroparesis 0.3, oesophageal ulcer 0.3 - Vascular complications/major bleeding 2.3 - Other: 0.7 (haemoptysis and hemomediastin)
Kuck, 2016(87) (multicenter RCT)	N=90 CB; N=279 CBA; CB 1x5; CBA 1x4	100	Phrenic nerve pacing	65	141 (p<0.001) N.A 17 (p<0.001)	- Cardiac tamponade/Effusion 0.3 - Stroke/TIA 0.5 and transient neurologic complications 0.3 - Transient an permanent PNP 2.7 (p=0.001) and0.3 - Gastrointestinal complication 0.3 ; oesophageal ulcer 0.3 - Vascular access 1.9 - Other: pulmonary or bronchial complication 0.5; other cardiac complications 0.8, anxiety 0.3
Luik, 2015 (161) (RCT)	N=156; CB 2x5; CBA 2x4	100	N.A.	61	161 (IQR 133-193) (p=0.006) N.A. 25 (IQR 18-31)	- Pericardial effusion 1.3 - Transient and permanent PNP 3.8 (p=0.002) and 1.9 - Vascular access 5.1

Table 2. Continued.

Author, year (study type)	Number of patients, ablation device and protocol*	PAF (%)	Preventive techniques	AAD free survival (1 year) (%)	Procedural, ablation time and fluoroscopy time (min)	Complications (%)
Mugnai, 2014 (88) (retrospective)	N=136; CB 2x5	100	Phrenic nerve pacing (12mA, 1000ms)	57	112 (P<0.001) N.A.	- Pericardial effusion/ Cardiac tamponade 7.3/ 0.7 - Transient ST-elevation 1.5 - Phrenic nerve palsy 8.1 (p<0.001); 0.7 at 12 months - Vascular access 1.5
Neumann,2008 (89) (observational)	N=346; CB2x5	85	N.A.	74	170 (IQR 140-195) 46 (IQR 26-60) 40 (IQR 30-57)	- Cardiac tamponade 0.6 - Transient PNP 7.5 - Vascular access 2.3
Providencia, 2017(162) (multicentre retrospective)	N=393; CB 2x4	100	N.A.	68–80 at 18m	120 (p<0.001) N.A. 23	- Pericardial effusion 0.3 (p=0.036) - Stroke/TIA 0.3/0.5 and coronary gas emboli 0.3 - PNP 1.8 (p=0.004) - Vascular access 2.0 - Other: 1.0 (haemoptysis and hemothorax)
Schmidt, 2014 (90) (multicentre retrospective)	N=905 CB; (discretion of the physician)	100	Phrenic nerve pacing	N.A.	160 (IQR 130-200) 45 (IQR 40-57) (p<0.001) 34 (26-46) (p<0.001)	- Cardiac tamponade 0.8 - Stroke/TIA 0.3 and myocardial infarction 0.1 - Permanent PNP 2.1 (p<0.001) - Vascular access 1.4 - Other: third-degree AV-block 0.1
Squara, 2015 (91) (multicenter retrospective)	N=198 CBA; 2x4	100	N.A.	82 DC testing	110 (p=0.003) N.A. 18	- Transient PNP 5.6 (p=0.001) - Vascular access 1.7

Table 2. Continued.

Author, year (study type)	Number of patients, ablation device and protocol*	PAF (%)	Preventive techniques	AAD free survival (1 year) (%)	Procedural, ablation time and fluoroscopy time (min)	Complications (%)
Straube, 2014 (93)	N=224 CB; N=308 CBA; CB 2x5 CBA 2x4	100	Temperature balloon Oesophageal temperature monitoring	N.A.	185 vs. 175 (p=0.038) N.A. 34 vs. 29 (P<0.001)	- Pericardial effusion/Cardiac tamponade 0.27 / 0.27 vs. none - Stroke/TIA 0.27 / 0.27 vs. none and transient amaurosis fugax none vs. 0.83 -Transient PNP 27.5vs.27.5 and permanent PNP 1.1 vs. 1.67 - Gastroparesis 0.27 vs. none. - Vascular access 1.10 vs. 0.83
Straube, 2016 (92) (multicenter observational)	N=193 (86% CBA; n=164) N.A.	100	N.A.	71	112 (P<0.001) 32 (P<0.001) 16	- Cardiac tamponade 0.4 - Stroke 0.5 - Transient/Permanent PNP 1.6/ 0.5 - Vascular access 7.5
Van Belle, 2008(94) (observational)	CB=141; N.A.	100	N.A.	48 (59 after second procedure)	207 N.A. 50	- Transient PNP 4 - Vascular access 4 - Other: haemoptysis 2
Vogt, 2013(95) (prospective observational)	N=605 CB; CB 2x6 (LSPV 3x5)	96	N.A.	62 (24 (IQR 12-42)	156 N.A. 25	- Pericardial effusion/Cardiac tamponade 0.2 / 0.2 - Stroke 0.3 - Transient PNP 2.5 - Asymptomatic pulmonary vein stenosis 0.3 - Other: hemoptysis 1.7
Wasserlauf, 2015 (96) (retrospective)	N=31 CB; N=70 CBA; 1x3-4	101	N.A.	60	193 (P<0.001) N.A. 46 (P<0.001)	- Transient PNP 1 - Vascular access 1 - Other: urinary tract infections 3

(only observational/retrospective studies and randomized clinical trials with n > 100 for are included) in patients with paroxysmal atrial fibrillation, showing the use of different ablation devices, outcomes, the use of preventive techniques and complication rates.AAD= anti-arrhythmic drugs, CB =cryoballoon (first-generation), CBA=cryoballoon advanced (second-generation), DC=dormant conduction, IQR=interquartile range, PAF=paroxysmal atrial fibrillation, PNP=phrenic nerve pacing and TIA=Transient ischemic attack. P-values indicated significant differences between catheters from the same technology (table 2) or between catheters from different technologies (table 2 vs. table 1). *protocol (number of freeze cycles x duration in minutes).

2.5 Hotballoon

2.5.1 Historical overview

The hotballoon (HotBalloon catheter, Sataka, Toray Industries, Tokyo, Japan) is a compliant RF-based balloon (25-35 mm) which is filled with saline and contrast. The balloon can be heated to a temperature of 65-75 °C through a coil electrode inside the balloon. Energy delivery is based on thermal conduction to the tissue in contact with the balloon surface. The first human study has shown that 2-3 applications of 2-3 minutes duration were required to achieve PVI resulting in AF free survival of 92% off AAD during a mean follow-up of 11±5 months (104). In consecutive studies, reported outcome off AAD was 78, 59 and 65% after 1, 6.3 and 3.6 years, respectively (105-107). Randomized studies comparing the hotballoon with other ablation technologies are lacking.

2.5.2 Complications

In an early animal study published in 2001, no major complications were reported (108). In a human feasibility study, oesophageal injury, however, occurred in 3 of the first 6 cases. After introduction of oesophageal cooling with saline, consisting of repeated injections of 10-20 ml mixture of contrast medium and saline, cooled at 10˚C during applications, only one additional injury was observed in the next 58 patients (109). In a series of 502 patients, the incidence of oesophageal injury could be further reduced by adapting the oesophageal temperature cut-off (39° C instead of 41° C) (107). Additional procedural related complications included PNP and PVS. In a series of 319 ablations performed in 238 patients, 16 major complications occurred: >70% PV stenosis in 4 (1.7%), temporary PNP in 8 (3.4%) and oesophageal injury in 4 (1.7%) (105). In a randomized controlled trial comparing hotballoon with AADs, for paroxysmal AF major complications were reported in 15 (11%) patients: PV stenosis of >70% in 5% and transient PNP in 3.7% (106). The hotballoon is still under investigation and optimal ablation energy and duration needs to be determined.

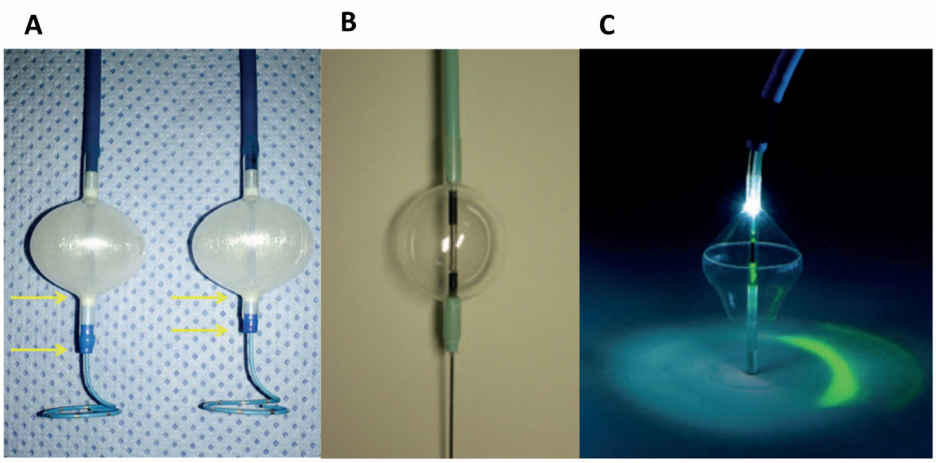

Figure 2. Different Balloon-based Ablation Devices for Pulmonary Vein Isolation.
The second and third-generation cryoballoon (with a shorter tip indicated with arrows for better pulmonary vein recordings) (A) with a spiral catheter inside the balloon. The hotballoon (B): the inflated balloon with a thermocouple and radiofrequency electrode inside and a central lumen for a guide wire and the laserballoon (C) with an endoscope and arc generator in the catheter shaft inside the balloon. Images are respectively derived from Chierchia *et al.* (169), Sohara *et al* (109) and Reddy *et al.* (110)

2.6 Laserballoon

2.6.1 Historical overview

The first-generation laserballoon (Endoscopic ablation system, Cardiofocus Inc. Marlborough, Massachusetts, USA) was available in three diameters (20, 25 and 30 mm). It consists of a delivery sheath with an endoscope and arc generator inside a balloon. With the endoscope, the intra-cardiac anatomy and adequate tissue contact can be visualised real-time. The arc generator delivers laser energy to perform PVI (110). Similar to other balloon-based devices, superior caval vein pacing and oesophageal temperature monitoring (39 °C cut off) is recommended to minimize the risk for PNP and oesophageal injury. After ablation, PV isolation needs to be evaluated with a separate spiral catheter. In the next-generation balloon (HeartLight, Cardiofocus, Inc., Marlborough, Massachusetts, USA), the arc of the laser was decreased from 90-150 to 30 degrees to improve safety. In addition, the balloon material was modified allowing variable sizing and deformation to prevent mismatch between the balloon size and the PV diameter (111). Based on data from 9 studies, including 1021 patients the efficacy of the HeartLight balloon procedure ranged between 58-88% at 1-1.5 year follow (off AAD) (112). A more compliant laserballoon is currently being developed (HeartLight Excalibur Balloon™, Cardiofocus Inc.).

2.6.2 Procedure time

The first-generation laserballoon was initially constructed as a two-operator device for positioning the balloon and directing the laser ablation (113). The second-generation laserballoon can be used by a single-operator. In addition, energy delivery has been modified leading to a shorter procedural duration from 334 min during first use (110) to 133-236 min in the improved laserballoon (112, 114).

2.6.3 Complications

A paper providing pooled data of 8 small studies (total 308 patients) reported PNP in 2.3% and cardiac tamponade in 1.9% of the patients (113). In a multi-center study including 200 patients with paroxysmal AF, similar complications rates were observed (2% cardiac tamponade and 2.5% PNP (115). However, in a recent multicenter prospective study 1 patient out of 68 showed PNP and 1 patients developed a stroke (both 1.5%) (114). Of concern, the incidence of asymptomatic cerebral embolism with the laserballoon was 24%, but not significantly higher (p=0.8) than for cryoballoon (18%) and irrigated RFCA (24%) in a randomized study (116). In a clinical trial comparing laserballoon with irrigated

RFCA (178 vs. 175 patients), the incidence of all adverse events was also similar (12% vs. 15%) (111). However, the incidence of PNP was significantly higher with the laserballoon (3.5% vs. 0.6%). PNP was also the major complication in another study with an incidence of 5.8%. Cardiac tamponade was reported in 3.5% of the patients (117). In these studies PVS was not reported.

2.7 Comparison of ablation devices

2.7.1 Ablation technology and efficacy

Outcome after cryoballoon ablation vs. point-by point RFCA has been well studied, also in randomized trials: a recent meta-analysis of 10 studies (total of 6473 patients; 3 randomized trials) showed similar efficacy (118). Data comparing other single-shot techniques with RFCA are limited. Smaller studies suggest no significant differences in efficacy. A randomized multi-center clinical trial comparing the laserballoon with RFCA (178 vs. 175 patients) reported a 61 vs. 62% AF free survival at 1 year (off AAD) (111). Also in another multi-center prospective trial comparing laserballoon (n=68) with RFCA (n=66) there was no difference in outcome (71 vs. 69%, p=0.40) at 1-year follow-up (off AAD)(114). In a study comparing laserballoon with cryoballoon (n=140) the efficacy at 1 year off AAD was comparable between the 2 techniques (73.vs.63%) (119).

2.7.2 Ablation technology and procedural time

The reported procedure times for cryoballoon ablation are significantly shorter compared to point-by-point RFCA (118) (table 1-2). Similar, procedural time using multi-electrode ablation catheters (PVAC) are shorter if compared to point-by-point RFCA, while the efficacy was similar (120, 121). Although in an early study longer procedural times were reported for laserballoon ablation compared to cryoballoon ablation and point-by-point RFCA (116), a recent study demonstrated similar procedural duration (laserballoon 144 minutes, cryoballoon 136 minutes) (119). This was also applicable when comparing laserballoon with RFCA (128 vs. 135 min)(114).

2.7.3 Pericardial Effusion/Cardiac Tamponade

Radiofrequency ablation, compared to balloon-based devices is associated with an increased risk for cardiac tamponade (1.5vs.0.1%) (122). This risk was higher in PVI plus additional lesions sets compared to PVI only (0.8vs.0.1%, p=0.024) (122). For CF catheters, the reported incidences are higher (2.5-8%)(123-125). Based on published data (table 1, table 2), the estimated incidence of pericardial effusion/cardiac tamponade is approximately 1.9% (144 of 9793; range 1-12%) for point-by-point RFCA and 0.7% (47 of 6772; range 0-8%) for the cryoballoon.

2.7.4 Stroke/TIA

Cryoballoon ablation has been associated with a lower risk for thrombus formation compared to RFCA (126). In line with this data is the observed lower incidence of silent cerebral embolism compared to irrigated RFCA and PVAC (51, 52, 127). However, in a randomized study comparing laserballoon (n=33), cryoballoon (n=33) and irrigated RFCA (n=33), the incidence of asymptomatic cerebral lesions was not significantly different (24%, 18% and 24%, respectively) (116). For PVAC, a higher rate of micro-embolic signals and asymptomatic cerebral embolism has been observed compared to cryoballoon or RFCA (51, 53, 56). However, the incidence of symptomatic cerebral events (stroke/TIA) is similar (0.3vs.0.2%).

2.7.5 Phrenic nerve palsy and oesophageal/vagal nerve injury

The incidence of PNP is significantly higher with the cryoballoon compared to RF, occurring in 3.9% of the ablations (264 of 6772 cases; range 0-15%), with permanent paralysis in <1% (table 1-2). Similar, laserballoon ablations are complicated by PNP in 5.8% of patients (111). In contrast, the reported risk for oesophageal injury is lower with cryoballoon compared to RFCA (128).

2.7.6 Pulmonary vein stenosis

In a clinical trial comparing laserballoon vs. RFCA, the incidence of PV stenosis was lower (0vs.3%) (111). In a study comparing the laserballoon with RFCA and cryoballoon, only mild stenosis was seen in 18, 10 and 3.6% of the PVs, respectively (129).

2.7.7 Groin complications and bleeding

Based on the published data summarized in table 1 and 2, there were no significant differences in groin related complications between cryoballoon ablation and RFCA: total reported cases for cryoballoon are 139 (1.8%) vs. 179 (1.8%) for RFCA.

2.7.8 Patient characteristics related to complications

The majority of patients included in ablation studies are male (130). Bleeding complications (groin-related) after catheter ablation were reported in 2.1% of female patients (total 3265 patients, n=518 females) undergoing AF ablation. These numbers exceed those reported in males (n=27; 0.9%) (130). Both female gender and higher age have been associated with major adverse events (29). In a large nationwide survey, significant predictors for complications were female gender, high burden of comorbidity and low ablation volume of the hospital (< 50 procedures/per year) (131). In addition, patient with diabetes mellitus are at risk specifically for thrombotic or haemorrhagic complications (132).

2.8 Prevention of Complications

Knowledge of all potential complications is important for prevention. Technical advances may help to improve safety. Three-dimensional electro-anatomical mapping and image integration can minimize radiation exposure. Careful procedural planning, close cooperation of different medical specialties (e.g. in hybrid AF treatment) and patient monitoring can further reduce complications (133).

2.8.1 Pericardial Effusion/Tamponade

For prevention of cardiac tamponade, limiting of radiofrequency power to 30-40 watts in the anterior wall and 20-30 watts in the posterior wall has been applied in most studies (table 1a/1b). Previous studies demonstrated that power limitation from 45-60 to ≤ 42 Watt in linear lesions during AF ablation limited the incidence of cardiac tamponade (134). With the introduction of force sensing catheters, RF power adjustment according to CF parameters became possible, however optimal values remain to be established (135).

2.8.2 Stroke/TIA

Trans-oesophageal echocardiography, computed tomography or cardiac magnetic resonance imaging may be used to exclude the presence of a left atrial thrombus (4). Symptomatic cerebral thromboembolic events are relatively rare (0.8%) (136). Independent risk factors are a CHADS2 score ≥2 and a history of stroke (137). Accurate sheath management can reduce the risk of air embolism (incidence <1%). Continued oral anticoagulation (INR ≥ 2) during the procedure and maintenance of an adequate ACT (>300) should be considered to impact catheter thrombogenicity and the risk for (asymptomatic) cerebral embolism (138). A meta-analysis of 13 studies comparing non-vitamin K antagonists (NOAC) with vitamin-k antagonists (including 3 RCT) could demonstrate that NOACs are safe and effective, but adequately-powered randomized controlled trials are required to confirm these results (139).

2.8.3 Phrenic Nerve Palsy

Superior caval vein phrenic nerve pacing with palpation of diaphragmatic excursions may allow discontinuation of ablation before permanent injury (140). Diaphragmatic compound motor action potential (CMAP) monitoring is a relatively new technique to prevent PNP (141). To measure the CMAP signal, the left and right arm electrocardiogram leads are placed respectively 5 cm above the xiphoid and 16 cm along the right costal margin. Peak-to-peak measurement is performed of the CMAP-signal with each phrenic nerve capture

during superior vena cava pacing with a decapolar catheter. CMAP signals were amplified using a bandpass filter between 0.5 and 100 kHz and recorded on a recording system (Prucka, GE Healthcare, Milwaukee, WI). The technique is well-described with figures by Lakhani *et al.* (142). The ablation is terminated after reaching a 30% reduction in CMAP, which resulted in a faster recovery of phrenic nerve injury compared to manual palpation (143). Abortion of the freeze cycle during cryoballoon ablation ('double stop' technique: immediately ablation termination with direct balloon deflation) is an important additional manoeuvre to prevent permanent nerve injury (143, 144). Measuring of CMAP has reduced PNP incidence to 1% compared to 4-11% with manual palpation (145).

2.8.4 Oesophageal/Vagal nerve injury

Reduction of radiofrequency power to 20-25 watts aims to prevent oesophageal injury, atrial-oesophageal fistulae and vagal nerve injury causing gastric hypo-motility (146). Oesophagus and /or vagal nerve damage can be prevented by monitoring of the oesophageal temperature during ablation (147-149), with a reduction from 36% to 6% in RFCA (150) and from 18.8% to 3.2% in cryoballoon ablation (148). Temperature cut-offs may be considered safe are <38.5˚C for RFCA and >15˚C for cryoballoon procedures (148, 150). However, the use of temperature monitoring during RFCA is still under debate. Employment of temperature probes during RFCA has been associated with a higher incidence of oesophageal injury (30vs.2.5%; $p<0.01$) and using the temperature probe has been identified as independent predictor (151). It has been hypothesized that the probe may act as an antenna drawing RF energy to the oesophagus (152). Other methods for prevention of oesophageal damage are active cooling with saline (153), changing the oesophagus position with a deviation tool and visualization of the posterior wall and oesophagus with image-integration and electro-anatomical mapping (154-157). Whether prescription of prophylactic proton-pump inhibitors can prevent oesophageal damage needs further investigation.

2.8.5 Pulmonary vein stenosis

Pulmonary vein stenosis is likely an underdiagnosed complication after AF ablation which may be due to the lack of specific symptoms (158). The most important step to reduce the risk of PV stenosis is to avoid ablation inside the PVs by careful determination of the PV ostia before ablation.

2.8.6 Groin complications and bleeding

Management of coagulation is important to prevent vascular complications. In addition, a three-point strategy tested in 324 patients with continued warfarin during ablation, a smaller needle for access (18G instead of 21G) and avoiding arterial access has resulted in a reduction in vascular access complications (3.7%vs.0%; p=0.03), while the rates of thromboembolic complications and cardiac tamponade were similar (159). Ultrasound-guided vs. conventional femoral puncture did not reduced major complication rate (0.6vs.1.9%; p=0.62) in 320 patients, however it was associated with significantly lower puncture time, higher rate of first pass success and less extra or arterial punctures (160).

2.9 Conclusion

Several ablation devices have been developed over the last 15 years to increase procedural efficacy. Improvement of safety profiles is often initiated after the occurrence of complications. Knowledge of potential and device specific complications and awareness of currently considered asymptomatic procedure related events (e.g. cerebral emboli) is important for patient counselling and selection – primum non nocere.

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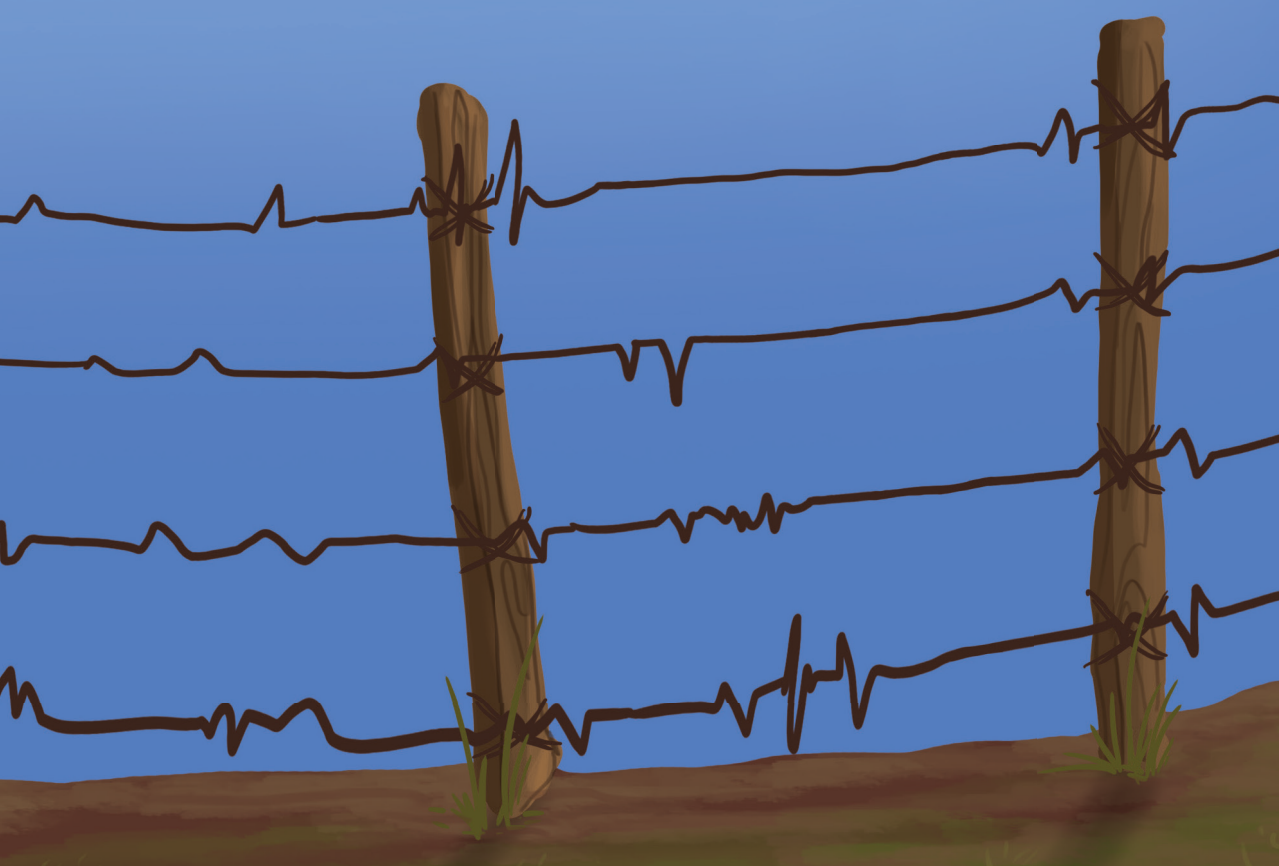
Part 1

Freedom from Complications



Chapter 3

Incidence and Clinical Significance of Cerebral Embolism during Atrial Fibrillation Ablation with Duty-Cycled Phased-RF versus cooled-RF: A Randomized Controlled Trial

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Abstract

Background

Pulmonary vein isolation (PVI) with the Pulmonary Vein Ablation Catheter (PVAC) is associated with asymptomatic cerebral embolism (ACE). The second-generation PVAC (PVAC-Gold) was designed to avoid this complication.

Objective

The purpose of this study was to randomly compare ACE incidence between the PVAC-Gold and the irrigated Thermocool catheter.

Methods

Patients with paroxysmal atrial fibrillation were 1:1 randomized to PVI with the PVAC-Gold or Thermocool catheter. Cerebral MRI was performed the days before and after ablation and repeated after 3 months in case of a new lesion. Monitoring for micro-embolic signals (MES) was performed by transcranial Doppler ultrasonography. Parameters of coagulation were determined before, during and after ablation. Neuropsychological tests and questionnaires were applied 10 days before and 3 months after ablation.

Results

Seventy patients were included (61±9 years, 43 male, CHA_2DS_2-VASc score 1.6±1.2, INR 2.7±0.5, ACT 374±24s, P>0.05 for all parameters). Procedural duration was shorter in the PVAC-Gold group (140±34 vs. 207±44 min, p<0.001). Eight (23%, 7 infarcts) patients in the PVAC-Gold group showed a new ACE, compared to 2 (6%, no infarcts) patients in the Thermocool group (p=0.042). Median number of MES was higher in the PVAC-Gold group (1111 [IQR 715-2234] vs. 787 [IQR 532-1053], p<0.001). There were no differences between groups regarding coagulation and neuropsychological outcomes.

Conclusion

PVI with the new PVAC-Gold catheter was associated with a higher incidence of ACE/cerebral infarcts and number of MES. Both catheters induced a comparable pro-coagulant state. As there were no measurable differences in neuropsychological status, the clinical significance of ACE remains unclear.

Clinical Trial Registration

Cerebral Embolism [CE] in Catheter Ablation of Atrial Fibrillation [AF] [CE-AF]; at clinicaltrials.gov- NCT01361295

3.1 Introduction

The Pulmonary Vein Ablation Catheter (PVAC; Medtronic Inc., Minneapolis, MN, USA) is a multipolar, non-cooled, duty-cycled radiofrequency (RF) device for pulmonary vein isolation (PVI). Although short procedure times with similar effectiveness compared to cooled point-by-point RF ablation were described (1), the reported incidence of asymptomatic cerebral embolism (ACE) up to 42% on cerebral magnetic resonance imaging (MRI) raised significant concern (2-4). Subsequent studies suggested temperature overshoot during intermittent tissue contact and electrical short-circuit between electrodes 1 and 10 as the main causes (5,6). Accordingly, the nine electrode PVAC-Gold was developed to prevent these issues, which led to a 2.1% incidence of ACE (7). This study lacked a control group however and the ACE definition did not comply with international consensus (3). Nonetheless, the clinical significance of ACE remains unclear (8,9).

The main purpose of this study was to randomly compare the ACE incidence between PVAC-Gold and irrigated RF catheter. The second aim was to deepen the understanding of ACE by analysis of trans-cranial Doppler and coagulation parameters. The third aim was to evaluate the clinical significance of ACE with neuropsychological tests.

3.2 Methods

3.2.1 Study Population

Consecutive patients referred for a first ablation of paroxysmal, drug-refractory atrial fibrillation (AF) between March 2015 and December 2016 were included and 1:1 randomized to PVI using the PVAC-Gold (n=35) or Thermocool catheter (Navistar Thermocool, Biosense Webster, Diamond Bar, CA, USA), n=35). Twenty patients with AF (*age and education matched*) not undergoing ablation served as a reference group for neuropsychological testing (baseline and 3 months). Patients with prior AF ablation, persistent AF, contra-indications for MRI and/or the inability to perform neuropsychological testing were excluded. To avoid bias based on different anticoagulant drugs, we chose to start only Vitamin K antagonists in all patients. Patients were kept on vitamin K antagonists from at least 2 months before until 3 months after the procedure For their anticoagulant control, all patients were monitored by the regional anticoagulation clinic. Because of the high expertise and structured protocols followed in these clinics, little deviation from the therapeutic INR range is normally observed. All anticoagulation clinics in the Netherlands follow, in fact, the guidelines of the Dutch Federation of Anticoagulation Clinics, which are published in “Kunst van het doseren”(10) and are updated regularly. Data collection was performed using our electronic patient information system (EPD-Vision). All patients gave written informed consent before study entry. The study was approved by the institutional ethical review board and registered at clinicaltrials.gov (NCT01361295).

3.2.2 Ablation

Pre-ablation Phase: Ablation was performed under continued vitamin K antagonist therapy with a targeted peri-procedural international normalized ratio (INR) of 2.0-3.0. Patients were treated under deep sedation using propofol/remifentanil or conscious sedation using midazolam/fentanyl. After venous access, a dose of 5000 IU of heparin was administered. Single (PVAC-Gold) or double transseptal access (Thermocool) were obtained with the needle introduced using the stylet and under intracardiac echocardiography guidance. Mapping of the left atrium (Thermocool) and pulmonary venography (both groups) was performed. ACT was checked every 30 min after transseptal access and maintain >350 s. Energy delivery was not commenced before ACT was >350 s. *Ablation Phase*: Only ablation lesions aiming at PVI were allowed. PVAC-Gold catheter: Duty cycled RF energy applications of 60s (Genius Generator software version 15.1 Medtronic Inc., Minneapolis, MN, USA) were delivered in a bipolar: unipolar ratio of either 4:1 (10 W) or 2:1 (8 W) until PVI was achieved. Pulmonary vein isolation was mainly (99%) performed in 2:1 energy mode. This

was common practice in our center already with the first generation PVAC, as in general we often failed to isolate pulmonary veins with 4:1 energy mode. No touch-ups with a single-tip catheter were performed. Thermocool catheter: A point-by-point ablation around both ipsilateral veins was performed until PVI was achieved. RF power was set at 30-35 W with a flow rate of 17-20 ml/min and a maximum temperature of 43°C. *Post-ablation Phase:* After a waiting period of 30 min, PVI was confirmed and 5000 IU protamine was administered before sheath removal. In this study no additional measures (e.g. adenosine testing) were taken to ensure lesion durability.

3.2.3 Cerebral MRI

A cerebral MRI (1.5 Tesla, Philips Medical Systems, Best, The Netherlands) was performed on the days before and after ablation. Hyperintensities on the diffusion-weighted image were identified and the corresponding apparent diffusion coefficient maps were calculated. In addition, turbo fluid attenuated inversion recovery (FLAIR) and T2-weighted turbo spin echo sequences were performed. Technical details of the MRI sequences are described in *Supplementary Table A*. White matter lesions were categorized with the modified Fazekas scale (11). ACE was defined as a new diffusion abnormality on the diffusion-weighted image sequence with an apparent diffusion coefficient reduced map. Cerebral infarcts were defined as positive ACE with a positive FLAIR. Patients with ACE or cerebral infarcts underwent follow-up MRI using the same protocol 3 months later. MRI results were confirmed by 2 independent radiologists.

3.2.4 Transcranial Doppler Ultrasonography

2 MHz transcranial Doppler ultrasonography (DWL Multi Dop P, DWL Sipplingen, Germany) of the right middle cerebral artery was continuously performed from venous access to catheter removal. Raw Doppler signals were recorded as MP3 (Eridol R-09, Roland Corporation Nakagawa, Japan) for off-line analysis. Micro-embolic signals (MES) were automatically detected and discriminated from artefacts using a locally developed MATLAB algorithm (MATLAB R2007b, The MathWorks Inc., Natrick, MA, USA)(12). Number and concentration of MES (MES per unit of time) were calculated for the entire procedure and per ablation phase: pre-ablation, ablation (10s before first RF until 60s after last RF) and post-ablation phase.

3.2.5 Laboratory Measurements

2x5 ml Citrated blood samples were collected the day before ablation (T1), during the procedure before the first RF application (T2), before sheath removal (T3) and the day after ablation (T4). Samples were centrifuged at 2700 *g* for 10 min at 18°C. Markers of intrinsic and extrinsic coagulation (APTT, PT/INR), fibrin-turnover (D-Dimer), acute phase markers and coagulant potential (fibrinogen) were measured directly. Other coagulation parameters were analyzed on frozen -70°C aliquots: Von Willebrand factor antigen as a marker of endothelial damage, Prothrombin fragment 1+2 as a marker of thrombin generation, tissue plasminogen activator as a marker of fibrinolysis and soluble P-selectin as a marker of platelet activation. Measurements are described in the *Supplemental Methods A.*

3.2.6 Neuropsychological Assessment

Two weeks before and 3 months after the ablation patients underwent neuropsychological tests for global cognitive functioning and intelligence level, memory function, attention and concentration, executive functioning, psychomotor speed and mood. The education-matched (13) reference group underwent the same tests. The tests are described in the *Supplemental Methods B.*

3.2.7 Statistical Analysis

Power analysis was based on the outcome of 3 prior studies (2,4,14) and the results of our pilot study (15). Taking the outcome of these studies together, 56 of the 142 patients (39.4%) showed ACE after PVAC-ablation and 8 of 82 (9.8%) patients showed ACE after cooled-tip ablation. The rate difference was therefore 29.6% ; with a required sample size of 64 to detect a difference in ACE with 80% power at a 0.05% probability level (SPSS Sample Power 2.0 (SPSS Inc. Chicago, Illinois, USA). Accordingly, the group size was set to 35. All continuous data was checked for normality with the Shapiro-Wilk or Kolmogorov-Smirnov test and expressed as mean±standard deviation or median and interquartile range (IQR), when appropriate and compared using an unpaired t-test or Mann-Whitney U test. For categorical data, numbers and frequencies were provided and compared using an chi-square test or Fisher's exact test for low expected count. A mixed linear model with between subject (group) and within subject (time) factors was used for the laboratory values and neuropsychological measures. Kaplan Meier survival curves were constructed (log-rank test) to compare the AF-free survival between the 2 groups. A p-value of <0.05 (two-sided) was considered statistically significant. Data were analyzed using SPSS (version 23).

3.3 Results

3.3.1 Baseline Characteristics

Mean age was 59±9 years in the PVAC-Gold group and 62±9 years in the Thermocool group. The groups were predominantly male (66% and 57%, respectively). There were no significant differences in any of the baseline characteristics between the two groups (Table 1).

Table 1. Baseline Characteristics.

	PVAC-Gold (n=35)	TC (n=35)	P-value
Age (years)	59±9	62±9	0.157
Male gender	23 (66)	20 (57)	0.461
BMI (kg/m2)	26.2±3.5	26.9±3.6	0.392
LA diameter (mm)	39±7	40±4	0.282
CHA_2DS_2-VASc score	1.6±1.2	1.6±1.3	0.924
ECV last 12 months	8 (23)	12 (34)	0.290
Ejection fraction (>55)	35 (100)	35 (100)	
Antiplatelet drugs	3 (4)	1 (1)	1.000
Comorbidity			
Hypertension	16 (46)	18 (51)	0.632
Dyslipidemia	14 (40)	11 (31)	0.454
Diabetes	2 (6)	1 (3)	1.000
Coronary artery disease	4 (11)	6 (17)	0.495
CVA/TIA history	6 (17)	5 (14)	0.743

Values are mean±standard deviation or n (%).
AF: atrial fibrillation, BMI: body mass index, CVA: cerebrovascular accident, ECV: electrical cardioversion, LA: left atrium, PVAC-Gold: Pulmonary Vein Ablation Catheter-Gold, TC: Thermocool, TIA: transient ischemic attack.

3.3.2 Procedural Details

Procedure time and RF duration with PVAC-Gold were shorter compared to the Thermocool group Table 2). During the ablation, 99% of the applications were performed in 2:1 bipolar: unipolar mode. The ACT values before electrical cardioversion was always above 350 s, except in 1 patient in the PVAC-Gold group (327s).

Table 2. Procedural Details.

	PVAC -Gold (n=35)	TC (n=35)	P-value
TEE prior to ablation	1 (3)	6 (17)	0.053
Procedural time (min)	149±34	207±44	<0.001
Ablation time (min)	28±9	48±12	<0.001
INR day of ablation	2.8±0.6	2.6±0.4	0.066
SR before ablation	30 (86)	28 (80)	0.526
Mean ACT during procedure (s)	369±26	378±24	0.118
ACT before energy delivery (s)	377±32	370±32	0.280
Minimum measured ACT (s)	337±47	348±41	0.286
Total administered heparin during procedure (IE)	8357±2095	8071±2579	0.613
ECV during procedure	5 (14)	12 (34)	0.051
Deep sedation	29 (83)	29 (83)	1.000
Postprocedural time to MRI (hours)	25±17	28±19	0.589

Values are mean±standard deviation or n (%).
ACT: activated clotting time, ECV: electro cardio version, INR: international normalized ratio, MRI: magnetic resonance imaging, SR: sinus rhythm, TEE: transesophageal echocardiography, PVAC-Gold: Pulmonary Vein Ablation Catheter-Gold, TC: Thermocool.

3.3.3 Cerebral Embolism

All patients underwent pre- and post-procedural MRI and no patients were excluded due to missing data. At pre-procedural MRI, 42 (60%) patients had white matter lesions, 25 PVAC-Gold and 17 Thermocool (p=0.087) with modified Fazekas scores of 0.7±0.6 and 0.7±0.8 (p=0.725), respectively. Ten Patients (5 in each group) had a previous infarction. In 8 patients the previous infarction was asymptomatic. MRI at a median of 21 (IQR 18-25) hours after ablation showed 16 new cerebral lesions in 8 (23%) patients (7 patients with cerebral infarction) of the PVAC-Gold group compared to 2 ACE in 2 (6%) patients (no cerebral infarction) of the Thermocool group (p=0.042, Figure 1). One patient in the PVAC-Gold group experienced symptomatic diplopia with corresponding embolism in the nucleus of the oculomotor nerve. Symptoms resolved a few hours after ablation. At follow-up MRI, 6 out of 16 (38%) ACE in 4 (11%) patients in the PVAC-Gold group but none in the Thermocool group persisted as cerebral infarcts. Figure 2 shows an example of a patient with 4 cerebral lesions. Details about lesion size and location are described in *Supplementary table B.* In the PVAC-Gold group, there was no significant difference in the total number of MES between patients with and without cerebral lesions. There was no relation between peri-procedural ECV and

ACE. The patient who underwent ECV with an ACT of 327s had no cerebral lesion after ablation. There were 9 patients (4 patients in the PVAC-Gold group vs. 5 patients in the Thermocool group) with an INR of 1.8-1.9 before ablation. However none of these patients experienced cerebral embolism.

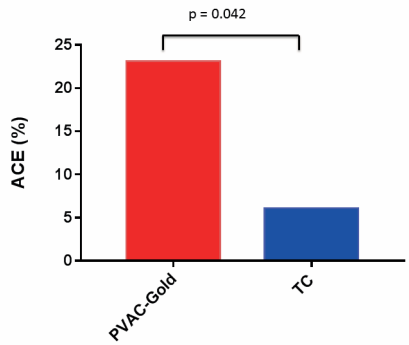

Figure 1. Incidence of Asymptomatic Cerebral embolism.
Asymptomatic cerebral embolism in the PVAC-Gold group (n=8/35) and the Thermocool Group (2/35). TC: Thermocool.

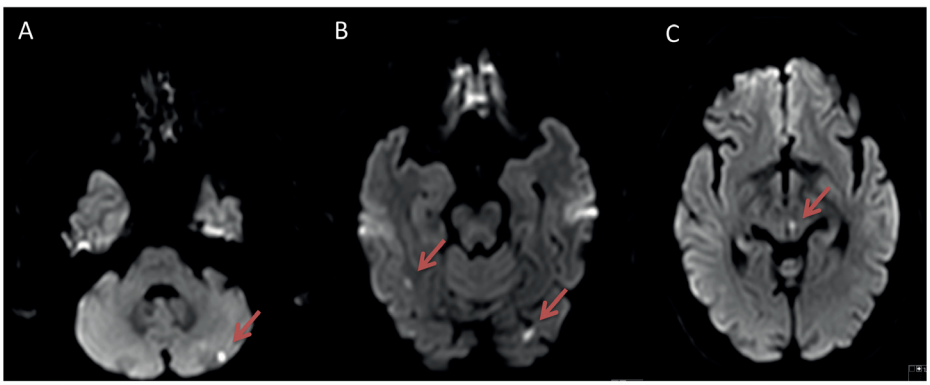

Figure 2. Diffusion weighted images of a patient with several cerebral lesions after PVAC-Gold ablation.
A: Lesion located left cerebellum, B: left occipital and right temporal and C: left midbrain (region of the nucleus of the oculomotor nerve)

3.3.4 Transcranial Doppler

Median number and concentration of MES during the total procedure were higher with the PVAC-Gold compared to Thermocool catheter (respectively 1111 [IQR 715-2234] vs. 787 [IQR 532-1053], p<0.001 and 8 [IQR 5-17] MES/min vs. 4 [IQR 3-5] MES/min, p<0.001) (Figure 3). Figure 4 shows an example of procedural MES detection. In the pre-ablation phase, median number but not median concentration of MES was higher in the Thermocool group. In contrast, in the ablation phase, median MES number and concentration were significantly higher in the PVAC-Gold group (respectively 819 [IQR 509-1608] vs. 354 [IQR 181-593], p<0.001 and 13 [IQR 7-24] MES/min vs. 3 [IQR 2-5] MES/min, p<0.001).

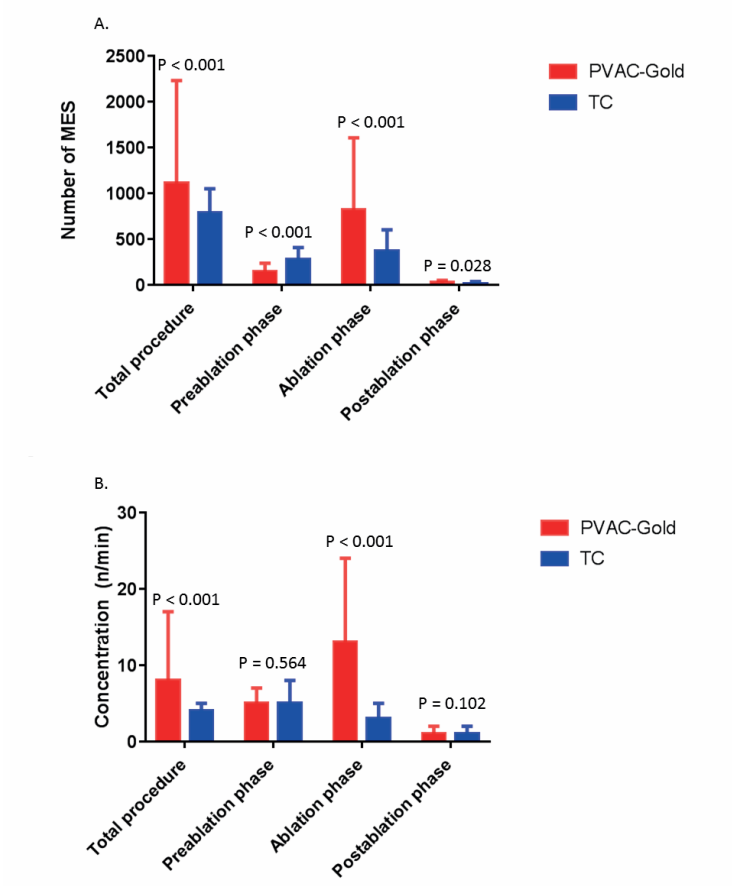

Figure 3. Number and concentration of micro-embolic signals.
Number (A) and concentration (B) of MES for the Pulmonary Vein Ablation Catheter-Gold (PVAC-Gold) catheter and Thermocool catheter for the entire procedure and per ablation phase. Median and interquartile range are displayed. MES: micrembolic signal; TC: Thermocool.

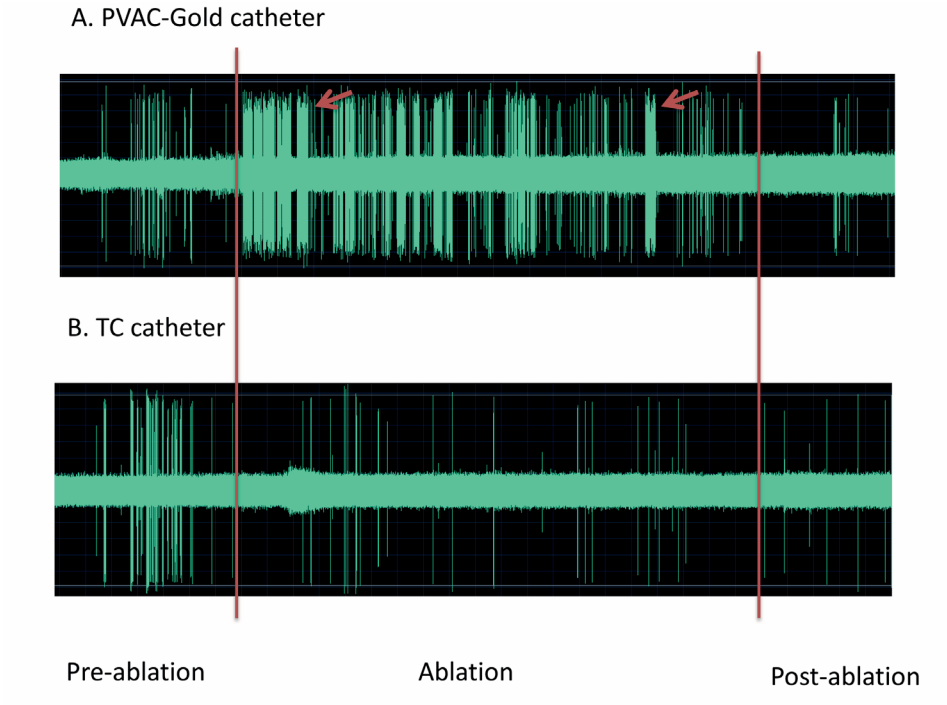

Figure 4. Example of transcranial Doppler recordings.
The procedure was divided in a pre-ablation, ablation and post-ablation phase. In the pre-ablation phase, contrast venography and catheter manipulation were associated with MES detection. This was more present in the TC group due to the additional mapping procedure. During the ablation phase, showers of MES were seen with the PVAC-Gold catheter during the RF applications. In the post-ablation phase, low MES numbers were seen for both catheters.

3.3.5 Parameters of Coagulation

Ablation with both catheters induced a pro-coagulant state. This was observed by an increase in D-dimer with no significant difference between the groups (Supplementary table C). In addition, fibrinogen and prothrombin fragment F1+2 were slightly lower during the procedure while Von Willebrand factor was elevated post-ablation. No differences in activation of coagulation were observed between the two catheters.

3.3.6 Neuropsychological Assessment

3.3.6.1 Study Group

No significant differences in test performance were observed between the PVAC-Gold and the Thermocool group for all cognitive domains (Supplementary table D). For both groups, an increase in the Groninger Intelligence Test-2 results, in memory functioning, executive

functioning and psychomotor speed were measured with several (sub)tests 3 months after the ablation. Both groups showed significantly better results on the Hospital Anxiety and Depression Scale after 3 months. No significant differences in neuropsychological test results were observed 3 months after the procedure between patients with and without cerebral infarcts.

3.3.6.2 Reference Group

The mean age (60 ± 8 years), sex (70% male) and education level (5.6 ± 1.5) in the reference group were not significantly different compared to the combined study groups. No significant differences in neuropsychological test results were found between the reference group and the combined study group (*Supplemental table E*).

3.3.7 Outcome and complications

One-year anti-arrhythmic drug-free AF survival was 49% in the PVAC-Gold group and 63% in the Thermocool group (p=0.229). In the PVAC-Gold group, 1 patient showed asymptomatic severe (>70%) pulmonary vein stenosis and 1 patient had a urinary tract infection. In the Thermocool group, there was 1 tamponade and 1 groin hematoma.

3.4 Discussion

To the best of our knowledge, this is the first randomized controlled trial comparing cerebral embolism with the new non-irrigated PVAC-Gold catheter and with the irrigated Thermocool catheter. The main findings are: (1) ablation with the PVAC-Gold catheter is associated with higher incidence of cerebral lesions (23% vs. 6%) and in addition, in the PVAC-Gold group the majority of these lesions were cerebral infarcts compared to none in the Thermocool group, (2) there was a significantly higher number of MES on transcranial Doppler in the PVAC-Gold group, (3) coagulation activity and cognitive functioning did not differ between the groups.

3.4.1 Incidence of ACE

In the first generation PVAC, a high incidence of ACE (up to 42%) was reported in several studies (2,3). Investigations revealed a suboptimal ACT, air entrapment during catheter introduction, peri-procedural cardioversion, temperature overshoot during intermittent catheter-tissue contact (6) and electrical interaction between electrodes 1 and 10 as possible causes (16). After implementation of procedural modifications (ACT >350 s, catheter submersion before introduction and deactivating of electrode 10), ACE incidence was reduced to 1.7% (17). Subsequently, the nine-polar PVAC-Gold was developed to prevent temperature overshoot and electrode interaction, which yielded an ACE incidence of 2.1% (7). However, discussions were raised about MRI timing and ACE definition in these studies (3). A positive FLAIR sequence was demanded for ACE diagnosis although scans were performed 16-72 hours post-ablation (7,17). As the FLAIR sequence usually becomes positive after 2-7 days, underestimation of the real ACE incidence may have occurred (3). In the current trial, ACE incidence with PVAC-Gold was 23%, more than 10-fold compared to the previous studies. In the PVAC-Gold group the majority of the patients (7 of 8) the lesions were cerebral infarctions compared to none in the Thermocool group. Although we performed the MRI 21 (IQR: 18-25) hours after ablation, FLAIR positivity was seen in 83% of all lesions. Therefore, MRI timing cannot fully explain the differences in ACE found. Additionally, the total duration of RF delivery was similar to other studies (7,17). However, in this study 99% of the applications were performed in the 2:1 mode. In prior studies, 57-67% of the ablations were performed with the 2:1 mode, 7% in 1:1 mode and 36-26% in 4:1 mode (7,17). Accordingly, the mixture in energy mode may have influenced the results. At 3 months follow-up, we detected a lower incidence of cerebral lesions compared to directly post-ablation. In a study with 3 instead of 1,5 Tesla MRI, the incidence of ACE was doubled to tripled due to the higher spatial resolution, a slice thickness of 2.5 instead of

5 mm and an improved signal-to-noise ratio (18). As the lesion size of ACE in our trial was between 3 and 6 mm and lesions tend to decrease in size during follow-up (14), lesions may have been missed on follow-up MRI.

3.4.2 Transcranial Doppler

Across the entire procedure, the number and concentration of MES were much higher in the PVAC-Gold group. In the pre-ablation phase however, the Thermocool catheter showed a higher number of MES. Besides energy delivery, catheter manipulation contributes to the generation of MES (6) The additional mapping procedure before ablation may therefore explain this finding. During ablation, a higher number and concentration of MES were detected with PVAC-Gold. In our pilot with the first-generation PVAC and ACT >300 s, we detected a mean MES number of 2324±1406 (15), comparable to other reports with relatively high MES numbers with this catheter (8,19). In the current study with ACT >350s, we still detected a higher number of MES with PVAC-Gold compared to the Thermocool catheter. We therefore believe that several factors (energy mode, temperature overshoot, anticoagulation protocol and aspect of non-irrigation) may contribute to the incidence of ACE in the PVAC-Gold.

3.4.3 Parameters of Coagulation Activity

There are no other studies comparing coagulation activity between cooled RF ablation and PVAC. During and after the procedure we observed a progressive increase in D-dimers levels which reflects fibrin formation and subsequent breakdown of fibrin, suggesting activation of coagulation during the procedure. In addition, we observed a progressive increase of Von Willebrand factor antigen reflecting endothelial damage and/or acute phase response. These observations may indicate that the ablation procedure in itself is pro-thrombotic. However, we did not observe significant differences between the two groups. Accordingly, the difference in ACE cannot solely be attributed to the observed in the pro-coagulant state. One study comparing PVAC to the Cryoballoon catheter also showed no significant differences in coagulation activity (7)(20), similar to our results.

3.4.4 Clinical Significance of ACE

In our study, 42 (60%) patients had pre-existent white matter lesions and 14% exhibited a previous lacunar infarction. It is known that pre-existent white matter lesions can cause cognitive decline (21). However, the additive cognitive effect of new ACE in AF-ablation patients is still a matter of debate. In previous studies, both presence (9) and absence (8) of negative cognitive effects of ACE have been described. In our study, we did not detect

a decline in cognitive function both in patients with and without ACE. It is difficult to determine which numerical decline (whether or not statistically significant) is also clinically meaningful. There is limited data about cognitive functioning after atrial fibrillation ablation (22). In several studies on other procedures (for example after CABG), statistical techniques have been implemented to determine "true" (i.e., statistically significant) cognitive decline at the individual level (23). In addition, for major neurocognitive disorder as defined by international diagnostic guidelines for mental disorders (24) a meaningful decrease in test performance is typically 2 or more standard deviations below appropriate norms or reference groups (3rd percentile or below). However, as we did not observe any significant difference but also not a trend towards impaired test results in patients with ACE, we believe that a clinically relevant decline in cognitive function is unlikely. Cerebral location of the lesions between studies may explain the differences in cognitive effects of ACE. Lesion-symptom mapping studies have shown that the impact on cognition depends on lesion volume but also on location (25). Lesions in strategic brain regions cause more cognitive impairment. It is more difficult to detect lesions in cortical regions with mechanisms compensating the affected neuropsychological function. In our study, most of the lesions were located in the cortical regions of the brain.

3.4.5 Adverse Events

In the PVAC-Gold group 1 patient experienced an asymptomatic pulmonary vein stenosis, which was detected during a second procedure. Since this patient underwent re-ablation of both left pulmonary veins, it is possible that the second ablation contributed to the progression of the stenosis. Importantly, it is well known that pulmonary vein stenosis might be underdiagnosed due to the lack of a specific clinical presentation (26) and the absence of systematic screening after ablation. In a cohort of 62 patients using the first generation PVAC, we also observed mild (25-50%) narrowing in 37% of the PV's, a moderate (50-70%) narrowing in 9% and severe narrowing (>70%) in 3% (27). Von Bary *et al.* reported a detectable narrowing of the PV diameter after first-generation PVAC ablation in 23% of the patients (28).

3.4.6 Limitations

This was a single center study with a relatively small number of patients in each arm. The size of the study sample was calculated based on the estimates of differences in ACE. Strong conclusions regarding the neuropsychological effects of ACE cannot be drawn and larger trials are required to confirm the results. We have no detailed information available on the INR values and time in therapeutic range for individual patients in the

weeks before and after the procedure. Impedance data could have revealed possible interaction between PVAC Gold electrodes. Impedance data was not available however. The final blood sample was taken one day after the ablation. Delayed coagulation effects 3 days after the ablation could not be detected. We did not correct ACE and MES for total RF duration or energy because total RF energy data was not available. Differentiation between solid and gaseous MES would widen the scope of transcranial Doppler MES detection. Dual-frequency insonation during trans-cranial Doppler could have aided in this differentiation. However, despite developments in both signal acquisition techniques and MES classification algorithms, it remains difficult to reliably determine MES composition, especially in clinical settings in which periods with numerous MES may occur. A complete neurological evaluation by a neurologist according to the National Institute of Health Stroke scale could have given more information on the neuropsychological status of patients with ACE. Only 20 patients were included in the reference group for neuropsychological testing. Neuropsychological tests may not have been sensitive enough to detect changes in complex cognitive functions. Long-term effects on cognitive functioning of the new ACE were not studied.

3.5 Conclusions

PVI with the new PVAC-Gold is associated with a higher incidence of ACE/cerebral infarctions and a higher number of MES on transcranial Doppler compared to ablation with an irrigated-tip catheter. Both ablation technologies induced a similar increase in pro-coagulant state. We could not detect a cognitive decline in patients using available tests. Since the purpose of the redesign of the PVAC-catheter was to reduce the high incidence of ACE, it can be stated that the improvement of this device was unsuccessful. Therefore, the manufacturer of the PVAC-Gold should continue to improve the device.

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3.7. Supplemental Methods

3.7.1 Laboratory Measurements

Intrinsic and extrinsic coagulation

APTT and PT/INR were respectively measured on an automated coagulometer using STA Neoplastin R (STA-R Max, Diagnostica Stago, Leiden, Netherlands) and using STA Cephascreen (STA-R Max, Diagnostica Stago, Leiden, Netherlands).

Fibrin turnover

For the measurement of D-dimer an automated coagulometer using STA Liatest D-DI Plus (STA-R Max, Diagnostica Stago, Leiden, Netherlands) was used.

Coagulant potential (acute phase marker)

Fibrinogen was measured with STA Liquid Fib (STA-R Max, Diagnostica Stago, Leiden, Netherlands).

Endothelial damage

For the measurement of Von Willebrand Factor Antigen, ELISA using rabbit polyclonal anti-human VWF antibody (A082, Dako, Denmark) and horseradish peroxidase conjugated rabbit anti-human VWF antibody (P0226, Dako, Denmark) was used.

Thrombin generation

Prothrombin Fragment 1+2 was measured with ELISA (Cloud-Clone Corp., Katy, TX, USA).

Fibrinolysis

Tissue plasminogen activator was measured using Elisa (Abcam, Cambridge, United Kingdom).

Platelet activation

Soluble P-selectin (sP-sel) was measured on ELISA (Affymetrix, part of the Thermo Fisher Scientific, Waltham, MS, USA).

3.7.2 Neuropsychological Assessment

Global cognitive function and intelligence

Global cognitive functioning was tested with MMSE (Mini Mental State Examination) (1). The MMSE is a 30-point questionnaire to assess global cognition; a higher score reflects better performance. For an estimation of the intelligence level, 7 subtests of the 10 of the GIT2 (Groninger Intelligence Test 2) (2) were used.

Memory functioning

Memory functioning was tested with WMS (Wechsler Memory Scale) (3). The score is presented in a memory quotient (MQ) based on the scores on various subscales. RAVLT (Rey Auditory Verbal Learning Test) was used to test verbal memory and learning (4). The test consists of 2 lists of 15 words, the first repeated over several trials, the second used once as interference trial. The number of correctly recalled words was counted for every trial and after a delay (only for words of the first list). With the figure test, drawing and visual memory was tested. A higher score indicates better visual memory.

Attention and concentration

Attention and concentration was tested with SART (Sustained Attention to Response Task) (5). The test assesses the capacity to attend. In the test, patients are asked to either press a button or to withhold in response to the appearance of numbers from 1 through 9 in random order. The number of errors and reaction times were noted.

Executive functioning

Executive functioning was tested with FFT (Figure Fluency Test) (6), TMT (Trail Making Test) Part B and Part B minus Part A (7), and STROOP (Stroop Color Word Test) Card 3 and Card 3 minus Card 2, the interference score (9). The FFT assesses nonverbal mental flexibility and fluency by the ability to draw new figures. The number of correct, wrong and repeated figures were counted. In TMT Part B, a patient needs to connect digits with letters in an ascending pattern. In TMT Part A, the patient connects digits in an ascending order. The time to complete the test parts was measured, more time indicating lower performance. With STROOP Card 3, the color of the ink in which color names are printed (color of the ink does not match the color names) needs to be named and reading the colored words needs to be inhibited, leading to a delay in reaction time. With STROOP Card 2, the patient needs to name different color patches.

Psychomotor speed

For psychomotor speed, LDST (Letter Digit Substitution Test) (10), PPT (Purdue Pegboard Test) (8) and TMT Part A were used. Psychomotor speed was also tested with STROOP Cards 1 and 2, the number of correct and wrong responses were counted. With LDST, the patient needs to correctly substitute numbers for letters within a time frame of 60 seconds. PPT measures the manual dexterity and bimanual coordination. In the first trial, the patient needs to place pegs in holes with one hand as quickly as possible. In the second trial, both hands need to be used to place 2 objects on each other. The test can be performed for the dominant or non-dominant hand. A longer duration indicates lower performance. With STROOP Card 1, the patient needs to read names of colors printed in black ink.

Anxiety and depression

HADS (Hospital Anxiety and Depression Scale)(11) measures anxiety and depression on a questionnaire with 14 items on a 4-point scale. Higher scores indicate more severe anxiety and/or depression.

3.8. Supplemental Tables

Table A. Details of the MRI sequences.

Sequence	TR (ms)	TE (ms)	TI (ms)	Angle (°)	Slices (n)	Thick-ness (mm)	NSA	Slide gap (%)	FOV (mm)	Orientation
Survey	15	5		15	9 (3-3-3)	10	1	10-20	250	Sagittal Coronal Transversal
FLAIR	11000	130	2800	120	28	5	1	10	220	Transversal
T2-TSE	80	3951		90	48	3	2		220	Transversal
DWI/ADC*	3323	79		90	29	5	1	10	220	Transversal

ADC = apparent diffusion coefficient; DWI = diffusion weighted images; FLAIR = fluid attenuated inversion recovery; FOV = field of view; NSA = number of signal averages; TE = echo time; TI = inversion time; TR = repetition time; TSE = turbo spin echo.
*For ADC mapping b-values (b=0 and b=1000)

Table B. Size and location of the cerebral lesions (n = 18).

	Patient ID	Location	Size (mm)	ACE	Cerebral infarcts	Repeated MRI
1	PVAC Gold-8	Left Gyrus Cingulate	6	1	1	1
2	TC-12	Left Temporal Cortical	3	1	0	0
3	TC-13	Left Occipital Subcortical	4	1	0	0
4	PVAC Gold-15	Right Nucleus Caudatus	6	1	1	1
5	PVAC Gold-17	Cortical Gyrus Precentralis	6	1	0	0
6	PVAC Gold-20	Right Gyrus Frontalis Medialis Cortical	5	1	1	0
7	PVAC Gold-21	Left Paramedian Mesencephalic	5	1	1	1
8	PVAC Gold-21	Left Cerebellum	5	1	1	1
9	PVAC Gold-21	Left Occipital	6	1	1	1
10	PVAC Gold-21	Right Gyrus Temporalis Inferior	5	1	1	0
11	PVAC Gold-28	Left Centrum Semiovale	5	1	1	1
12	PVAC Gold-29	Right Gyrus Precentralis	3	1	1	0
13	PVAC Gold-29	Right Gyrus Postcentralis	5	1	1	0
14	PVAC Gold-29	Right Gyrus Postcentralis	3	1	1	0
15	PVAC Gold-29	Left Parietal	4	1	1	0
16	PVAC Gold-29	Left Gyrus Postcentralis	4	1	1	0
17	PVAC Gold-29	Left Frontal Periventricular	4	1	1	0
18	PVAC Gold-30	Left Cerebellum	4	1	1	0
	16:2		**4.6 ± 1**	**18:0**	**15:3**	**6:16**

Asymptomatic cerebral embolism (ACE, no scar) is defined as a diffusion – positive (DWI hyperintense) + ADC reduced map on MRI and a cerebral infarct (scar) is defined as diffusion – positive (DWI hyperintense) + ADC reduced map plus a FLAIR positive scan. ADC = apparent diffusion coefficient; DWI = diffusion weighted image; FLAIR = fluid-attenuated inversion recovery.

Table C. Coagulation activity.

	Ablation Technology	T1	T2	T3	T4	P -value (group)	P-value (time)	P -value (interaction)
Intrinsic (APTT) and extrinsic (PT) coagulation								
APTT (s)	PVAC Gold	37 ± 4	120 ± 0	120 ± 3	38 ± 5	0.830	0.001	0.607
	TC	37 ± 3	120 ± 0	120 ± 0	38 ± 3			
PT (s)	PVAC Gold	37 ± 7	43 ± 10	37 ± 8	35 ± 7	0.307	0.001	0.009
	TC	36 ± 9	39 ± 7	37 ± 7	35 ± 7			
INR	PVAC Gold	2.4 ± 0.5	2.8 ± 0.6	2.5 ± 0.5	2.3 ± 0.4	0.359	0.001	0.021
	TC	2.6 ± 0.4	2.6 ± 0.4	2.5 ± 0.4	2.3 ± 0.4			
Fibrin turnover (Marker of activated fibrinolysis)								
DD (µg/L)	PVAC Gold	291 ± 145	266 ± 114	285 ± 115	329 ± 150	0.778	0.001	0.042
	TC	259 ± 53	278 ± 66	279 ± 75	328 ± 139			
Coagulant potential (Acute phase coagulation marker)								
Fib (g/L)	PVAC Gold	3.4 ± 0.6	2.9 ± 0.6	3.0 ± 0.6	3.5 ± 0.7	0.306	0.001	0.002
	TC	3.6 ± 0.6	3.2 ± 0.5	3.1 ± 0.6	3.7 ± 0.6			
Endothelial damage (Main alterations of coagulation)								
VWF (kIU/mL)	PVAC Gold	1.3 ± 0.3	1.1 ± 0.3	1.3 ± 0.5	1.7 ± 0.5	0.191	0.001	0.243
	TC	1.5 ± 0.6	1.3 ± 0.6	1.4 ± 0.7	1.8 ± 0.7			
Thrombin generation (Markers of activated coagulation)								
F1+2 (ng/L)	PVAC Gold	1239 ± 595	1256 ± 608	1086 ± 539	1279 ± 692	0.183	0.001	0.567
	TC	1089 ± 392	1178 ± 397	902 ± 313	1117 ± 560			

Table C. Continued.

	Ablation Technology	T1	T2	T3	T4	P -value (group)	P-value (time)	P -value (interaction)
				Fibrinolysis (Main alterations of fibrinolysis)				
t-PA (µg/L)	PVAC Gold	3.5 ± 4.6	3.0 ± 4.2	3.2 ± 4.2	2.5 ± 1.6	0.505	0.001	0.437
	TC	3.2 ± 2.9	2.5 ± 1.9	2.5 ± 1.7	3.1 ± 3.8			
				Platelet Activation				
sP-sel (µg/L)	PVAC Gold	82 ± 24	70 ± 19	72 ± 19	82 ± 20	0.224	0.001	0.111
	TC	86 ± 17	78 ± 16	76 ± 16	87 ± 19			

Values are mean ± standard deviation.

APTT = activated partial thromboplastin time; DD = D-dimer; F1+2 = prothrombin fragment F1+2; Fib = fibrinogen; INR = international normalized ratio; PT = prothrombin time; PVAC Gold = Pulmonary Vein Ablation Catheter-Gold; sP-sel = soluble P-selectin; TC = Thermocool catheter; t-PA = tissue plasminogen activator; vWF = von Willebrand Factor antigen.

T1 = day before ablation; T2 = during the procedure before the first RF application; T3 = after the last RF application, before sheath removal; T4 = day after ablation.

Table D. Neuropsychological test results for the PVAC Gold group vs. the Thermocool group.

	Ablation Technology	T1	T2	P-value (group)	P-value (time)	P-value (interaction)
Global Cognitive Functioning and Intelligence						
MMSE total score	PVAC Gold	29 ± 1	29 ± 2	0.706	0.708	1.000
	TC	29 ± 1	29 ± 1			
GIT2 total score (7/10 subtests)	PVAC Gold	95 ± 16	100 ± 15	0.688	0.001	0.564
	TC	93 ± 17	99 ± 18			
Memory Functioning						
WMS MQ total score	PVAC Gold	122 ± 15	127 ± 14	0.532	0.001	0.941
	TC	119 ± 17	126 ± 16			
RAVLT Imprinting score	PVAC Gold	13 ± 3	13 ± 3	0.879	0.006	0.894
	TC	12 ± 2	12 ± 3			
RAVLT Delayed Cued Recall score	PVAC Gold	13 ± 3	12 ± 3	0.412	0.001	0.679
	TC	12 ± 3	11 ± 3			
RAVLT Delayed Recognition score	PVAC Gold	42 ± 3	42 ± 2	0.893	0.069	0.867
	TC	41 ± 3	41 ± 2			
Attention and Concentration						
SART mean reaction time (s)	PVAC Gold	330 ± 51	332 ± 51	0.652	0.688	0.456
	TC	339 ± 54	330 ± 51			
SART no. errors	PVAC Gold	12 ± 8	11 ± 6	0.150	0.129	0.762
	TC	13 ± 10	12 ± 9			
Executive Functioning						
FFT no. patterns	PVAC Gold	58 ± 28	65 ± 30	0.955	0.001	0.354
	TC	55 ± 33	67 ± 29			

Table D. Continued.

	Ablation Technology	T1	T2	P-value (group)	P-value (time)	P-value (interaction)
FFT no. repeats	PVAC Gold	6 ± 6	5 ± 3	0.481	0.182	0.888
	TC	7 ± 10	6 ± 6			
FFT no. errors	PVAC Gold	1 ± 1	0 ± 1	0.840	0.761	0.711
	TC	1 ± 1	1 ± 2			
TMT Part B (s)	PVAC Gold	49 ± 10	72 ± 35	0.315	0.001	0.639
	TC	50 ± 12	78 ± 31			
TMT Part B - Part A (s)	PVAC Gold	47 ± 37	40 ± 29	0.389	0.014	0.874
	TC	53 ± 33	46 ± 24			
STROOP Card 3 (s)	PVAC Gold	52 ± 9	54 ± 8	0.623	0.214	0.689
	TC	52 ± 7	52 ± 7			
STROOP Interference score	PVAC Gold	52 ± 9	53 ± 8	0.998	0.312	0.590
	TC	53 ± 8	53 ± 8			
Psychomotor Speed						
LDST no. of correct	PVAC Gold	34 ± 5	35 ± 7	0.287	0.120	0.316
	TC	33 ± 6	33 ± 6			
PPT Dominant Hand score	PVAC Gold	34 ± 4	34 ± 5	0.776	0.419	0.247
	TC	34 ± 5	34 ± 6			
PPT Assembly score	PVAC Gold	28 ± 6	28 ± 7	0.925	0.084	0.287
	TC	27 ± 7	29 ± 7			
TMT Part A (s)	PVAC Gold	32 ± 8	32 ± 11	0.981	0.772	0.979
	TC	32 ± 13	32 ± 12			
STROOP Card 1 (s)	PVAC Gold	43 ± 9	42 ± 10	0.426	0.067	0.821
	TC	45 ± 9	44 ± 9			

Table D. Continued.

	Ablation Technology	T1	T2	P-value (group)	P-value (time)	P-value (interaction)
STROOP Card 2 (s)	PVAC Gold	46 ± 10	46 ± 11	0.650	0.525	0.885
	TC	47 ± 10	47 ± 10			
			Anxiety and Depression			
HADS total score	PVAC Gold	9 ± 7	7 ± 6	0.673	0.001	0.341
	TC	8 ± 5	7 ± 6			

Values are mean ± standard deviation.

FFT = Figure Fluency Test; GIT2 = Groninger Intelligence Test 2; HADS = Hospital Anxiety and Depression Scale; LDST = Letter Digit Substitution Test; MMSE = Mini Mental State Examination; MQ = memory quotient; PPT = Purdue Pegboard Test; PVAC Gold = Pulmonary Vein Ablation Catheter Gold; RAVLT = Rey Auditory Learning Test; SART = Sustained Attention to Response Task; STROOP = Stroop Color Word Test; TC = Thermocool catheter; TMT= Trail Making Test; WMS = Wechsler Memory Scale.

T1 = two weeks before ablation; T2 = 3 months after ablation.

Table E. Neuropsychological test results for the combined study group vs, the reference group.

Test	Ablation Technology	NPO I test score	NPO II test score	P (group)	P (time)	P (interaction)
		Global Cognitive Functioning				
MMSE total score	Ablation group	29 ± 1	29 ± 2	0.859	0.513	0.775
	Reference Group	30 ± 1	29 ± 1			
GIT2 total score (7/10 subtests)	Ablation group	94 ± 16	99 ± 17	0.388	0.001	0.264
	Reference Group	98 ± 19	102 ± 17			
		Memory Functioning				
WMS MQ total score	Ablation group	120 ± 16	127 ± 15	0.044	0.001	0.654
	Reference Group	128 ± 13	134 ± 13			
RAVLT Imprinting score	Ablation group	12 ± 2	13 ± 3	0.992	0.001	0.042
	Reference Group	12 ± 2	13 ± 2			
RAVLT Delayed Cued Recall score	Ablation group	12 ± 3	12 ± 3	0.565	0.001	0.005
	Reference Group	11 ± 3	13 ± 2			
RAVLT Delayed Recognition score	Ablation group	41 ± 2	42 ± 2	0.754	0.082	0.979
	Reference Group	41 ± 2	42 ± 3			
		Attention and Concentration				
SART mean reaction time (s)	Ablation group	335 ± 52	332 ± 58	0.834	0.611	0.921
	Reference Group	333 ± 56	329 ± 48			
SART no. errors	Ablation group	12 ± 9	11 ± 8	0.503	0.001	0.006
	Reference Group	16 ± 10	10 ± 8			
		Executive Functioning				
FFT no. patterns	Ablation group	57 ± 30	66 ± 30	0.076	0.001	0.500
	Reference Group	71 ± 20	77 ± 25			

Table E. Continued.

Test	Ablation Technology	NPO I test score	NPO II test score	P (group)	P (time)	P (interaction)
FFT no. repeats	Ablation group	7 ± 8	5 ± 5	0.248	0.118	0.713
	Reference Group	8 ± 7	7 ± 6			
FFT no. errors	Ablation group	1 ± 1	1 ± 1	0.330	0.099	0.057
	Reference Group	0 ± 0	1 ± 2			
TMT Part B (s)	Ablation group	82 + 39	75 + 33	0.669	0.001	0.669
	Reference Group	73 + 28	64 + 26			
TMT Part B - Part A (s)	Ablation group	48 ± 11	51 ± 9	0.168	0.008	0.776
	Reference Group	51 ± 9	54 ± 8			
STROOP Card 3 (s)	Ablation group	48 ± 10	49 ± 9	0.736	0.037	0.378
	Reference Group	48 ± 9	50 ± 8			
STROOP Interference score	Ablation group	52 ± 8	53 ± 7	0.331	0.629	0.591
	Reference Group	54 ± 10	54 ± 10			
		Psychomotor Speed				
LDST no. of correct	Ablation group	33 ± 6	34 ± 7	0.614	0.001	0.075
	Reference Group	32 ± 6	35 ± 5			
PPT Dominant Hand score	Ablation group	34 ± 5	34 ± 6	0.275	0.015	0.092
	Reference Group	35 ± 6	36 ± 6			
PPT Assembly score	Ablation group	27 ± 6	29 ±7	0.280	0.288	0.630
	Reference Group	26 ± 7	26 ± 8			
TMT Part A (s)	Ablation group	32 ± 10	32 ± 12	0.601	0.604	0.807
	Reference Group	31 ± 12	30 ± 15			

Table E. Continued.

Test	Ablation Technology	NPO I test score	NPO II test score	P (group)	P (time)	P (interaction)
STROOP Card 1 (s)	Ablation group	44 ± 9	43 ± 10	0.565	0.747	0.040
	Reference Group	42 ± 8	43 ± 7			
STROOP Card 2 (s)	Ablation group	46 ± 10	47 ± 11	0.605	0.015	0.069
	Reference Group	44 ± 8	47 ± 8			
Anxiety and Depression						
HADS total Score	Ablation group	8 ± 6	7 ± 6	0.967	0.005	0.340
	Reference Group	8 ± 4	7 ± 5			

Values are mean ± standard deviation.

FFT = Figure Fluency Test; GIT2 = Groninger Intelligence Test 2; HADS = Hospital Anxiety and Depression Scale; LDST = Letter Digit Substitution Test; MMSE = Mini Mental State Examination; MQ = memory quotient; PPT = Purdue Pegboard Test; RAVLT = Rey Auditory Learning Test; SART = Sustained Attention to Response Task; STROOP = Stroop Color Word Test; TMT= Trail Making Test; WMS = Wechsler Memory Scale.

T1 = two weeks before ablation; T2 = 3 months after ablation.

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Chapter 4

Biophysical parameters associated with micro-embolic signals using the PVAC-Gold catheter: results from the CE-AF trial

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Submitted

Abstract

Micro-embolic signals (MES) during atrial fibrillation ablation are associated with asymptomatic cerebral embolism. In the CE-AF trial, we detected a high MES count with the PVAC-Gold catheter. In the current sub-analysis, the influence of biophysical parameters was investigated. Besides differences between the pulmonary veins, parameters indicating poor electrode-tissue contact (average power, total effective energy, temperature at 2 seconds, average impedance) were predictors of MES genesis. Parameters of influence with the first generation PVAC (electrode proximity, electrode interaction, temperature overshoot) occurred infrequently and could not be associated with MES count. A re-design including monitoring and improving catheter contact is desirable.

4.1 Introduction

Asymptomatic cerebral emboli (ACE) on magnetic resonance imaging after atrial fibrillation (AF) ablation are of concern. Emboli formation may be diagnosed by recording micro-embolic signals (MES) with transcranial Doppler ultrasonography during ablation. A high incidence of ACE has been reported following ablation with the first generation non-irrigated multi-electrode ablation catheter (PVAC) and was attributed to temperature overshoot, electrode interaction, and poor electrode-tissue contact (1,2). Therefore, three major design changes were incorporated in the second generation PVAC-Gold: gold-electrodes to prevent temperature overshoot, removal of the 10th electrode to prevent electrode interaction, and a 20° angle between the catheter ring and shaft to improve contact. Despite these advances, we found ACE/cerebral infarctions in 23% of paroxysmal AF patients using PVAC-Gold compared with in 6% of patients using a Thermocool catheter in a recent randomized trial (3). Of importance, the median number of micro-embolic signals (MES) was significantly higher with PVAC-Gold compared with Thermocool. In this study biophysical parameters of PVAC-Gold applications associated with MES are analyzed to gain insight into the potential mechanism of MES generation using the redesigned catheter.

4.2 Methods

This analysis included 945 PVAC-Gold radiofrequency applications in 32 patients (age 58±9 years, 23 men). The biophysical parameters of each application that could be extracted from the generator for off-line analysis included average power (Watt), average and maximum temperature (°C), temperature 2 seconds after ablation onset (indicative for the speed of temperature rise), average and total effective contact time (seconds), average and total effective energy (J), average impedance (Ω), electrode proximity (1-9) and interaction (1-8, 2-9), and temperature overshoot (>75˚C). MES were recorded from the onset of the application until 20 seconds after termination. To explore the association between individual biophysical parameters and log-transformed MES counts, single predictor linear mixed model analysis was used with patient and ablation site as random effects. Significant predictor variables were candidates to construct the final optimal multivariable model based on the AIC. Fixed-effects predicted values of this model were calculated for graphic representation.

4.3 Results

The median MES count per application was 9 (IQR 1-37). The median MES count was highest for the left superior pulmonary vein (PV; 31 [IQR 6-72]), followed by the left inferior PV (10 [IQR 2-41]), the right superior PV (5 [IQR 1-15]), and the right inferior PV (2 [IQR 0-9]; p<0.001). Electrode proximity, 1-8 and 2-9 electrode interaction, and temperature overshoot were seen in only 1.3%, 0.7%, 0.3%, and 5.0%, respectively, and were excluded from the analysis. Univariable linear mixed models showed that average power (p<0.001), average and total effective energy (p=0.001 and p<0.001, respectively), and average impedance (p=0.039) were positively associated with MES count, while average temperature (p<0.001) and temperature 2 seconds after ablation onset (p<0.001) were negatively associated. Other patient and procedural characteristics were not associated with MES count. Due to collinearity, only 4 variables (average power, total effective energy, average impedance, temperature 2 seconds after ablation start) were included in the final multivariable model. Observed median MES count showed a stepwise increase with every quartile of the multivariable model-based predicted MES count (Figure 1).

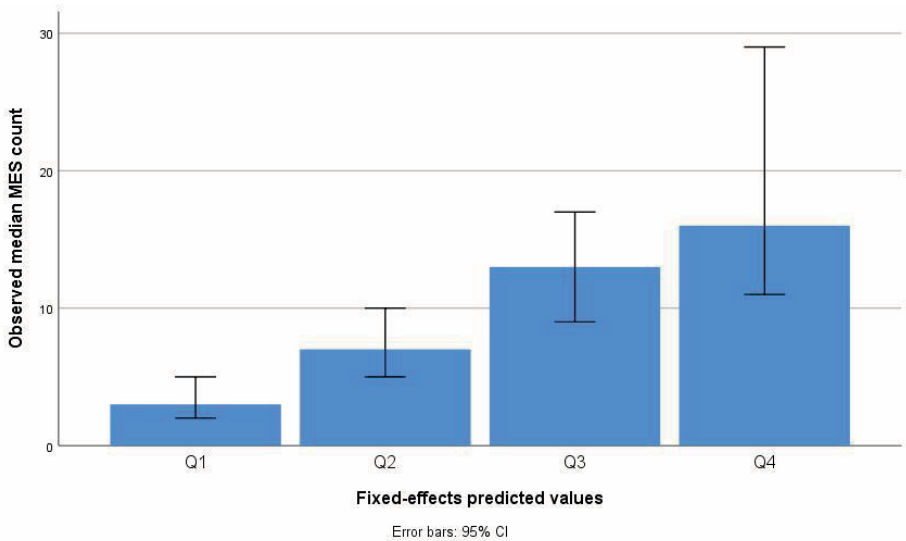

Figure 1. Observed median MES count within quartiles of the multivariable model-based predicted MES count (fixed-effects predicted values) with confidence bounds.

4.4 Discussion/Conclusion

In line with previous reports, the MES count was particularly high for the left superior PV, which may be due to a steep angle between the catheter and the vein resulting in poor contact. In ablations with high power and high total effective energy, the higher MES count may be explained by stronger tissue devolution. A low temperature after 2 seconds may also be related to poor catheter contact, increasing the MES count. Increased impedance may be due to denaturization of blood proteins (MES particles). A slower temperature rise requires higher power to achieve the target temperature, and hence is related to a higher MES count. Electrode proximity/interaction and temperature overshoot (responsible for high MES counts in the first-generation PVAC) occurred infrequently and could not explain MES occurrence. In conclusion, in PVAC-Gold ablation, catheter contact-related biophysical parameters are associated with the increased amount of MES. A re-design including monitoring and improving catheter contact is therefore desirable.

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Chapter 5

Micro-embolic signals and Coagulation markers in ablation with the PVAC-Gold and Thermocool catheter: results from the CE-AF trial

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Submitted

Abstract

Micro-embolic signals (MES) on transcranial Doppler ultrasound are associated with asymptomatic cerebral embolism in patients undergoing atrial fibrillation ablation. We studied the association between coagulation markers and MES during PVAC-Gold ablation. Early changes in an acute phase marker (fibrinogen) and von Willebrand factor (endothelial damage) as a result activation of the fibrinolytic pathway (elevated D-dimer) were associated with MES during PVAC-Gold ablation. Analysis of these markers to screen patients for cerebral ischemia may be useful. Further research is needed to explore the relationship between the origin of MES and coagulation activation.

5.1 Introduction

In the prospective randomized CE-AF trial from our centre 8 (23%) of the patients undergoing ablation with the non-irrigated PVAC-Gold catheter showed multiple cerebral infarcts (1). In addition, a high median number of micro-embolic signals (MES) on transcranial Doppler ultrasound was detected with this catheter (1111 [interquartile range, 715-2234]. Moreover, during the PVAC-Gold applications, a high incidence of so-called embolic showers was observed. MES represent microbubbles and microparticles within the blood flow (2). We hypothesised that activation of the coagulation cascade may play a role in the genesis of the micro-embolism observed with the PVAC-Gold catheter and studied the relationship between MES and activation of coagulation with this catheter.

5.2 Methods

Thirty-two patients (age 58±9 years, 23 men) with paroxysmal AF undergoing ablation with the PVAC-Gold catheter were included in the analysis. Doppler signals were recorded throughout the ablation and MES were automatically identified offline using an in-house developed MATLAB algorithm. Coagulation markers were measured before ablation (T1), after the last application (T2), and 1 day after the ablation (T3). Expected early changes (T2-T1) in coagulation markers (prothrombin fragment as a marker of thrombin generation, fibrinogen as an acute phase marker, von Willebrand factor antigen as a marker of endothelial damage, and soluble p-selectin as a marker of platelet activation) and expected late changes (T3-T1) in coagulation markers (D-dimer as a marker of fibrin turnover and tissue plasminogen activator as a marker of fibrinolysis) were univariably correlated with (log-transformed) MES counts.

5.3 Results

The average temperature with the PVAC-Gold catheter in 997 applications was 52±3 °C. The PVAC-Gold catheter induced a pro-coagulant state which was characterized by significant changes in the coagulation markers (p=0.001 for all markers). The mentioned changes in the different coagulation markers were 17% for prothrombin fragment (1337 to 1111 ng/L), 17% for fibrinogen (3.5 to 2.9 g/L), 45% for von Willebrand factor antigen (1.1 to 1.6 kIU/mL), 23% for D-Dimer (266 to 327 µg/L), 16% for soluble p-selectin (81 to 68 µg/L), and 17% for tissue plasminogen activator (3.6 to 3.0 µg/L). Early changes in fibrinogen (b=0.429, p=0.014) and von Willebrand factor (b=0.418, p=0.022) and late changes in D-dimer (b=0.387, p=0.038) were related with MES counts. Other early and late changes in coagulation markers were not related with MES.

5.4 Discussion/Conclusion

In this study, a higher activation of an acute phase marker (fibrinogen) and more endothelial damage (a higher von Willebrand factor) and activation of fibrinolysis (increased D-dimer) were associated with MES with the PVAC-Gold catheter. These results suggest that in ablations with a stronger acute phase and endothelial damage response more micro-embolism occurs, which eventually results in a stronger activation of the fibrinolytic pathway with elevated D-dimer. During radiofrequency application with open-irrigated catheters, it has been shown that microparticles are especially seen in high energy ablations, drag ablations, and when high-temperature steam pops occur (3). The higher temperatures during ablation with non-irrigated catheters compared to temperature controlled irrigated catheters (3) may cause a stronger activation of the coagulation cascade (with a stronger acute phase response), and may thus result in an higher amount of silent cerebral embolism.

Consequently, measuring coagulation markers in AF ablation may be helpful to identify patients with a high embolic burden to be referred for additional imaging to exclude cerebral infarcts. Currently, measuring D-dimer is proposed for the prediction of ischemic stroke in patients with AF during anticoagulation therapy (4). It may be useful to use this marker in patients undergoing AF ablation also. Larger studies are needed to explore the relationship between coagulation markers and MES in more depth and to define cut-off values for the prediction of silent cerebral ischemia during and after AF ablation.

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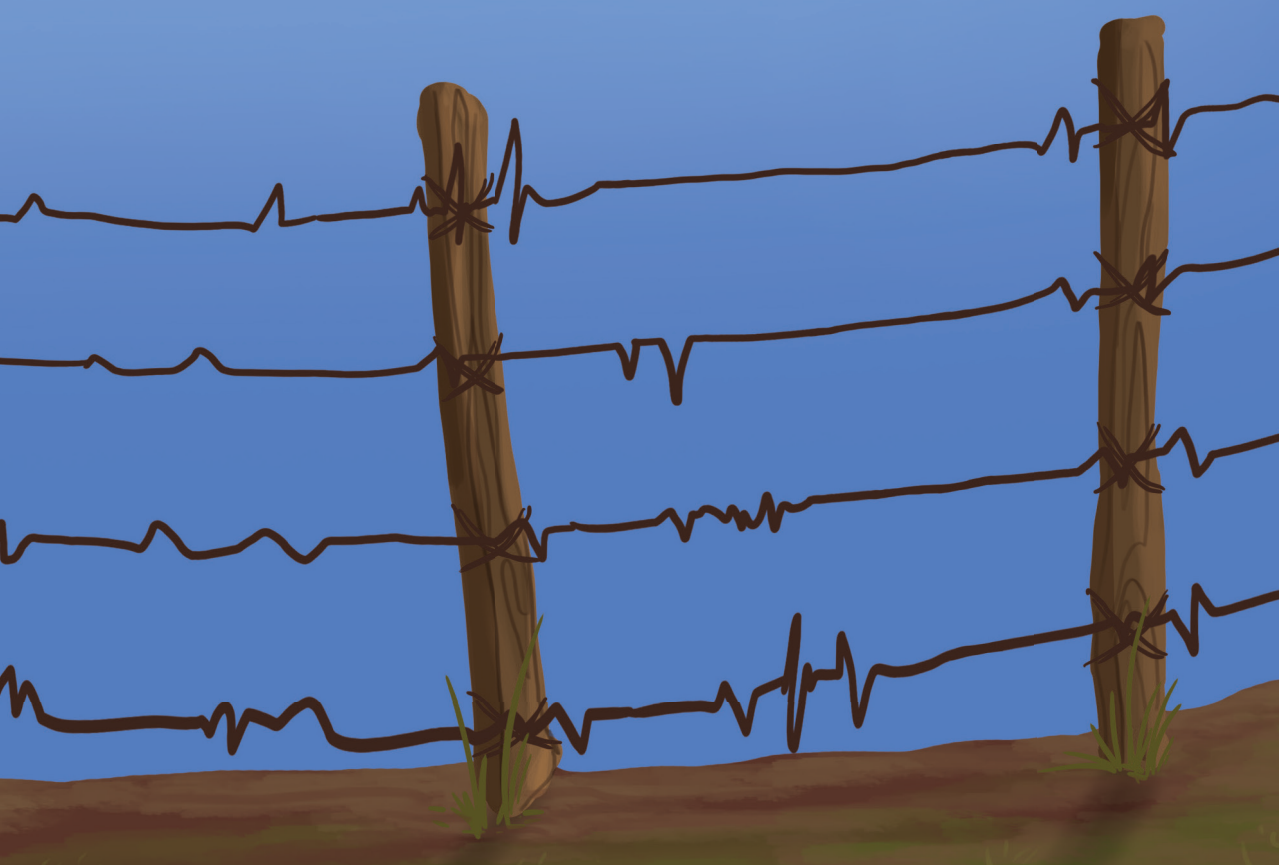
Part 2

Freedom from Recurrences



Chapter 6

Optimizing ablation duration using dormant conduction to reveal incomplete isolation with the Second Generation Cryoballoon: A Randomized Controlled Trial

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Abstract

Introduction

Efficacy of cryoballoon ablation depends on balloon-tissue contact and ablation duration. Prolonged duration may increase extra-cardiac complications. The aim of this study is to determine the optimal additional ablation duration after acute pulmonary vein isolation (PVI).

Methods

Consecutive patients with paroxysmal AF were randomized to 3 groups according to additional ablation duration (90, 120 or 150s) after acute PVI (time-to-isolation). Primary outcome was reconnection/dormant conduction (DC) after a 30 minutes waiting period. If present, additional 240s ablations were performed. Ablations without time-to-isolation <90s, esophageal temperature <18°C or decreased phrenic nerve capture were aborted. Patients were followed with 24-hour Holter monitoring at 3, 6 and 12 months.

Results

Seventy-five study patients (60±11 years, 48 male) were included. Reconnection/DC per vein significantly decreased (22, 6 and 4%) while aborted ablations remained stable (respectively 4, 5 and 7%) among the 90, 120 and 150s groups. A shorter cryo-application time, longer time-to-isolation, higher balloon temperature and unsuccessful ablations predicted reconnection/DC. Freedom of AF was respectively 52, 56 and 72% in 90, 120 and 150s groups (p=0.27), while repeated procedures significantly decreased from 36% to 4% (p=0.041) in the longer duration group compared to shorter duration group (150s vs 90s group). In multivariate Cox-regression only reconnection/DC predicted recurrence.

Conclusion

Prolonging ablation duration after time-to-isolation significantly decreased reconnection/DC and repeated procedures, while recurrences and complications rates were similar. In a time-to-isolation approach, an additional ablation of 150s ablation is the most appropriate.

Clinical Trial Registration – Dutch National Trial Register- NL47833.058.14.

6.1 Introduction

Cryoballoon ablation is an effective single-shot technique for the treatment of paroxysmal atrial fibrillation (AF) and is non-inferior to radiofrequency catheter ablation (1). Several ablation protocols for cryoballoon ablation have been proposed (2, 3). Optimizing the ablation duration to obtain durable ablation lesions without causing extra-cardiac complications is crucial.

It has been shown that time to pulmonary vein (PV) isolation (time-to-isolation) is related to balloon-tissue contact, with a shorter time-to-isolation indicating a better contact (4). It can be expected that with a fixed ablation duration, a better balloon-tissue contact will lead to an earlier lesion transmurality and a potentially higher risk for extra-cardiac complications. It may be beneficial to adapt the application duration according to the time-to-isolation.

The most common extra-cardiac complications related to cryoballoon ablation are right phrenic nerve palsy (7-8%) and esophageal ulceration (12%) (5, 6). Right phrenic nerve palsy can be permanent and may lead to significant dyspnea (7). A rare, but severe complication is the development of an atrio-esophageal fistula, which can be fatal (8). Optimizing the ablation duration may prevent these complications.

After ablation, testing for dormant conduction (DC) with adenosine can be used to reveal incomplete pulmonary vein isolation (PVI) (9, 10). The absence of reconnection/DC after 30 minutes waiting period may be considered as parameter for durable PVI and is therefore selected as a clinical outcome parameter. The primary objective of this randomized clinical trial was to determine the optimal additional ablation after time-to-isolation with absence of reconnection/DC as the primary endpoint.

6.2 Methods

6.2.1 Study Population

Patients eligible for a first cryoballoon ablation of paroxysmal AF were prospectively included between May 2014 and October 2016 and 1:1:1 randomized to an additional ablation of 90, 120 or 150 seconds (s) after time-to-isolation (Figure 1). Eligibility was determined with a pre-procedural CT-scan (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) and defined as no PV diameter >26mm. Patients with previous catheter or surgical AF ablation or persistent AF were excluded. Study patients gave written informed consent for participation in the study and were blinded to group allocation. Data were collected using the departmental Cardiology Information System (EPD-Vision). The study was approved by the institutional ethical review board and registered at the Dutch national trial register (NL47833.058.14).

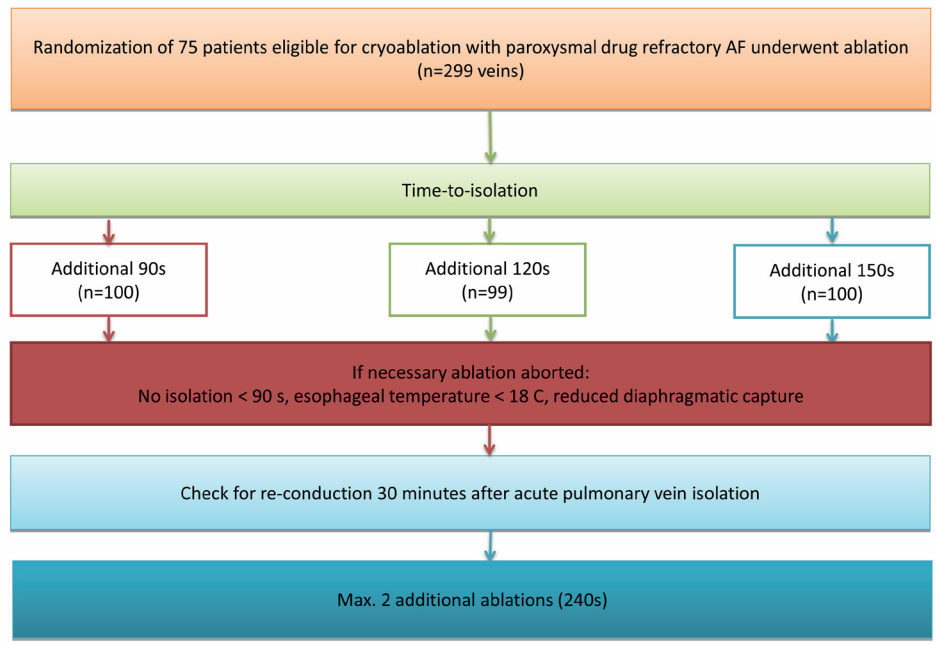

Figure 1. Study protocol.
Seventy-five patients were enrolled and 1:1:1 randomized into 3 groups of respectively 90, 120 and 150 additional ablation time after reaching isolation of the pulmonary vein. Additional ablations were applied in case of reconnection/dormant conduction. Ablations were aborted if no isolation occurred within 90s, in case of reduced phrenic nerve capture or endoluminal esophageal temperature below 18 °C.

6.2.2 Ablation procedure

Anti-arrhythmic drugs (AAD) except amiodarone were discontinued 5-half-lives before ablation. In all patients, a single ablation with the 28 mm second-generation cryoballoon (Arctic Front Advance, Medtronic Inc., Minneapolis, MN, USA) was initially performed. The 23 mm balloon was only used as bail-out in veins with a maximal diameter ≤20 mm when PV occlusion could not be obtained. Total ablation duration for the right superior PV was limited to 180s to prevent phrenic nerve palsy. Time-to-isolation was defined as the time from the start of ablation to the disappearance of PV potentials, registered with a 20 mm intraluminal circumferential mapping catheter (Achieve, Medtronic, Minneapolis, MN). If time-to-isolation was not achieved within 90s, ablation was aborted ('unsuccessful ablation') and the balloon repositioned. If time-to-isolation could not be determined, time-to-isolation was set to 90s to calculate ablation duration. Thirty minutes after ablation, PV isolation was confirmed and adenosine was infused in order to identify DC. Initial adenosine dose was 18 mg and increased to a maximum of 30 mg to obtain ≥ 1 sinus beat with blocked AV-conduction. In case of DC, a maximum of 2 additional ablations with a fixed 240s duration were performed to abolish DC. During ablation of the right veins, absence of phrenic nerve palsy was confirmed by pacing the phrenic nerve from the superior caval vein at 20mA/2ms with manual verification of diaphragmatic movement. A nasal temperature probe (Sensitherm, St. Jude Medical, Saint Paul, MN, USA) was used to monitor endoluminal esophageal temperature. Ablation was discontinued immediately ("aborted ablation") using the "double-stop technique" if a reduced diaphragmatic movement or an esophageal temperature <18 °C was reached. Repeated ablations were always performed by point-by-point ablation using a Lasso and Thermocool Smarttouch SF Catheter (CARTO, Biosense Webster Inc., Diamand Bar, CA, USA) or the Advisor circular mapping and Tacticath catheters (Ensite, Abbott, St. Paul, MN, USA).

6.2.3 Follow-up

Patients were followed 3, 6 and 12 months after ablation with a 24h Holter and exercise test. AAD were restarted after the ablation and maintained until the first follow-up at 3 months after ablation. Success was defined as the absence of any recording of AF/Atrial tachycardia on ECG or recording of >30s on a 24h Holter registration off AAD after a blanking period of 3 months.

6.2.4 Statistical Analysis

Sample size for the prospective randomized groups was calculated based on the incidence of DC in our hospital with the first generation balloon (42%, expected to be comparable with the additional 90s group) and second generation balloon (5%, expected to be comparable with the additional 150s group). For the additional 120s group an expected incidence of 21% was used. A Cochran-Armitage test for linearity was performed to obtain a sample size for the three groups using STATA software, V.12 (Stata Corp, College Station, Texas, USA). With α=0.05 the necessary total sample size was 66 patients to detect a significant trend in DC with 80% power. The group size was therefore set at a total sample size of 75 patients. Baseline characteristics were compared between the randomized groups using one-way ANOVA for continuous variables and Chi-square tests or Fisher's exact test for categorical variables. Predictors for reconnection/DC were tested using multivariate regression analysis. Multivariate Cox-regression was used to identify predictors for recurrence. Variables with a $p<0.1$ in univariate analyses were entered in the multivariate analysis using the enter method. The log-rank test was used to test differences for AF recurrences. A p-value of <0.05 was considered statistically significant. SPSS (version 23, SPSS Inc., Chicago, IL, USA) was used.

6.3 Results

6.3.1 Baseline characteristics

Table 1 shows the baseline clinical characteristics of the 75 randomized patients. There were no significant differences in age, gender and co-morbidities between the 90, 120 and 150s groups. All patients had a normal ejection fraction and the mean left atrial diameter was 40±5mm.

Table 1. Baseline characteristics.

	90s (n=25)	**120s(n=25)**	**150s (n=25)**	***P value***
Age (years)	61±11	59±11	60±11	0.857
Male gender	15 (60)	15 (60)	18 (72)	0.594
AF duration (months)	51 [37-112]	24 [12-54]	41 [18-69]	0.066
CHA_2DS_2-VASc score	1.6±1.4	1.1±1.0	1.4±1.1	0.380
LA diameter (mm)	39±6	38±5	40±5	0.542
Body Mass Index (kg/m^2)	25.5±3.5	25.0±3.9	25.7±3.4	0.847
AAD at baseline	21 (84)	19 (76)	20 (80)	0.329
Hypertension	11 (44)	7 (28)	14 (56)	0.133
Dyslipidemia	12 (48)	5 (20)	8 (32)	0.109
Diabetes	1 (4)	1 (4)	1 (4)	1.000
Coronary Artery Disease	1 (4)	2 (8)	1 (4)	0.768
Structural Heart Disease	4 (16)	4 (16)	1 (4)	0.372

Values are reported as the mean±standard deviation, median (interquartile range), or n (%).

6.3.2 Procedural details

The mean procedure time and mean ablation duration for all groups were respectively 126±31 minutes and 17±5 minutes and no significant differences were seen between the three groups (p=0.053 and p=0.132, respectively, Table 2). The mean cryo-application duration was significantly different among the groups (146±28s, 167±30s and 192±34s respectively, p<0.001). The mean number of cryo-applications per patient was 6±2 (p=0.339). Time-to-isolation could be determined for 262 veins (88%). In the remaining veins the disappearance of PV potentials were unclear. Analyses on the differences in biophysical data of the cryoballoon, on the incidence of reconnection and DC and on the predictors of reconnection/DC with exclusion of these pulmonary veins did not influence the results (online supplement). There were no significant differences in time-to-isolation between the four pulmonary veins. In addition, there were no differences in

time-to-isolation, minimum balloon temperature, warming time and minimum esophageal temperature between the three groups. Single-shot isolation was achieved in respectively 81, 79 and 72% of the PVs in the 90, 120 and 150s (p=0.254). There were no significant differences in single-shot isolation rates between the PVs (76% for the left superior PV, 81% for the left inferior PV, 82% for the right superior PV and 72% for the right inferior PV, p=0.465).

Table 2: Procedural details.

	90s (n=25)	**120s (n=25)**	**150s (n=25)**	***P value***
Procedure Time (min	138±32	118±26	126±31	0.053
Total cryoapplication time (min)	18±6	15±4	17±4	0.132
Balloon size (28 mm)	24 (96)	23 (92)	23 (92)	1.000
Balloon size (23 mm)	1 (4)	1 (4)	2 (8)	1.000
Ballloon size (23 and 28 mm)	0	1 (4)	0	1.000
Fluroscopy time (min)	24±11	19±9	23±12	0.296
Dose-area product (mSV)	2.4±1.5	1.9±1.0	2.8±2.1	0.184
Cavotricuspid isthmus ablation	7(28)	4(16)	4(16)	0.472
Mean time-to-isolation (s)	51±25	49±26	52±27	0.641
Mean cryo-application time (s)	146±28	167±30	192±34	<0.001
Warming Time (s)	40±18	41±20	39±19	0.836
Min. balloon Temperature (°C)	-43±7	-45±7	-45±7	0.038
Min. oesophageal temperature (°C)	34±5	32±6	33±6	0.249

Values are reported as the mean±standard deviation or n (%).

6.3.3 PV reconnection/DC

The numbers of patients and PVs with reconnection/DC are specified in Table 3. A significant decrease in reconnection/DC and a corresponding decrease in the number of additional cryo-applications was shown with increasing ablation durations. The procedural duration was also prolonged by the additional applications to abolish dormant conduction and an additional waiting-period of 30 minutes.

6.3.4 Predictors of PV reconnection/DC

In multivariate analysis, a shorter cryo-application time, longer time-to-isolation, a higher nadir balloon temperature and more unsuccessful ablations were associated with a higher incidence of PV reconnection/DC (Table 4). Warming time was not a significant predictor in multivariate analysis.

Table 3. Incidence of reconnection/ DC per patient and per vein.

	90s (n=25/100)	120s (n=25/99)	150s (n=25/100)	*P value*
Reconnection	8 (32)	3 (12)	0	0.005
Reconnection (per vein)	9 (9)	3 (3)	0 (0)	0.003
DC	9 (36)	3 (12)	4 (16)	0.085
DC (per vein)	15 (15)	3 (3)	4 (4)	0.002
Reconnection/DC	16 (64)	6 (24)	4 (16)	0.001
Reconnection/DC (per vein)	22 (22)	6 (6)	4 (4)	0.001

Values are reported as the mean±standard deviation or n (%). DC indicates dormant conduction.

Table 4: Univariate and multivariate regression analyses of the predictors of reconnection/DC in the pulmonary veins.

Variables	**Univariate**		**Multivariate**	
	Hazard ratio (95% confidence interval)	***P* value**	**Hazard ratio (95% confidence interval)**	***P* value**
Cryoapplication time (s)	0.991 [0.982-0.999]	0.035	0.975 [0.962-0.988]	<0.001
Time-to-isolation (s)	1.012 [0.999-0.1025]	0.079	1.027 [1.009-1.046]	0.004
Warming time (s)	0.947 [0.955-0.994]	0.011		0.500
Nadir balloon temperature (˚C)	1.139 [1.070-1.212]	<0.001	1.163 [1.068-1.266]	0.001
Number of unsuccessful ablations	1.393 [0.998-1.944]	0.052	1.722 [1.113-2.664]	0.015

6.3.5 Outcome

During a follow up of 1-year, the single-procedure success rate off AAD was 60% in the total group (68% on/off AAD). Median time to recurrence was 7 [5-13] months. The single-procedure success rates off AAD in the 90, 120 and 150s groups were respectively 52, 56 and 72% (p=0.27) after 1 year. Total AF-free single-procedure success on/off AAD was respectively 56, 72 and 77% (p=0.384). During follow-up a repeated procedure was performed in 15 patients (20%). During the repeated procedure, PV reconnections were observed in 14 patients (19%) and additional ablations were performed in 9 (12%) patients (4 superior vena cava, 3 mitral isthmus line, 1 posterior left atrial box lesion, 1 posterior line and 1 left atrium anterior wall ablation). During these repeated procedures 53% of the left superior veins were reconnected, 53% of the left inferior veins, 40% of the right superior veins and 20% of the right inferior veins (p=0.217). The rate of repeated procedures significantly decreased with increasing additional ablation time: 36% in the 90s group, 20% in the 120s group and 4% in the 150s group (p=0.041).

6.3.6 Predictors of recurrence

In multivariate analysis, only PV reconnection/DC was associated with a higher incidence of AF recurrence (Table 5).

Table 5. Univariate and multivariate cox proportional regression analyses of the predictors of recurrence per patient.

Variables	Univariate		Multivariate	
	Hazard ratio (95% confidence interval)	***P* value**	**Hazard ratio (95% confidence interval)**	***P* value**
Age		0.397		
Male Gender		0.119		
BMI (kg/m²)		0.782		
LA diameter (mm)		0.819		
AF duration (months)		0.483		
Group		0.152		
Reconnection/DC	4.0 [1.465-10.919]	0.007	4.037 [1.446-11.271]	0.008
CTI Ablation		0.084		0.096
Diabetes		0.359		

AF indicates atrial fibrillation; BMI, body mass index; CTI, cavotricuspid isthmus; LA, left atrium; DC, dormant conduction.

6.3.7 Complications

One patient from the 150s group showed persistent phrenic nerve palsy at discharge that was resolved at 1-year follow up. Two patients had complications related to the vascular femoral access, including one patient with a severe bleeding requiring transfusion. In Figure 2 a 'safety profile' is made using the number of reconnection/ DC, aborted ablations, phrenic nerve palsy and repeated procedures.

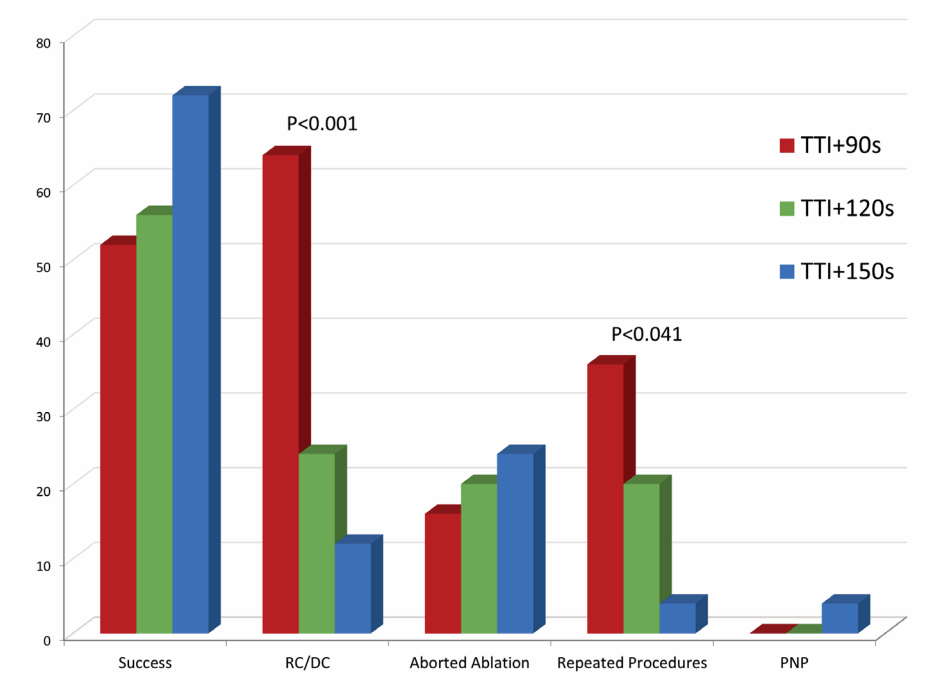

Figure 2. Safety profile of the different ablation groups.
One-year AF-free survival off anti-arrhythmic drugs, percentage of reconnection(RC)/dormant conduction(DC) (per patient), aborted ablations (per patient), phrenic nerve palsy and repeated procedures across the different groups. There were no significant difference in single-procedure success off AAD, aborted ablations and phrenic nerve palsy (PNP), however significant differences were seen in the percentage of reconnection/dormant conduction ($p<0.001$) and repeated procedures ($p=0.041$).
PNP=phrenic nerve palsy, RC/DC=reconnection and dormant conduction and TTI=time-to-isolation.

6.4 Discussion

6.4.1 Main Findings

The major finding of this study is that an additional ablation with 90, 120 or 150s after time-to-isolation showed a stepwise decrease in reconnection/DC. Consequently, additional ablations for the treatment of reconnection/DC decreased similarly while the success rates at one-year off AAD were not significantly different. During follow-up the rate of repeated procedures decreased with increasing additional ablation. To the best of our knowledge, this is the first trial studying single cryoballoon applications with the ablation duration based on time-to-isolation.

6.4.2 Decreasing ablation duration with the second-generation cryoballoon

The second-generation cryoballoon with more injection ports for more homogenous and faster cooling was introduced to achieve more durable PVI. At the cost of a higher success rate, more transient and persistent phrenic nerve palsies were described (11). Instead of a double 300s fixed ablation duration, a double 240s fixed duration was proposed by the manufacturer. Subsequently, studies showed that a single ablation per vein is sufficient (12). In addition, shortening the ablation duration from 4 to 3 minutes did not increase AF recurrence (2, 13).

6.4.3 Making ablation duration dependent on time-to-isolation

Cryothermal energy delivery does not only depend on ablation duration, but also on adequate balloon-tissue contact (14). As balloon gas flow is constant, time to PVI is related to balloon-tissue contact, with a shorter time-to-isolation indicating a better contact (15). Indeed, time-to-isolation predicted durable PVI in several studies with significantly lower PV reconnections at 1 year follow up (4, 16). In a canine model, a 60s additional ablation after time-to-isolation showed 100% durable PVI on histology (17). In addition, extending ablation duration based on a longer time-to-isolation was not associated with durable PVI. Furthermore, a perfect score for the assessment of occlusion was more relevant than total ablation duration in predicting gaps. Therefore, balloon-tissue contact remains the most important factor for durable PVI. Moreover, making ablation dependent on time-to-isolation is feasible, since in a majority of the veins (88%) time-to-isolation could be observed, while other researchers report 72-81% (18, 19). This percentage may become even higher with the future introduction of the third-generation cryoballoon with a shorter-tip, which facilitates PV electrogram registration.

6.4.5 Outcome in time-to-isolation dependent ablation

Two prior studies report on time-to-isolation cryoballoon based ablation. A recent randomized trial by Ferrero-de-Loma-Osorio et al. showed in 140 patients that applying 60s additional ablation after time-to-isolation with a second 120s application was similar to a double 180s fixed duration protocol (70.5 vs. 74.3% success off AAD at one year, p=0.61) (19). In a multicenter trial by Aryana et al. an additional ablation of 120s in 355 patients was applied after time-to-isolation, but a second 120s ablation was added when time-to-isolation was >60s. They compared this strategy to conventional ablation performed in 400 pts, which was defined as 2-3 applications of 2-4 min at the discretion of the operator. Outcomes were similar at 83% and 78% at one year off AAD (p=0.14)(18). Although we performed no additional ablations in our protocol, our results in the 150s group (72% off AAD at one year) are similar to the first study. Interestingly, although we aimed at abolishment of all dormant conducting veins, outcomes were numerically smaller in both the 90s and 120s groups (52 and 56%) compared to the 150s group (72%), suggesting inferiority of this approach. A possible explanation is that during the first incomplete ablation edema occurs(20), making the second ablation less effective. Indeed, in multivariate analysis we observed that reconnection/DC was the only predictor of recurrence while the number of unsuccessful ablations was a predictor of reconnection/DC. Therefore, a complete lesion formation with a single (durable) freeze may be desirable. In addition, success on AAD was 16% higher than success off AAD in the 120s group, compared to only 4 and 3% difference in the 90s and 150s groups respectively. This may indicate that 120s additional ablation creates enough PV activation delay to maintain sinus rhythm with AAD in this group.

6.4.6 Repeat ablation in time-to-isolation dependent ablation

The study of Aryana *et al.* reported 9.9% vs. 15.7% re-ablations in the study and control groups, respectively, with 18.5% vs. 5.0% of the veins reconnected(18). In our study a significant less repeated procedures were required when the additional ablation duration was increased from 90s to 150s (36 vs. 4%; p=0.041). As repeated procedures are clinically meaningful, these results suggest that 90s or 120s additional ablation after time-to-isolation is insufficient.

6.4.7 Reconnection/dormant conduction in time-to-isolation dependent ablation

Acute PV reconnection is also reported in the trial of Ferrero-de-Loma-Osorio *et al*. In this trial in 140 patients, 3.5% and 2.3% of the veins were acutely reconnected in the study and control groups, respectively (p=0.6)(19). This is comparable to the 4% dormant conduction in our 150s group, while the 90s and 120s groups showed a significant increase in reconnection/DC with decreasing additional ablation.

6.4.8 Complications in time-to-isolation dependent ablation

A multicenter comparison of 352 patients undergoing an additional ablation of 120s after time-to-isolation with both a double (152 patients) and single (59 patients) 240s application found 3.7%, 7.9% and 8.5% complications, respectively(3). However, numbers were mainly driven by remote complications (groin and respiratory tract infections: 0.6%, 1.3% and 5.1%), while phrenic nerve palsy was present in 2.0%, 5.7% and 3.4%. In the study of Aryana *et al.* comparing a protocol guided by time-to-isolation (n=355) versus a conventional group (n=400), adverse events were similar at 2.0% and 2.7%, with a numerically lower phrenic nerve palsy incidence of 0.6% in the time-to-isolation group vs. 1.2 in the control group (p=0.33)(18). The randomized trial of 140 patients reported 8% complications with 3.6% phrenic nerve palsy and no differences between the groups (19). Our results are comparable to these numbers and were not significantly different between the groups.

6.4.9 Limitations

This is a small-size single-center randomized study. The study was powered to detect differences in reconnection/DC and not to detect significant differences in complications and recurrence rates. Therefore, a substantial conclusion cannot be drawn regarding outcome and complications. In this study only ablation duration and not contact force and ablation energy were optimized, as contact force cannot be measured by the current technology and ablation energy (balloon gas flow) cannot be adjusted by the operator. Indirect measurements for balloon occlusion, such as fluoroscopic contrast stasis or intracardiac echo doppler measurements were not routinely documented in this study. Due to the small number of patients these factors may have biased the results. In addition, dormant conduction was used to reveal incomplete pulmonary vein isolation, which is only a surrogate for durable PV isolation. In this study the 90s dosing protocol was the least successful with a significant higher number of reconnection/DC. Given the low number of patients in each group, it is possible that there is no significant differences in reconnection/DC between the 120 and 150s group. During follow up only 24-h Holter monitoring was used, longer rhythm monitoring could have detected more AF-episodes. However, we consequently encouraged patients to seek healthcare support for additional ECG recordings if symptoms occurred.

6.5 Conclusions

An additional ablation with 90, 120 or 150s after time-to-isolation in cryoballoon ablation caused a stepwise decrease in reconnection/DC, a decrease in additional ablations for the treatment of reconnection/DC, while recurrences and complication rates at one year were not significantly different. In addition, the rate of repeated procedures during follow-up decreased with increasing additional ablation. Therefore, based on our data selecting an additional ablation of 150s is the most appropriate approach in time-to-isolation based ablation.

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Chapter 7

Predicting early reconnection after cryoballoon ablation with procedural and biophysical parameters

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Submitted

Abstract

Background

Predicting early reconnection/dormant conduction (ERC) immediately after pulmonary vein isolation (PVI) can avoid a waiting-period with adenosine testing.

Objective

To identify procedural and biophysical parameters predicting ERC.

Methods

Consecutive AF patients undergoing a first cryoballoon ablation (Arctic Front Advance) between 2014 and 2017 were included. ERC was defined as manifest or dormant pulmonary vein (PV) reconnection with adenosine 30 min after PVI. Time-to-isolation (TTI), balloon temperatures (BT) and thawing times were evaluated as potential predictors for ERC. Based on a multivariable model, cut-off-values were defined and a formula was constructed to be used in clinical practice.

Results

A total of 136 patients (60±9 years, 108 males, 95% paroxysmal AF) were included. ERC was found in 40 (29%) patients (ERC group) and in 53/575 (9%) veins. Procedural and total ablation time and the number of unsuccessful freezes were significantly longer/higher in the ERC group compared to the non-ERC group (150±40 vs. 125±34min; 24±5 vs. 17±4min and 38% vs. 24% respectively (p=0.028). Multivariable analysis showed that a higher nadir balloon temperature (HR 1.17[1.09–1.23, p<0.001), a higher number of unsuccessful freezes (HR 1.69[1.15-2.49], p=0.008) and a longer TTI (HR 1.02[1.01–1.03], p<0.001) were independently associated with ERC leading to the following formula: 0.02*TTI + 0.5*number of unsuccessful freezes + 0.2*nadir BT with a cut-off value of ≤-6.7 to refrain from a waiting-period with adenosine testing.

Conclusion

Three easily available parameters were associated with ERC. Using these parameters during ablation can help to avoid a 30-min waiting period and adenosine testing.

7.1 Introduction

Cryoballoon ablation is an effective treatment for drug-resistant atrial fibrillation (AF) due to its ease of use, its low complication rates and shorter procedural times compared to radiofrequency catheter ablation (1). AF-recurrence rates after cryoballoon ablation can be decreased if a 30-minute waiting period for detecting early pulmonary vein (PV) reconnection is applied, followed by testing with adenosine for identifying dormant conduction (2-6). However, this approach is time-consuming and infusion of adenosine is associated with patient discomfort. Therefore, predicting the absence of early PV reconnection and dormant conduction immediately after a cryoballoon application would be desirable.

In a prior study, a time-to-isolation ≤60 seconds and a thawing time to 0°C of ≥10 seconds during the index cryoablation were associated with durable PV isolation assessed during a repeat ablation 14±3 months after the index procedure (7). However, sites of early (after 30-min) reconnection may differ from sites of late (repeated procedure) reconnection (6) and biophysical data associated with late reconnection may not predict early reconnection/dormant conduction (ERC).

The purpose of this study was therefore to identify procedural and biophysical parameters to predict the absence of ERC at the time of the index procedure.

7.2 Methods

7.2.1 Study Population

Consecutive patients undergoing a first AF ablation with cryoballoon at the Leiden University Medical Center between 2014 and 2017 were included. Patient characteristics and procedural data were collected using the departmental Cardiology Information System (EPD-Vision). The ablation files were extracted from the ablation console to derive biophysical parameters of each cryo-application. This retrospective study was approved by the institutional ethical review board.

7.2.2 Ablation procedure

All anti-arrhythmic drugs (except amiodaron) were discontinued for at least 3 days before ablation. Ablation was performed with a 28-mm second-generation cryoballoon (Arctic Front Advance, Medtronic Inc., Minneapolis, MN, USA). The 23-mm balloon was only used in PVs with a diameter <20 mm in which PV isolation could not be achieved with the 28mm balloon. A single cryo-application was performed per PV. The ablation duration was set to 240 s except for the right superior PV in which the application duration was decreased to 180 s to prevent phrenic nerve palsy(2, 8). During ablation, time-to-isolation was measured, defined as the time from start of the application until disappearance of the PV potentials recorded from a 20 mm intraluminal circumferential mapping catheter with 8 electrodes (Achieve, Medtronic, Minneapolis, MN). The cryo-application was aborted and the balloon repositioned if isolation was not achieved within 90 seconds. After a waiting period of 30-minutes, PV isolation was re-assessed. If a given PV was reconnected, additional cryo-applications were performed until PVI was achieved. In the presence of PVI, dormant PV conduction was tested during adenosine infusion. An increasing dose of adenosine (18 up to 30mg i.v.) was administered until >1 sinus beat with blocked AV-conduction was observed. In case of dormant conduction, additional applications were performed, with a maximum of 2. Early reconnection was defined as acute reconnection directly after the application or reconnection or dormant conduction tested with adenosine after a waiting-period of 30 minutes. For the prevention of phrenic nerve palsy, high-output pacing (20mA/2ms) of the phrenic nerve from the superior caval vein was performed with manual palpation of the diaphragmatic movement to confirm and control capture. Endoluminal esophageal temperature was monitored with a nasal temperature probe (Sensitherm, St. Jude Medical, Saint Paul, MN, USA). Applications were terminated with a ‘double stop technique’ if the temperature of the esophagus reached <18

°C or a reduced diaphragmatic movement was observed. Procedural characteristics including number of applications and unsuccessful freezes per vein (defined as aborted applications because of absence of PV isolation within 90 s) and time-to-isolation as well as biophysical data were evaluated as potential predictors for ERC (7).

7.2.3 Follow-up

Patients were followed 3, 6 and 12 months after ablation with a 24-Holter and an exercise test. In addition, all symptomatic patients were encouraged to immediately visit the outpatient clinic for rhythm documentation on 12-lead ECGs or additional 24-Holter registration during palpitations. After the procedure, anti-arrhythmic drugs were restarted and stopped at the first follow-up visit if no AF/Atrial tachycardia recurrence was documented. After a blanking period of 3 months, ablation success was defined as the absence of any documentation of AF/atrial tachycardia lasting longer than >30 seconds on ECG, Holter or device recording.

7.2.4 Statistical analysis

Categorical variables were compared using the Chi-square test (or Fisher exact test when appropriate) and continuous variables with the independent T-test (or Mann-Whitney U test). Predictors of ERC were identified by multivariable logistic regression using variables with statistically significant differences in the univariable analysis between the groups. This resulted in a model providing odds ratios and 95% confidence intervals for the primary outcome. A receiver operating characteristics (ROC) curve corresponding to the selected logistic regression was constructed and the area under the curve was calculated to provide a summary measure of the accuracy of the prediction model. Based on the individual coefficients of the regression model a formula was created and based on the ROC curve, a combined cut-off-value was determined for the significant parameters. Finally, the AF-free survival was compared between groups using the log-rank test. A p-value of <0.05 was considered statistically significant. R-studio (Version 1.0.143 – © 2009-2016 RStudio, Inc.) was used for data extraction and calculation of biophysical data from the console files and SPSS (version 23, SPSS Inc., Chicago, IL, USA) was used for data analysis.

7.3 Results

7.3.1 Baseline characteristics

A total of 151 patients (60±9 years, 108 males, 95% paroxysmal AF) were included. Fifteen patients and 52 veins were excluded from the analysis, because dormant conduction testing was not performed due to contraindications for adenosine (asthma)). The final population consisted of 136 patients and 575 veins were analysed. ERC was found in 40 (29%) patients (ERC group) and in 53 (9%) veins. ERC was more prevalent in males (83% vs. 66%, p=0.049). Other baseline clinical characteristics were comparable between groups (table 1).

Table 1. Baseline Characteristics.

	No ERC (n=96)	**ERC (n=40)**	***P value***
Age (y), mean	60±10	60±9	0.789
Male gender, n (%)	63 (66%)	33 (83%)	0.049
AF duration, years	4.4±3.8	3.9±3.1	0.473
Paroxysmal AF	93 (97%)	36 (90%)	0.098
CHA_2DS_2-VASc score	1.6±1.4	1.4±1.2	0.333
Body Mass Index, kg/m²	26.9±3.8	27.3±3.8	0.538
AAD at baseline, n (%)	82 (85%)	33 (83%)	0.668
Amiodaron	14 (15%)	5 (13%)	0.749
Comorbidity			
Hypertension, n (%)	44 (46%)	13 (33%)	0.151
Dyslipidemia, n (%)	24 (25%)	15 (38%)	0.142
Diabetes, n (%)	6 (6%)	5 (135%)	0.300
Sleep Apnea, n (%)	5 (5%)	4 (10%)	0.449
Coronary Artery Disease, n (%)	13 (14%)	6 (15%)	0.823
Structural Hearth Disease, n (%)	6 (6%)	3 (8%)	0.722
Imaging			
LA diameter (mm), mean, SD	40±4	41±5	0.706

AF: atrial fibrillation; AAD: anti-arrhythmic drugs; LA: left atrium.

7.3.2 Procedural details

Procedure and total ablation time were longer in the ERC group compared to the non-ERC group (150±40 min vs. 125±34 min and 24±5 min vs. 17±4 min; both p<0.001). The total number of applications (8±2 v. 5±1, p<0.001) and the number of unsuccessful freezes 38%

vs 24% (p=0.028) of the PVs were significantly higher in the ERC group. Time-to-isolation could be measured in 80% of the PVs during ablation and was significant longer in the ERC group (70±30 vs 48±28 s). Procedural details are displayed in table 2.

Table 2. Procedural Characteristics.

Per patient (n=136) or per vein (n=575)	No ERC (n=96/522)	ERC (n=40/53)	*P value*
Procedure Time (min), mean	125±34	150±40	<0.001
Total Ablation Time (min), mean	17±4	24±5	<0.001
Number of applications per patient, mean	5±1	8±2	<0.001
Balloon size (28 mm), n (%)	89 (93%)	37 (93%)	1.000
Balloon size (23 mm), n (%)	5 (5%)	1 (3%)	0.670
Ballloon size (23 and 28 mm), n (%)	2 (2%)	2 (5%)	0.581
Effective radiation dose (mSV), mean	2.7±2.6	3.5±2.5	0.081
Time to isolation (s)	48±28	70±39	0.001
Total ablation time (s)	213±41	219±43	0.302
Minimal oesophagus temperature (°C)	33±6	31±12	0.254
Unsuccessful freezes, n (%)	125 (24%)	20 (38%)	0.028
Aborted freezes, n (%)	56 (11%)	8 (15%)	0.336

7.3.3 Biophysical data

The balloon temperature at 60 s (-35±6 vs -39±6 °C, p=0.004) and the nadir balloon temperature were significantly lower in the non-ERC-group (-42±9 °C vs.-47±7 °C, p<0.001). In addition, significantly shorter thawing times were achieved at 0, 15 and 20°C in the ERC group. The mean balloon temperature below 0°C was-35±7 °C in the ERC group compared to -38±5 °C in the non-ERC group (p<0.001). In table 3, an overview of all biophysical parameters is shown.

7.3.4 Early reconnection/dormant conduction

Reconnection without adenosine was seen in 28 (19%) of the patients and 30 (5%) of the veins, while dormant conduction was observed in 21 (14%) patients and 28 (4%) veins.

7.3.5 Predictors of Early reconnection/dormant conduction

Multivariable analysis showed that a higher number of unsuccessful freezes (HR 1.69[1.15-2.49], p=0.008), a longer time-to-isolation (HR 1.02[1.01 – 1.03], p=0.001) and a higher nadir balloon temperature (HR 1.17[1.09 – 1.27], p<0.001) were independently associated with ERC.

Table 3. Biophysical parameters.

	No ERC (522)	ERC (n=53)	*P value*
Temperature at 30 seconds (°C)	-31±5	-29±8	0.058
Temperature at 60 seconds (°C)	-39±6	-35±8	0.004
Nadir Balloon Temperature (°C)	-47±7	-42±9	<0.001
Temperature at time-to-isolation (°C)	-34±8	-34±8	0.789
Freeze (AUC)	7999±7285	7285±1961	0.007
Freeze magnitude (Freeze AUC/total application time)	38±5	35±7	<0.001
Warming time to 0 °C (s)	9±6	6±4	0.001
Warming time to 15 °C (s)	35±16	25±16	<0.001
Warming time to 20 °C (s)	42±18	31±18	<0.001

AUC=Area-under-the-curve (sum of temperature x time)

Table 4. Biophysical and procedural predictors for early reconnection/dormant conduction.

Variables	**Univariable**		**Multivariable**	
	Odds ratio (95% confidence interval)	***P value***	**Odds ratio (95% confidence interval)**	***P value***
Procedural				
Time to isolation	1.0 [1.01-1.03]	<0.001	1.1 [1.01 – 1.03]	0.001
Number of Unsuccessful freezes	1.5 [1.18-2.01]	<0.001	1.7 [1.15 – 2.49]	0.008
Biophysical				
Temperature at 30 seconds	1.1 [1.02 – 1.13]	0.006	0.9 [0.82-1.0]	0.057
Temperature at 60 seconds	1.1 [1.05 – 1.17]	<0.001		
Nadir Temperature	1.1 [1.06-1.15]	<0.001	1.2 [1.09 – 1.23]	<0.001
Temperature at time-to-isolation	1.0 [0.95 – 1.04]	0.885		
Freeze (area under the curve)	1.0 [1.0 – 1.0]	0.008		
Freeze magnitude	0.9 [0.83 – 0.93]	<0.001		
Warming time to 0	0.9 [0.78-0.93]	<0.001		
Warming time to 15	1.0 [0.94-0.98]	<0.001		
Warming time to 20	1.0 [0.95-0.98]	<0.001		

In figure 1, a ROC-curve is constructed with the three available parameters with an area under the curve of 0.75. Based on the coefficients, 0.02, 0.5 and 0.2 for respectively time-to-isolation, number of unsuccessful freezes and nadir balloon temperature, a combined cut-of-value of ≥-6.7 was calculated to predict ERC with a 86% specificity and 70% sensitivity. By applying the derived formula on different values of the respective parameters, we constructed table 5 for clinical decision making to either apply a waiting period with adenosine testing (ERC testing) or to refrain from it.

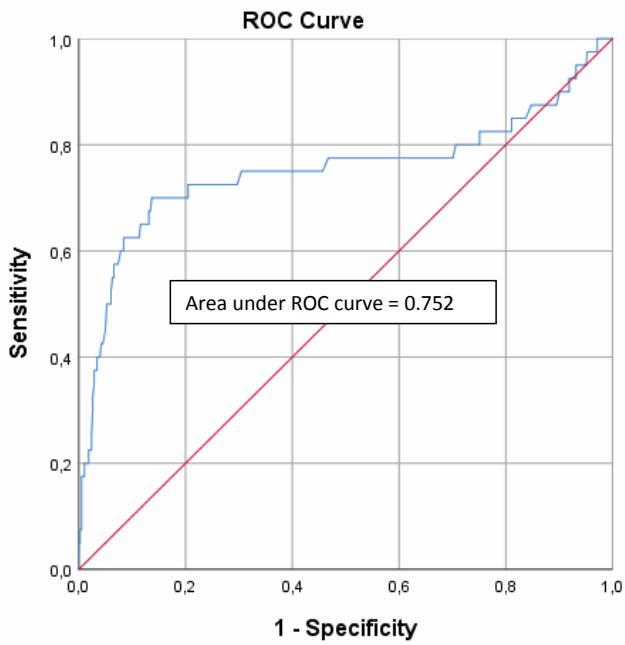

Figure 1. ROC curve predicting early reconnection/dormant conduction using the three parameters.

7.3.6 Acute complications and follow-up

In 2 patients, groin-related complications (1.3%) and in 4 patients, phrenic nerve palsy persisting after one year (2.6%) occurred. The one-year off anti-arrhythmic drug AF-free survival in the total group was 69% and was not significantly different between the two groups (68% vs. 71%, p=0.983). Eleven patients were lost to follow up.

7.4 Discussion

7.4.1 Main Findings

The purpose of this study was to identify procedural and biophysical parameters associated with the absence of early reconnection and dormant pulmonary vein conduction (ERC) during AF ablation with the cryoballoon. We found that unsuccessful freeze attempts, a longer time-to-isolation and a higher (warmer) nadir balloon temperature were associated with ERC. Based on these parameters, we constructed an easy-to-use table which may help to decide for or refrain from a 30-min waiting period followed by adenosine testing.

7.4.2 Prognostic significance of dormant conduction

Adenosine testing to reveal and subsequently treat dormant conduction during AF ablation is associated with lower recurrence rates (5, 9). An international multicentre randomised study showed an improvement of arrhythmia-free survival using this strategy compared to no-adenosine-testing, with an absolute risk reduction of 27% and a hazard ratio of 0.44 ($p<0.0001$) (5).

In addition, applying a waiting period before adenosine testing also appears to be an important tool to detect impending PV reconnections (10). We previously could demonstrate that the incidence of dormant conduction was higher after a waiting period of 30 minutes than immediately after PVI. In this study, additional applications for the treatment of dormant conduction resulted in an improved 1-year AF-free survival(4). In the current study a comparable outcome between groups with and without ERC was observed after 1 year, regardless of the number of unsuccessful attempts, lower balloon temperatures and longer time-to-isolation in the PV. Again this suggests the effectiveness of treating ERC after a waiting period followed by adenosine testing.

The prevalence of dormant conduction can be influenced by the duration of the cryo-application(2). In a prior study, we could show that increasing the duration of the cryo-application from 90 to 150 seconds after acute PV isolation, resulted in a decreased incidence of dormant conduction from 22% to 4% of the veins (2). In the current study, we could demonstrate that dormant conduction after 30 minutes was more prevalent in veins in which more than one cryo-application had to be performed to achieve isolation. This may be explained by anatomical properties of the PV ostium causing insufficient PV occlusion and incomplete balloon-tissue contact. Another explanation might be related to the occurrence of oedema after the first application, making a second application less effective (11, 12). However, although tissue oedema (diffuse wall thickening of the antra

and ostium of the PVs) is thought to occur immediately after ablation, the time-frame of this development is not yet clarified (13). Nonetheless, it seems reasonable to perform a single effective freeze instead of an ineffective freeze followed by a second application to treat dormant conduction.

7.4.3 Biophysical and procedural parameters

In a prior study, a time-to-isolation ≤65 seconds and a longer-time-cycle integration (which is the integration of time-to-isolation and the number of freeze-cycles)) were associated with the absence of acute PV reconnection after a single freeze of 180 seconds and a waiting period of 30-minutes without adenosine testing (14). In another study, a time-to-isolation ≤60 seconds and a thawing time at °0 C of ≥10 seconds were associated with durable PV isolation in patients undergoing a repeat ablation 14±3 months after the index cryo-ablation procedure (7). Biophysical parameters as a predictor of early reconnection have been previously analysed. In this study isolation durability was tested without adenosine after a waiting period of 30 minutes. Only the temperature slope (which was strongly correlated with nadir temperature) predicted acute isolation (15). The authors suggested that this information might be useful to decide for an pull-down manoeuvre or aborting a cryoablation. Our results extend the results of these studies as we found that the number of unsuccessful freeze attempts, the nadir balloon temperature and time-to-isolation were the most important predictors of ERC with incorporation of a waiting period of 30-minutes and adenosine testing.

7.4.4 Clinical Implications

This study identified three parameters that can predict the absence of ERC and may be helpful to avoid a waiting period of 30 minutes and adenosine testing in selected patients. Implementing these parameters can shorten the total procedure time. By avoiding a 30 min waiting period, it may, in addition, also decrease the occurrence of oedema that might influence additional application success. Based on the cut-off values of the three parameters we constructed a table for clinical decision making which can be easily applied during the procedure to decide for 30 min of waiting with adenosine testing. In prior studies, single parameter cut-off values have been defined for time-to-isolation and nadir balloon temperature (16). As three different parameters predicted ERC in our study we suggested a multivariable prediction model, which was stronger than a single parameter prediction model in our data. In the new version of the cryoconsole, biophysical data will be directly available, which facilitates peri-procedural decision-making. Larger studies, preferably with adenosine testing to reveal dormant reconnection sites, should be performed to develop

a model for a cryoballoon ablation score, similar to the ablation index or Lesion Index (17, 18). It has been demonstrated that the prospective use of an ablation score system, for example the 'ablation index' can improve clinical outcome (19). Similarly, a cryoballoon ablation score may further optimize cryoablation and related outcome.

7.4.5 Limitations

This is a single center study analyzing procedural and biophysical parameters predicting ERC. Despite the relative large study population (n=151), the incidence of ERC in the PVs was only 9%. Therefore the results of this study may be considered hypothesis generating and need to be validated in larger cohorts. We had to use a statistical script to derive the biophysical parameters from text files from the cryoconsole. However, when the new cryoconsole will be available, data collection will be easier. This study only investigated the predictors of early reconnection; for a final model it may be important to also analyse data of late reconnection, since this can be dissimilar. We did not include indirect measurements for balloon occlusion, such as fluoroscopic contrast stasis or intracardiac echo doppler measurements into our prediction model. 24-Hour Holter monitoring was used to detect recurrences; longer rhythm monitoring could have detected more AF-episodes.

7.5 Conclusion

We identified three parameters predicting early reconnection/dormant conduction in cryoballoon ablation: higher nadir balloon temperature, higher number of unsuccessful freezes and longer time-to-isolation. From these parameters we constructed a multivariable prediction model. This prediction model may help to avoid a 30-min waiting period and adenosine testing in selected patients with a significant reduction of the total procedural duration.

Tabel 5. Cut-off-values for time-to-isolation to predict early reconnection/dormant conduction.

Unsuccessful freezes (n)	**0**	**1**	**2**	**3**
Balloon temperature (°C)	Time-to-isolation (s)	Time-to-isolation (s)	Time-to-isolation (s)	Time-to-isolation (s)
-30	ERC test	ERC test	ERC test	ERC test
-31	ERC test	ERC test	ERC test	ERC test
-32	ERC test	ERC test	ERC test	ERC test
-33	ERC test	ERC test	ERC test	ERC test
-34	≥5: ERC test	ERC test	ERC test	ERC test
-35	≥15: ERC test	ERC test	ERC test	ERC test
-36	≥25: ERC test	ERC test	ERC test	ERC test
-37	≥35: ERC test	≥10: ERC test	ERC test	ERC test
-38	≥45: ERC test	≥20: ERC test	ERC test	ERC test
-39	≥55: ERC test	≥30: ERC test	≥5: ERC test	ERC test
-40	≥65: ERC test	≥40: ERC test	≥15: ERC test	ERC test
-41	≥75: ERC test	≥50: ERC test	≥25: ERC test	ERC test
-42	≥85: ERC test	≥60: ERC test	≥35: ERC test	≥10: ERC test
-43	≥95: ERC test	≥70: ERC test	≥45: ERC test	≥20: ERC test
-44	NO ERC test	≥80:ERC test	≥55: ERC test	≥30: ERC test
-45	NO ERC test	≥90: ERC test	≥65: ERC test	≥40: ERC test
-46	NO ERC test	NO ERC test	≥75: ERC test	≥50: ERC test
-47	NO ERC test	NO ERC test	≥85: ERC test	≥60: ERC test
-48	NO ERC test	NO ERC test	≥95: ERC test	≥70: ERC test
-49	NO ERC test	NO ERC test	NO ERC test	≥80:ERC test
-50	NO ERC test	NO ERC test	NO ERC test	≥90: ERC test

Based on the coefficients a formula is created for the three significant parameters (0.02* time-to-isolation + 0.5 * number of unsuccessful freezes and 0.2* nadir balloon temperature). With a 86% specificity and 70% sensitivity a combined cut-off-value of-6.7 is predictive for early reconnection. In clinical practice this means that in case of a longer time-to-isolation than the given numbers, peri-procedural adenosine testing (ERC test) or additional freezing is advised.

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Chapter 8

Impact of Left Atrial Box Surface Ratio on the Recurrence after Ablation for Persistent Atrial Fibrillation

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Abstract

Background

The posterior wall of the left atrium (LA) is a well-known substrate for atrial fibrillation (AF) maintenance. Isolation of the posterior wall between the pulmonary veins (box lesion) may improve ablation success. Box lesion surface area size varies depending on the individual anatomy. This retrospective study evaluates the influence of box lesion surface area as a ratio of total LA surface area (box surface ratio) on arrhythmia recurrence.

Methods

Seventy consecutive patients with persistent AF (63±11 years, 53 men) undergoing CT imaging and ablation procedure consisting of a first box lesion were included in this study. Box lesion surface area was measured on electroanatomical maps and total LA surface area was derived from CT. Patients were followed with 24-hour electrocardiography and exercise tests at 3, 6 and 12 months after AF ablation. Arrhythmia recurrence was defined as any AF/atrial tachycardia (AT) beyond 3 months without anti-arrhythmic drugs.

Results

During a median follow-up of 13 (IQR 10-17) months, 42 (60%) patients had AF/AT recurrence. Multivariate Cox proportional regression analysis showed that a larger box surface ratio protected against recurrence (Hazard Ratio (HR) 0.81; 95% confidence interval (CI) (0.690–0.955); p=0.012). Left atrial volume index (HR 1.01 (0.990-1.024, p=0.427) and a history of mitral valve surgery (HR 2.90; 95% CI 0.970–8.693; p=0.057) were not associated with AF recurrence in multivariate analysis.

Conclusion

A larger box lesion surface area as a ratio of total LA surface area is protective for AF/AT recurrence after ablation for persistent AF.

8.1 Introduction

Wide circumferential pulmonary vein isolation (PVI) is the first step in atrial fibrillation (AF) ablation as the pulmonary veins (PV's) and their antrum harbour the majority of triggers and are an important substrate for the maintenance of AF (1) . However, PVI alone in patients with progressively diseased atria has a poor outcome and additional ablation strategies may be required (2-5). Both histological and electrophysiological determinants of AF such as fibrosis, drivers and rotors are frequently found within the (inferior part of the) posterior wall of the left atrium, which may be explained by a common embryologic origin with the PV's (6-10). Several studies have demonstrated that catheter ablation of the posterior wall in addition to PVI improves ablation outcome (11, 12). Similar, a surgical approach aiming to isolate the posterior wall resulted in 76% free of AF recurrences in patients with long standing persistent AF (13).

The insertion of the PV's in the LA can be highly variable between patients. A larger distance between the insertion of the superior pulmonary veins and inferior pulmonary veins increases the box lesion surface area. As the potentially arrhythmogenic posterior LA is not confined to the area between the PV's but may extend caudally towards the coronary sinus (9, 10, 14), a variable part of the posterior LA will not be included in the box lesion, depending on the insertion of the inferior veins. In addition, with progressive left atrial dilation, the box lesion surface area as a ratio of total left atrial surface area may decrease further. We therefore hypothesized that differences in box lesion surface area normalized to total left atrial surface area may be an important factor influencing ablation outcome.

8.2 Methods

8.2.1 Inclusion

Consecutive patients with symptomatic drug-refractory persistent AF who underwent PVI and isolation of the posterior LA between the PV's (box lesion) between 2013 and 2017 at the Leiden University Medical Center (LUMC) were retrospectively analyzed. During this period all patients in the LUMC with persistent atrial fibrillation referred for ablation were treated with PVI plus box lesion. All consecutive patients with an (attempted) box lesion were included in the study. In all patients, a box lesion was performed in addition to a circumferential PVI referred to/defined as index procedure. Patients were treated according to the institutional clinical protocol and provided informed consent. Approval for the current retrospective analysis was obtained from the Institutional Review Board.

8.2.2. Ablation procedure

Prior to the procedure, patients underwent a 320-slice Computer Tomography (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) and image segmentation to visualize the anatomy of the LA and PV's and to guide the ablation (15). The CT-scan was performed in a phase window between 65-85% of R-R interval in patients with an HR ≥ 60 beats per minute and 75% of R-R interval in patients with a heart rate below 60 (16). Antiarrhythmic drugs (AAD) were discontinued for 5 half-lives before ablation, with the exception of amiodarone which was continued until 1 month after ablation. Catheter mapping and ablation was performed under uninterrupted anticoagulation with a double transseptal approach using a 3D electroanatomical mapping system (CARTO3, Biosense Webster, Diamond Bar, CA, USA or Ensite Velocity System, Model EE3000, St. Jude Medical, MN, USA), an irrigated 3.5-mm ablation catheter (Biosense Thermocool, Biosense Thermocool Smarttouch or St. Jude Medical Coolpath Duo) and a 10-polar circular mapping catheter (Lasso 2515, Biosense Webster). During the index procedure, a box lesion was applied in all patients in addition to a circumferential first or redo PVI. A roof line between the superior ostia of the superior PV's and a posterior line between the inferior ostia of the inferior PV's were created to complete the LA box lesion. The posterior line was drawn directly across the posterior wall between the inferior ostia of the inferior pulmonary veins. The operators did not extend the box lesion inferiorly below this level. Radiofrequency energy was delivered with a power of 25 W at the roof and the posterior LA wall and with 30 W at the anterior LA (maximum temperature, 43°C; flow rate, 17-20 ml/min, 30 seconds). If patients were

not in sinus rhythm after ablation an electrical cardioversion was performed. Entrance block in the PV's and the box lesion was confirmed using maximal signal amplification. In addition, exit block from the box lesion was demonstrated by pacing with high output (10mA/2ms) at the posterior LA. PVI and box lesion isolation were reconfirmed ≥30 minutes after the last RF application.

8.2.3 Follow-up

Follow-up at the outpatient clinic was performed in all patients at 3, 6 and 12 months after the procedure. Follow-up included clinical history for symptoms suggestive of recurrent AF, 12-lead Electrocardiography (ECG), 24 hour Holter monitoring and an exercise test (at 3 and 12 months). AAD's were continued until the first outpatient clinic visit at 3 months. After this blanking period of 3 month, the AAD's were stopped in all patients. Patients were encouraged to obtain ECG recordings in case of symptoms to determine recurrence. Recurrence was defined as any AF or atrial tachycardia (AT) on a 12-lead ECG or lasting > 30 seconds on Holter monitoring beyond 3 months.

8.2.4 Calculation of left atrial and box lesion surface areas

The total LA surface area of all patients was measured on the segmented CT data after importing the original CT data into the CARTO system using the CARTO Merge software. The box lesion surface area, bordered by the posterior circumferential ablation lines adjacent to the PV ostia, the roofline and the posterior line was measured on the EA maps using dedicated software of CARTO and Ensite Velocity systems (figure 1). In addition, the ratio of the box lesion surface area to the total LA surface area (box surface ratio) was calculated. The distances between the contra-lateral pulmonary veins (box lesion width), between the roof and posterior line (box lesion height) and the distance between the middle of the posterior line to the mitral annulus was measured. Both in patients with and without atypical/mitral isthmus dependent flutter at follow-up, the distance between the posterior line and the mitral annulus was measured. For outcome comparison, the study subjects were divided into 2 groups according to the box surface ratio (above and below the median).

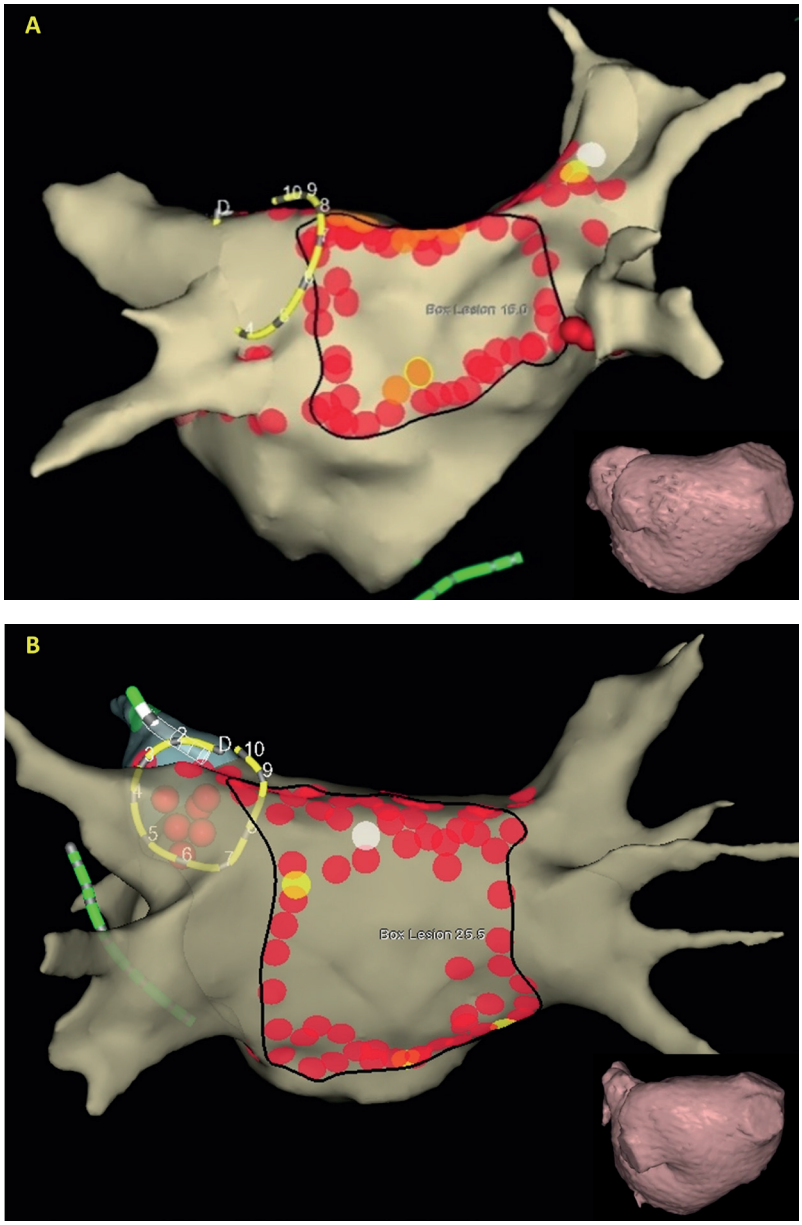

Figure 1. Box lesion area surface measurement.
Box Surface area measurement on electroanatomical maps in Ensite. Panel A: a posteroanterior view of the posterior wall of the left atrium with an example of a small box surface ratio (Box surface area 16.0 cm², Total LA surface area on CT 203.0 cm² measured in CARTO, box surface ratio: 0.08). Panel B: a posteroanterior view of the posterior wall of the left atrium with an example of a large box surface ratio (Box surface area 25.5 cm², Total LA surface area on CT 184.9 cm², box surface ratio: 0.14).

8.2.5 Statistical Analysis

Clinical, echocardiographic, and ablation data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Centre, Leiden, The Netherlands) and retrospectively analysed. Continuous variables were expressed as mean ± standard deviation or median (interquartile range (IQR)) and compared by an unpaired t-test or Mann-Whitney U-test when indicated. Categorical variables were presented as numbers and percentages, and compared by the chi-square or Fisher's exact test when appropriate. Kaplan Meier survival curves were constructed to compare the AF-free survival between the 2 groups. Multivariable Cox proportional regression analysis was performed to detect any independent significant predictors of AF/AT recurrence reported as hazard ratio (HR) with 95% confidence interval (CI). Previously reported predictors of AF recurrence (17) after catheter ablation were tested in the univariate model. Variables with a $p < 0.1$ in the univariate analyses were included in the multivariate analyses using the 'enter' method. $P < 0.05$ was considered as significant. All analyses were performed with the SPSS version 23 statistics software package (SPSS, Chicago, IL).

8.3 Results

8.3.1 Study group

During the study period, 76 patients underwent box lesion isolation in addition to PVI. From this group, 6 patients were excluded (EA maps were of insufficient quality to delineate the box lesion surface area (n=4), EA maps were not retrievable (n=1), multi-slice CT-scan was not performed prior to ablation (n=1)). The remaining 70 patients (63 ± 11 years, 53 men) comprised the study population.

8.3.2 Baseline characteristics

Persistent AF was diagnosed in 39 (56%) and long-standing persistent AF in 31 (44%) patients. The median duration of AF from first diagnosis to the index ablation procedure was 70 (IQR 40–114) months. The left atrium volume index was 50±22 ml/m² in the recurrence group and 41±13 ml/m² in the non-recurrence group (p=0.050). Thirty-one patients (56%) had undergone prior PVI. This was not significantly different between the recurrence and the non-recurrence group. In the entire population, the median LA surface area was 196 (IQR 172-233) cm², the box lesion surface area 20 ± (IQR 18-24) cm² and the median box surface ratio 0.10 (IQR 0.09 – 0.14). Eighty-four percent of the population was on AAD before the ablation. Fifty-one patients (73%) were using beta-receptor blocking drugs (sotalol: n=27, 38%), 11 (16%) patients were using flecainide, 19 patients (27%) were using amiodarone and 2 patients (3%) were using disopyramide. Four patients (6%) were on rate control with digoxin. Baseline characteristic are provided in table 1.

8.3.3 Procedural Characteristics and complications

Table 2 provides the procedural details of the index ablation including additional ablation lesions beyond pulmonary vein and box isolation. The box lesion was successfully isolated in 67 patients (96%), while isolation could not be achieved in 3 patients despite extensive ablation. Thirty-five patients (50% of the cases in which the index procedure was a re-ablation) underwent a redo PVI. Additional ablation (focal AT ablation, CFAE ablation, SVC ablation and Mitral isthmus ablation) during the index procedure was performed in 10 (14%) patients. This was equally distributed between the groups and not significantly different. One patient (1%) had a complication related to the vascular access (femoral pseudo-aneurysm). No other complications occurred during the index procedure. During the repeated procedure a single patient experienced cardiac tamponade that required drainage. No other complications were reported during the repeated procedures.

Table 1. Demographic and baseline characteristics between patients with and without AT/AF recurrence.

	All (n=706)	AF/AT recurrence (n=42)	No AF/AT recurrence (n=28)	*P value*
Age, years	63 ± 11	63 ± 11	63 ± 10	0.950
Male gender, n (%)	53 (76)	33 (79)	20 (71)	0.495
Body Mass Index (kg/m²)	27 ± 4	27± 4	27 ± 4	0.529
Comorbidity				
Hypertension, n (%)	37 (53)	22 (52)	15 (53)	0922
Hyperlipidemia, n (%)	27 (39)	20 (47)	7 (25)	0.057
Diabetes Mellitus, n (%)	6 (9)	5 (12)	1 (4)	0.390
Structural Heart Disease, n (%)	21 (30)	15 (36)	6 (21)	0.201
OSAS, n (%)	6 (9)	4 (10)	2 (7)	1.000
GFR <30, n (%)	1 (1)	1 (2)	0 (0)	1.000
Duration of AF, months	59 (41–116)	59 (36–112)	57 (43–115)	0.405
Type of AF				
Persistent, n (%)	39 (56)	25 (60)	14 (50)	0.432
Long-standing, n (%)	31 (44)	17(41)	14 (50)	0.432
Prior PVI, n (%)	39 (56)	26 (62)	13 (46)	0.202
Prior mitral valve surgery, n (%)	8 (11)	6(14)	2 (7)	0.462
LV ejection fraction <35	1 (1)	1 (2)	0 (0)	1.000
LA volume index (ml/m²)	46 ± 19	50 ± 22	41 ± 13	0.050
CHA_2DS_2-VASc	2 ± 1	2 ± 1	2 ± 1	0.697
AAD, n (%)	59 (84)	36 (85)	23 (82)	0.745

Values are reported as the mean ± standard deviation, median (interquartile range), or n (%). AAD indicates anti-arrhythmic drug; AF atrial fibrillation; LA, left atrium; eGFR, estimated glomerular filtration rate; LV, left ventricle; NOAC, novel oral anticoagulant; OSAS, obstructive sleep apnea and PVI, pulmonary vein isolation.

8.3.4 Follow-up

After a median follow-up of 13 (IQR 10-17) months, 42 Patients (60%) experienced AF/AT recurrence after a median duration of 10 months (IQR 5-14). Of these patients, 28 (67%) had recurrence of atrial fibrillation, 12 (29%) recurrence of atypical flutter/atrial tachycardia and 2 (5%) of both. In 16 (24%) patients there was improvement of their symptoms and the tachycardia improved from persistent to paroxysmal. Atrial fibrillation free survival off ADD was 40%. AF-free survival on/off AAD was higher (59%). There was no significant difference in recurrence between patients undergoing ablation with and

without contact force sensing (62 vs. 55% P=0.589). Before the ablation, anti-arrhythmic drugs usage (84% in the total group) was not significantly different between the groups. In the no-recurrence group after the blanking period of 3 months, 38 patients (90%) stopped all AAD's, 4 patients (10%) continued with sotalol in a lower dosage at the discretion of the treating physician as beta blockade therapy was indicated for concomitant coronary artery disease.

Table 2. Procedural details of the index procedure between patients with and without AT/AF recurrence.

	All (n=70)	**AT/AF recurrence (n=42)**	**No AT/AF recurrence (n=28)**	***P value***
Successful box isolation, n (%)	67 (96)	40 (95)	27 (96)	0.810
CARTO, n (%)	48 (69)	29 (69)	19 (68)	0.916
Force sensing catheter, n (%)	20 (29)	11 (26)	9 (32)	0.589
Additional ablation, n (%)	10 (14)	6 (14)	4 (14)	1.000
CFAE, n (%)	3 (4)	1 (2)	2 (7)	0.335
SVC isolation, n (%)	3 (4)	2 (5)	1 (4)	0.810
Mitral isthmus, n (%)	4 (6)	2 (5)	2 (7)	0.674
Focal AT, n (%)	3 (5)	2 (6)	1 (5)	0.810

Values are reported as the mean ± standard deviation, median (interquartile range), or n (%). AF indicates atrial fibrillation; AT, atrial tachycardia; CFAE, Continuous Fractionated Atrial Electrogram; and LA, left atrium.

8.3.5 Predictors of AF/AT recurrence

In univariate analysis, a larger LA volume, a history of prior mitral valve surgery and a smaller box surface ratio were associated with AF/AT recurrence ($p \leq 0.1$). Male gender, type and duration of AF, Body Mass Index, CHA_2DS_2-VASc score, previous PVI box lesion width, height and surface area were not associated with AF recurrence (Table 3).

On multivariate Cox proportional regression analysis only a smaller box surface ratio (Hazard Ratio (HR) 0.81; 95% confidence interval (CI) (0.690–0.955); p = 0.012) was independently associated with AF/AT recurrence (table 3). The box lesion width and height were not significantly different between the recurrence and non-recurrence group (respectively 38±5 and 38±8 mm and 45±8 and 44±9 mm). The distance between the posterior line to the mitral annulus was 53 ± 8 mm in the recurrence group and 54±8 in the no-recurrence group (p=0.639). In addition, no correlation between the box surface ratio and the distance from the posterior line to the

mitral annulus was observed (p=0.266). The distance between the posterior line to the mitral annulus was also not significantly different in patients with and without documented atypical/ mitral isthmus dependent flutter (51±9 vs. 54±8 mm; p=0.236). Kaplan-Meier survival curves showed that patients with a larger box surface ratio had a lower incidence of AF/AT recurrence. The median survival (free from AT/AF) after the index LA box lesion was 8 months in the large box surface ratio group and 14 months in the small box surface ratio group (p=0.0324 by log-rank test; HR 0.57 [CI 0.3086 – 1.058) (Figure 2).

Table 3. Univariate and Multivariate Cox Proportional Regression Analyses for predictors of AF/ AT recurrence.

Variables	Univariate		Multivariate	
	Hazard ratio (95% confidence interval)	***P value***	**Hazard ratio (95% confidence interval)**	***P value***
Age	0.990 (0.961–1.021)	0.536		
Female sex	0.716 (0.342–11.502)	0.377		
BMI	1.012(0.936-1.094)	0.759		
SR at admission	1.493(0.703-3.169)	0.297		
Previous PVI	1.631 (0.859-3.096)	0.134		
Additional Ablation	1.584 (0.719-3.490)	0.253		
AF duration	1.003 (998-1.009)	0.245		
CHA_2DS_2-VASc	0.961(0.744-1.240)	0.758		
Distance posterior line to mitral annulus	0.992 (0.953-1.033)	0.705		
Box lesion width	1.038 (0.978-1.101)	0.217		
Box lesion height	0.999 (0.950-1.050)	0.968		
Box lesion surface area	1.004 (0.938-1.074)	0.916		
LA volume index	1.015 (1.000-1.031)	0.046	1.007 (0.990-1.024)	0.427
Prior mitral valve surgery	2.263 (0.936–5.476)	0.070	2.903 (0.970–8.693)	0.057
Box surface ratio	0.850 (0.729–0.991)	0.038	0.812 (0.690–0.955)	0.012

AF indicates atrial fibrillation; BMI, body mass index; LA, left atrium; EF, ejection fraction; PVI, pulmonary vein isolation and SR, sinus rhythm.

8.3.6 Repeat procedures

In 15 patients, a re-ablation was performed after the index box lesion isolation. In all patients, isolation of the pulmonary veins and of the box lesion was checked and/or an additional ablation was performed. Two patients underwent a His-ablation after permanent

pacemaker insertion. In the remaining 13, re-PV isolation (n=9), re-isolation of box lesion (n=9), superior vena cava isolation (n=1), mitral isthmus ablation (n=4), anterior box lesion isolation (n=1), and other LA atrial tachycardia ablation (n=4) was performed. Out of 13 patients, follow-up data was available in 10 (2 patients lost to follow-up). In 1 patient, the procedure was aborted because of a cardiac tamponade and AF was accepted. During a median follow up of 9 (IQR 5-18) months after the repeat procedure, 4 (40%) patients maintained sinus rhythm without AAD's and 6 (60%) patients had recurrent AF after a period of 5 (IQR 4-8) months. In summary AF-free survival after the index procedure was 40% and after the repeated procedures 51% off AADs. AF-free survival on/off AAD in the entire group after repeated procedures was 64%.

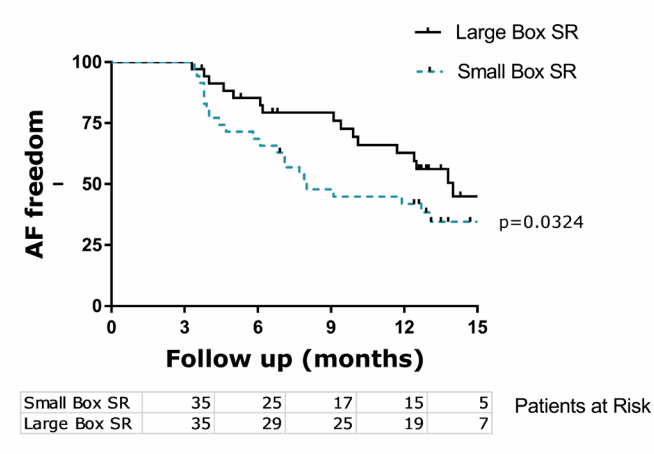

Figure 2. Atrial fibrillation-free survival off AAD according to box surface ratio (Box SR).

8.4 Discussion

8.4.1 Main Findings

The major finding of this study is that a larger box lesion surface area as a ratio of total left atrial surface area is protective for AF/AT recurrence after ablation for persistent atrial fibrillation. To the best of our knowledge, this is the first study that investigated box lesion surface area ratio in relation to ablation outcome.

8.4.2 Benefit of substrate modification beyond PVI

The necessity of extending the ablation beyond PVI by performing substrate modification in patients with persistent AF is currently controversial due to the STAR-AF II trial, in which no benefit was demonstrated of additional ablation beyond PVI (18). Studies reporting on favourable outcome after isolation of the posterior wall are not in direct contradiction with the STAR AF II trial as this trial did not include a group undergoing isolation of a part of the left atrium in addition to PVI. Isolation of a part of the posterior left atrium may be a promising strategy, as there is evidence that the LA posterior wall harbours triggers and substrate for AF: animal studies have demonstrated that 80% of AF triggers are located in the posterior wall including the PV region, based on electrophysiological and molecular findings (19-21). In addition, imaging studies could demonstrate that fibrotic areas (atrial delayed enhancement) are mainly located in the posterior wall (6-8). More specific, the preferential distribution of drivers and atrial fibrosis, beside the PV-antrum, is located in the inferior part of the posterior wall (9, 10). The importance of targeting the posterior wall in patients with persistent atrial fibrillation is also demonstrated by the encouraging results (62% overall freedom of AF) of surgical ablation (22) of the posterior wall. In line with these results, we recently published a 76% success rate with a stand-alone surgical box lesion in persistent AF (13). A meta-analysis comparing catheter ablation of PVI vs. PVI with box lesion also showed a benefit of adding a box lesion to PVI in patients with persistent atrial fibrillation (11). In the current study, 1-year success was 40% after a single procedure off AADs and 64% after repeated procedures on/off AAD. Bai *et al*. recently reported an anti-arrhythmic drug free survival of 65%, 50% and 40% after respectively 1, 2 and 3 years follow up in persistent AF after catheter ablation of the posterior wall. (23). Lim *et al.* reported a 2-years AT/AF drug free survival of 53% in patients with persistent atrial fibrillation (24). The difference in outcome between surgical and catheter based isolation of a box lesion can be explained by the higher durability of surgical compared to catheter based ablation lesions (25). It is unknown if the area of the box lesion in patients undergoing a surgical box lesion is larger than patient undergoing catheter ablation.

As ablation lines have to be connected to anatomical barriers to prevent scar-related reentry, the roof line of a box lesion is connected to the superior ostia of the superior veins and the posterior line of a box lesion is connected to the inferior ostia of the inferior PV's. However, the anatomical posterior LA is not limited to the area between the veins but extends more caudally towards the coronary sinus (14, 26). In the current study, patients with a small box surface ratio had a decreased arrhythmia-free survival compared to patients with a large box surface ratio, while box lesion width, height and surface area, total LA surface area and LA volume were not predictive. A possible explanation is the extent of isolation of the posterior wall which shares the same embryologic origin with that of the pulmonary veins, containing substrate for AF maintenance. Although the ratio of the isolated box lesion surface area and the total LA surface was calculated, box lesion surface area as a ratio of total left atrial posterior wall surface area could be superior to sustain our hypothesis. However, as the borders of the posterior wall of the LA are not well defined in the literature we did not adopt this parameter. A second explanation of our findings may be that an increase in left atrial size outside the area between the pulmonary veins will also decrease the box surface ratio. It may be hypothesized that enlargement of the left atrium will be more distinct outside the box lesion while the box lesion itself may be more resistant to dilation, as this area is bounded by the pulmonary veins. Therefore, the combination of anatomical variation and left atrial dilation outside the box lesion may explain why box surface ratio was predictive of outcome while box lesion length, width and surface area were not. It remains to be proven that the positive influence of a large box lesion is dependent on substrate modification of the LA posterior wall and not on extensive atrial debulking per se. Pre-procedural visualization of a small posterior LA box as a ratio of left atrial surface could be an important factor to predict failure in patients in whom a box lesion is considered.

8.4.3 Clinical implications

The box lesion surface area and total left atrial surface area can be measured during the procedure irrespective from prior imaging. In concordance with the fact that the AF substrate in the LA posterior wall is not confined to the area between the PV's, it may be hypothesized that ablation of a relatively larger box lesion is beneficial. This may support a decision to increase the size of the box lesion, e.g. extending it inferiorly below the level of the PV's towards the coronary sinus, especially in patients with a relatively small anatomical box lesion. This hypothesis needs to be proven in further studies, however. Concordantly, Di Biase *et al.* described PVI together with an extensive box lesion extended down to the coronary sinus and to the left sided atrial septum in patients with persistent

AF and heart failure (29). Two-years follow up demonstrated 70% freedom from AF/AT off antiarrhythmic drugs. This is a very respectable outcome considering that heart failure patients with persistent atrial fibrillation are at high-risk for recurrence of AF (30). It may be reasoned that the extensive box lesion performed in this study explains the high success rate in these patients with heart failure and persistent atrial fibrillation.

8.4.5 Limitations

The present study is a single-centre, retrospective study in a small group of patients. Due to the small group of patients this study may have been underpowered to detect other parameters influencing arrhythmia recurrence. Therefore, this study should be considered as 'hypothesis generating'. Several prior studies already have presented data on the value of isolating the posterior wall, however the aim of this study was not to evaluate the value of posterior wall isolation, but the influence of the size of the ablated anatomical box lesion surface area as a ratio of total left atrial surface area on the outcome of this procedure. Our study did not show that extending the inferior line between the inferior poles of the inferior pulmonary veins improved outcome. Further larger and randomised studies need to confirm that a relatively larger box lesion or extension of the box lesion inferior from the inferior ostia of the PV's protects against arrhythmia recurrence. In the study population 56% had undergone a prior PVI, which can have influenced the results. However, this was not significantly different between the groups. During the index-procedure in 10 patients (14%) additional ablation was performed, this was however not significantly different between the groups. Moreover, when these 10 patients were excluded from the analysis, the study results remained unchanged. Only repeated 24h Holter monitoring was used during follow-up. Therefore, asymptomatic AF episodes may have been missed. The recurrence group had more often LA enlargement compared to the no-recurrence group. However, this number was not significant in multivariate analysis. During the procedure durable isolation of the pulmonary veins and box lesion was not enhanced using manoeuvres such as the pace/ablate method (31) or adenosine infusion, which could have improved outcomes in both groups. No atrial substrate analysis was performed in this study. Distinguishing the presence of fibrotic areas based on MRI findings and/or high resolution voltage mapping and comparing the posterior LA with other LA regions could be helpful. Despite the limitations, we believe that this study is an important scientific contribution with potentially valuable suggestions for further research. Box lesion surface ratio is a new parameter to predict outcome in persistent AF ablation and we think that our hypothesis-generating study will trigger new research on extending the box lesion in patients with a small box lesion surface ratio to improve outcome.

8.5 Conclusion

When applying a box lesion in persistent AF ablation, a larger box lesion surface area as a ratio of total LA surface area is protective for AF/AT recurrence after ablation for persistent AF.

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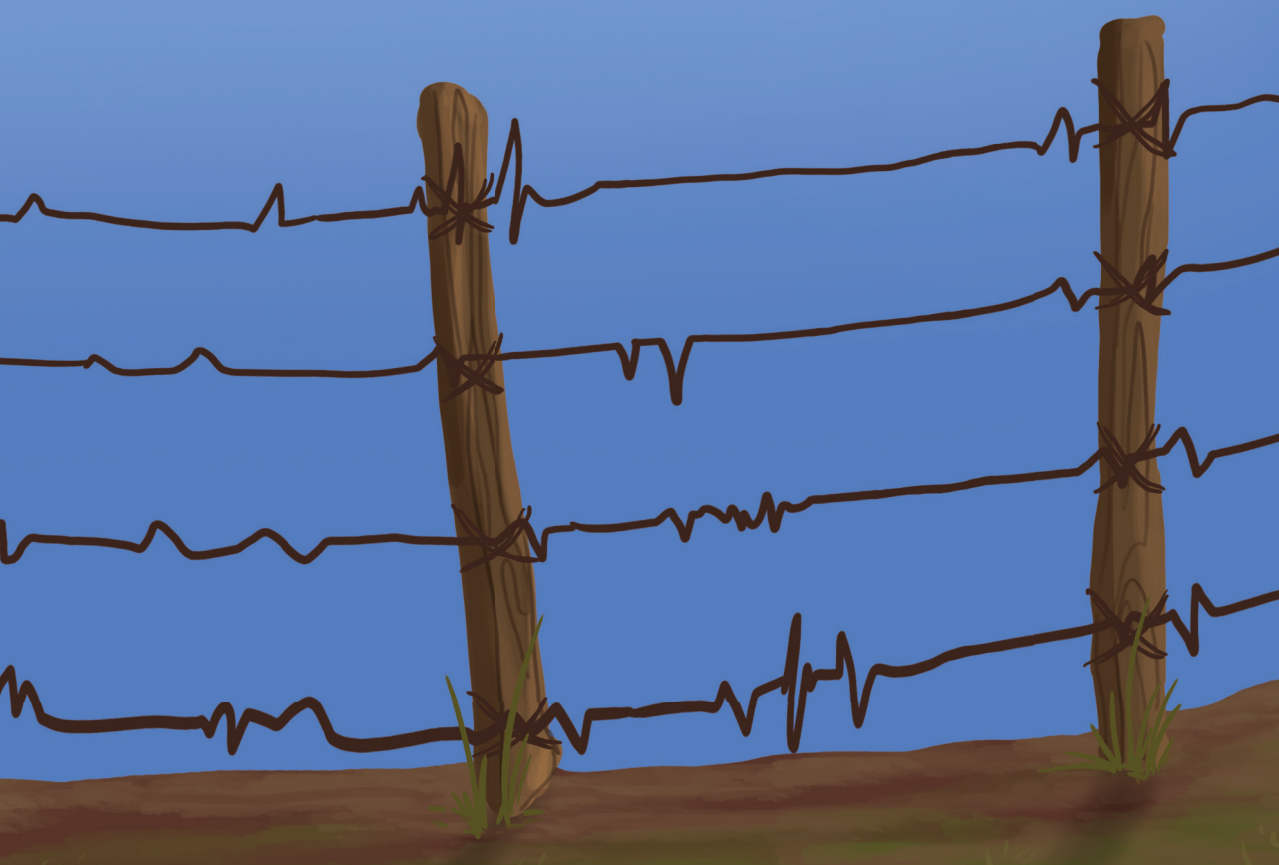
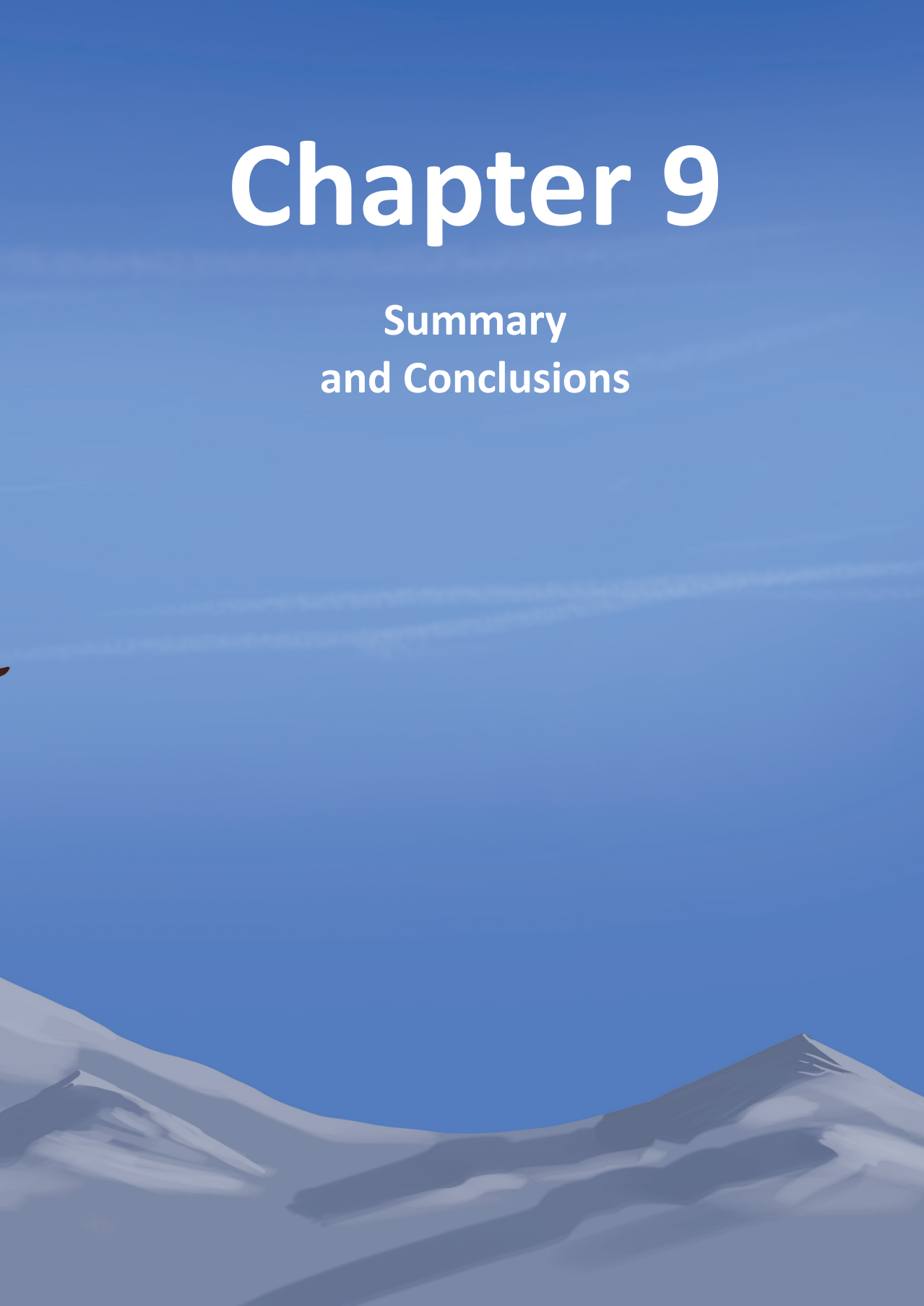
Summary and Conclusions



Chapter 9

Summary and Conclusions



9.1 Aim of this thesis

The aim of the first part of this thesis was to study the impact of advances in the development of AF devices on the incidence of complications. More specifically, the safety of the improved non-irrigated catheter (PVAC-Gold) was investigated. The first generation of this catheter showed a high incidence of asymptomatic cerebral embolism. Subsequently, the ablation device and protocol were revised to improve the safety of this device. Therefore, we investigated whether these revisions improved the incidence of cerebral infarcts by comparing it in a randomized fashion with an irrigated catheter. In addition, we performed in-depth analyses on the relationships between cerebral infarcts, activation of the coagulation system and the genesis of cerebral micro-embolisms.

In the second part of this thesis, the ablation protocol for another new ablation device for pulmonary vein isolation, the cryoballoon ablation catheter, was investigated to prevent complications by optimizing the ablation duration. The development of the second-generation cryoballoon brought a significant improvement in terms of efficacy. To prevent complications however, the ablation duration still needed to be optimized. The second aim of this thesis was therefore to optimize the ablation duration by randomizing patients to different ablation durations using the incidence of dormant conduction as an indicator for incomplete isolation. Furthermore we tried to predict the absence of incomplete cryoballoon applications, making the standard waiting period after ablation unnecessary.

The third aim of this thesis was to improve the ablation protocol in patients with persistent AF. We focused on posterior left atrial box isolation in patients with progressive left atrium illness and investigated the effect of the ablation surface area on the outcome of the ablation.

In the general introduction, **chapter 1** of this thesis, it is explained that with improvement of the ablation tools and techniques, AF ablation evolved to a first-line therapy over the last 20 years. In this chapter the knowledge about the AF mechanisms and the different ablation methods and tools are summarized.

In **chapter 2** the introduction continues by describing the advances in AF ablation devices and the incidence and prevention of complications. An overview of point-by-point, multi-electrode and balloon-based devices for pulmonary vein isolation is given with a detailed description of the ablation tools, reported complications and device-related specific aspects. The development of new ablation devices is often directed at increasing procedural efficacy, improvement of the safety profile is often delayed until unexpected complications occur. For point-by-point irrigated contact-force radiofrequency

catheter ablation, cardiac tamponade remains an important complication compared to balloon-based techniques. Due to three-dimensional mapping the procedural duration has been shortened and with the development of high-power short duration ablation further shortening of the duration is expected. For cryoballoon ablation the incidence of phrenic nerve palsy is of importance and higher compared to radiofrequency ablation. Improvement of the cryoballoon ablation system led to shorter procedural and fluoroscopy times with similar efficacy and complication rates. Other single shot devices are in development with unknown safety profiles. A potential drawback of non-irrigated multi-electrode catheters is the association with asymptomatic cerebral embolism of which the clinical significance is not yet clarified. Together with the improvement of ablation devices also the ablation protocol is improved with implementation of safety maneuvers for the prevention of complications and pre-selection of patients undergoing ablation.

In **chapter 3** a randomized controlled trial on the incidence and clinical significance of cerebral embolism during AF ablation with the duty-cycled phased radiofrequency catheter versus a cooled radiofrequency catheter is described. With the first generation pulmonary vein ablation catheter (PVAC), the incidence of asymptomatic cerebral embolism was up to 42% on cerebral magnetic resonance imaging. Studies suggested that temperature overshoot during intermittent catheter-tissue contact and an electrical short-circuit between electrode 1 and 10 were the main causes of these cerebral infarcts in the pulmonary vein ablation catheter. The technical development of the next generation PVAC-Gold consisted therefore by substitution of platinum electrodes by gold to prevent temperature overshoot and removal of electrode 10 to prevent short-circuiting. Furthermore, the ablation protocol was optimized by aiming at higher Activated Clotting Time (ACT) values and submersion of the catheter in saline before introduction to minimize air embolism. In this chapter we show that the incidence of asymptomatic cerebral embolism/cerebral infarctions with this new catheter and ablation protocol is still higher (23%) compared to an irrigated catheter (6%). While both ablation technologies induced a similar increase in the procoagulant state, we observed a significantly higher number of micro-emboli on transcranial doppler with the PVAC-Gold catheter. The median concentration of micro-embolic-signals during the total procedure was 8 [IQR, 5 to 17] MES/min with the pulmonary vein ablation catheter versus 4 [IQR 3 to 5] MES/min with the irrigated catheter. We detected no cognitive decline in patients using extensive neuropsychological testing. As the purpose of the redesigned catheter was to reduce the high incidence of asymptomatic cerebral embolism, we state that the improvement of this device was only partly successful with only a 45% reduction of ACE and MES compared to the first generation device. As the incidence is still higher compared to point-by-point ablation, the manufacturer should continue to improve the device.

In **chapter 4** we focused in more depth on the genesis of these micro-embolic signals with the PVAC-Gold catheter. The analysis included 945 PVAC-Gold radiofrequency applications in which biophysical parameters of the applications were investigated to reveal potential pathophysiological mechanisms. We found that left superior vein ablation, average power, total effective energy, average impedance and temperature 2 seconds after ablation were associated with MES count. Possibly due to the new catheter design, a low percentage of electrode interaction (1%) and temperature overshoot (5%) were detected and could not explain the high number of MES. These results suggest that firstly a poor electrode contact, especially in the left superior vein due to a sleep angle between the catheter and the pulmonary vein, is responsible for the micro-embolic signals. A low temperature after 2 seconds may also be related to poor catheter contact, increasing the MES count. Secondly, ablation power was related to MES as in ablations with high power and high total effective energy a higher MES was seen which may be explained by a stronger tissue devolution. Also a slower temperature rise requires a higher power to achieve the target temperature. Thirdly, increased impedance may be due to denaturization of blood proteins explaining the relationship between impedance and MES. In conclusion, the re-design of the PVAC-Gold abolished temperature overshoot and electrode interaction but the other causes of MES remained unaffected.

In **chapter 5** the activation of coagulation during ablation with the PVAC-Gold was studied. In this chapter we showed that early changes in fibrinogen and von Willebrand Factor antigen and late changes in d-dimer were associated with increases in MES. These results suggest that in ablation with a stronger acute-phase response and endothelial damage, a stronger activation of the coagulation cascade occurs, causing more micro-emboli, eventually resulting in a stronger activation of the fibrinolytic pathway with an increased d-dimer. We hypothesized that a stronger activation of the coagulation cascade results in silent cerebral embolism. This may explain why 7 patients showed multiple infarcts in the PVAC-Gold group compared to none in the Thermocool group. We suggest that routine measurement of coagulation markers during AF ablation may be useful to identify patients with a high embolic burden to be referred for post-ablation cerebral imaging to exclude ablation-related ischemic events.

In **chapter 6** the results of a randomized trial to optimize the ablation duration with the second-generation cryoballoon are presented. The second-generation cryoballoon with more injection ports for more homogenous and faster cooling was introduced to achieve more durable pulmonary vein isolation. However, at the cost of a better efficacy, more transient and persistent phrenic nerve palsy and esophageal ulcera were described. With the first generation cryoballoon the advised ablation protocol was two 300 second

applications, while the advised protocol for the second generation was two 240 second applications. Subsequent studies showed that a single application was sufficient. In addition, shortening the ablation duration from 240 seconds to 180 seconds did not increase AF recurrence. Apart from ablation duration, adequate balloon-tissue contact is required to achieve durable pulmonary vein isolation. With a more adequate balloon-tissue contact, pulmonary vein isolation will be achieved more early causing a shorter time-to-isolation. Indeed, it has been shown that time-to-isolation in pulmonary vein ablation predicts durable PVI. The aim of this chapter was therefore to make ablation duration dependent on time-to-isolation and to determine the optimal ablation duration after time-to-isolation. To this end, patients were randomized to three groups with an additional ablation duration of 90, 120 or 150 seconds after PVI was achieved. Spontaneous or adenosine induced PV reconnection (early reconnection) was selected as primary outcome parameter. We showed that increasing the additional ablation duration caused a stepwise decrease in early reconnection and a decrease in additional cryoballoon applications, while recurrences and complication rates at one year were not significantly different. In addition, the rate of repeat procedures during follow-up decreased with increasing additional ablation duration. In conclusion based on these data, an additional ablation of 150s after PVI is the most appropriate approach in time-to-isolation based ablation.

In **chapter 7** we focused on the procedural and biophysical predictors of early reconnection. Predicting the absence of early reconnection may shorten the procedure and abolish the need for adenosine testing. For this chapter biophysical data of the cryoballoon ablation was analyzed in 151 patients with a 240 seconds fixed ablation duration. We found that three easily available parameters were associated with early reconnection. A higher number of unsuccessful freezes, longer time-to-isolation and higher nadir balloon temperature predicted early reconnection. We constructed a simple formula with cut-off values for these parameters. Using this formula during ablation may help to avoid a 30-min waiting period and adenosine testing in selected patients. While for the purpose of this chapter offline calculations were necessary, with the upcoming improvements of the cryo-console these biophysical parameters will be easily available and the implementation of this formula in the form of a cryoballoon ablation score, similar to ablation index, will be possible. With a cryoballoon ablation score the ablation procedure may be further optimized to improve AF-free survival.

Finally, in **chapter 8** we focused on isolation of the left atrial posterior wall in patients with persistent atrial fibrillation. The posterior wall is a well-known substrate for atrial fibrillation maintenance as it shares a common embryological origin with the pulmonary veins. Isolation of the posterior wall between the pulmonary veins, a so-called box lesion,

may improve outcome in persistent AF ablation. In this chapter we have shown that a larger box surface ratio, which is a larger box lesion as a ratio of total left atrial surface area, decreases AF recurrence in these patients. The box lesion surface area can be measured peri-procedurally in the electro-anatomical mapping system and the total left atrial surface area can be measured on pre-procedural CT-scans. We showed that box surface ratio is a stronger predictor for recurrence than left atrium volume index. This study may therefore support a decision to increase the size of the box lesion, e.g. extending it inferiorly below the level of the pulmonary veins towards the coronary sinus, especially in patients with a relatively small anatomical box lesion. Measurement of the box surface ratio and the decision to extend the size of the ablated area in selected patients may improve ablation outcome.

9.2 Future perspectives

The number of patients with AF is increasing and it is expected that this number will be doubled in the next 50 years as a consequence of prolonged life expectancy, metabolic syndrome associated diseases and better recovery after (surgical) treatment of cardiac diseases (i.e. myocardial infarction). In the past 20 years, catheter ablation evolved from a rare and difficult procedure to a first-line therapy in many patients with AF. The understanding of the pathogenesis of AF and the equipment and techniques specifically designed for AF ablation improved hand in hand. However, it has also become clear that AF is not just a rhythm disorder that can be treated with a simple intervention. It is quite the opposite, AF is an ongoing multifactorial disease with a very complicated pathophysiology and treatment.

Despite the technological development of catheter ablation tools, the incidences of both early and late recurrences after pulmonary vein isolation will remain an important issue, together with ablation safety. The improvement of ablation tools can be challenging but we still believe that optimization of ablation tools and protocols can be successful with better efficacy, reduction of procedural duration and reduction of device-specific complications. In this thesis the results for two randomized clinical trials were described applying improved tools or techniques. Improvement may come in small steps but compared to the very first catheter ablation a huge progress is made.

Several diagnostic tools, i.e. high-resolution multi-electrode mapping catheters and imaging techniques, are being developed and implemented to analyze AF. Hereby we are heading to an ablation technique which is primarily based on 'individual' substrate analyses. All patients are different and initial substrate-analysis is required, before a specific treatment can be given. This means that we need to adapt a new definition for AF based on the underlying substrate, instead of the arbitrary clinical definitions of paroxysmal and persistent AF. Pulmonary vein isolation, which is currently the cornerstone of the ablation, may become the treatment of just one of the several important pathophysiological mechanisms. Furthermore, more attention is needed for the different pathways responsible for the progression of AF. A more holistic approach is required with attention to patients' comorbidities (obesity, sleep apnea, hypertension, alcohol abuse, etc.) and underlying individual pathophysiological pathways.

The cornerstone of a future ablation procedure will be the understanding and delineation of the substrate, which will be facilitated by high-resolution 3D electro-anatomical mapping systems allowing the integration of anatomical and structural/ functional information from imaging techniques such as magnetic resonance imaging and

electrophysiological information. Larger, randomized and prospective trials are needed to carefully evaluate the safety and efficacy of novel approaches targeting ‘the substrate’. In the first 20 years of this century, the spring of AF ablation has become to an end and in the summer of this era further optimization of the ablation techniques is expected. Hopefully the struggle for this purpose will ultimately free the heart of this rhythm disorder.

Chapter 10

Samenvatting
en Conclusies

10.1 Doel van dit proefschrift

Het doel van het **eerste deel** van dit proefschrift was om de impact van de ontwikkeling van AF-katheters op de incidentie van complicaties te bestuderen. Meer specifiek werd de veiligheid van de verbeterde niet-gekoelde katheter (PVAC-Gold) onderzocht. De eerste generatie van deze katheter vertoonde een hoge incidentie van asymptomatische cerebrale embolieën. Vervolgens is de ablatiekatheter en het ablatieprotocol herzien om de veiligheid van deze katheter te verbeteren. We hebben op gerandomiseerde wijze onderzocht of de verbeteringen in deze katheter de incidentie van herseninfarcten verminderden vergeleken met een geïrrigeerde katheter. Daarnaast hebben we analyses uitgevoerd om de relaties tussen herseninfarcten, activering van het coagulatiesysteem en het ontstaan van cerebrale micro-embolieën te analyseren.

In het **tweede deel** van dit proefschrift werd het ablatieprotocol van een ander nieuw ablatie-apparaat voor pulmonaalveneisolatie, de cryoballon ablatiekatheter, onderzocht met als doel het voorkomen van complicaties door optimalisatie van de ablatieduur. De ontwikkeling van de tweede generatie cryoballon bracht een aanzienlijke verbetering in termen van werkzaamheid. Om complicaties te voorkomen, moest echter de ablatieduur nog worden geoptimaliseerd. Het tweede doel van dit proefschrift was daarom het optimaliseren van de ablatieduur waarbij patiënten werden gerandomiseerd naar verschillende ablatietijden met incidentie van dormant conduction als een indicator voor onvolledige isolatie. Verder hebben we geprobeerd de afwezigheid van onvolledige cryo ballon applicaties te voorspellen, waardoor de standaard wachttijd voor controle van de pulmonaal venen na ablatie overbodig werd.

Het derde doel van dit proefschrift was het verbeteren van het ablatieprotocol bij patiënten met persisterend AF. We concentreerden ons op de boxisolatie bij patiënten met een progressieve fibrose van het linker atrium en onderzochten het effect van het ablatie-oppervlak op de uitkomst van de ablatie.

In de algemene inleiding, **hoofdstuk 1** van dit proefschrift, wordt uitgelegd dat de laatste 20 jaar met verbetering van de ablatietools en -technieken, ablatie van AF is geëvolueerd naar een eerstelijnsbehandeling. In dit hoofdstuk wordt de pathofysiologie van AF, de verschillende ablatie-methoden en katheters samengevat.

In **hoofdstuk 2** gaat de introductie verder met het beschrijven van de vooruitgang in AF-ablatiekathers en de incidentie en preventie van complicaties. Een overzicht van point-by-point, multi-elektrode en ballon gebaseerde katheters voor pulmonaalvenenisolatie wordt weergegeven met een gedetailleerde beschrijving van de ablatietools, gerapporteerde complicaties en katheter gerelateerde specifieke aspecten. De ontwikkeling van

verschillende nieuwe ablatiekatheters is vaak gericht op het verhogen van de procedurele effectiviteit, maar verbetering van het veiligheidsprofiel volgt vaak na het optreden van complicaties. Voor punt-bij-punt gekoelde radiofrequentiekatheter ablatie blijft cardiale tamponade een belangrijke complicatie vergeleken met ballon gebaseerde technieken. Door driedimensionale mapping is de procedurele duur verkort en met de ontwikkeling van high-power short duration ablatie wordt een verdere verkorting van de ablatieduur verwacht. Voor cryoballon ablatie is de incidentie van nervus phrenic parese een belangrijk complicatie met hogere incidentie in vergelijking met radiofrequentie ablatie. Verbetering van het cryoballoon-ablatiesysteem leidde tot kortere procedurele en fluoroscopietijden met vergelijkbare werkzaamheid en complicaties. Andere single shot-katheters zijn in ontwikkeling met onbekende veiligheidsprofielen. Een mogelijk nadeel van niet-gekoelde katheters met meerdere elektroden is de associatie met asymptomatische cerebrale embolieën waarvan de klinische betekenis nog niet is opgehelderd. Samen met de verbetering van ablatiekatheters wordt ook het ablatieprotocol verbeterd met de implementatie van veiligheidsmanoeuvres voor het voorkomen van complicaties en selectie van patiënten die een ablatie ondergaan.

In **hoofdstuk 3** wordt een gerandomiseerde gecontroleerde studie beschreven naar de incidentie en klinische betekenis van cerebrale embolieën tijdens AF-ablatie met een zgn. 'duty-cycled phased-radiofrequente' katheter (PVAC-Gold) versus een gekoelde radiofrequente katheter. Met de eerste generatie PVAC katheter was de incidentie tot wel 42% van asymptomatische cerebrale embolie op MRI. Studies suggereerden dat temperatuuroverschrijding tijdens intermitterend katheter-weefsel contact en elektrische kortsluiting tussen elektrode 1 en 10 de hoofdoorzaken waren van deze herseninfarcten in de PVAC-katheter. De technische ontwikkeling van de volgende generatie PVAC-Gold bestond daarom uit vervanging van platina-elektroden door gouden elektroden om temperatuur overschrijding te voorkomen en verwijdering van elektrode 10 om kortsluiting te voorkomen. Bovendien werd het ablatieprotocol geoptimaliseerd door te streven naar hogere waarden voor geactiveerde stollingstijd (ACT) en werd de katheter in zoutoplossing ondergedompeld, voordat deze werd ingebracht in het lichaam om zo het ontstaan van luchtembolieën te minimaliseren. In dit hoofdstuk laten we zien dat de incidentie van asymptomatische cerebrale embolieën / herseninfarcten met deze nieuwe katheter en ablatieprotocol nog steeds hoog (23%) is vergeleken met een geïrrigeerde katheter (6%). Hoewel beide ablatietechnologieën een vergelijkbare toename van de coagulatie laten zien, zagen we een significant hoger aantal micro-embolieën op transcraniële doppler met de PVAC-Gold-katheter. De mediane concentratie van micro-embolische signalen tijdens de totale procedure was 8 [IQR, 5 tot 17] MES / min met de PVAC-Gold katheter versus 4 [IQR

3 tot 5] MES / min met de gekoelde katheter. Met neuropsychologische testen werd er geen cognitieve achteruitgang geconstateerd. Aangezien het doel van de opnieuw ontworpen katheter gericht was op het verminderen van de hoge incidentie van asymptomatische cerebrale embolie, stellen we dat de verbetering van dit apparaat slechts gedeeltelijk succesvol was met vermindering van slechts 45% ACE en MES vergeleken met de eerste generatie katheter. Omdat de incidentie nog steeds hoger is vergeleken met punt-bij-punt gekoelde ablatie moet de fabrikant het apparaat blijven verbeteren.

In **hoofdstuk 4** zijn we dieper ingegaan op het ontstaan van deze micro-embolie signalen met de PVAC-Gold katheter. De analyse omvatte 945 PVAC-Gold-radiofrequentie applicaties waarin biofysische parameters werden onderzocht om potentiële pathofysiologische mechanismen te onthullen. We ontdekten dat ablatie van de linker bovenste pulmonaal vene, het gemiddeld vermogen, de totale effectieve energie, de gemiddelde impedantie en temperatuur 2 seconden na ablatie geassocieerd was met het aantal MES. Vanwege het nieuwe katheterontwerp, werd mogelijk een laag percentage kortsluiting van de elektrodes (1%) en temperatuuroverschrijding (5%) gedetecteerd. Dit kon echter het hoge aantal MES niet verklaren. Deze resultaten suggereren dat ten eerste slecht elektrodecontact, vooral in de linker bovenste pulmonaal venen, vanwege de scherpe hoek tussen de katheter en de longvene, verantwoordelijk is voor het ontstaan van micro-embolieën. Een lage temperatuur na 2 seconden kan ook verband houden met slecht kathetercontact, waardoor het aantal MES toeneemt. Ten tweede was de ablatie power gerelateerd met MES: bij ablaties met een hoog vermogen en een hoge totale effectieve energie kan een hogere MES worden waargenomen, wat kan worden verklaard door een sterkere weefseldegeneratie. Bij een langzamere temperatuurstijging is ook een hoger vermogen nodig om de gewenste temperatuur te bereiken. Ten derde kan een verhoogde impedantie het gevolg zijn van afbraak van bloedeiwitten, wat de relatie tussen impedantie en MES verklaart. Concluderend, het herontwerp van de PVAC-Gold maakte een einde aan de temperatuuroverschrijding en de interactie met de elektrode, maar de andere oorzaken van MES zijn hetzelfde gebleven.

In **hoofdstuk 5** werd de activering van coagulatie tijdens ablatie met de PVAC-Gold bestudeerd. In dit hoofdstuk lieten we zien dat vroege veranderingen in fibrinogeen en von Willebrand Factor antigeen en late veranderingen in d-dimeer geassocieerd waren met toenames in MES. Deze resultaten suggereren dat bij ablatie met een sterkere coagulatie respons in de acute fase en endotheelcel beschadiging een sterkere activering van de coagulatiecascade optreedt, waardoor meer micro-embolieën ontstaan, wat uiteindelijk resulteert in een sterkere activering van de fibrinolytische pathway met een verhoogd d-dimeer. Onze hypothese is dat een sterkere activering van de coagulatiecascade resulteert

in stille cerebrale embolieën. Dit verklaart ook waarom 7 patiënten meerdere infarcten vertoonden in de PVAC-Gold-groep in vergelijking met 0 patiënten in de Thermocool-groep. We suggereren dat routinematige meting van stollingsmarkers tijdens AF-ablatie nuttig kan zijn om patiënten met een hoge embolische load te identificeren, die na de ablatie moeten worden doorverwezen voor cerebrale beeldvorming om ablatie gerelateerde ischemische events uit te sluiten.

In **hoofdstuk 6** worden de resultaten gepresenteerd van een gerandomiseerde studie die gericht is op het optimaliseren van de ablatieduur met de tweede generatie cryoballon. De tweede generatie cryoballon die meer injectieopeningen heeft voor een meer homogene en snellere koeling werd geïntroduceerd om een duurzamere isolatie van de longvenen te bereiken. Ten koste van een betere werkzaamheid werden echter meer en tijdelijke en persisterende nervus phrenicus parese en slokdarmbeschadigingen beschreven. Bij de eerste generatie cryoballon was het geadviseerde ablatietijd, twee applicaties van elk 300 seconden, terwijl het geadviseerde protocol voor de tweede generatie twee applicaties van 240 seconden was. Latere studies toonden aan dat één enkele applicatie voldoende was. Bovendien verhoogde het verkorten van de ablatieduur van 240 seconden naar 180 seconden de AF-recidief niet. Afgezien van de ablatieduur is het een vereiste dat er voldoende contact is tussen de ballon en de weefsel om een duurzame isolatie van de longvene te bereiken. Met beter contact tussen ballon en weefsel zal isolatie van de longvene eerder worden bereikt, wat een kortere isolatietijd tot gevolg heeft. Er is inderdaad aangetoond dat de tijd tot isolatie bij ablatie van de longvene een duurzame ablatie voorspelt. Het doel van dit hoofdstuk was daarom om de ablatieduur afhankelijk te maken van de tijd tot isolatie en om de optimale ablatieduur te bepalen op basis van isolatietijd. Daartoe werden patiënten gerandomiseerd naar drie groepen met een extra ablatieduur van 90, 120 of 150 seconden nadat pulmonaalveneisolatie was bereikt. Met als primaire uitkomstparameter spontane reconnectie of adenosine geïnduceerde dormant (vroege reconnectie) conductie. We toonden aan dat het verhogen van de extra ablatieduur een stapsgewijze afname veroorzaakte van vroege reconnectie van de venen. Bovendien werd een afname gezien van aanvullende ablaties die nodig waren voor de behandeling van reconnectie en dormant conduction, terwijl bij toenemende ablatie duur de recidieven en complicaties na één jaar niet significant verschillend waren. Ook nam het aantal herhaalprocedures tijdens follow-up af. Concluderend is op basis van onze data een extra ablatie tijd van 150 seconden na isolatie van de pulmonaalvenen de meest geschikte benadering bij ablaties die gebaseerd zijn op isolatie van de pulmonaalvene.

In **hoofdstuk 7** hebben we ons gericht op de procedurele biofysische voorspellers van vroege reconnectie. Het voorspellen van de afwezigheid van reconnectie zou de procedure verder verkorten en adenosinetesten overbodig maken. In dit hoofdstuk worden biofysische gegevens van de cryoballoon ablatie geanalyseerd bij 151 patiënten met een vaste ablatieduur van 240 seconden. We ontdekten dat drie eenvoudig beschikbare parameters geassocieerd waren met vroege reconnectie. Een hoger aantal niet-succesvolle vries pogingen, een langere isolatietijd en een hogere nadir-ballontemperatuur voorspelden vroege reconnectie. Met een eenvoudige formule werden voor deze parameters afkapwaardes gedefinieerd. Het gebruik van deze formule tijdens ablatie zou zinvol kunnen zijn om de procedure te verkorten door niet te wachten op adenosine-tests. Terwijl in dit hoofdstuk offline berekening nodig waren, zal met de verbetering van de cryoconsole de biofysische parameter gemakkelijker beschikbaar zijn en zou een cryoballon-ablatiescore, vergelijkbaar met de ablatie-index, mogelijk zijn. Met een cryoballoon-ablatiescore kan het ablatieprotocol verder geoptimaliseerd worden om AF-vrije overleving te verbeteren.

Ten slotte hebben we ons in **hoofdstuk 8** gericht op het isoleren van de linker atrium achterwand bij patiënten met persisterend atriumfibrilleren. De achterwand van de linkerboezem is een bekend substraat voor het blijven bestaan van boezemfibrilleren, omdat het een gemeenschappelijke embryologische oorsprong heeft met de longvenen. Isolatie van de achterwand tussen de longvenen, een zogenaamde boxlaesie, kan de uitkomst bij AF-ablatie bij persisterend atriumfibrilleren verbeteren. In dit hoofdstuk hebben we laten zien dat een grotere box-oppervlakverhouding, wat een grotere box-laesie is in verhouding met het totale linker atriumoppervlak, het recidief van atriumfibrilleren vermindert. Het oppervlak van de boxlaesie kan worden gemeten op elektro-anatomische mappen en het totale linker atriumoppervlak kan worden gemeten op pre-procedurele CT-scans. We hebben laten zien, dat de box surface ratio een sterkere voorspeller is voor recidieven dan het linker atrium volume-index. Deze studie kan daarom een beslissing ondersteunen om de omvang van de boxlaesie te vergroten, b.v. door de onderlijn van de ablatie, onder het niveau van de longvenen richting de sinus coronarius te plaatsen. Dit zal vooral zinvol zijn bij patiënten met een relatief kleine anatomische boxlaesie. Door meting van de boxsurface ratio kan men besluiten om de grootte van het ablatie gebied bij geselecteerde patiënten te vergroten, wat de effectiviteit van de ablatie kan verbeteren.

10.2 Toekomstperspectieven

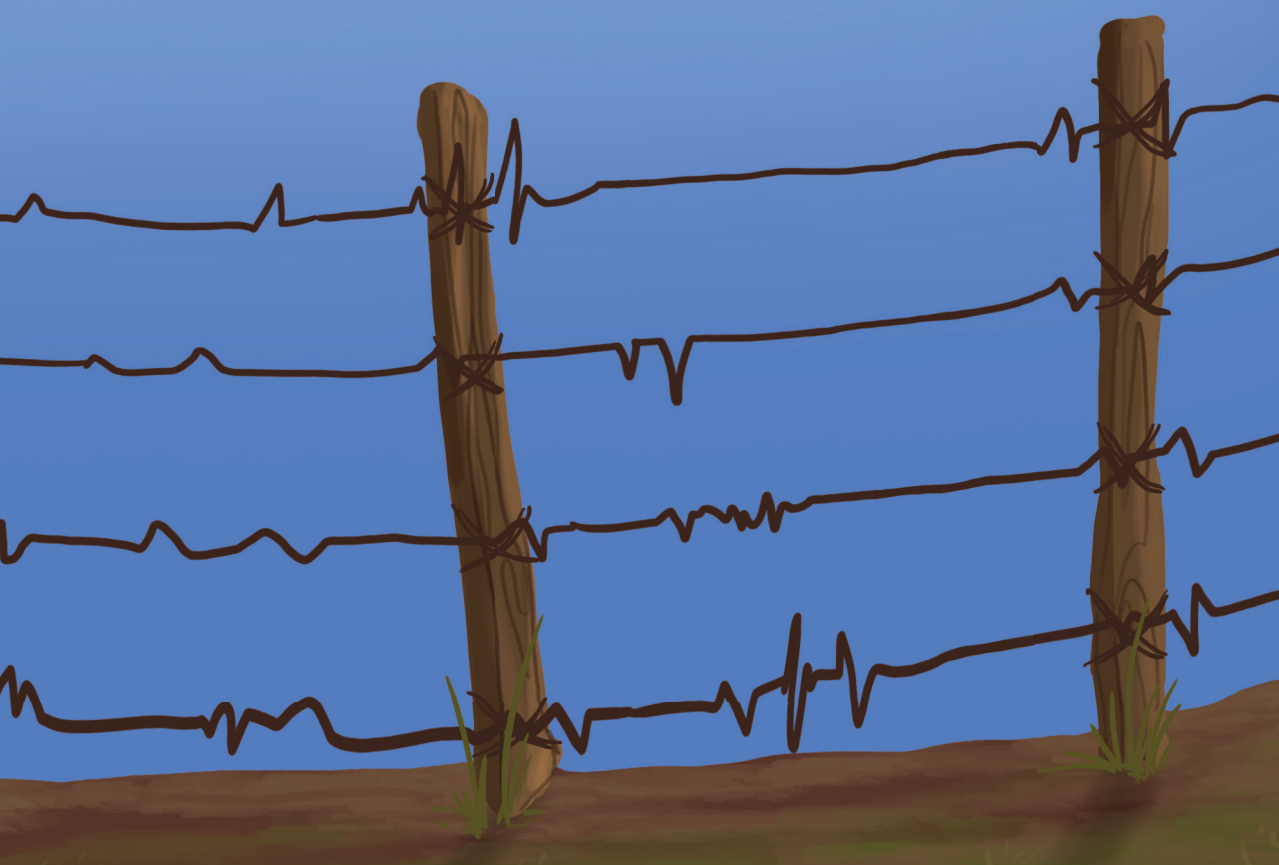
Het aantal patiënten met AF neemt alsmaar toe en naar verwachting zal dit aantal de komende 50 jaar worden verdubbeld als gevolg van een toegenomen levensverwachting, metabool syndroom gerelateerde ziekten en beter herstel na (chirurgische) behandeling van hartaandoeningen (myocardinfarct). In de afgelopen 20 jaar is katheterablatie bij veel patiënten met AF geëvolueerd van een zeldzame en moeilijke procedure naar een eerstelijnsbehandeling. Dit is samengegaan met het begrijpen van de pathogenese van AF en de verbetering van de apparatuur en de technieken. Het is duidelijk geworden dat AF niet alleen een ritmestoornis is die met een simpele ingreep kan worden behandeld. Integendeel, AF is een aanhoudende multifactoriële ziekte met een zeer gecompliceerde pathofysiologie en behandeling.

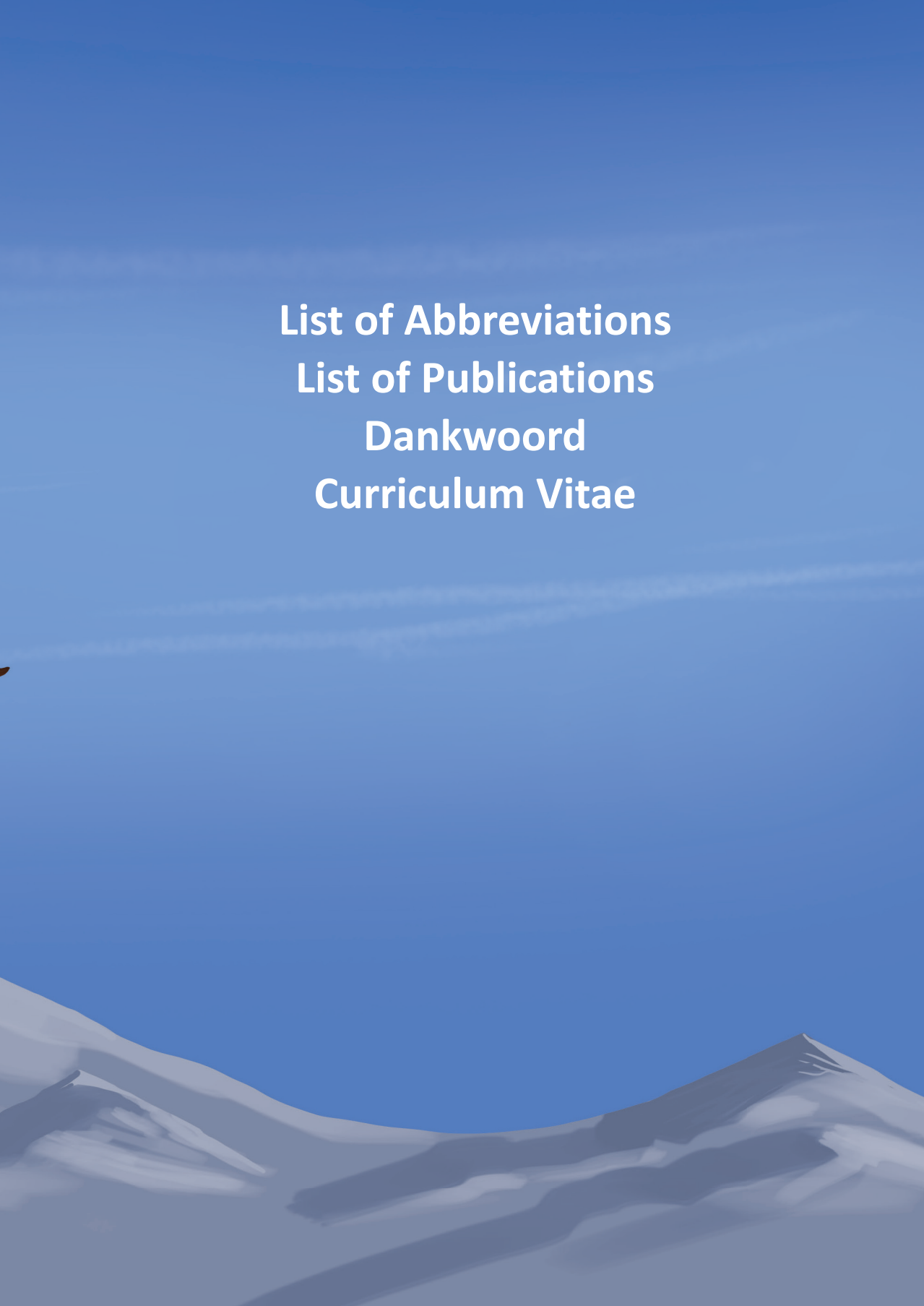
Ondanks de technologische ontwikkeling van hulpmiddelen voor katheterablatie, blijft de incidentie van zowel vroege als late recidieven na pulmonaalveneisolatie een belangrijk probleem, samen met veiligheid van de ablatie. De verbetering van ablatie-instrumenten kan een uitdaging zijn, maar we zijn nog steeds van mening dat optimalisatie van ablatie-instrumenten en -protocollen succesvol kan zijn met een betere effectiviteit, verkorting van de procedurele duur en vermindering van katheter specifieke complicaties. In dit proefschrift werden de resultaten van twee gerandomiseerde klinische onderzoeken beschreven. Verbetering kan dan misschien in kleine stapjes komen, maar vergeleken met de allereerste katheterablatie is reeds een enorme stap vooruit gemaakt.

Verschillende diagnostische hulpmiddelen, d.w.z. katheters die de atrium in kaart kunnen brengen met behulp van multi-elektrode katheters die met hoge resolutie worden ontwikkeld en geïmplementeerd om AF te analyseren. We wijn hiermee een weg ingeslagen, naar een ablatietechniek die voornamelijk is gebaseerd op 'individuele' substraatanalyse. Alle patiënten zijn verschillend en er is in eerste instantie substraatanalyse nodig voordat een specifieke behandeling kan worden gegeven. Dit betekent dat we een nieuwe definitie voor AF moeten gebruiken die gebaseerd is op het onderliggende substraat, in plaats van de huidige klinische definities van paroxismale en persistente AF. Pulmonaalveneisolatie, die momenteel de hoeksteen is van de behandeling, is slechts de behandeling van de belangrijkste pathofysiologische mechanisme. Verder is er meer aandacht nodig voor de verschillende pathways die verantwoordelijk zijn voor de progressie van AF. Een meer holistische benadering is vereist met aandacht voor de co-morbiditeit van patiënten (obesitas, slaapapneu, hypertensie, alcoholabusus enz.) En onderliggende individuele pathofysiologische pathways die die ziekte laat ontstaan of de ziekte onderhoud.

De hoeksteen van toekomstige ablatieprocedures zal het begrijpen en afbakenen van het substraat zijn, wat zal worden vergemakkelijkt met 3D-elektro-anatomische mappingsystemen met hoge resolutie die de integratie van anatomische en structurele / functionele informatie van beeldvormingstechnieken zoals magnetische resonantiebeeldvorming en elektrofysiologische informatie. Er zijn grotere, gerandomiseerde en prospectieve onderzoeken nodig om de veiligheid en effectiviteit van nieuwe benaderingen die gericht zijn op 'het substraat' zorgvuldig te evalueren. In de eerste 20 jaar van deze eeuw is het voorjaar van AF-ablatie ten einde gekomen en in de zomer van dit tijdperk wordt een verdere optimalisatie van de ablatietechniek verwacht. Hopelijk zal het vechten voor dit doel, het hart uiteindelijk van deze ritmestoornis bevrijden.

Appendices





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List of abbreviations

ACE: Asymptomatic Cerebral Embolism
ACT: Activated Clotting Time
AF: Atrial Fibrillation
APTT: Activated Partial Thromboplastin Time
CI: Confidence Interval
ECG: Electrocardiography
FLAIR: Fluid Attenuated Inversion Recovery
HR: Hazard ratio
INR: International Normalized Ratio
IQR: Interquartile Range
LA: Left atrium
MES: Micro-embolic Signals
MRI: Magnetic Resonance Imaging
PVAC: Pulmonary Vein Ablation Catheter
PVI: Pulmonary Vein Isolation
RF: Radiofrequency

List of publications

Optimizing Ablation Duration with the Second Generation Cryoballoon: A Randomized Controlled Trial. Keçe F, de Riva M, Naruse Y, Alizadeh Dehnavi R, Wijnmaalen AP, Schalij MJ, Zeppenfeld J, Trines SA. J Cardiovasc Electrophysiol. 2019 June;30(6):902-909.

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Curriculum Vitae

Fehmi Keçe is 26 augustus 1983 te Amsterdam geboren. In 2003 heeft hij zijn diploma voor het voorbereidend wetenschappelijk onderwijs met profiel Natuur en Gezondheid én Natuur en Techniek behaald aan het Hervormd Lyceum West in Amsterdam. Hij heeft geneeskunde gestudeerd aan de Vrije Universiteit van Amsterdam en behaalde zijn propedeutisch examen in 2005, het doctoraal examen in 2009 en het artsenexamen in 2011. Na zijn studie geneeskunde heeft hij in de kliniek gewerkt in het huidige Onze Lieve Vrouwe Gasthuis in Amsterdam en Isala Klinieken in Zwolle. In 2015 maakt hij de overstap naar het Leids Universitair Medisch Centrum om te kunnen promoveren onder supervisie van professor doctor Katja Zeppenfeld. Vanaf 2018 heeft hij naast zijn promotie in deeltijd gewerkt als echocardiografist bij Cardiologie Centra Nederland. Het onderwerp van zijn thesis richt zich op het optimaliseren van verschillende ablatie technologieën en de incidentie en preventie van complicaties. Hij heeft 2 prospectieve gerandomiseerde onderzoeken uitgevoerd en de resultaten van zijn onderzoeken staan beschreven in dit proefschrift. In april 2020 is hij met zijn opleiding tot cardioloog gestart aan de Universiteit van Keulen.