

Advances in atrial fibrillation ablation technologies

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ISBN: 978-94-6361-530-3

Cover design: Annie van Houten

Layout: Optima Grafische Communicatie

Print: Optima Grafische Communicatie

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Financial support for publication of this dissertation by ChipSoft is gratefully acknowledged.

Financial support by Wetenschapsfonds Medisch Specialisten Isala for the publication of this thesis is gratefully acknowledged.

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Advances in atrial fibrillation ablation technologies

Ontwikkelingen in atriumfibrilleren ablatie technologie

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
dinsdag 20 april 2021 des ochtends te 10.30 uur

door

Thomas Jelmer Buist

geboren op 4 juli 1990
te Groningen

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1

General introduction

Atrial fibrillation ablation strategies and technologies: past, present, and future.

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Clinical Research in Cardiology 2020 Oct 22. doi: 10.1007/s00392-020-01751-5.

ABSTRACT

Catheter ablation is an established treatment option for atrial fibrillation (AF), and pulmonary vein isolation (PVI) has become the gold standard in AF ablation. AF recurrence after PVI remains an important clinical problem. Recovery of conduction from the pulmonary veins (PVs) is considered the dominant mechanism for AF recurrence in paroxysmal AF. However, the underlying mechanism of AF recurrence after PVI is more complex in patients with persistent and longstanding persistent AF. Different ablation technologies and energy sources have been developed aimed at improving lesion quality and durability with an acceptable safety profile. Novel technologies are under evaluation which have a great potential to produce permanent PVI after a single ablation procedure. However, clinical value of these novel devices needs to be tested in adequately powered randomized controlled trials. In this article, we review the history of catheter ablation for AF and discuss the present and future ablation technologies.

INTRODUCTION

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia¹ and is associated with reduced quality of life², increased mortality³ and morbidity, including enhanced risk of stroke⁴, heart failure⁵, and repeated hospitalizations⁶. Due to its significant impact on cardiovascular morbidity and mortality, researchers have sought ways to successfully treat and even cure some types of AF. Over the past decades, percutaneous catheter ablation (CA) has become an important AF treatment modality to restore and maintain sinus rhythm. Pulmonary vein isolation (PVI) is now considered the cornerstone of catheter-based treatment for paroxysmal and early persistent AF.^{7,8} Since the introduction of CA, major advances have been made. Different ablation technologies and energy sources have been designed and the search for improving ablation safety and clinical outcome continues. This article outlines the history and evolution of CA, reviews the currently available AF ablation technologies, and provides a glimpse into future ablation techniques.

HISTORY OF CATHETER ABLATION

The first intra-cardiac use of catheters was described in the 1960s, where the application was limited to signal recording and cardiac stimulation. One of the earliest reports of catheter use is a study performed by Durrer et al. in which application of intracardiac electrical pulses and signal recording was described in patients with Wolff-Parkinson-White (WPW) syndrome.⁹ Together with electrophysiological studies performed by Zipes and Wellens in the 1970s, insights into tachycardia mechanisms, including the WPW syndrome, markedly improved.^{10,11,12}

Probably the first described catheter-mediated ablation was permanent atrioventricular conduction (AV) block accidentally caused in a patient undergoing an electrophysiological study for recurrent syncope in 1979.¹³ During the procedure, the patient required electrical cardioversions for ventricular tachycardia while the intracardiac bipolar recording catheter was reportedly in contact with the bundle of His. Presumably, this led to inadvertent transfer of externally delivered direct current energy over the recording catheter electrodes resulting in complete AV block.

This unintended catheter-mediated induction of AV block was further investigated in the following years, leading to the first described in-human catheter ablation in 1982. In a study by Scheinman et al., five patients suffering from drug refractory supraventricular tachycardia received a permanent pacemaker followed by AV junction ablation using high-energy DC shocks.¹⁴ From this point, the use of the electrode catheters was no longer limited to diagnostic electrophysiological studies alone, and DC ablation was applied in ablation of accessory pathways¹⁵, atrial tachycardias¹⁶, and ventricular tachycardias¹⁷.

While these early results of high-energy DC catheter ablation appeared potentially promising, the occurrence of significant adverse events, including cardiac tamponade and sudden death, were major drawbacks of the technique.^{18,19,20,21} High-energy DC shocks were associated with arcing, gas formation and shockwave generation leading to barotrauma.^{22,23,24}

In the late 1980s, radiofrequency (RF) energy for catheter ablation was introduced. In the early 1990s, many studies on RF ablation followed, showing better efficacy and safety in ablation of accessory pathways, atrial flutter, modification of the AV junction in AV nodal reentrant tachycardia and ventricular tachycardia.^{25,26,27,28,29} The use of RF catheter ablation skyrocketed, and high-energy DC ablation became abandoned.

HISTORY OF ATRIAL FIBRILLATION ABLATION

While insights obtained from electrophysiological studies led to surgical and catheter-based treatment of several supraventricular tachyarrhythmias, such as WPW syndrome and AV nodal reentrant tachycardia, treatment options for more complex arrhythmias like AF were limited to drugs or pacemaker implantation followed by AV junction ablation. In 1987, the first surgical strategy for AF treatment was reported by Cox and colleagues. Their group performed computerized mapping of atrial fibrillation in animals and man, eventually leading to the development of a surgical procedure for the treatment of drug refractory AF, known as the surgical Maze procedure.^{30, 31} The original Maze procedure involved creation of multiple surgical incisions in the left and right atrium during open heart surgery. The rationale for the Maze procedure was derived from experimental studies by Allesie and Schuessler.^{32, 33} Allesie et al. experimentally validated Moe's multiple wavelet hypothesis by mapping the activation pattern in isolated canine atria during rapid pacing-induced cholinergic atrial fibrillation.^{34,35,36} Complete mapping of both atria was performed, and it was estimated that a critical number of four to six simultaneously present wavelets were required to maintain AF. Although the underlying mechanisms involved in the initiation and perpetuation of AF were incompletely understood, the main goal of the initial Maze procedure was to compartmentalize the atria, thereby creating an electrical maze, using the "cut and sew" technique or alternative means of creating linear lesions of electrical block in both atria to eliminate reentrant wavelets and restore sinus rhythm or an atrial rhythm within the atrial myocardium.³⁰ Further improvements to the surgical technique eventually resulted in the Cox Maze III procedure, which is still used today.³⁷ Long-term follow-up of 198 patients with paroxysmal and persistent AF who underwent a Cox Maze III procedure showed that 95% were AF free after a mean follow-up of 5.3 years. Major complications occurred in 12%, including two perioperative deaths.³⁸ Due to the complex and invasive nature of the Maze procedure several investigators in the early 90s tried to replicate the ablation lesion sets using the catheter. Morillo et al. performed a study with 22 dogs in which structural remodeling of the atria was achieved

by rapid pacing for 6 weeks, resulting in inducibility of sustained AF. In 11 of the dogs, attempted cryoablation of an area in the posterior left atrium resulted in restoration of sinus rhythm and non-inducibility of AF.³⁹ In that same year, Elvan et al. published a study in which AF was induced by burst pacing in 27 dogs. The creation of epicardial and endocardial RF ablation lesions targeting the left and right atrium, the superior vena cava, and transverse sinus resulted in reduced inducibility of AF (by high doses of methacholine).⁴⁰ In the mid-90s, feasibility of CA as treatment of AF in humans was reported by Haïssaguerre et al. The ablation involved the creation of multiple linear lesions in the right atrium using RF energy. After ablation AF could not be induced with pacing, and during short-term follow-up of 3 months the patient remained free of arrhythmias without antiarrhythmic drugs.⁴¹ The first patient series on catheter ablation of AF soon followed. In a study by Swartz et al. patients with chronic AF received RF CA in both the left and right atria.⁴² Arrhythmia-free survival after 12 months was considered satisfying; however, the complication rate was high including pericardial effusion and cerebrovascular accidents. In a study by Haïssaguerre et al. 45 patients with paroxysmal AF received RF ablation with the creation of linear lesions mainly in the right atrium. Follow-up showed a poor 1-year arrhythmia-free survival, but no serious complications were observed.⁴³ Long-term follow-up of clinical trials that applied transcatheter linear ablation lesions in the right atrium in a Maze-like approach showed limited success.^{44, 45} An historically important AF ablation approach targeting foci that triggered AF was reported by Jaïs et al. These arrhythmogenic foci were found near the sinus node, at the coronary sinus ostium, and at the ostium of the left and right sided pulmonary veins, and were successfully eliminated by RF ablation.⁴⁶ In 1998, Haïssaguerre and colleagues published their milestone study on ablation of AF initiating triggers that were mainly localized in the pulmonary veins (PVs) and which could be successfully eliminated using CA.⁷ These findings led to a different approach of AF ablation, focusing on the elimination of AF triggers, and the Maze-like linear lesions in the right atrium became abandoned. Subsequently, a method was developed to electrically isolate AF triggers in the PVs by creation of circumferential ablation lesions in the PVs, now known as pulmonary vein isolation (PVI).⁴⁷

Many studies on electrical isolation of the PVs as treatment for AF followed, and currently PVI has become the cornerstone treatment in catheter-based ablation of AF.⁸ Randomized trials showed better efficacy rates for RF ablation compared to antiarrhythmic drugs.^{48,49,50} Furthermore, PVI resulted in better quality of life compared to drug therapy.⁵¹ However, AF recurrence after ablation was still frequently observed, especially in patients with persistent and long-standing persistent AF. In patients with persistent forms of AF, it was recognized that triggers that initiated and maintained AF frequently originated outside the PVs, including the PV antrum, the posterior wall of the LA, the superior vena cava, the crista terminalis, the coronary sinus, ligament of Marshall and the left atrial appendage.⁸ Ablation strategies were adapted to wider ablations at the PV antrum, also known as wide-area circumferential ablation (WACA), and strategies complementary to PVI were investigated.⁵² These strategies

included linear lesions in the left and right atria, ablation of the left atrial appendage, and ablation of complex fractionated atrial electrograms (CFAE).^{53, 54} Some observational studies have suggested a beneficial effect of additional ablations on treatment outcome.^{55, 56} However, results from the randomized STAR AF II trial demonstrated that additional ablation lines or CFAE ablation did not result in better efficacy in patients with persistent AF.⁵⁷ Whether selected groups of patients benefit from these additional ablation strategies remains uncertain and subject for future research.

RATIONALE BEHIND AF ABLATION

The major impact of AF on cardiovascular morbidity and mortality has driven researchers and physicians to find ways to restore and maintain sinus rhythm. It is generally accepted that the pathophysiology of AF includes a trigger to initiate AF, a substrate to maintain AF, and modulating risk factors, ultimately resulting in progression to more persistent forms of AF.⁵⁸ Over the years, AF ablation strategies have targeted elimination of AF triggers or modification of the arrhythmogenic substrate. Ablation lesions are created to produce non-conductive tissue isolating triggers that initiate AF, and interrupt arrhythmogenic pathways in patient-specific AF substrate, or modulate autonomic innervation of the atria.^{7, 59, 60}

Recent results from the randomized CABANA trial comparing ablative therapy to medical therapy for the treatment of AF showed no significant benefit of CA over medical therapy in reduction of the composite end point of death, disabling stroke, serious bleeding, or cardiac arrest.⁶¹ However, treatment crossover and lower event rates than anticipated might have affected the disappointing results of the CABANA trial. Of note, the trial did show more favorable quality of life outcomes at 12 months following CA compared to medical therapy.⁶² Therefore, whether AF ablation can reduce morbidity or mortality remains unclear. Meanwhile, symptom reduction and QOL improvement remain the primary indication for catheter ablation.⁸

AF ablation and heart failure

Recent studies suggested AF ablation with restoration of sinus rhythm can improve morbidity and mortality in patients with heart failure. The AATAC study comparing CA with amiodarone resulted in reduction of hospitalization and mortality in persistent AF patients with heart failure.⁶³ The prospectively randomized CASTLE-AF trial reported similar results, in which CA of AF resulted in a lower rate of hospitalization and mortality in patients with heart failure compared to medical therapy.⁶⁴

PRESENT AF ABLATION TECHNIQUES AND ENERGY SOURCES

3D mapping and creation of a transmural and contiguous ring of scar tissue around the PVs with point-by-point RF ablation can be technically challenging, particularly at less experienced centers. Over the past years, different 3D mapping and catheter ablation systems using various energy sources have been developed to improve catheter handling, thereby enhancing safety, efficiency and efficacy of these ablation procedures. Among these are balloon-based technologies using a variety of energy sources, circular multielectrode, and contact force tip electrode systems. For surgical ablation, clamp devices have been developed to improve lesion quality. In this section, we will review different ablation technologies that are used for AF ablation.

Radiofrequency point-by-point ablation

RF myocardial ablation is a thermal-mediated method in which localized heat generation is used to create tissue necrosis and formation of ablation lesions. Continuous lesions are created in a point-by-point manner usually guided by a dedicated 3D electro-anatomical mapping system. The thermal effect is generated by delivering an electrical current through myocardial tissue from the tip electrode of the ablation catheter to a large dispersive electrode patch (unipolar) or between a pair of electrodes from adjacent ablation catheters (bipolar), causing resistive heating of the underlying tissue at the electrode tip (unipolar) or resistive heating of tissue between two catheter electrodes (bipolar). Myocardial cells become irreversibly damaged when exposed to temperatures of 50 °C or higher, leading to necrosis and eventually to nonconducting myocardial fibrotic scar tissue. If the temperature at the electrode exceeds 100 °C, boiling of blood occurs, resulting in clot and char formation.⁶⁵ If the intramyocardial temperatures exceeds 100 °C, boiling of tissue can lead to steam formation (pop lesion) potentially causing intramyocardial rupture and tissue perforation.⁶⁶ Factors that affect lesion size include electrode size, temperature, electrode–tissue contact, power and duration of RF energy delivery.^{65, 67} Furthermore, heat loss to circulating blood on endocardial side and to epicardial coronaries can compromise lesion formation.⁶⁵ RF ablation lesions in PVI often consist of a combination of myocardial necrosis and tissue edema, often resulting in partially reversible myocardial lesions.⁶⁸ This latter can appear as irreversible lesions but lead to PV-reconnection later, which is associated with recurrence of atrial arrhythmias after ablation.^{69,70,71} Higher power RF energy delivery can increase lesion size and depth but also increases the risk of temperature rise and char formation and collateral damage to structures such as esophagus and phrenic nerve. To allow higher power RF energy delivery, saline irrigation of the catheter tip electrode was developed to improve conductive heating of the underlying tissue while reducing temperature rise in the circulating blood. Saline-irrigated RF ablation results in deeper and larger lesions.⁶⁶ Currently, point-by-point RF

ablation is most commonly performed using ablation catheter tip electrode irrigation with saline. To improve electro-tissue contact, catheters have been developed that are capable of measuring contact force between the catheter tip and tissue during ablation.^{72,73} RF ablation catheters with a contact force sensor improved outcome of AF ablation in the hands of experienced operators. Contact force of more than 10 g was associated with higher rates of arrhythmia-free survival.⁷⁴

Although point-by-point RF ablation is the most commonly applied technique to achieve PVI, the procedure remains technically challenging, even in experienced centers. Potential complications associated with the RF point-by-point ablation technique include cardiac tamponade (0.2–5%)^{8,75}, stroke and transient ischemic attack (0–2%)^{8,76}, esophageal damage including atrio-esophageal fistulae (0.02–0.11%)^{8,77}, and PV stenosis (<1%)^{8,78}.

Multielectrode circumferential RF catheter

Multielectrode circumferential RF ablation catheters were designed to make PVI procedures less complex and time consuming. The currently available multielectrode PV ablation catheters contain nine to ten electrodes with a circular configuration when deployed. These catheters can be navigated to the PV ostium by fluoroscopy, enabling both mapping and ablation. The circumferential placement of the electrodes allows the creation of a circular ablation lesion at the PV ostium after multiple applications, eventually resulting in PVI. The first-generation multielectrode catheter is no longer in use due to its association with asymptomatic cerebral embolisms, which was related to overlap of the first and tenth electrode leading to tissue and blood overheating causing thromboembolisms.^{79,80} Currently, one multielectrode circumferential ablation catheter system is available for clinical practice; the second-generation gold multielectrode ablation catheter (PVAC GOLD™, Medtronic, Minneapolis, MN, USA) containing 9 gold-plated electrodes. PVI with the use of PVAC multielectrode ablation was associated with significantly shorter procedure, fluoroscopy, and radiofrequency energy times.⁸¹ However, comparison of multielectrode PVAC PVI to standard point-by-point irrigated RF ablation PVI showed conflicting data; some studies showed comparable outcomes while others significantly lower long-term atrial arrhythmia-free survival with the PVAC. Currently, available data on efficacy of multielectrode PVAC ablation are scarce and conflicting. Therefore, more prospective and randomized studies on this subject are needed.

Cryoballoon ablation

In cryoballoon ablation (Arctic Front Advance™, Medtronic, Inc., Minneapolis, MN, USA; POLARx™ Cryoablation Catheter, Boston Scientific, Marlborough, MA, USA), PVI is achieved by freezing tissue using a pressurized balloon that occludes the PV ostium and injecting liquid nitrous oxide as refrigerant into the balloon. Freezing tissue below –40 °C causes irreversible cell death due to freezing of intracellular water that results in irreversible disruption of organelles and cell membranes.⁸² The commonly used second-generation cryoballoon

(Arctic Front Advance, Medtronic, Inc. Minneapolis, MN, USA) catheter has a refrigerant injection system with 8 injection jets. The catheter has a lumen that can be used to pass a guide wire or a mapping catheter to guide balloon position and record PV potentials during ablation. The balloon catheter can be placed at the PV ostia without the use of 3D electro-anatomic navigation systems, and the balloon design allows circumferential ablation in a so called 'single shot' manner. The aim of this balloon design was to shorten and simplify PVI ablation procedures. Cryoablation has become the most frequently used alternative energy source to RF for AF ablation. In the multicenter randomized Fire and Ice trial, cryoballoon and point-by-point RF ablation were shown to be equally effective and safe for the treatment of paroxysmal AF.⁸³ However, procedure duration and left atrial dwell time were shorter in the cryoballoon group, whereas fluoroscopy time was shorter in the RF group.⁸³ The most commonly reported complication in cryoballoon ablation is phrenic nerve injury with a reported incidence between 2 and 5%, fortunately often of temporary nature.^{84, 85} Recently, presented results from the YETI registry containing data from 5371 patients treated with second-generation cryoballoon shows an incidence of phrenic nerve injury incidence of 3.9%, of which 57.5% were resolved at the end of the procedure. After 12 months, most of the phrenic nerve injuries were recovered, with an incidence of persistent phrenic nerve injury of only 0.08%.⁸⁶

Laser balloon

Laser balloon ablation (Heartlight™, CardioFocus, Marlborough, MA, USA) is a balloon-based technology using laser energy to create circumferential cell necrosis and achieve PVI. The laser balloon consists of a compliant balloon that fits into the PVs irrespective of variability in PV sizes and shapes. Unique to the device is the incorporation of a fiber optic endoscope to provide direct visualization of the target tissue in the antrum of the PVs.⁸⁷ Once positioned in the PV, the laser source emits energy to the exposed PV antral tissue. The intensity of the laser energy application can be titrated from 5.5 to 12 W, usually during 20–30 s for the formation of each ablation lesion. Lower laser energy setting is usually applied to reduce the risk of heating blood and charring when the occlusion is suboptimal and blood is present in the targeted ablation field. Laser energy output is also lowered when the targeted tissue is in the vicinity of the esophagus or phrenic nerve. Higher laser energy dose can be applied to the remaining PV segments resulting in more durable PVI lesions.⁸⁸ A frequently observed complication in laser balloon ablation is phrenic nerve injury, fortunately often of a temporary nature.⁸⁹ In a meta-analysis, efficacy and safety of the laser balloon were comparable to other AF ablation techniques.⁸⁹ (Fig. 1).

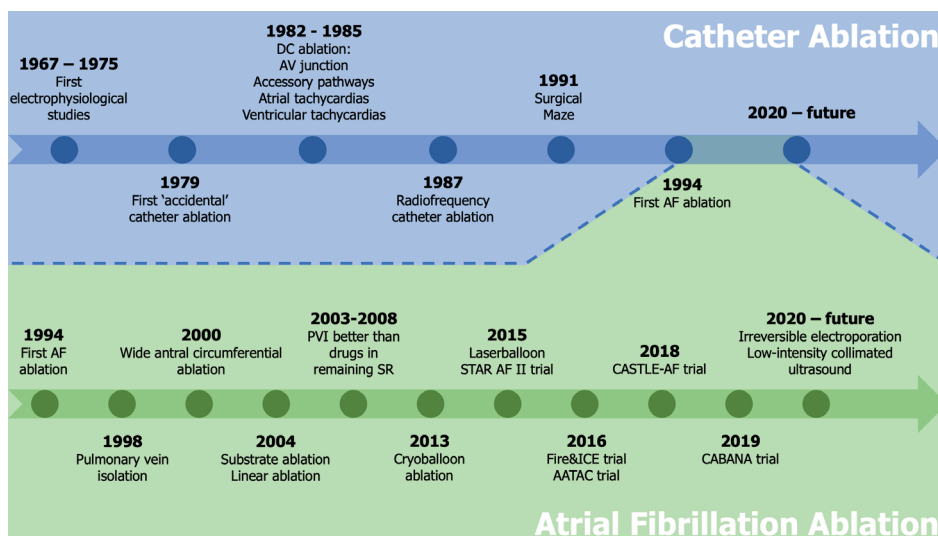


Figure 1. Timeline of key findings in catheter ablation of atrial fibrillation research.

AF atrial fibrillation, AV atrioventricular, DC direct current, PVI pulmonary vein isolation, SR sinus rhythm. AATAC Ablation versus Amiodarone for Treatment of AF in Patients With Congestive Heart Failure and an Implanted ICD/CRD, CABANA Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation, CASTLE-AF Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and AF, FIRE&ICE Cryoballoon or Radiofrequency Ablation for Paroxysmal AF. STAR-AF II trial the Substrate and Trigger Ablation for Reduction of AF Trial Part II

FUTURE ABLATION STRATEGIES AND TECHNOLOGIES

Over the past years, advances have been made in catheter-based AF ablation technologies and strategies. Achieving durable PVI lesions safely and rapidly remains challenging. Driven by AF recurrences after ablation and the occurrence of severe complications including cerebral embolism, esophageal damage, phrenic nerve palsy, investigators continue their search for more effective and safe ablation strategies and technologies.

Ablation line contiguity index

Although contact force-guided PVI is associated with improved arrhythmia-free outcome compared to conventional RF, reconnection of the PVs after ablation is still observed. The PV reconnection is explained by discontinuous and insufficient lesion depth in the circular lesion sets. Optimized and protocolized ablation strategies are developed aiming at creating contiguous and transmural RF lesions that might improve PV isolation durability.

The ablation line contiguity index (ablation index) is a novel measure assessing both contiguity and lesion depth, which can be used as a measure to detect weak spots in the set of created PV antral ablation lesions and LA anterior lines.^{90, 91} The ablation index incorporates ablation contact force, time, and power in one marker using a weighted formula, and pro-

vides an accurate estimation of lesion depth.⁹² Studies that used target values of 550 for anterior and 400 for posterior LA regions demonstrated to prevent PV reconnection.^{93, 94} The measure has been integrated in automated lesions tagging software for 3D electro-anatomic mapping to visualize lesion ablation index and target values. Performing contact force RF ablation according to a specific ablation protocol that incorporates the ablation index improved procedural and 1 year outcome of contact force PVI while shortening procedure time.^{95, 96}

High power short duration RF ablation

Recent studies investigated higher RF energy output with shorter pulses in AF ablation to improve safety and create more durable lesions.^{97,98,99} This high-power short-duration (HPSD) ablation strategy comprises the use of higher RF power (45–50 W) and shorter duration of each RF energy application (5–15 s) instead of conventional lower RF power (25–30 W) and longer duration of applications (30–60 s). With HPSD, the short duration of RF energy application results in more local resistive heating and local atrial tissue destruction without conductive heating of more distant tissues, such as the esophagus, preventing collateral damage.^{99,100}

The HPSD ablation strategy has been shown to improve contiguity and transmural of atrial linear lesions in animal models.⁹⁷ Furthermore, HPSD was associated with shorter procedural and RF time compared with conventional RF ablation and, appears to be a safe approach.^{98,99,100} Recent studies have investigated even higher power settings. PVI is achieved with 90 W applications for 4 s per ablation point, with a computerized algorithm modulating power to maintain target temperature.^{97, 101} A first-in-human study showed feasibility of achieving PVI with 90 W HPSD ablation in 52 patients. At 3 month follow-up, 49 patients (94.2%) were in sinus rhythm, and the occurrence of serious adverse events was low (3.8%).¹⁰¹ In another recently published study, a HPSD ablation protocol with 70 W for 5–7 s was compared to conventional (30–40 W for 20–40 s) ablation, in patients undergoing PVI for paroxysmal AF. The HPSD group showed significantly less AF recurrences 1 year after ablation, with 83.1% freedom from AF compared to 65.1% in the conventional group. Safety profiles were similar between the groups, and significantly shorter radiofrequency and procedural time were observed with HPSD.¹⁰²

Novel technologies in multielectrode RF balloon ablation

Several multielectrode RF balloon catheters have been developed for PVI. Similar to point-by-point RF ablation, PVI is achieved by RF energy resulting in thermal injury. The balloon design aims to shorten and simplify PVI ablation procedures. Data on these multielectrode RF balloon systems are limited to experimental and first-in-human studies. The Heliostar multielectrode RF balloon catheter (Biosense Webster Inc, Irvine, CA, USA) contains 10 gold-plated and irrigated electrodes mounted around a balloon in a circular configuration. The RF balloon is advanced to the left atrium using an over-the-wire design and positioned at the PV ostia.

Different RF energy settings can be programmed for each individual electrode to control temperature during ablation, particularly at sites that are in vicinity of sensitive structures (e.g. phrenic nerve and esophagus). This device allows the operator to create circumferential PVI lesions in a single shot manner without the need for catheter extensive manipulation, while preventing collateral damage. First-in-human results from the RADIANCE trial, showed feasibility and safety of achieving PVI in 39 patients with paroxysmal AF. Acute PVI was achieved in all the patients, and 79.6% of the PVs was isolated with a single application. In this limited series, one case of phrenic nerve palsy was observed.¹⁰³

The Luminize™, another RF balloon system (Boston Scientific, Marlborough, MA, USA) formerly known as the Apama RF balloon (Apama Medical Inc, Campbell, CA, USA), is an over-the-wire balloon catheter, containing 12 proximal (equatorial) electrodes and 6 distal electrodes. The technology incorporates four built-in cameras and LED illumination that allows direct visualization of the targeted area of interest for ablation. Furthermore, both mapping and pacing from the ablation electrodes are possible. The first-in-human results presented at the European Heart Rhythm Association Congress (Lisbon, Portugal, 2019) demonstrated safety and efficacy in achieving PVI in patients with paroxysmal AF.¹⁰⁴ Successful PVI was achieved in 98% of all the PVs and no serious adverse events were observed during a follow up of 30 days.

The Globe system (The Globe® system, Kardia Inc., Burnaby, BC, Canada) is a multielectrode catheter containing globe-shaped expanding array of 122 electrodes that can be deployed in the left atrium. Each individual electrode can perform sensing, pacing, and measurement of tissue contact, temperature and impedance. Ablation is achieved using RF energy that can be applied on each individual electrode up to 24 electrodes simultaneously. The catheter is designed to combine diagnostic mapping capabilities of basket catheters with the simplicity of the use of balloon catheters for ablation. First-in-human experience showed that PV isolation could be performed using this new multielectrode array catheter.¹⁰⁵ The safety and efficacy of the catheter are still under investigation.

Although feasibility and safety were shown for these novel multielectrode RF balloon catheters, more patient data and long-term follow-up are warranted. Furthermore, randomized studies are needed to assess the potential benefit regarding procedural time, safety and efficacy of these novel catheters compared to other (balloon based) ablation techniques.

Irreversible electroporation

Irreversible electroporation (IRE), also referred to as pulsed field ablation, is a novel nonthermal ablative modality in which ultrarapid (< 1 s) electrical fields (monophasic waveforms 900–1000 V and biphasic waveforms, 800–2000 V per application) are applied to target tissue. This approach destabilizes cell membranes by forming irreversible nanoscale pores and leakage of cell contents, culminating in cell death.¹⁰⁶ Importantly, various tissues have specific characteristic thresholds to field strengths that induce necrosis by electroporation.

Of note, myocardial tissue has the lowest threshold and is thus most sensitive tissue for irreversible electroporation. Therefore, in contrast to any other energy source, IRE spares collateral structures such as the esophagus, arteries and nerves while effectively ablating myocardial tissue. Potential benefits of IRE include the tissue selectivity of the ablation, and the rapid delivery of the energy, potentially resulting in shorter procedure times. Experimental data demonstrated that IRE can be a safe treatment modality for ablation in the vicinity of important structures such as the coronary arteries, the right phrenic nerve, and the esophagus, consistent with the tissue selectivity data derived from animal studies.^{107,108,109} The first-in-human experience with IRE ablation for PVI in patients with AF was recently reported.^{110, 111} Feasibility of achieving acute PVI by IRE ablation was shown using different catheter designs, including a 14-polar circular catheter¹¹⁰ and an over-the-wire catheter with a deployable basket containing 20 separate electrodes¹¹².

Low-intensity collimated ultrasound

Low-intensity collimated ultrasound (LICU) (VytronUS, Inc., Sunnyvale, California) is a novel ablation technique designed to integrate anatomic mapping and ablation capabilities in a single catheter.¹¹³ The catheter contains an irrigated tip with an ultrasound transducer. The catheter tip allows automatic construction of two- and three-dimensional maps of the scanned left atrial area of interest with a maximal depth of 40 mm. Ablation is performed using a highly collimated ultrasound beam that is absorbed by the atrial tissue and results in thermal injury with an estimated maximum depth of 17 mm. Ablation is performed with the support of a robotic system after definition of the ablation trajectories on a two-dimensional map by the operator. Feasibility of producing continuous transmural lesions in PVI ablation was shown in a porcine model.¹¹³ However, available data on this novel ablation technique are limited to an experimental study. Results from the first-in-human study are awaited.

CONCLUSION

Catheter ablation is an established treatment option for AF. Isolation of the PVs is the gold standard of catheter ablation of AF, but reconnection and conduction from the PVs is the dominant mechanism of recurrences of AF after PVI, especially in patients with paroxysmal AF. Novel technologies are under evaluation that have a great potential to facilitate creation of durable lesions with permanent PVI after a single ablation procedure. However, many of these novel technologies need to be tested clinically in well powered RCTs.

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AIM AND OUTLINE

Part I - Present atrial fibrillation ablation technologies

In the first part of this thesis we explore and evaluate existing ablation methods for atrial fibrillation (AF) ablation that are applied in common practice. The focus lies on comparing ablation techniques and the identification of factors that influence ablation outcome. In **chapter 2** we describe anatomical factors that affect ablation outcome in multi-electrode pulmonary vein isolation (PVI). **Chapter 3** describes clinical data of a gold plated multi-electrode ablation catheter, while studying the relationship between the number of transmural lesions and ablation success. In **chapter 4** we compare the second-generation cryoballoon with contact force radiofrequency point-by-point PVI for treatment of AF. Results are described regarding pulmonary vein reconnection patterns and arrhythmia-free survival. In **chapter 5** a direct comparison in a randomized controlled trial is made between minimally invasive thoracoscopic PVI with left atrial appendage ligation (surgical MIPI) versus percutaneous catheter ablation as primary treatment of AF. Results are presented regarding efficacy and safety of the treatment modalities of the so called SCALAF trial. Subsequently, in **chapter 6** we evaluate the quality of life of these patients.

Part II - Novel ablation technologies and future perspectives

The second part of this thesis explores the novel irreversible electroporation (IRE) ablation technique for the application in adjunctive substrate modification in AF ablation. This part consists of two experimental animal studies on IRE. In **chapter 7** we investigated the efficacy of linear multi-electrode IRE ablation in a porcine model, while assessing the relation between magnitude of IRE application and lesion size. In **chapter 8** we investigated the feasibility of IRE in the coronary sinus in a porcine model. The section ends with a discussion in **chapter 9** in which study results from this thesis are reviewed and interpreted in context of previous research, as well as suggestions for future research are provided.

PART I

Present atrial
fibrillation ablation
technologies

2 | Association between pulmonary vein orientation and ablation outcome in patients undergoing multi-electrode ablation for atrial fibrillation

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Journal of Cardiovascular Computed Tomography, Volume 10, Issue 3,
251 – 257

ABSTRACT

Background: Previous studies reported on the impact of pulmonary vein orientation on pulmonary vein isolation (PVI) outcome in atrial fibrillation patients undergoing laser balloon PVI and point-by-point radiofrequency ablation.

Objective: Demonstrate the association between pulmonary vein orientation and PVI outcome after multi-electrode radiofrequency ablation.

Methods: 120 patients undergoing PVI with a circular MER catheter were included. A left atrial ECG-triggered CT was performed in all patients prior to PVI. The orientation of all pulmonary veins at the insertion into the left atrium was measured in the axial and coronal planes. pulmonary veins were classified as having a ventral/dorsal and caudal/cranial orientation depending on the pulmonary vein trunk angle as compared to the median angle.

Results: Mean age was 56 years, arrhythmia-free survival after a median follow-up of 20 months was 54.2%. Left upper pulmonary vein orientation within the coronal plane was associated with arrhythmia-free survival, ranging from 58% with a cranial pulmonary vein orientation to 21% with a caudal orientation ($p = 0.003$). Similarly, arrhythmia-free survival was 50% in patients with a caudal orientation and 33% in patients with a cranial orientation of the left lower pulmonary vein in the coronal plane ($p = 0.036$). Pulmonary vein orientation in the axial plane and orientation of the right-sided pulmonary veins were not associated with arrhythmia-free survival. Multivariable analysis showed an independent association between both left upper (hazard ratio 2.8, $p = 0.001$) and left lower (hazard ratio 0.490, $p = 0.034$) pulmonary vein orientation and arrhythmia-free survival.

Conclusion: In MER ablation, orientation of the left upper and lower pulmonary veins in the coronal plane were independently associated with arrhythmia-free survival after multi-electrode PVI.

Keywords: atrial fibrillation, pulmonary vein isolation, multi-electrode ablation, PVAC, pulmonary vein anatomy, pulmonary vein orientation.

INTRODUCTION

Pulmonary vein isolation (PVI) is an effective treatment for atrial fibrillation (AF),^{1,2} although ablation success varies between 60-80% after long-term follow-up.³⁻⁵ Besides conventional radiofrequency (RF) ablation, several other techniques have been developed to perform PVI, including endoscopically assisted laser balloon ablation^{6,7} and multi-electrode RF (MER) ablation.⁸⁻¹⁰ We recently reported that pulmonary vein orientation significantly influences ablation outcome in laser balloon ablation,¹¹ but not in contact force sensing ablation.¹² These results suggest that efficacy of ablation catheters with a circular design may be impacted by pulmonary vein orientation. Therefore, we aimed to determine the association between pulmonary vein orientation and arrhythmia-free survival in patients with AF undergoing MER PVI.

METHODS

Data from 120 consecutive patients suffering from highly symptomatic, drug-refractory AF who underwent a first PVI using the MER ablation catheter (PVAC, Medtronic Inc.) and in whom CT imaging had been performed were entered in a prospective registry. Exclusion criteria were: a previous PVI attempt, left atrium diameter exceeding 50 mm in the parasternal long-axis view, severe valvular heart disease and contraindications to postinterventional oral anticoagulation. Directly prior to the ablation procedure, all patients underwent transesophageal echocardiography to rule out LA thrombus.

CT characteristics

All patients underwent CT scanning of the LA to guide the procedure. Cardiac multislice CT (MSCT) angiography was performed by a team of experienced CT technologists using a 64-slice scanner (Lightspeed VCT XT, GE Healthcare). A bolus of 70 ml of nonionic contrast medium of agent (Optiray 350, Mallinckrodt, The Netherlands) was infused through a large antecubital vein at a rate of 5 ml/s, followed by 50-ml saline solution flush. Automatic detection of the contrast bolus in the LA was used to time the start of the scan. Delay times varied significantly because of flow rate differences in patients, but were generally in the range of 5-15 seconds. Craniocaudal scanning was performed during breath-hold and using retrospective ECG gating (to be able to determine volume changes of the LA, but not used in this study). The collimation was 64 x 0.5 mm, rotation time 400 ms, and the tube voltage was 120 kV with mA dose modulation variable between 80 - 200 mA. All images were checked for adequacy before the end of the procedure to guarantee adequate image quality in all patients. In accordance with local guidelines, pulmonary vein analysis was performed at 40% of the RR interval, to ensure maximum contrast enhancement in the atrium. After

acquisition, the raw MSCT data were exported, post-processed, and analyzed on a dedicated workstation (GE Healthcare, Little Chalfont, UK). The images were reviewed by an independent investigator who was not involved in the ablation procedures and was not informed about the PVI outcome in these patients to prevent unconscious bias.

Pulmonary vein orientation measurement

The pulmonary vein trunk orientation measurement has been described in previously published reports.^{11, 13, 14} The orientation of the pulmonary vein trunk at the site of insertion into the LA was assessed for all pulmonary veins in both the axial and coronal (coronal) plane. A line was drawn in the direction of each pulmonary vein trunk in both the axial and coronal plane. Thereafter, the angle between the pulmonary vein trunk direction and the intersection line of the sagittal plane was measured in the axial and coronal plane (figure 1). Median pulmonary vein trunk angles were calculated in the axial and coronal plane for all four pulmonary vein trunks. Pulmonary veins were classified as having a ventral or dorsal orientation and caudal or cranial orientation, respectively depending on the individual angle as compared to the median angle in the axial and coronal plane. Common pulmonary veins¹⁵ were excluded from analysis.

Ablation protocol

All ablation procedures were performed under general anesthesia supervised by a cardiovascular anesthesiologist. After placement of a 6F quadripolar catheter in the coronary sinus, a single transseptal puncture was performed using a Brockenbrough needle under fluoroscopic and pressure guidance. Immediately after the transseptal puncture, 10,000 IU of unfractionated heparin was administered. An 8.5F sheath (SL-1, St. Jude Medical, Minnetonka, MN, USA) was used for pulmonary vein angiography. All sheaths were continuously flushed with saline containing 2500 IU heparin per 500 mL saline. An activated clotting time between 300 and 350 seconds was targeted. Additional heparin was administered when needed. The activated clotting time was checked during the procedure at regular intervals of 30 minutes.

Multi-electrode catheter ablation

The MER catheter (PVAC™, Medtronic, Minneapolis, MN, USA) is a mapping and ablation catheter with a 25 mm diameter circular electrode array. This catheter has a bidirectional steering mechanism and an over-the-wire design. The details of this device have been described previously.⁸ Using a 0.032" guidewire placed in the pulmonary vein, the catheter was positioned at the antrum of each pulmonary vein to record local electrical activity at the veno-atrial junction prior to radiofrequency energy application, creating pulmonary vein templates. Radiofrequency energy was applied with a target temperature setting of 60 °C, energy setting of 4:1 or 2:1 ratio between bipolar and unipolar energy, and 60 s duration (Medtronic GENius, Minneapolis, MN, USA). Multiple circular ablation sets of radiofrequency

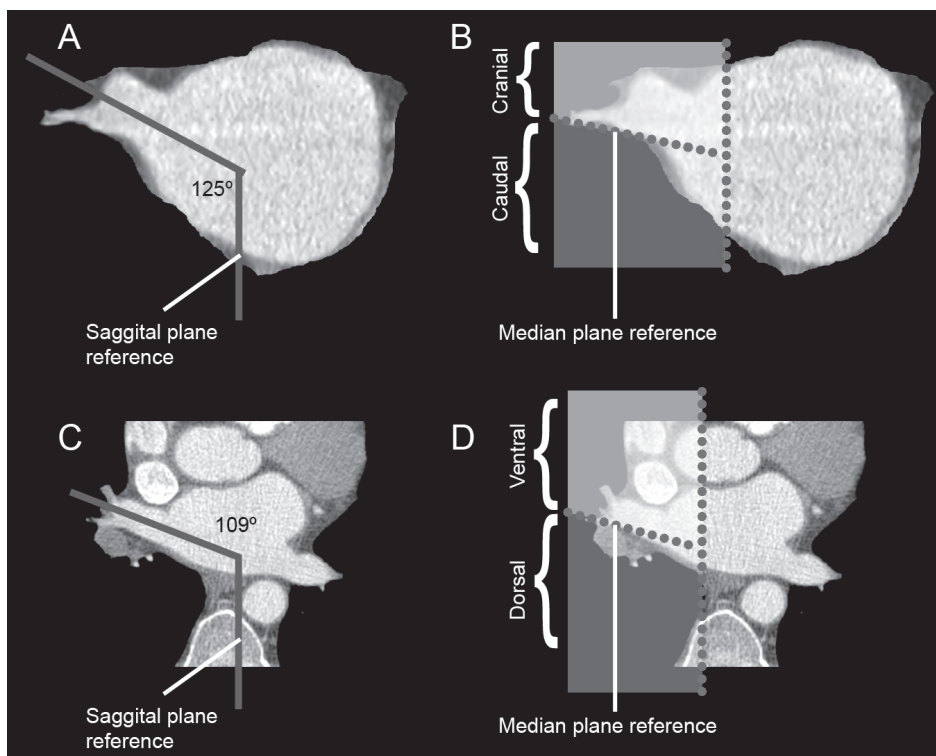


Figure 1. Example of right lower pulmonary vein orientation measurement in the coronal plane.

This figure displays the PV orientation measurement in the coronal and axial plane of the RUPV. As displayed in panel A, the angle between the PV and the sagittal plane reference is 125° in the coronal plane. The median RUPV direction is 116° in the coronal plane, as can be observed in table 2, categorizing the RLPV in this patient to the cranial RUPV orientation group, as is displayed in panel B. As displayed in panel C, the angle between the PV and the sagittal plane reference is 109° in the axial plane. The median RUPV direction is 102° in the axial plane, as can be observed in table 2, categorizing the RLPV in this patient to the ventral RUPV orientation group, as is displayed in panel D. PV: pulmonary vein; RUPV: right upper pulmonary vein.

energy were delivered using the available energy settings until isolation of each pulmonary vein was achieved. After ablations were performed at all veno-atrial junctions, the MER was used to remap all pulmonary vein ostia. If pulmonary veins appeared to be incompletely isolated, additional radiofrequency energy applications were delivered using the MER until full isolation was achieved. No adenosine testing was performed.

Post-ablation management

Patients were hospitalized for at least 24 h and monitored telemetrically. Oral anticoagulants were resumed immediately after the procedure, with a target INR of 2.5-3.5, in accordance with local guidelines. Low molecular weight heparin was administered in a patient-weight dependent dose until INR was adequate.

Follow-up

A blanking period of 3 months was defined after PVI. Patients had outpatient visits at 3, 6 and 12 months after PVI, including 24-72 hour Holter ECG. Follow-up after the 12 month outpatient clinic visit was performed by the referring physician. Patients were immediately referred to the emergency room in case of symptoms. If no arrhythmia could be detected, patients underwent Holter ECG monitoring to exclude arrhythmia recurrence. Furthermore, patients were contacted telephonically at the end of the study period when they were discharged from follow-up and were inquired about any arrhythmia symptoms and use of anti-arrhythmic drugs (AADs).

Study endpoints

The primary endpoint of our study was arrhythmia-free survival, defined as patients without AF/atrial flutter/atrial tachycardia recurrence after a blanking period of 3 months. Arrhythmia recurrence was defined as an ECG showing the characteristics of AF/atrial flutter/atrial tachycardia, or on a 30 second telemetry strip, in accordance with the European consensus statement on AF ablation.² Patients who were still using antiarrhythmic drugs at the end of the study period were considered arrhythmia recurrences, in accordance with the European consensus statement.²

Statistical analysis

Continuous data were expressed as mean \pm standard deviation in case of normal distribution or median \pm interquartile range when variables were not normally distributed. The association between arrhythmia-free survival and pulmonary vein orientation was assessed with a log-rank test. Uni- and multivariate Cox proportional hazard models were used to determine predictors of AF free survival. Since only pulmonary vein orientation was associated with AF recurrences post-ablation, and none of the other variables in the univariate analysis had a p-value <0.100 , age, BMI, AF duration and AF type were entered into the model, since these had been reported to influence arrhythmia-free survival in previous studies. The multivariate model demonstrated that left upper pulmonary vein (LUPV) and left lower pulmonary vein (LLPV) orientation in the coronal plane were independently associated with ablation outcome. Therefore, LUPV and LLPV orientation groups were combined, resulting in four groups: caudal LUPV and LLPV orientation; caudal LUPV and cranial LLPV orientation; cranial LUPV and LLPV orientation and cranial LUPV and caudal LLPV orientation. These 4 groups were compared with a log-rank test. Statistical analysis was performed using IBM SPSS statistics version 22.0 (IBM inc., Armonk, NY, USA). A p-value ≤ 0.05 was considered statistically significant.

RESULTS

The study population consisted of 120 consecutive patients. Table 1 describes the baseline characteristics. There were 5 left common PVs (1.1%), which were excluded from the analysis. There were no accessory pulmonary veins or right common pulmonary veins. No LA thrombi were found during pre-operative transesophageal echocardiography. Table 2 describes the characteristics of the pulmonary veins orientation in all patients. As an example, for the LLPV, the median angle in the coronal plane between the LLPV and the sagittal reference plane was 88°. This means that, by definition, in 50% (n=57) of patients, the angle between the left lower pulmonary veins and the sagittal plane was less than 88°, and in 50% (n=58) of patients, the angle between the left lower pulmonary veins and the sagittal plane was more than 88°.

Table 1. Baseline characteristics

	Total (n= 120)
Age (years)	56.2 (±10.0)
Gender men (%)	94 (78.3%)
BMI (kg/m²)	27.8 (±4.1)
LA size in PSLAX (mm)	42.4 (±4.4)
CHA₂DS₂VASc score	
0	46 (38.3%)
1	42 (35.0%)
2	22 (18.3%)
3	10 (8.3%)
4-7	0 (0%)
Co-morbidity (%)	
Hypertension	44 (36.7%)
Diabetes mellitus	6 (5.0%)
Previous TIA / Stroke	10 (8.3%)
Structural heart Disease	12 (10.0%)
Type AF: paroxysmal	98 (81.7%)
AF duration (years)	8.2 (±4.7)

Data are presented as absolute numbers or means ± their SD or absolute numbers with percentages where appropriate.; BMI: body mass index; LA: left atrium; PSLAX: parasternal long axis echocardiographic view; TIA: transient ischemic attack; AF: atrial fibrillation.

Procedural characteristics

In 474 out of 475 pulmonary veins (99.8%), acute pulmonary vein isolation after MER ablation was confirmed. Median follow-up was 19.6 months (interquartile range 5.4 to 35.5). 37 patients (30.8%) underwent 2 PVI attempts and 16 (13.3%) patients underwent 3 PVI

attempts. Overall arrhythmia-free survival was 54.2% after a mean of 1.58 PVI procedures without the use of class I or III AADs. Mean procedure time was 134 ± 39 minutes, mean ablation time was 33 ± 12 minutes. Only procedure time was significantly different among orientation groups in the left lower pulmonary vein orientation in the axial plane (ventral: 128 ± 33 minutes; dorsal: 143 ± 46 minutes, $P=0.040$)

Table 2. Distribution of pulmonary vein orientation

Pulmonary vein	Median in axial plane	Median in coronal plane
Left upper	92 (74 - 101)	124 (113 - 130)
Left lower	72 (61 - 78)	88 (83 - 94)
Right upper	102 (97 - 109)	116 (109 - 124)
Right lower	59 (53 - 68)	83 (74 - 88)

This table details the cut-off values used to designate PVs to the cranial/caudal orientation or ventral/dorsal orientation, respectively. As an example, for the left lower PV, the median angle in the coronal plane was 88° . This means that, by definition, in 50% ($n=57$) of patients, the angle between the left lower PV and the sagittal plane was less than 88° , and in 50% ($n=58$) of patients, the angle between the left lower PV and the sagittal plane was more than 88° . Data are presented as median, with their interquartile range between brackets.

Pulmonary vein orientation and arrhythmia-free survival

The orientation of the left upper pulmonary vein in the coronal plane was associated with arrhythmia-free survival, i.e. arrhythmia-free survival was 57.6% in patients with a cranial orientation and 20.9% in patients with a caudal orientation of the left upper pulmonary vein ($p = 0.003$). Left upper pulmonary vein orientation in the axial plane was not associated with arrhythmia-free survival. Figure 2, panel A depicts the association between left upper pulmonary vein orientation and arrhythmia-free survival. Orientation of the left lower pulmonary vein in the coronal plane was also associated with arrhythmia-free survival. Arrhythmia-free survival was 32.5% in patients with a cranial orientation as compared to 50.1% in patients with a caudal orientation of the left lower pulmonary vein ($p = 0.036$). Orientation of the left lower pulmonary vein in the axial plane was not associated with arrhythmia-free survival. Figure 2, panel B depicts the association between left lower pulmonary vein orientation and arrhythmia-free survival.

Right upper pulmonary vein orientation and right lower pulmonary vein orientation in both the coronal and the axial plane were not associated with arrhythmia-free survival.

Subsequently, left upper and left lower pulmonary vein orientation in the coronal plane were combined, resulting in four groups: caudal left upper and left lower pulmonary vein orientation; caudal left upper with cranial left lower pulmonary vein orientation; cranial left upper and left lower pulmonary vein orientation and caudal left upper with cranial left lower pulmonary vein orientation. The different configurations are depicted in figure 3. There was a significant difference in arrhythmia-free survival post-ablation between the four. Arrhythmia-

free survival 60 months after the initial ablation procedure was 31.8% in patients with a caudal orientation of both pulmonary veins, 12.0% in case of a caudal left upper with cranial left lower pulmonary vein orientation, 48.9% in case of cranial orientation of both pulmonary veins and 70.7% in case of a cranial left upper pulmonary vein orientation in combination with a caudal left lower pulmonary vein orientation ($p = 0.003$), as displayed in figure 4.

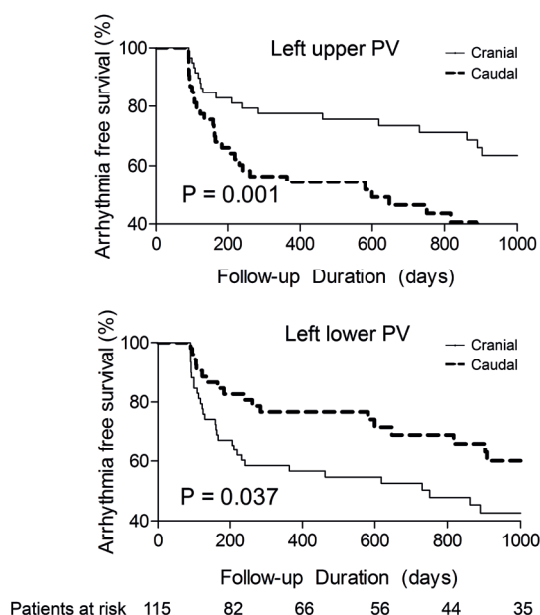


Figure 2. PV orientation and AF free survival in left upper and left lower PV orientation.

This figure displays the significant association between arrhythmia-free survival and left upper PV orientation in the coronal plane (top panel) and left lower PV orientation (bottom panel). PV: pulmonary vein.

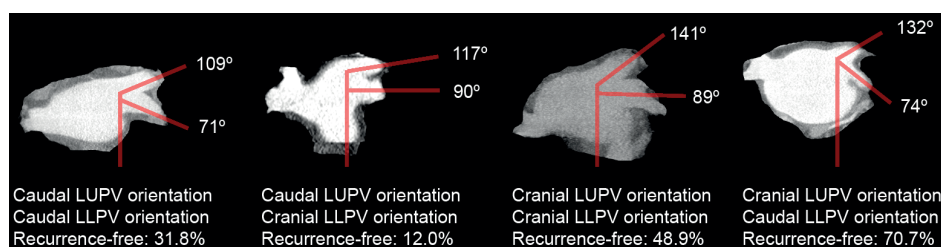


Figure 3. Orientation configurations of the left upper and left lower PV.

This figure displays the 4 configurations for the left PVs. Panel A displays the configuration with a caudal orientation for both PVs, corresponding to an arrhythmia-free survival of 31.8%. Panel B displays a caudal LUPV and a cranial LLPV configuration, corresponding to an arrhythmia-free survival of 12.0%. Panel C displays a cranial orientation for both PVs, corresponding to an arrhythmia-free survival of 48.9%. Panel D displays the a cranial LUPV orientation and a caudal LLPV orientation, corresponding to an arrhythmia-free survival of 70.7%.

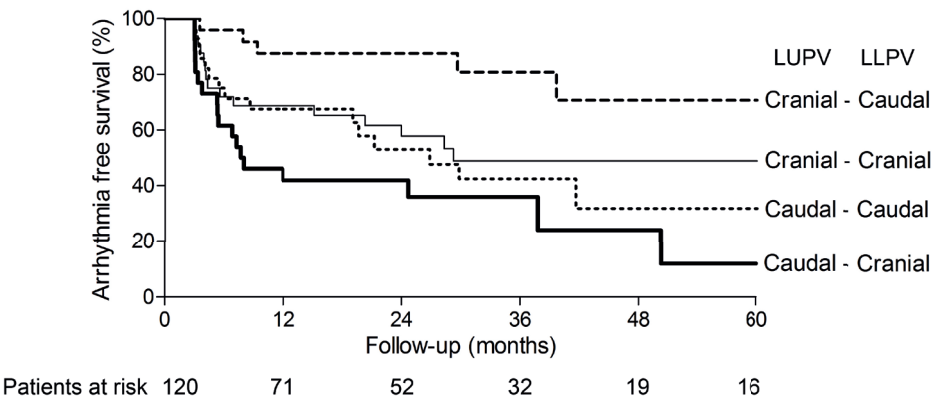


Figure 4. Arrhythmia-free survival for left upper and left lower PV orientation configurations. This figure depicts the significant association between left upper and left lower PV orientation and arrhythmia-free survival after MER ablation. LUPV: left upper PV orientation, LLPV: left lower PV orientation, PV: pulmonary vein; MER: multi-electrode radiofrequency ablation catheter.

Pulmonary vein orientation and AF type

In the 98 paroxysmal AF patients, the association between left upper pulmonary vein orientation in the coronal plane and ablation outcome was statistically significant (65% vs. 25%, log-rank, $p = 0.009$). The association between left lower pulmonary vein orientation in the coronal plane and ablation outcome did not reach statistical significance, even though a clear trend was visible (55% vs. 35%, $p = 0.105$).

In the 22 persistent AF patients, the association between left upper and left lower pulmonary vein orientation and ablation outcome did not reach statistical significance, although again, a trend was suggested (left upper pulmonary vein: 70% vs. 20%, $p = 0.102$; left lower pulmonary vein: 65% vs. 30%, $p = 0.187$). Since only 22 patients with persistent AF were included, this analysis may have been underpowered to detect a statistically significant difference.

Multivariable analysis

In a multivariable model which included age, body mass index, AF type and AF duration, only left upper and left lower pulmonary vein orientation in the coronal plane were independently associated with arrhythmia-free survival post-ablation (adjusted HR 2.8, $p = 0.001$ for left upper pulmonary vein orientation and adjusted HR 0.49, $p = 0.034$ for left lower pulmonary vein orientation), as displayed in table 3.

Table 3 Univariate and multivariate analysis

Univariate Analysis	p-value	Hazard Ratio	95% CI	Multivariate analysis	p-value	Hazard Ratio	95% CI
Female gender	0.846	0.955	0.598 – 1.523	Age (per year)	0.357	0.985	0.954 – 1.017
Age (per year)	0.226	1.012	0.993 – 1.032	BMI	0.705	0.984	0.908 – 1.068
BMI	0.871	1.004	0.955 – 1.056	Persistent AF	0.429	0.748	0.364 – 1.536
Persistent AF	0.455	1.220	0.724 – 2.058	AF duration (per year)	0.807	1.008	0.945 – 1.075
AF duration (per year)	0.833	1.004	0.967 – 1.042	LUPV Caudal orientation*	0.001	2.824	1.490 – 5.354
LA dimension	0.116	1.086	0.980 – 1.204	LLPV Caudal orientation*	0.034	0.490	0.253 – 0.948
CHA ₂ DS ₂ VASc score	0.569	1.056	0.875 – 1.275				
Hypertension	0.805	1.052	0.703– 1.575				
Diabetes Mellitus	0.365	1.428	0.661 – 3.087				
Structural heart disease	0.292	1.384	0.756 – 2.532				
LUPV Caudal orientation*	0.003	2.349	1.344 – 4.107				
LUPV Dorsal orientation**	0.738	0.912	0.531 – 1.566				
LLPV Caudal orientation*	0.040	0.558	0.320– 0.973				
LLPV Dorsal orientation**	0.750	0.916	0.533 – 1.574				
RUPV Caudal orientation*	0.389	0.791	0.464 – 1.349				
RUPV Dorsal orientation**	0.168	0.682	0.396 – 1.175				
RLPV Caudal orientation*	0.660	1.126	0.663 – 1.913				
RLPV Dorsal orientation**	0.146	0.667	0.387 – 1.151				

Univariate and multivariate analysis of the association between patient and PV characteristics and AF free survival after EAS PVI. *: as compared to cranial orientation. **: as compared to ventral orientation BMI: body mass index; AF: atrial fibrillation; AAD: anti-arrhythmic drugs; LA: left atrium; PSLAX: parasternal long axis view; LVEF: left ventricular ejection fraction. P-values: comparison between AF free and AF recurrence groups. LUPV: left upper pulmonary vein; LLPV: left lower pulmonary vein; RUPV: right upper pulmonary vein; RLPV: right lower pulmonary vein.

DISCUSSION

This study reports that in MER ablation, pulmonary vein orientation has a significant impact on ablation outcome. In the present study, orientations of the left upper and left lower pulmonary veins in the coronal plane were independently associated with arrhythmia recurrences 60 months after the initial ablation procedure. These findings suggest that pulmonary vein orientation may be a useful parameter to selecting the most suitable patients for MER ablation.

Pulmonary vein anatomy and arrhythmia-free survival

In a previous report on the association between accessory pulmonary veins, pulmonary veins with a common ostium, pulmonary vein diameter and arrhythmia-free survival after MER ablation, no significant association could be found.¹⁶ Several studies have reported the impact of pulmonary vein geometrical characteristics such as pulmonary vein diameter,¹⁷ atypical anatomy,^{18,19} ostium shape^{17,20} and branching level^{17,21} and arrhythmia-free survival post-ablation in multiple PVI techniques. Our group recently reported on the significant association between pulmonary vein orientation and arrhythmia-free survival after endoscopic laser balloon PVI,¹¹ demonstrating an association between left lower, left upper, and right lower pulmonary vein orientation and arrhythmia-free survival after PVI. Conversely, pulmonary vein orientation did not impact arrhythmia-free survival after contact force sensing point-by-point catheter ablation.¹²

Catheter design

The MER catheter contains 10 platinum electrodes in an over-the-wire design that only requires 1 transseptal puncture because the catheter system allows for both ablation as well as pulmonary vein mapping.⁸ Previous reports already showed a high rate of acute PVI success, with favorable procedure times and an arrhythmia-free survival rates compared to other PVI techniques.^{4,22-24} The catheter is guided to the pulmonary vein by fluoroscopy, where several ablations are performed with the catheter system being rotated in between ablations. Despite achieving acute isolation in 99.8% of pulmonary veins, the overall arrhythmia-free survival after ablation in this patient population was 54.2% after a median follow-up of 19.6 months. Arrhythmia recurrences, especially in patients with paroxysmal AF, are generally considered a sign of local electrical reconnection between the pulmonary vein and left atrium.²⁵⁻²⁷ Creating durable pulmonary vein lesions is therefore important to achieve long-term arrhythmia-free survival. Pulmonary vein orientation may affect the creation of durable lesions by influencing positioning of the MER in the pulmonary vein. In other words, MER catheter positioning may be suboptimal depending on pulmonary vein orientation. Potentially, a caudal orientation of the left lower pulmonary vein may allow a more direct pathway compared to a cranial orientation, with the catheter system approaching from the

right atrium, through the interatrial septum and positioned in the left lower pulmonary vein. Hypothetically, a more direct pathway allows for improved positioning and tissue contact of the MER catheter in the pulmonary vein and thereby influences the quality of the ablation lesion set. The observation that different pulmonary vein orientation subsets are associated with favorable arrhythmia-free survival between different PVI techniques seems to support this hypothesis.

Pulmonary vein anatomy and AF substrate

Several previous studies reported the influence of AF on left atrial and pulmonary vein anatomy. Kato et al. showed that AF was associated with an increased pulmonary vein length compared to control patients. Moreover, left atrial geometrical characteristics, such as left atrial size²⁸⁻³¹ and left atrial fibrosis³²⁻³⁴ are altered in patients with AF. An increased left atrial size is usually associated with an increased AF substrate. Although we did not find an association in the present study (data not shown), pulmonary vein orientation can potentially be influenced by left atrial size, and this may explain the association between pulmonary vein orientation and AF-free survival. Multivariable analysis of our data showed that left pulmonary vein orientation was independently associated with arrhythmia-free outcome, whereas left atrial size was not.

Limitations

With regards to interpreting our data, the following limitations should be considered. This is a single center study with a limited number of patients and was not designed to differentiate whether the influence of pulmonary vein orientation on arrhythmia-free survival is due to factors related to the PVI technique or differences in AF substrate.

CONCLUSION

In this study, orientation of the left upper and left lower pulmonary veins in the coronal plane were independently associated with arrhythmia-free survival in patients undergoing PVI using a MER catheter. Whether this is related to the ablation technique or other factors remains to be delineated. Potentially, pulmonary vein orientation assessment may be useful to predict arrhythmia-free survival after PVI depending on the technique used, and operators may tailor the type of ablation therapy by selecting the PVI technique most suitable for each patient's pulmonary vein anatomy and orientation.

CONFLICT OF INTEREST

None.

FUNDING SOURCES

None.

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3 | Effective contact and outcome after pulmonary vein isolation in novel circular multi-electrode atrial fibrillation ablation

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Netherlands Heart Journal 2017 Jan; 25(1): 16–23.

ABSTRACT

Introduction: Pulmonary vein (PV) reconnection is frequently the cause of recurrence of atrial fibrillation (AF) after ablation. The second-generation gold multi-electrode ablation (Gold-MEA) catheter has a new design possibly resulting in improved lesion formation compared with its predecessor. We aimed to determine the association between effective radiofrequency applications with the Gold-MEA catheter and outcome after AF ablation.

Methods: 50 consecutive patients with paroxysmal AF underwent Gold-MEA (PVAC GOLD™, Medtronic Inc.) ablation. The Gold-MEA catheter was navigated to the PV ostium by fluoroscopy. Duty-cycled radiofrequency ablations were performed at all PV ostia. Lesions were considered transmural when electrode temperature was $>50^{\circ}\text{C}$ and power $>3\text{ W}$ for >30 seconds. After the ablation procedure, patients visited the outpatient clinic at 3-month intervals including 24-hour Holter ECGs.

Results: Mean age was 56 years. All PVs were acutely isolated with the Gold-MEA catheter. Procedure time was 111 ± 22 minutes, ablation time was 24 ± 6.7 minutes and fluoroscopy time was 20 ± 8.1 minutes. No procedure-related complications were observed. One year after ablation, 60 % of patients were still free of arrhythmia recurrences after a single PV isolation attempt. The number of transmural lesions was associated with arrhythmia-free survival: 25.0 % in <72 transmural lesions, 64.3 % in 72–108 transmural lesions and 71.4 % in >108 transmural lesions ($p = 0.029$).

Conclusion: PV isolation can be performed successfully with the Gold-MEA catheter, with a favourable safety profile. Transmurality of lesions was associated with ablation success and may improve AF ablation success.

Keywords: Atrial fibrillation, Ablation, Multi-electrode ablation, Effective energy, PVAC Gold

INTRODUCTION

Pulmonary vein isolation (PVI) has become an important treatment modality for symptomatic atrial fibrillation (AF).^{1,2} The dominant triggers for paroxysmal AF come from the pulmonary veins (PVs). During PVI, a circumferential lesion set is created at the base of the PVs so that these PVs are electrically isolated from the left atrium.^{1,2} Several techniques are used to perform the ablation, including point-by-point radiofrequency (RF) catheter ablation^{3,4}, cryoballoon ablation⁵, laser balloon ablation⁵⁻⁸ and multi-electrode ablation (MEA).^{3,9,10} The last-mentioned is no longer in use due to its association with asymptomatic cerebral embolism,¹¹⁻¹⁴ but the newly designed gold multi-electrode ablation (Gold-MEA) catheter, building on its predecessor, combines several characteristics that may improve lesion formation and reduce complications. Although PVI has proven to be an effective treatment for AF, some patients develop recurrences.^{3,15} Electrical reconnection of the PVs is considered the most important mechanism for AF recurrence.² In contrast to other ablation techniques, there is no surrogate marker for transmuralty of lesions for the Gold-MEA catheter. We aimed to report the ablation characteristics of 50 patients, determine transmuralty of lesions with the Gold-MEA catheter and describe its association with ablation outcome.

METHODS

Patient population

Fifty consecutive patients with symptomatic paroxysmal AF who were accepted for primo PVI in our centre were included in this study. Data were collected in a prospective hospital database. All patients consented to their data being registered and used for publication, as did the Board of Hospital Administrators.

Preablation protocol

All patients underwent a CT scan, to assess left atrial and pulmonary vein (PV) anatomy. Patients with common PV ostia, both left and right, were excluded from this analysis, as well as patients with accessory PVs. Patients were admitted 24 hours before the ablation procedure. During hospitalization, the cardiac rhythm was continuously monitored in all patients. Transthoracic echocardiography was performed routinely 1 day before ablation to determine right and left ventricular function, valvular abnormalities, and left and right atrial dimensions. Transesophageal echocardiography was performed directly pre-ablation to assess the interatrial septum and to rule out intracardiac thrombus and/or severe aortic plaques. Routine blood tests were performed, including electrolytes and cardiac enzymes. Patients who used oral anticoagulants were 'bridged' using low-molecular-weight heparins up to 3 days prior to the ablation procedure, in accordance with local guidelines.

Ablation protocol

All ablation procedures were performed under general anaesthesia supervised by a cardiovascular anaesthesiologist. After placement of a 6F quadripolar catheter in the coronary sinus via a transfemoral approach, a single transseptal puncture was performed using a Brockenbrough needle under fluoroscopic and pressure guidance. Immediately after the transseptal puncture, 10,000 IU of unfractionated heparin was administered. An 8.5F sheath (SL-1, St. Jude Medical, Minnetonka, MN, USA) was used for PV angiography. All sheaths were continuously flushed with saline containing 2500 IU heparin per 500 ml saline. An activated clotting time between 300 and 350 seconds was targeted. Additional heparin was administered when needed. The activated clotting time was checked during the procedure at regular intervals of 30 minutes.

Multi-electrode catheter ablation

The multi-electrode pulmonary vein RF ablation catheter (PVAC Gold™, Medtronic, Minneapolis, MN, USA) is a mapping and ablation catheter with a 25 mm diameter circular electrode array. This catheter has a bidirectional steering mechanism and an over-the-wire design. Compared with its predecessor, the novel Gold-MEA catheter consists of 9 gold electrodes positioned with 3.75 mm inter-electrode spacing at a 20° forward tilt for optimal electrode-tissue energy transfer, as displayed in Figure 1. The GENius generator (Medtronic, Minneapolis, MN, USA) delivers duty-cycled bipolar and unipolar phased RF energy to all or selected electrode pairs. RF is delivered in a temperature-controlled and power-limited fashion (60 °C, maximum 10 W) with a typical ablation duration of 60 seconds.

The Gold-MEA catheter was introduced into the left atrium via a 10F SL-1 sheath. Using a 0.032 inch guidewire placed in the PV, the catheter was positioned at the antrum of each PV to record local electrical activity at the veno-atrial junction prior to RF energy application, creating PV templates. RF energy was applied using the RF generator (Medtronic GENius, Minneapolis, MN, USA) with a target temperature setting of 60 °C, RF energy setting of 2:1 ratio between bipolar and unipolar energy, and 60-second RF application duration. After each application, PV triggers were assessed. Multiple applications of RF were delivered using the available energy settings until isolation of each PV was achieved. Furthermore, after phased RF ablations were performed at all veno-atrial junctions, the Gold-MEA catheter was used to remap all PV ostia. If the PVs appeared to be incompletely isolated, additional RF applications were delivered using the Gold-MEA until the PV isolation was achieved. No adenosine testing was performed.

To aid in delivering adequate lesions, the RF generator displays temperature and RF power in a green bar when the temperature is >50 °C and RF power >3 W. If either the temperature is <50 °C or the RF power is <3 W, the colour of the bar changes to yellow. This is based on previous research in animal studies which demonstrated that the positive predictive value of an ablation with a temperature >50 °C and RF power >3 W for >30 seconds to predict

a transmural lesion was 99 %.¹⁶ In the current study, electrodes with a temperature <50 °C or RF power <3 W were switched off during phased RF energy application.

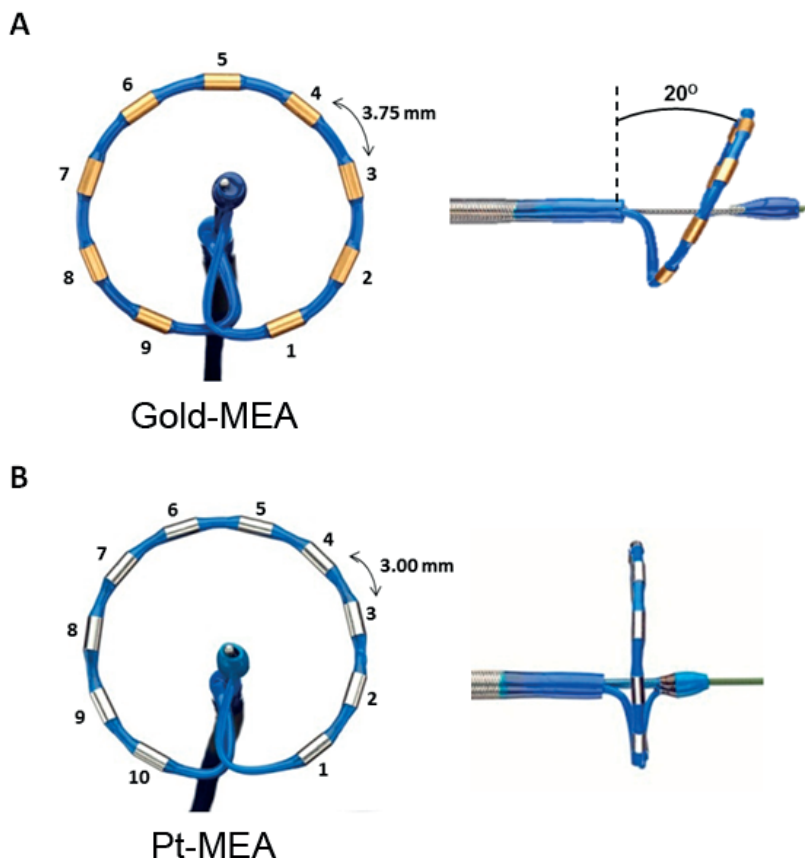


Figure 1. PVAC Gold Design

Panel A displays the newly designed Gold-MEA catheter; Panel B displays the Pt-MEA catheter. Several key improvements have been implemented: the ablation electrodes are made of Gold (Au) instead of Platinum (Pt); the new catheter consists of 9 electrodes, to prevent overlap of the 1st and 10th ablation electrode; the interelectrode spacing is increased to 3.75 mm to retain the effective arc length and finally the electrodes are at a 20° forward tilt. MEA: multi-electrode ablation.

Post-ablation management

Patients were hospitalized for at least 24 hours and monitored telemetrically. Oral anti-coagulants were resumed immediately after the procedure, with a target INR of 2.5–3.5, in accordance with local guidelines. Low-molecular-weight heparin was administered in a patient-weight dependent dose until the INR was adequate. Complications were defined according to the HRS/EHRA/ECAS expert consensus statement on AF ablation.² Cerebral imaging was not performed routinely to assess asymptomatic cerebral embolism.

Follow-up

A blanking period of 3 months was defined after PVI. Patients visited the outpatient clinic at 3, 6 and 12 months after PVI; this included a 24-hour Holter ECG. All patients were >12 months after their first AF ablation attempt. Patients were immediately referred to the emergency room in case of symptoms. If no arrhythmias could be detected, patients underwent Holter ECG monitoring to exclude arrhythmia recurrence. An attempt was made to discontinue antiarrhythmic drugs in all patients 3 months after the ablation.

Study endpoints

The primary endpoint of our study was arrhythmia-free survival, defined as patients without AF/atrial flutter/atrial tachycardia recurrence after a blanking period of 3 months. Arrhythmia recurrence was defined as an ECG showing the characteristics of AF/atrial flutter/atrial tachycardia, or on a 30-second telemetry strip, in accordance with the HRS/EHRA/ECAS expert consensus statement on AF ablation.² Patients who were still using antiarrhythmic drugs 3 months after the ablation were considered arrhythmia recurrences, in accordance with the HRS/EHRA/ECAS expert consensus statement.²

Statistical analyses

Data are mentioned as means \pm standard deviation, interquartile range or percentage where appropriate. Statistical significance between variables was calculated by the Student's t-test (unpaired) for continuous variables and Chi-square test for categorical variables. Effective electrode-tissue contact creating a transmural lesion was defined as any ablation with a temperature $>50^{\circ}\text{C}$ and RF power $>3\text{ W}$ for over 30 seconds.¹⁶ Patients were categorized into <72 transmural lesions, 72–108 transmural lesions and >108 transmural lesions. Kaplan-Meier analysis with a log-rank test was used to compare transmural lesion groups. To assess the learning curve, the first 25 patients were categorized to the first cohort and the following 25 patients to the second cohort. The follow-up duration between cohorts was compared with a Mann-Whitney U test. A p -value of ≤ 0.05 was regarded significant. Statistical analysis was performed using IBM Statistics version 22.0 (IBM SPSS Statistics for Windows, 2011: Armonk, New York, USA).

RESULTS

Fifty consecutive patients with paroxysmal AF were included, mean age was 57.1 ± 11.7 years. No left atrial thrombi were found during the preoperative transesophageal echocardiogram. Of note, no patients had common left or right PV ostia and no patients had accessory PVs on the pre-ablation CT scan. Baseline characteristics are displayed in Table 1.

Table 1. Baseline characteristics.

Patient Characteristic	Total (n=50)
Gender female (%)	15 (30%)
Age (years)	57.1 (\pm 11.7)
BMI (kg/m ²)	28.3 (\pm 4.2)
Paroxysmal AF	50 (100%)
AF duration (years)	5.1 (\pm 7.4)
CHADS ₂ VA ₂ Sc (range)	1.3 (0-5)
Congestive heart failure	5 (10%)
LA ventral-dorsal dimension (mm)	41.1 (\pm 3.9)
LVEF (%)	58.8 (\pm 3.2)
History of hypertension	16 (32%)
History of diabetes mellitus	2 (4%)
History of TIA/CVA	7 (14%)

Data are presented as percentages or means \pm their SD or ranges where appropriate; BMI: body mass index; AF: atrial fibrillation; AADs: anti-arrhythmic drugs; LA: left atrium; LVEF: left ventricular ejection fraction; TIA: transient ischemic attack; CVA: cerebrovascular accident.

Procedural characteristics

In all 200 PVs, acute PVI was achieved. The mean procedure duration was 111 ± 22 minutes, with a range of 60 to 150 minutes. The mean ablation time was 23.5 ± 6.7 minutes, with a range of 12 to 42 minutes. The mean fluoroscopy time was 20.1 ± 8.1 minutes, with a range of 9 to 45 minutes. None of the patients developed complications related to the procedure and, in particular, no patients developed symptomatic thromboembolic events.

Ablation outcome

All patients were >1 year after their initial ablation procedure when the present analysis was conducted. One year after ablation, 20 (40 %) patients developed an arrhythmia recurrence, whereas 30 (60 %) remained free of arrhythmia recurrences and off antiarrhythmic drugs after a single PVI attempt. The arrhythmia-free survival is displayed in figure 2.

Transmural lesions

Transmural lesions, defined as any ablation with a temperature >50 °C and RF power >3 W for over 30 seconds,¹⁶ was achieved in 44.6 % (range 23–62 %) of the total number of lesions delivered. Patients were categorized into: <72 transmural lesions (8 patients); 72–108 transmural lesions (28 patients) and >108 transmural lesions (14 patients). Arrhythmia-free survival after one year was significantly associated with the number of transmural lesions, 25 % in patients with <72 transmural lesions, 64.3 % in patients with 72–108 transmural lesions and 71.4 % in patients with >108 transmural lesions ($p = 0.029$), as displayed in figure 2. Of note, none of the patient characteristics were associated with the number of transmural lesions.

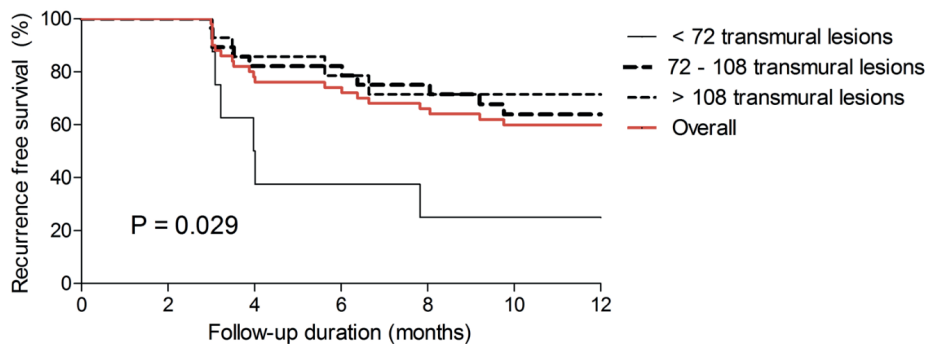


Figure 2. Arrhythmia recurrence free survival after ablation with the Gold-MEA catheter. This figure displays the AF free survival after ablation with the Gold-MEA catheter. The overall recurrence free survival is displayed in red. P-value between transmural lesion groups. MEA: Multi-electrode ablation.

Learning curve

The first 25 patients were compared with the following 25 patients in terms of procedural characteristics. As mentioned, acute PVI was achieved in all PVs. Between the cohorts, procedure time (106 ± 25 vs. 116 ± 18 minutes, $p = 0.11$), ablation time (24 ± 7.4 vs. 23 ± 6.0 minutes, $p = 0.94$) and fluoroscopy time (20 ± 9.5 vs. 20 ± 6.4 minutes, $p = 0.87$) were comparable. The number of transmural lesions was comparable in the latter cohort (91 vs. 101, $p = 0.32$). The differences in procedural characteristics are displayed in table 2 and figure 3. In terms of ablation outcome, there was no difference between the two cohorts: of the first 25 patients, 14 (46.7 %) were still arrhythmia-free whereas 16 (53.3 %) patients from the second group of 25 patients were still arrhythmia-free ($p = 0.55$). Furthermore, there were no significant differences between operators in number of applied transmural lesions ($p = 0.47$) as well as arrhythmia recurrences ($p = 0.15$).

Table 2 Procedural characteristics of the first versus second half of the study cohort

	First cohort (n=25)	Second cohort (n=25)	P
Acute isolation (n)	100/100 (100%)	100/100 (100%)	>0.99
Procedure time (min)	106 \pm 25	116 \pm 18	0.11
Ablation Time (min)	24 \pm 7.4	23 \pm 6.0	0.94
Fluoroscopy Time (min)	20 \pm 9.5	20 \pm 6.4	0.87
Complications (n)	0 (0%)	0 (0%)	>0.99
Transmural lesions (n)	91 \pm 28	101 \pm 24	0.32

Data are presented as percentage or means \pm their SD where appropriate.

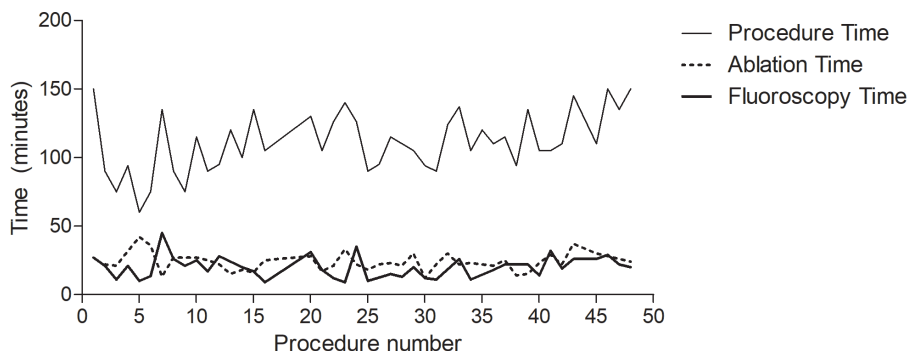


Figure 3. Procedure, Ablation and Fluoroscopy time.

This figure displays the procedure time, ablation time and fluoroscopy time. Note that there appears to be no difference in any of these variables between the first and the second cohort, thus there appears to be no learning curve with the Gold-MEA catheter for operators who are experienced with the Pt-MEA catheter. MEA: Multi-electrode ablation.

DISCUSSION

The present study reports on the association between transmuralities of lesions and AF ablation outcome in Gold-MEA catheter ablation. In conclusion, ablation outcome is poor in case of <72 transmural lesions, but is comparable with other ablation techniques for >108 transmural lesions. Gold-MEA catheter ablation is characterized by a relatively short procedure time, and safety outcome seems to be favorable, although this was a small study.

Catheter design

The newly designed Gold-MEA catheter builds on its predecessor, but several key improvements have been implemented. First, the new catheter consists of 9 electrodes, to prevent overlap of the 1st and 10th ablation electrode. Second, the ablation electrodes are made of gold instead of platinum. In an animal study with the new Gold-MEA catheter, gold electrodes produced more consistent power delivery than platinum¹⁷ without an increase in micro emboli production, potentially due to better passive convective cooling of the electrodes¹⁸. Last, the catheter system now boasts a 20 forward tilt to improve catheter-wall contact, which improves contact by 56 % according to unpublished data by Medtronic.¹⁹

Procedure duration

In the present study, we observed that the new Gold-MEA catheter achieved acute PVI in all PVs, with a relatively short procedure time which will result in a more cost-effective approach, since more procedures can be performed in the same amount of time compared with, for example, conventional RF catheter ablation^{3,20} or laser balloon ablation,^{6,21} which are characterized by procedures lasting 2.5–3.5 hours.²²

Complications

We did not observe any complications with the new Gold-MEA catheter, although this study consists of a limited patient population size. In a previous study performed in our centre, complications after ablation with the Platinum-MEA catheter were only 1.8 %, ³ significantly less than conventional point by point RF catheter ablation. However, as mentioned previously, the Platinum-MEA catheter is no longer in use due to its association with asymptomatic cerebral embolisms. Thromboembolisms were related to overlap between the 1st and 10th electrode in the Platinum-MEA catheter system.²³ This resulted in local overheating of blood and PV tissue, resulting in thromboembolisms.¹⁴ The new Gold-MEA catheter has been re-designed to prevent this local overheating, thereby reducing thromboembolic complications. Furthermore, the Precision Gold Trial²⁴ will allow assessment of the incidence of asymptomatic cerebral emboli in patients treated with the Gold-MEA catheter. The present study was not aimed at assessing the association between Gold-MEA catheter ablation and asymptomatic cerebral emboli.

Ablation success

The present study shows that the overall ablation success after a limited follow-up period seemed to be lower compared with other techniques.^{3,6,20,21} However, our reported success rate is comparable with the first-generation MEA catheter.^{25,26} Moreover, ablation outcome was clearly associated with the number of transmural lesions. To date, no techniques are available to assess actual lesion depth, and therefore true transmural lesions cannot be determined. Other AF ablation techniques use surrogates to ascertain if a lesion is transmural. Contact force sensing for conventional RF ablation with a mapping catheter was recently introduced, allowing operators to assess the contact force and force vector.^{27,28} Lesions with a force-time integral >400 gs were significantly associated with more durable PVI lesions and improved ablation outcome.^{5,29} The cryoballoon allows assessment of freezing and thawing temperature, which is indicative of the tissue temperature and thus lesion delivery.^{30,31} Laser balloon ablation allows operators to visually perform lesions that overlap, to ensure transmural lesions and circumferentiality. Based on experimental data, effective contact is considered a useful marker of transmural lesions for the Gold-MEA catheter. A previous animal study already demonstrated a high positive predictive value of 99 % for effective contact in achieving histologically confirmed acute and chronic transmural lesions.¹⁶ In the present study, we found an association between the number of transmural lesions based on effective contact and ablation outcome. Less than 72 transmural ablations were associated with a significantly poor ablation outcome. Implementation of effective contact into the Gold-MEA catheter ablation may improve ablation outcome. However, this study was not designed to determine the optimal number of transmural lesions to achieve durable PV isolation.

The operators who performed Gold-MEA were experienced with the Platinum-MEA catheter system. No differences between operators were found regarding the number of transmural lesions and arrhythmia recurrences.

However, although lesion quality displayed a significant association with ablation outcome, this was predominantly caused by patients with <72 transmural lesions. The 42 patients with >72 ablation lesions displayed a comparable ablation outcome, even though there was still a substantial variation in the number of transmural lesions and proportion of patients suffering from arrhythmia recurrences. These observations suggest that there are other factors at play that have an impact on ablation success, on top of lesion transmurality. Although the present study was not designed to investigate other factors that impact Gold-MEA ablation results, geometrical variation between patients may be one of these factors. Previous research by our group demonstrated that PV orientation was associated with ablation outcome after multi-electrode ablation³² and laser balloon ablation,³³ but not after contact force sensing catheter ablation.³⁴ Future research is necessary to determine if PV orientation may also impact ablation outcome after Gold-MEA ablation.

Limitations

The present study consists of a limited patient sample size, and therefore claims on safety and PVI success may be overestimated. Future research is warranted including more patients with a more extended follow-up period. Single procedure ablation success is reported, whereas most previous studies reported success after multiple PVI attempts. No adenosine testing was performed to assess for dormant conduction of PVs, which could potentially result in a higher success rate.

CONCLUSION

AF ablation can be performed successfully with the Gold-MEA catheter, with a favorable safety profile. A higher number of effective lesions, as a surrogate marker for transmurality of lesions, was associated with freedom of AF during follow-up.

ACKNOWLEDGEMENTS

We acknowledge Evelien Kolkman for statistical support.

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4

Arrhythmia-free survival and pulmonary vein reconnection patterns after second-generation cryoballoon and contact-force radiofrequency pulmonary vein isolation

Cryoballoon versus contact-force radiofrequency pulmonary vein isolation

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Clinical Research in Cardiology. 2018 Jun;107(6):498-506.

ABSTRACT

Introduction: The aim of this study was to compare second-generation cryoballoon and contact force radiofrequency point-by-point pulmonary vein isolation (PVI) in atrial fibrillation (AF) patients with regard to pulmonary vein reconnection and arrhythmia-free survival.

Methods and results: 269 consecutive patients with drug-refractory AF undergoing PVI were included and randomly allocated to second-generation cryoballoon or contact-force point-by-point radiofrequency ablation. Median follow-up duration was 389 days (interquartile range 219 to 599). Mean age was 59 years (71% male). 136 patients underwent cryoballoon and 133 patients underwent radiofrequency ablation. Acute electrical PVI was 100% for both techniques. Procedure duration was significantly shorter in cryoballoon versus radiofrequency (166.5 vs 184.13 min $P=0.016$). Complication rates were similar (6.0% vs 6.7%, $P=1.00$). Single procedure freedom of atrial arrhythmias was significantly higher in cryoballoon compared to radiofrequency (75.2% vs 57.4%, $P=0.013$). In multivariate analysis persistent AF, AF duration, and cryoballoon ablation were associated with freedom of atrial tachyarrhythmias. Number of repeat ablation procedures was significantly lower in the cryoballoon compared to radiofrequency (15.0% vs 24.3%, $P=0.045$). At repeat ablation pulmonary vein reconnection rate was significantly lower after cryoballoon compared to radiofrequency ablation (36.8% vs 58.1%, $P=0.003$).

Conclusions: Improved arrhythmia-free survival and more durable pulmonary vein isolation is seen after PVI using second-generation cryoballoon compared to contact-force radiofrequency, in patients with drug-refractory paroxysmal AF. Complication rates for both ablation techniques are low.

Keywords: atrial fibrillation; pulmonary vein isolation; cryoballoon; radiofrequency; pulmonary vein reconnection.

INTRODUCTION

Pulmonary vein isolation (PVI) has become the cornerstone of catheter-based treatment for paroxysmal and early persistent atrial fibrillation.^{1,2} Since the introduction of PVI several ablation technologies have been developed including point-by-point radiofrequency (RF) ablation, multi-electrode radiofrequency ablation, and cryoballoon ablation.^{1,3,4} In conventional RF PVI, the RF energy is delivered to the tissue in a point-by-point force-controlled manner resulting in cellular necrosis by heating.² In cryoballoon (CB) ablation, PVI is achieved by freezing tissue in a 'single shot' manner resulting in circumferential cell necrosis.³ RF PVI guided by 3D electro-anatomic mapping techniques is an effective treatment modality and requires only limited use of fluoroscopy. However, the technique is also considered technically challenging, especially for less experienced operators.^{2,5} CB PVI can be performed without 3D navigation systems and seems to be more accessible, however is associated with a higher risk of phrenic nerve injury.^{3,6} In a recent randomized trial, CB and RF ablation were shown to be equally effective for the treatment of paroxysmal atrial fibrillation. Furthermore, there were no significant differences in overall safety.⁶ Importantly, different generation cryoballoons and RF-ablation catheters with and without contact force were used in that study. Although a post-hoc analysis was performed for newer generation catheters, only a small proportion constituted of contact force RF ablation, and the study was not powered to detect differences. We therefore aimed to report single center ablation success, incidence of repeat ablation, extent and rate of pulmonary vein (PV) reconnection, and safety outcomes after second-generation CB and contact-force guided RF ablation for drug-refractory paroxysmal atrial fibrillation.

METHODS

Patient population

Patients who were suitable for primo PVI for drug-refractory paroxysmal or early persistent atrial fibrillation were randomly allocated to cryoballoon or contact-force radiofrequency catheter ablation and included in the Isala Heart Centre AF database. Procedures in which additional ablation strategies (e.g. complex fractionated atrial electrograms[CFAE], linear ablations, right atrium ablations) were applied, were excluded from the present study.

Pre-ablation protocol

All patients underwent cardiac computed tomography (CT) to assess left atrial and pulmonary vein (PV) anatomy. Transthoracic echocardiography was routinely performed to assess left ventricular function, valve abnormalities, and atrial dimensions. Patients were admitted one day before the ablation procedure. During hospitalization, cardiac rhythm was continu-

ously monitored in all patients. On admission and after ablation routine blood samples were taken for screening purposes. Pre-ablation transoesophageal cardiac echocardiography was performed to assess the interatrial septum and rule out left atrial thrombus.

Ablation protocol

PVI ablation procedures were performed under conscious sedation or under general anaesthesia supervised by a cardiovascular anesthesiologist, in accordance with HRS/EHRA/ECAS expert consensus on AF ablation. The ablation catheter was introduced in the left atrium via a transseptal puncture under pressure and fluoroscopic guidance, using a Brockenbrough needle. During the procedure anticoagulation was checked at intervals of 30 minutes, with a targeted activated clotting time between 300-350 seconds.

Catheter ablation technique

Cryoablation

Cryoballoon ablations were performed using the second-generation Artic Front cryoballoon catheter (Medtronic, Inc., Minneapolis, Minnesota, USA). This catheter has a bidirectional steering mechanism and an over the wire design. The 28-mm diameter balloon was used to create “single shot” circular antral lesions at all four PV ostia (left superior PV [LSPV], left inferior PV [LIPV], right superior PV [RSPV], right inferior PV [RIPV]) in order to create electrical PV isolation. Balloon selection was based on the PV size assessed by pre-ablation cardiac CT. Catheter placement and PV occlusion was checked by fluoroscopy. Cryo-energy applications were performed up to 240 seconds, with additional number of Cryo applications at operator discretion. After all ablations were performed electrical PV isolation of PVs was checked with a standard circular mapping catheter. Adenosine testing was not performed. Ablation of the RSPV and RIPV was performed under continuous phrenic nerve stimulation with palpation of diaphragmatic excursions and direct fluoroscopic visualization of the diaphragm in case of any diminished activity. Cryoablation was immediately terminated on any signs of phrenic nerve palsy.

Radiofrequency ablation

A steerable circular multipolar catheter (Lasso™, Biosense Webster Inc., Diamond Bar, CA, USA) and an irrigated RF contact-force ablation catheter with a 3.5-mm tip (Smarttouch Thermocool™, Biosense Webster Inc., Diamond Bar, CA, USA) were introduced in the left atrium through 2 transseptal sheaths. Electro-anatomical mapping of the left atrium and PV signal recordings were then performed, using 3D navigation system (Carto3™, Biosense Webster Inc., Diamond Bar, CA, USA). RF energy was applied in a point-by-point manner to create continuous circular lesions in order to achieve electrical PV isolation. Power setting was adjusted between 30W and 40W with a continuous 0.9% NaCl flow rate of 2ml/min

and 20-30ml/min during RF energy application. RF energy was applied with a targeted force-time integral (FTI) of >400gs with an RF application duration of 20 to 40 seconds, targeting an impedance drop of at least 10 Ohm, or until elimination of the local electrogram. The endpoint of the ablation procedure was defined as the absence or dissociation of PV potentials within the PVs ≥ 30 minutes post-ablation.

Post ablation protocol

Patients were hospitalized for at least 24 h with continuous telemetry monitoring. Anti-coagulation was continued after the procedure with a target international normalization ratio (INR) of 2.0 to 3.0 for at least 3 months after ablation. In patients using non vitamin K antagonist oral anticoagulation (NOAC), this was resumed after the ablation procedure. After 3 months anticoagulation therapy was (dis)continued at the discretion of the referring physician and in accordance with atrial fibrillation guidelines. Complications were defined in accordance with HRS/EHRA/ECAS expert consensus on AF ablation.²

Follow-up

A blanking period of 90 days was defined after PVI. Outpatient clinic visits were planned at 3, 6, and 12 months after PVI. Follow-up included physical examination, electrocardiography (all visits), event monitoring and 24-72 hours Holter ECG (at 6 and 12 months). In case of symptoms patients were immediately referred to the emergency department. Additional Holter ECG monitoring was performed if no arrhythmia could be detected. AF occurrence in the blanking period was not considered a relapse. After the blanking period antiarrhythmic drugs were discontinued. The need for a repeat ablation for recurrent symptomatic atrial arrhythmias was left at discretion of the physician.

Redo-procedures

Patients with recurrences, not sufficiently suppressed by AAD or not willing to use AAD, and with sufficient symptoms, underwent a redo-procedure. The redo procedure was performed with Carto 3D electro-anatomical mapping using a circular decapolar mapping catheter (Lasso™, Biosense Webster Inc., Diamond Bar, CA, USA) and RF ablation with an irrigated contact-force ablation catheter with a 3.5-mm tip (Smarttouch Thermocool™, Biosense Webster Inc., Diamond Bar, CA, USA). After the creation of a 3D electro-anatomical map and voltage map of the left atrium and pulmonary veins, the antra were ablated with the primary goal of pulmonary vein isolation. Additional ablation was left to the discretion of the operator.

Study endpoints

The primary effectiveness endpoint was single procedure arrhythmia-free survival, defined as patients without AF/atrial flutter (AFI)/atrial tachycardia (AT) recurrence, after the blanking period of 90 days after PVI. Arrhythmia recurrence was defined as AF/AFI/AT recorded on an

ECG or a 30 second telemetry strip, in accordance with HRS/EHRA/ECAS expert consensus statement on AF ablation.

Statistical analysis

Data are mentioned as mean \pm standard deviation (SD), median with interquartile range (IQR), or percentage where appropriate. Statistical significance between groups was calculated using Student's t-test for continuous variables and Chi-square test for categorical variables. Arrhythmia-free survival differences between catheter groups were assessed with a log-rank test. Univariate and multivariate analysis were performed using Cox Regression. A P-value of ≤ 0.05 was considered statistically significant. Statistical analysis was conducted using IBM statistics version 22.0 (IBM SPSS Statistics for Macintosh, 2013: IBM Corp., Armonk, New York, USA).

RESULTS

Patient population

Altogether, 269 consecutive patients with drug-refractory paroxysmal or early persistent AF undergoing PVI were included and randomly allocated to cryoballoon or radiofrequency ablation. Mean age was 58.9 ± 10.4 years, 191 (71%) were men. 136 patients underwent CB and 133 patients underwent RF ablation. General patient characteristics were similar in both treatment groups. Baseline characteristics are presented in table 1.

Acute PVI

Acute PVI was achieved in all patients. A total number of 1103 PVs were ablated (1068 standard PVs, 4 left common PVs, 2 left middle PVs [LMPV], 29 right middle PVs [RMPV]). Acute PVI results are described in table 2.

Procedural characteristics

Mean procedure duration was significantly shorter in CB ablation compared to RF ablation (166.5 ± 36.8 vs. 184.1 ± 40.0 minutes, $P=0.016$). Procedural characteristics are shown in table 2. Fluoroscopy times of the ablation groups were not significantly different (11.5 ± 8.5 vs. 9.1 ± 14.3 min, $P=0.26$).

Complications

There were no significant differences with regard to overall complication rate between CB and RF ablation (6.0% vs 6.7%, $P=1.00$). Temporary phrenic nerve palsy did occur more often in the CB group compared to RF, although this did not reach statistical significance (2.9% vs 0%, $P=0.058$). All complications were of a temporary nature. Complication characteristics are shown in table 3.

Table 1. Baseline characteristics

Characteristic	Overall (n=269)	CB (n=133)	RF (n=136)	P-value*
Age - years	58.9 ± 10.4	59.7 ± 9.9	58.2 ± 10.8	0.21
Male sex - no. (%)	191 (71%)	92 (69.2%)	99 (72.8%)	0.59
Type AF - no. (%)				0.12
Paroxysmal	229 (85.1%)	117 (88.0%)	112 (82.4%)	
Persistent	40 (14.9%)	16 (12.0%)	24 (17.6%)	
AF duration - years	4.9 ± 5.9	5.1 ± 6.1	4.8 ± 5.6	0.59
Body-mass index - kg/m ²	27.4 ± 4.2	27.8 ± 4.4	27.1 ± 3.9	0.25
CHA ₂ DS ₂ -VASc				
Mean	1.36 ± 1.29	1.37 ± 1.32	1.25 ± 1.26	0.49
0	90 (34.6%)	44 (34.9%)	46 (34.3%)	
1	67 (25.8%)	27 (21.4%)	40 (29.9%)	
2	60 (23.1%)	32 (25.4%)	28 (20.9%)	
3	25 (9.6%)	14 (11.1%)	11 (8.2%)	
4	13 (5.0%)	7 (5.6%)	6 (4.5%)	
5	4 (1.5%)	1 (0.8%)	3 (2.2%)	
6	1 (0.4%)	1 (0.8%)	0 (0.0%)	
Medical history - no. (%)				
Hypertension	109 (40.8%)	57 (43.2%)	52 (38.5%)	0.46
Diabetes Mellitus	23 (8.6%)	14 (10.6%)	9 (16.7%)	0.28
CVA/TIA	18 (6.7%)	8 (6%)	10 (7.4%)	0.81

AF atrial fibrillation, CB cryoballoon, RF radiofrequency

* P-value for statistical difference between cryoballoon and radiofrequency group

Table 2. Procedural characteristics

	CB (n=133)	RF (n=136)	P-value
Acute PV isolation - no. (%)	543 (100%)	560 (100%)	1.0
Left			
LSPV	132 (100%)	133 (100%)	
LIPV	132 (100%)	133 (100%)	
Common PV	1 (100%)	3 (100%)	
LMPV	1 (100%)	1 (100%)	
Right (n)			
RSPV	133 (100%)	136 (100%)	
RIPV	133 (100%)	136 (100%)	
RMPV	11 (100%)	18 (100%)	
Radiation dose (mGy)	11.5 (±8.5)	9.1 (±14.3)	0.26
Procedure duration (min)	166.50 (±36.7)	184.1 (±40.0)	0.016*

* significant P-value

CB cryoballoon, RF radiofrequency, PV pulmonary vein, LSPV left superior pulmonary vein, LIPV left inferior pulmonary vein, RSPV right superior pulmonary vein, RMPV right middle pulmonary vein, RIPV right inferior pulmonary vein

Table 3. Complications

Complication	CB (n=133)	RF (n=136)	P-value
Overall	8 (6.0%)	9 (6.6%)	1.000
Death	0 (0%)	0 (0%)	-
Vascular access	3 (2.3%)	3 (2.2%)	1.000
Temporary PNP	4 (3.0%)	0 (0%)	0.058
Permanent PNP	0 (0%)	0 (0%)	-
Pericarditis	1 (0.8%)	2 (1.5%)	1.000
Pericardial effusion	0 (0%)	1 (0.7%)	1.000
Pneumonia/bronchitis	0 (0%)	1 (0.7%)	1.000
TIA	0 (0%)	1 (0.7%)	1.000
Coronary spasm	0 (0%)	1 (0.7%)	1.000

CB cryoballoon, RF radiofrequency, PNP phrenic nerve palsy, TIA transient ischemic attack

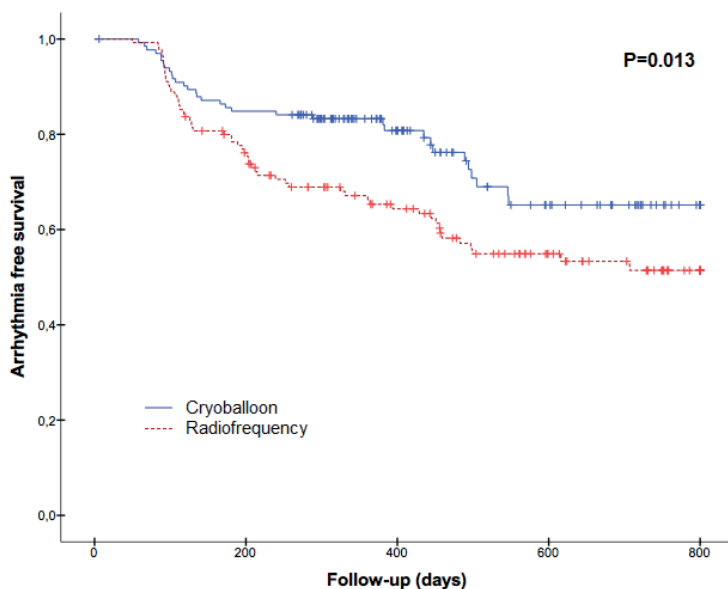
Arrhythmia-free survival

Median follow-up was 389 days (IQR 219 – 599) and did not differ in CB and RF group respectively ($P=0.98$). In the CB group arrhythmia-free survival after a single PVI-procedure was 75.2% with a median follow-up duration of 381 days (IQR 292 - 563). In the RF group arrhythmia-free survival after a single PVI-procedure was 57.4% with a median follow-up duration of 394 days (IQR 189 - 622). There was a significant difference in arrhythmia-free survival between catheter groups (log-rank test, $P=0.013$) favoring CB. Arrhythmia-free survival among catheter groups is shown in figure 1. In univariate and multivariate analysis RF ablation, persistent AF, and AF duration were significantly associated with decreased arrhythmia-free survival. Univariate and multivariate analysis results are displayed in table 4. Analysis in paroxysmal AF patients only show arrhythmia-free survival of 76.9% in CB group versus 60.7% in RF group, log-rank $P=0.019$. There was no significant difference in type of atrial arrhythmia (AF/AFL/AT) recurrence between treatment groups (Chi-square test: $P=0.90$), as described in table 5.

Repeat ablation and PV reconnection

In total, 53 patients (19.7%) required a repeat ablation for recurrent atrial arrhythmias. Incidence of repeat ablation procedures was significantly lower after CB ablation as compared to RF ablation (14.7% vs 24.8%, $P=0.045$). As mentioned, in all patients all PV were isolated in the index procedure. A total number of 211 PVs were assessed for electrical PV reconnection. In 49 of 53 patients (92.5%) PV reconnection was found, without a significant difference between CB versus RF (85.0% vs 97.0%, $P=0.15$).

However, the proportion of reconnected PVs at repeat ablations was lower after CB ablation compared to RF (36.8% vs 58.1%, $P<0.01$), as shown in figure 2 and 3. The reconnection rate of the right-sided PVs was significantly higher after RF ablation compared to CB (90.9% vs 50.0%, $P<0.01$). PV reconnection is shown in table 6.



Numbers at risk	0	100	200	300	400	600	800
Cryoballoon	133	123	102	84	63	29	6
Radiofrequency	135	121	98	81	67	37	12
Total	268	244	200	165	130	66	18

Figure 1. Kaplan-Meier curve showing atrial arrhythmia-free survival after first pulmonary vein isolation procedure for cryoballoon and radiofrequency ablation.
Log rank: P=0.013

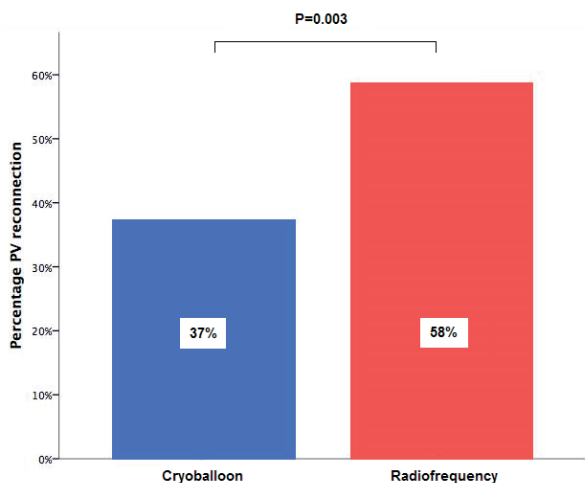


Figure 2. Percentage of PVs that exhibited reconnection at repeat PVI procedure.
PV pulmonary vein, PVI pulmonary vein isolation
Chi square test: P=0.03

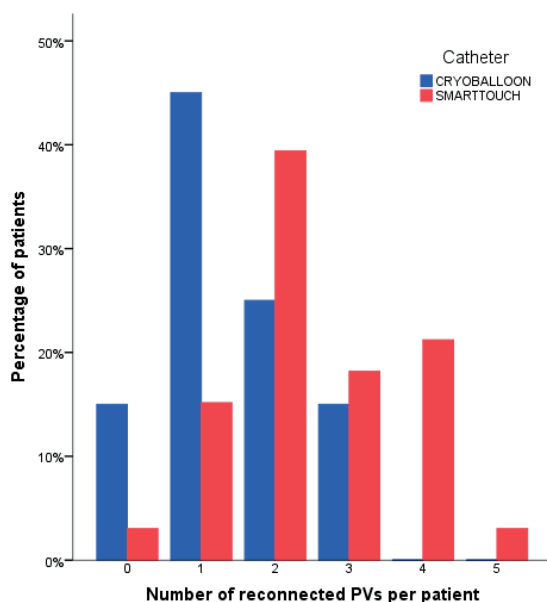


Figure 3. Number of PVs per patient that exhibited reconnection for each ablation catheter. PV pulmonary vein

Table 4. Univariate and multivariate analysis

Univariate analysis	Hazard Ratio	95% CI	p-value
Male gender	1.044	0.662 – 1.647	0.854
Age	1.008	0.987 – 1.030	0.465
BMI	0.978	0.922 – 1.039	0.474
Persistent AF	1.792	1.090 – 2.946	0.022
AF duration	1.027	1.000 – 1.056	0.054
Structural heart disease	1.626	0.659 – 4.012	0.292
Hypertension	1.081	0.712 – 1.640	0.715
Diabetes Mellitus	0.603	0.245 – 1.485	0.271
CHA2DS2VASc score	1.099	0.940 – 1.284	0.236
Previous TIA/stroke	1.191	0.551 – 2.576	0.657
Cryoballoon ablation**	0.537	0.380 – 0.898	0.014*
Multivariate analysis	Hazard ratio	95% CI	p-value
Persistent AF	1.667	1.006 – 2.761	0.047
AF duration	1.032	1.003 – 1.061	0.028
Cryoballoon ablation	0.578	0.369 – 0.905	0.017

Univariate and multivariate analysis of the association between procedural and patient characteristics and atrial arrhythmia recurrence after PVI.

* significant P-value

** as compared to radiofrequency ablation

BMI: body mass index; AF: atrial fibrillation; TIA: transient ischemic attack

Table 5. Type of atrial arrhythmia recurrence

Atrial arrhythmia	Cryoballoon (n=33)	Radiofrequency (n=58)
Atrial Fibrillation – no. (%)	24 (72.7%)	41 (70.7%)
Atrial Flutter – no. (%)	5 (15.2%)	8 (13.8%)
Atrial Tachycardia – no. (%)	4 (12.1%)	9 (15.5%)

There was no significant difference in type of atrial arrhythmia recurrence between catheter groups, Chi-square test: $P=0.90$

Sensitivity analysis

We performed Cox-regression analysis and plotted a Kaplan Meyer curve (figure 4) in patients with paroxysmal AF only, and similar results were observed, i.e. a higher arrhythmia-free survival rate in patients undergoing cryoablation. Additionally, our multivariate analysis provided insight into the independent association of the sort of ablation (cryoablation/RF ablation) and the type of AF (paroxysmal/persistent) and with arrhythmia-free survival after ablation.

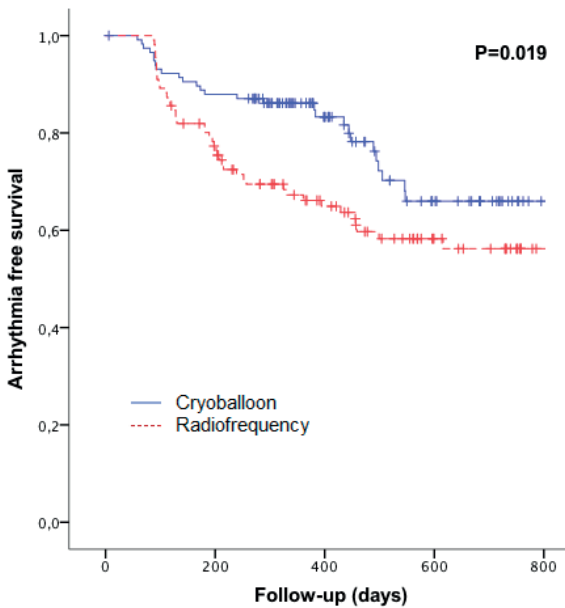


Figure 4. Kaplan–Meyer curve showing atrial arrhythmia-free survival after first pulmonary vein isolation procedure for cryoballoon and radiofrequency ablation in paroxysmal AF patients.

Log rank: $P=0.019$

Table 6. Pulmonary vein reconnection patterns

	CB (n=133)	RF (n=136)	P-value
Repeat procedure - no. (%)	20 (15.0%)	33 (24.3%)	0.045
Total number PVs assessed	76	135	0.046
Reconnection PVs - no. (%)			
LSPV	9 (45.0%)	20 (60.6%)	0.39
LIPV	6 (30.0%)	17 (51.5%)	0.16
RSPV	6 (30.0%)	22 (66.7%)	0.012*
RMPV	-	1 (33.3%)	-
RIPV	7 (35.0%)	22 (66.7%)	0.045*
Total	28/76 (36.8%)	79/135 (58.1%)	0.003*
Number PV reconnection per patient - no. (%)			0.032*
0	3 (15.0%)	1 (3.1%)	
1	9 (45.0%)	5 (15.6%)	
2	5 (25.0%)	13 (40.6%)	
3	3 (15.0%)	6 (15.6%)	
4	0 (0.0%)	7 (25.0%)	
5	-	1 (3.0%)	
Side PV reconnection per patient - no. (%)			
Left	13 (65.0%)	25 (75.8%)	0.53
Right	10 (50.0%)	30 (90.9%)	0.002*
Upper	13 (65.0%)	29 (87.9%)	0.079
Lower	11 (55.0%)	25 (75.8%)	0.14
≥ 2 PVs reconnection	8 (40.0%)	27 (81.8%)	0.003*

AF atrial fibrillation, CB cryoballoon, RF radiofrequency, PV pulmonary vein, LSPV left superior pulmonary vein, LIPV left inferior pulmonary vein, RSPV right superior pulmonary vein, RMPV right middle pulmonary vein, RIPV right inferior pulmonary vein. * significant P-value

DISCUSSION

This study reports single center data on single ablation success, safety outcomes, and pulmonary vein reconnection patterns after PVI, comparing second-generation cryoballoon ablation to point-by-point contact-force radiofrequency ablation. Acute PVI was always reached using both ablation strategies. However, higher arrhythmia-free survival, lower rate of repeat ablation and a lower rate of reconnected PV's per patient was found after CB compared to RF ablation. Both techniques had a high safety profile, and all observed complications were of a temporary nature.

Procedural characteristics

High acute ablation success (100%) was achieved using both ablation strategies. Procedure duration was significantly shorter in CB ablation compared to RF, in accordance with a recently reported randomized multicenter trial.⁶ This might be explained by easier catheter handling, and the single shot ablation strategy of the CB. However, adequate CB placement was checked by using fluoroscopy after contrast injections, whereas RF ablations were guided by electro-anatomic and force controlled mapping and RF ablation. In our study, fluoroscopy time in CB ablation was comparable to RF ablation. This is in contrast with the results of a recent trial that showed a higher fluoroscopy time in the CB arm.⁶ Although a trend to lower radiation dose was observed in RF ablation, we did not find a statistical significant difference compared to CB, possibly due to a lower number of patients that were involved in our study.

Complications

The reported overall complication rate of 6.3% is in line with previous reports.^{6,7} We found no significant difference in complication rate between both ablation strategies. Furthermore, all observed complications were of temporary nature. The most common complication in the CB group was temporary phrenic nerve palsy, with a rate of 2.9%, which is considerably lower than reported in the Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) trial (13.5%) and in line with the Fire&Ice trial (2.7%).^{3,6} The most reported complication in the RF group was vascular access complication (2.2%). Although not different from CB ablation (2.2%), the groin complication rate was lower than the reported 4.3% in the Fire&Ice trial. In this study, there was one (0.8%) transient ischemic attack (TIA), which is comparable to other PVI techniques.

Arrhythmia-free survival

Our main finding of improved success rate after a single procedure CB ablation compared with point-by-point RF, is in line with earlier reports.^{8,9} However, in a recent multi-center randomized trial (Fire&Ice) CB ablation was shown to be noninferior to point-by-point RF ablation regarding efficacy.⁶ Success of the CB might have been compromised in this trial, due to inclusion of first-generation CB procedures.^{10,11} The design of the second-generation CB with improved circumferential cooling, results in more extensive circumferential lesions, and might have contributed to improved lesion formation.¹² In addition, previous studies demonstrated that Cryo ablation creates more extensive lesions such as, at least partial, posterior wall ablation or ablation of ganglionated plexi, which might have incremental benefits, resulting in a higher arrhythmia-free survival.^{13,14} Indeed, results of the FIRE&ICE study show a trend of higher success rate after second-generation CB compared to the first-generation, however the trial was not powered to test superiority of one of the catheters.⁶ Of notice, the proportion of patients treated with the nowadays commonly used contact force RF catheter was small in the Fire&Ice.

In multivariate analysis, persistent AF was an independent predictor of reduced arrhythmia-free survival (hazard ratio 1.667; 95%CI 1.006 to 2.761; $P=0.047$). Catheter ablation of persistent AF remains challenging and is associated with less favorable outcome.^{15,16} There is a need for further improvement of ablation techniques, and knowledge of substrate modification to improve AF ablation outcome in this subgroup of patients. In our present analysis however, we performed sensitivity analyses in paroxysmal AF patients only, and observed similar results in this subgroup. Moreover, multivariate analysis showed an independent association of cryoablation with arrhythmia-free survival, with the type of AF in the multivariate model, suggesting that possibly also in persistent AF patients cryoablation could be superior. The number of patients with persistent AF was too little however to perform separate analysis. The proportion of patient with persistent AF was not significantly different between treatment groups, although relatively small cohorts are always at risk for selection bias. We realize that this could be a potential limitation.

PV reconnection

Significantly less patients required a repeat ablation after CB compared to RF (14.7% versus 24.8% $P=0.045$), which was in line with the lower recurrence rate. At repeat intervention all PVs were assessed using a circular mapping catheter. We found a lower number of reconnected PVs after CB ablation compared to point-by-point RF, as shown in figure 2. This finding is in line with previous studies that showed improved lesion durability following PVI with the second-generation cryoballoon.^{17,18} Moreover, the right sided PVs were more likely to exhibit electrical reconnection after RF ablation compared to CB ablation. This finding might be explained by a more challenging catheter approach to the right sided PVs, resulting in reduced durability of the RF ablation lesions. Compared to the RF catheter, the circular design of CB allows a relative simple positioning and alignment of the catheter, which might lead to improved lesion quality. In contrast to prior reports, we did not find higher reconnection rates of the right inferior PVs and left common PVs after CB ablation.¹⁸ Although a waiting period is constituted before assessing acute PV isolation, when starting ablation in the left pulmonary veins, the waiting period is always shorter for the right sided PV's. Furthermore, a steerable sheath was not systematically used in the RF-ablation group, but only when deemed necessary in order to reach adequate catheter contact (>10 grams and FTI >400 gs). We did not systematically test for durable PV isolation with adenosine, which might possibly have influenced these results. It could be that cryoablation is less prone to edema induced acute PV isolation that reconnects in the days to weeks after the procedure. Pre-procedural assessment of PV anatomy may aid in utilization of CB or RF catheter. Limitation of the CB size should be considered in case of increased PV diameter of left common PVs.

Future perspectives

AF recurrences after PVI still remain an important clinical problem. Acute PV isolation does not assure long-term electrical PV isolation, and this might partially explain AF recurrence. Future research is needed to give more insight into mechanisms of conduction recovery. Furthermore, continuous improvement of catheter design and characteristics might improve catheter handling and lesion quality. This might result in better lesion durability and improved clinical outcome.

Limitations

There are several limitations that should be considered for interpretation of the results of this study. This is a single center prospective non-randomized study reviewing results of primo pulmonary vein isolation procedures using second-generation CB versus contact-force radiofrequency RF in patients with atrial fibrillation. Unadjusted confounding factors might be present in the study, i.e. no data on PV reconnection in patients without recurrence of arrhythmia is available. Pulmonary vein reconnection was only assessed at repeat ablation procedures, and therefore by definition in symptomatic patients with AF recurrence.

CONCLUSIONS

In this single center prospective study, improved arrhythmia-free survival and more durable PV isolation is seen after PVI using second-generation CB compared to contact-force RF, in patients with drug-refractory paroxysmal AF. Complication rates for both ablation techniques are low, and all occurred complications were of a temporary nature.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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5 | Randomized Controlled Trial of Surgical Versus Catheter Ablation for Paroxysmal and Early Persistent Atrial Fibrillation

Surgical versus Catheter ablation of AF

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Circulation: Arrhythmia and Electrophysiology. 2018;11(10):e006182.

ABSTRACT

Background: Current guidelines recommend both percutaneous catheter ablation and surgical ablation in the treatment of atrial fibrillation (AF), with different levels of evidence. No direct comparison has been made between minimally invasive thoracoscopic pulmonary vein isolation (PVI) with left atrial appendage ligation (surgical MIPI) versus percutaneous catheter ablation (CA) comprising of PVI as primary treatment of AF. We therefore conducted a randomized controlled trial comparing the safety and efficacy of these 2 treatment modalities.

Methods: Eighty patients were enrolled in the study and underwent implantable loop recorder (ILR) implantation. 28 patients did not reach randomization criteria. A total of 52 patients with symptomatic paroxysmal or early persistent AF were randomized, 26 to CA and 26 to surgical MIPI. The primary endpoint was defined as freedom of atrial tachyarrhythmias, without the use of anti-arrhythmic drugs (AAD). The safety endpoint was freedom of complications.

Results: Median age was 57 years (range 37-75) and 78% was male. Paroxysmal AF was present in 74%. Follow-up duration was ≥ 2 years in all patients. CA was noninferior to MIPI in terms of single procedure arrhythmia-free survival after 2 years follow-up (56.0% versus 29.2%, hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.26 to 1.20), log-rank $P=0.059$). Procedure related major adverse events occurred significantly more often in MIPI than CA (20.8% versus 0%, $P=0.029$).

Conclusions: Percutaneous pulmonary vein isolation was noninferior to MIPI in terms of efficacy and resulted in less complications.

Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT00703157

Funding: This study was supported by Medtronic External Research Programme (Medtronic ERP, Medtronic Inc, Minneapolis, MN, USA) and Medtronic Bakken Research Center (The Netherlands)

INTRODUCTION

Percutaneous electrical isolation of the pulmonary veins (PVs) by catheter ablation (CA) is an effective treatment modality for atrial fibrillation (AF) and is indicated in drug-refractory paroxysmal and persistent AF.¹⁻⁴ However, AF recurrence after PV isolation (PVI) is common. Electrical reconnection of the PVs is considered the most important mechanism for AF recurrence. The surgical Cox-Maze-III procedure is recognized as an effective treatment of AF, but because of its invasiveness and complexity, it is not widely used as a stand-alone procedure nowadays. As an alternative, minimally invasive thoracoscopic PVI (MIPI) was introduced in 1999 by Wolf et al,⁵ which allows an epicardial approach for PVI on a beating heart through less invasive incisions. According to the European Society of Cardiology guidelines for AF management, surgical AF ablation should be considered for either patients who failed CA in the past (class IIa, level B) or as a treatment option for patients with symptomatic drug-refractory persistent AF (class IIa, level C).² Previous studies including a systematic review found better efficacy of surgical ablation (SA) as compared with CA for AF, although much heterogeneity was present between groups and procedures. Furthermore, a significant proportion of patients undergoing surgical AF ablation has a history of CA.⁶ The aim of the present study, therefore, was to perform a randomized controlled trial to compare the efficacy and safety of CA and MIPI as primary ablative treatment of AF. Patients with drug-refractory paroxysmal or early persistent AF were randomized to either percutaneous CA with the objective of PVI without additional lesion sets or surgical MIPI ablation in a 1:1 ratio. All patients were implanted an implantable loop recorder (ILR) to detect atrial arrhythmia recurrence and burden.

METHODS

Purpose

The purpose of this prospective randomized clinical study was to compare the success rate of surgical and percutaneous AF ablation in patients without structural heart disease. Furthermore, we assessed the safety of both invasive treatment strategies. The study was approved by the internal review board and registered (URL: <https://www.clinicaltrials.gov>; unique identifier: NCT00703157). The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Patients in the Isala Heart Centre (Zwolle, the Netherlands) with symptomatic paroxysmal or early persistent AF (continuous AF duration, <3 months) with failure of at least 1 class 1 or 3 antiarrhythmic drugs (AADs) were eligible. Patients had to be aged ≥ 18 years. At least 1

symptomatic episode of AF was required within 6 months before inclusion. Structural heart disease, like coronary ischemia, cardiomyopathy or more than mild valvular heart disease, had been excluded by appropriate tests. Patients were excluded when they had permanent or persistent AF >3 months, ejection fraction <40%, left atrial size >50 mm (parasternal long axis), use of amiodarone (no use within 6 months before study entry), history of cerebrovascular disease, pregnancy, life expectancy of <1 year, and previous left atrial ablation.

Enrollment

After written informed consent had been obtained, consecutive patients were implanted a continuous looprecorder (Reveal XT; Medtronic). This ILR is a single-lead electrocardiographic subcutaneous monitoring device able to monitor atrial tachyarrhythmia burden. Patients were followed for a minimum of 1 week after ILR implantation and a maximum of 6 months to establish the required AF burden.

If a patient had demonstrated a minimum of 10% AF burden after 1 week ILR monitoring and had complaints associated with AF, this patient was randomized to one of the treatment arms. Because many patients were highly symptomatic also with a burden <10% or did not reach 10% burden because of early electrical cardioversion, we observed that many patients could not be randomized. A protocol amendment was initiated, therefore, after approval in October 2012, allowing an AF burden of 2% in 1 week as a threshold for randomization. Moreover, patients were followed for a maximum of 2 months instead of 6 months to establish the required AF burden before randomization. The majority (75 of 80) of patients were included in the study before the amendment was effectuated. Patients were randomized electronically at a 1:1 ratio to CA or SA.

Ablation Techniques

Catheter Ablation

The ablation procedure was performed under general anesthesia. Vitamin K antagonists were discontinued for 3 to 5 days before ablation and in selected cases bridged with low-molecular-weight heparin in accordance with local guidelines. Transesophageal echocardiography was performed directly preablation procedure to assess interatrial septum and to exclude left atrial thrombus or other significant structural heart disease. Venous access was obtained through the femoral vein. A 6F deflectable quadripolar catheter (Bard, Lowell, MA) was positioned in the coronary sinus. Transseptal access to the left atrium (LA) was achieved guided by fluoroscopy and pressure with a Brockenbrough needle, transseptal sheath (SL1, St. Jude), and a guidewire. An initial bolus of 10.000 units of heparin was given and additional administration to achieve an activated clotting time between 300 and 350 seconds. All sheaths were continuously flushed with saline containing 2500 IU heparin per 500 mL saline. PV angiography was performed for ipsilateral PV ostia to provide a geometric reference for catheter navigation and localization of the antrum. A 3-dimensional electroanatomic map

of the LA was constructed (CARTO, Biosense Webster). Isolation of all PVs was performed using circumferential periosteal applications of radiofrequency energy, with a power limit of 40 W on the anterior LA and 30 W on the posterior LA, and verified with a decapolar circular mapping catheter (Lasso, Biosense Webster). The ablation was performed with a 3.5-mm irrigated tip catheter (Thermocool, Biosense Webster). Radiofrequency energy was applied for 20 to 60 seconds until the local electrogram amplitude was eliminated. The end point of the ablation procedure was defined as the absence or dissociation of PV potentials documented with a circular decapolar mapping catheter within the PVs ≥ 30 minutes post-ablation.

Surgical Ablation

MIPI and left atrial appendage ligation was performed by a highly experienced cardiothoracic surgeon who performed >1000 radiofrequency maze procedures. The MIPI procedure was performed under general anesthesia. In supine position, a double-lumen tracheal tube was introduced. In the right hemithorax, a 5- to 10-cm incision in the fourth intercostal space in the anterior axillary line was placed. A soft tissue retractor was used to introduce the scope through the sixth intercostal space (submammary). The pericardium was opened anterior to the phrenic nerve. Two stay sutures were placed in the pericardium. Blunt dissection of Waterstone groove was performed followed by a blunt dissection and opening of the oblique sinus caudal of the right inferior PV. Then, blunt dissection and opening of the oblique sinus cranial of the right superior PV between right superior PV and right pulmonary artery was performed. Hereafter a silastic tape was placed around the right sided PVs to facilitate proper positioning of the device.

An irrigated bipolar clamp device (Cardioblate; Medtronic) was introduced for PVI. This device has a self-regulating ablation protocol based on an impedance feedback system. Transmurality feedback is indicated based on a steady-state plateau in tissue impedance. After introduction of the device, antral tissue around the right-sided PVs was clamped after gentle traction of the tape, and radiofrequency energy was applied to ablate the left atrial wall adjacent to the junction with the right-sided PVs. After radiofrequency energy application, the clamp was repositioned approaching the antrum of the PV pair from 180°, and then a second radiofrequency application was performed. Isolation of the PVs was confirmed with pacing maneuvers at the LA-PV junction. After 30 minutes, pacing maneuvers were repeated to check for electrical reconnection. The left hemithorax was opened similar to the right hemithorax, except for the incision of the pericardium, that was incised posterior to the phrenic nerve. Additional left atrial appendage ablation or removal or exclusion with stapler or preferably with endoloop was performed. The left atrial appendage exclusion was verified on transesophageal echocardiography. Ganglionated plexi ablation and additional ablation lines were not performed.

End Points

The primary end point was defined as freedom from atrial tachyarrhythmias with a duration of ≥ 30 seconds during follow-up, without the use of antiarrhythmic drugs. A 3-month blanking period was initiated. Secondary end points were AF burden $< 0.5\%$ and reduction of absolute AF burden during follow-up. AF burden post-ablation was calculated per month. The absolute decrease in average AF burden post-ablation was determined as compared with the average AF burden ≤ 6 months before the procedure. The safety end point was the absence of procedure-related complications. Complications were regarded as major if they resulted in death, irreversible damage to structures or organs, stroke, atrioesophageal fistula, conversion to sternotomy, or need for reoperation. Pericardial effusion not needing intervention and managed conservatively, small groin hematoma not requiring blood transfusion and without significant drop in hemoglobin, and procedure-related mild infection (such as urinary tract infection or respiratory tract infection) were regarded as minor complications.

Postprocedural Care

Anticoagulation was reinitiated as soon as possible, after control of bleeding, and was continued at least 3 months after the ablation procedure. When CHADS₂VASC score was ≥ 1 , patients were kept on anticoagulation. During the blanking period of 3 months, the AADs were tapered off.

Follow-Up

During follow up, patients were seen at 3 months followed by outpatient clinic visits every 6 months after the ablation procedure or at other occasions when patients had symptoms. At each visit, a 12-channel ECG and ILR device download was performed to assess any recurrence of arrhythmias.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences, version 24 (IBM Nederland B.V., Amsterdam, the Netherlands). A 2-sided *P* value of < 0.05 was considered significant. To assess the primary efficacy end point, we performed both intention-to-treat analysis and as-treated patient analysis because of the small sample size. As-treated analysis was performed to assess the safety end point. Categorical variables were reported as frequencies and percentages with 95% CI where appropriate. Quantitative/continuous variables were described using the mean and SD when normally distributed or using the median with the interquartile range when not normally distributed. To determine whether the data were normally distributed, the Shapiro-Wilk and Kolmogorov-Smirnov tests were used in combination with Q-Q plots and histograms. Data were not normally distributed, and, therefore, *t* test could not be used. The Mann-Whitney *U* test was used for the continuous variables. The χ^2 test or Fisher exact test was used for the comparison

of categorical variables. We performed Cox survival analysis for efficacy of both treatment strategies. The proportional hazards assumption was graphically and statistically verified. Time to first documented recurrence was analyzed by the log-rank statistic and plotted using Kaplan-Meier survival curve. We assessed the proportion of patients with AF burden <0.5 during follow-up with a χ^2 test for differences between the 2 treatment arms. We additionally tested for differences in absolute AF burden reduction.

RESULTS

Patient Characteristics

Eighty patients were enrolled in the study and underwent ILR implantation. Twenty-eight patients did not reach randomization criteria. Twenty-seven patients did not reach the required AF burden, and 1 patient was excluded because of an LA size >50 mm. A total of 52 patients were randomized, 26 to CA and 26 to SA. Figure 1 shows the patient distribution. All patients in the catheter group received CA. In the SA group, 23 patients underwent MIPI, and 2 patients received CA because after randomization, these patients refused SA. One patient in the SA group was excluded because of significant coronary artery disease necessitating coronary artery bypass surgery combined with radiofrequency maze. In the CA group, 1 patient was excluded from analyses after ablation because on the preprocedural transthoracic echocardiography and transesophageal echocardiography, a much larger LA was seen than expected (>50 mm anteroposterior diameter, with LA volume >50 mL/m²). Baseline characteristics are demonstrated in Table 1.

Procedural Characteristics

Table 2 demonstrates the procedural characteristics. The total median procedure time was not significantly different ($P=0.14$) between CA (168 minutes; range, 124–195) and MIPI (176 minutes; range, 155–221). In the CA group, complete electrical isolation was achieved in all PVs (100%). In 1 patient with AF which could not be converted to sinus rhythm using electrical cardioversion after PVI, an additional roofline and fractionation guided ablation was performed. Afterward, the patient was converted to sinus rhythm. In the MIPI group, PVI and left atrial appendage ligation was successful in all patients. In 1 patient, the ligament of Marshall was cut in addition to PVI, again because of recurrent AF after electrical cardioversions. This patient could subsequently not be converted to sinus rhythm. Hospitalization duration was significantly longer ($P<0.001$) in MIPI with a median of 9 days (range, 8–10) versus a median of 3 days (range, 2–3) after CA.

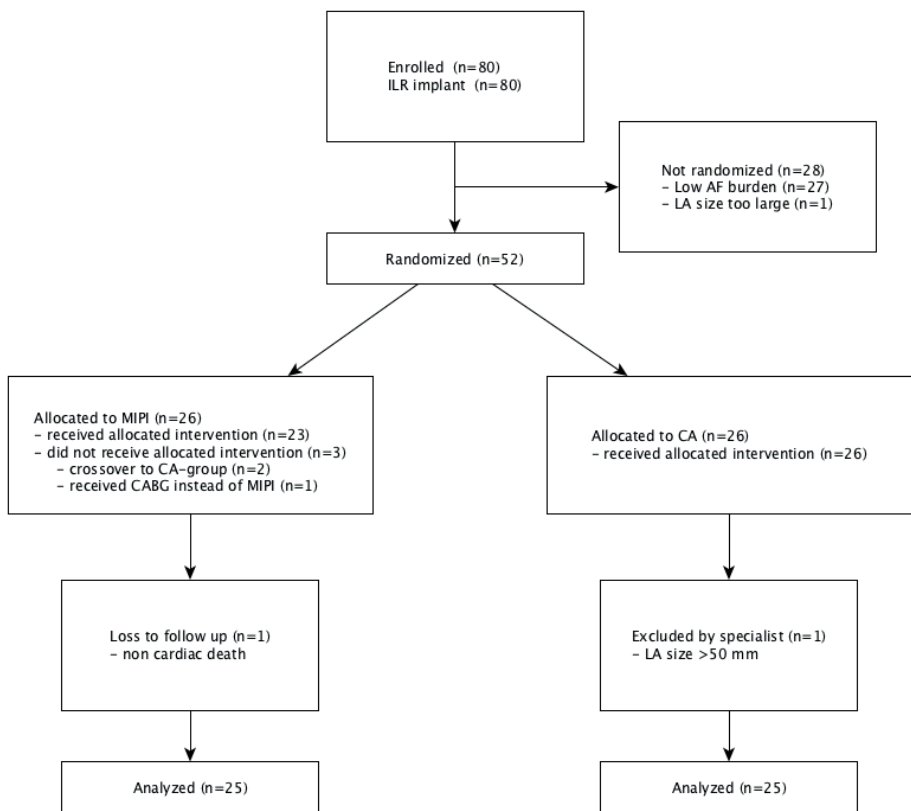


Figure 1. Patient distribution

Study design and patient distribution. AF: atrial fibrillation; CA: catheter ablation; CABG: coronary artery bypass grafting; ILR: implantable looprecorder; LA: left atrium; MIPI: minimal invasive thoracoscopic pulmonary vein isolation.

Efficacy of Catheter Versus Surgical AF Ablation

In intention-to-treat analysis of the primary end point CA, single-procedure arrhythmia-free survival without the use of AAD after 2 years of follow-up was noninferior to SA (2-year Kaplan-Meier event rate estimates, 56.0% and 29.2%, respectively; log-rank $P=0.059$; hazard ratio [HR], 0.56; 95% CI, 0.26–1.20), as shown in Figures 2 and 3. There was no significant interaction of age with arrhythmia-free survival (HR, 0.98; 95% CI, 0.94–1.02; $P=0.28$). In the as-treated population, difference in single-procedure arrhythmia-free survival between CA and MIPI was statistically significant (2-year Kaplan-Meier event rate estimates, 55.6% and 27.3%, respectively; log-rank $P=0.048$; HR, 0.55; 95% CI, 0.26–1.16). Univariate and multivariate Cox regression analysis results are described in Table I in the Data Supplement.

Similar results for CA and MIPI were seen after 1-year follow-up in intention-to-treat analysis (1-year Kaplan-Meier event rate estimates, 56.0% and 33.3%, respectively; log-

Table 1. Baseline characteristics

	CA (N=27)	MIPI (N=23)
Age (years)	59 (54-66)	55 (48-61)
Men	20 (74.1%)	19 (82.6%)
AF duration (years)	3.9 (1.5-8.0)	3.6 (1.6-8.7)
LVEF (%)	55 (50-60)	55 (50-60)
LA size, PLAX(mm)	40 (38-44)	39 (37-42)
Failed AAD before randomization		
Flecainide	18 (66.7%)	16 (69.6%)
Propafenone	0	2 (8.7%)
Sotalol	14 (51.9%)	14 (60.9%)
Amiodarone	3 (11.1%)	2 (8.7%)
Beta-blocker	14 (51.8%)	16 (69.5%)
Verapamil/diltiazem	6 (22.2%)	1 (4.3%)
Digoxine	4 (14.8%)	2 (8.7%)
CHADS₂VASC-score		
0	9 (36%)	9 (36%)
1	8 (32%)	11 (44%)
2	5 (20%)	4 (16%)
3	3 (12%)	1 (4%)
AF burden pre-ablation	29.2 (13.0-79.2)	26.3 (15.0-74.7)
Diabetes mellitus	2 (7.4%)	2 (8.7%)
Hypertension	11 (40.7%)	11 (47.8%)

AAD: anti arrhythmic drugs; AF: atrial fibrillation; CA: catheter ablation; CHADS₂VASC-score CHF, 1. HTN, 1. Age > 75, 2. Diabetes, 1. Stroke/TIA/systemic embolism, 2. Vascular disease (CAD, MI, PAD, aortic plaque); LA: left atrium; LVEF: left ventricular ejection fraction; PLAX: parasternal long axis

rank $P=0.103$; HR, 0.60; 95% CI, 0.28–1.30) and as-treated analysis (1-year Kaplan-Meier event rate estimates, 55.6% and 31.8%, respectively; log-rank $P=0.09$; HR, 0.59; 95% CI, 0.28–1.27).

The decrease in AF burden, 2 years after ablation, was 24.4% (interquartile range, 11.0%–61.5%) in CA compared with 14.1% (interquartile range, 10.4%–47.3%) in MIPI ($P=0.76$). In as-treated patient analysis, a significantly greater proportion of patients had an AF burden <0.5% after CA compared with MIPI (60.0% versus 27.3%; $P=0.047$), in intention-to-treat analysis, the difference did not reach statistical significance ($P=0.058$). Table II in the Data Supplement demonstrates the AF burden during the 2 years of follow-up.

Table 2. Procedural characteristics

	CA (n=27)	MIPI (n=23)	P-value*
Total procedure time (min)	168 (124-195)	176 (155-221)	0.14
Fluoroscopy time (min)	23 (17-31)	-	
Total ablation time (min)	31 (24-41)		
RF energy (sec)		200 (177-278)	
Additional ablation			
roofline	1	0	
Marshall's ligament	0	1	
Left atrial appendage ligation	..	23/23 (100%)	
Hospitalization (days)	3 (2-3)	9 (8-10)	<0.001

CA: catheter ablation; MIPI: minimal invasive thoroscopic pulmonary vein isolation; RF: radio frequency
* Mann-Whitney U test

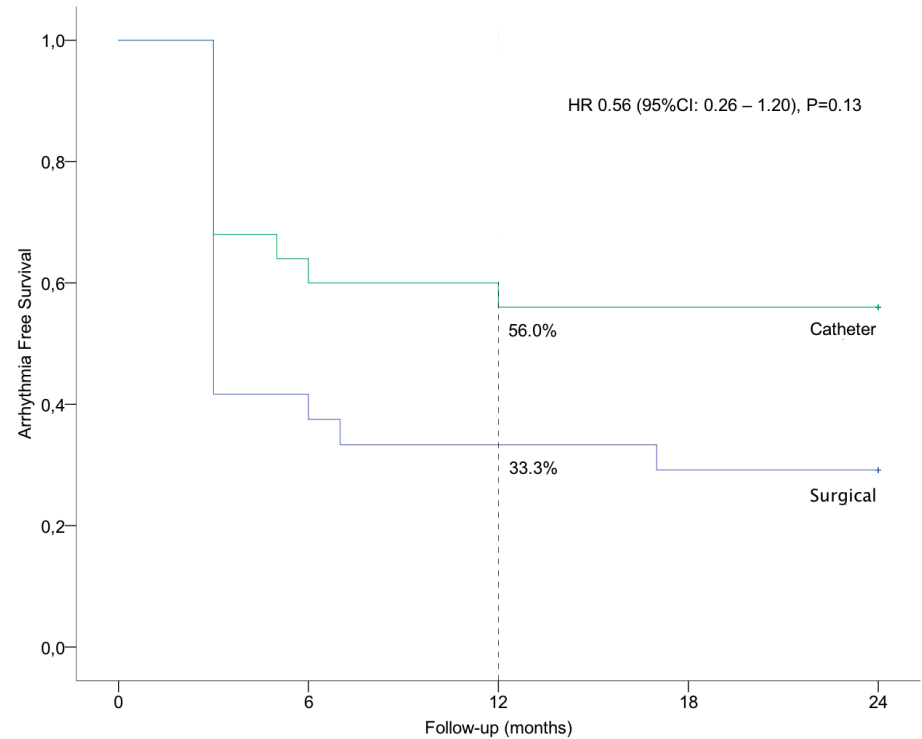


Figure 2. Kaplan–Meier curves displaying time to first atrial tachyarrhythmia with 3-month blanking period (intention-to-treat analysis).
Log-rank: $P = 0.059$. HR: hazard ratio.

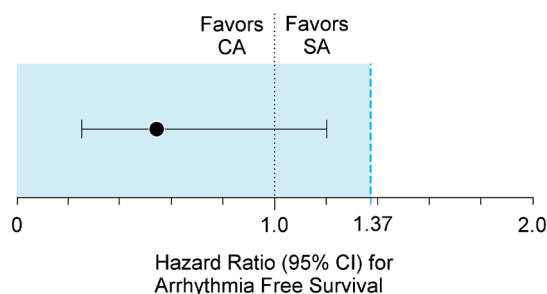


Figure 3. Hazard ratios (HRs) comparing arrhythmia-free survival between catheter (CA) and surgical ablation (SA) groups. Blue dashed line at HR = 1.37 indicates noninferiority margin, error bar indicates 2-sided 95% confidence interval (CI).

Table 3. Procedural and nonprocedural related adverse events

	CA (n=27)	MIPI (n=23)	P value
Pericarditis	1	2	
Pleuropericarditis with blood cloth	0	1	
Pericardial effusion	0	1	
Conversion to sternotomy	0	1	
TIA/stroke	0	0	
Pneumothorax	0	0	
Phrenic nerve paralysis	0	1	
Upper respiratory tract infection	1	0	
infection of unknown origin	0	1	
Pacemaker implant	0	0	
Death	0	0	
Other	1 (urosepsis)	2 (lung herniation requiring surgical correction, laryngeal nerve palsy)	
Total	3 (11%)	9 (37.5%)	0.046*
Minor	3	4	
Major	0	5	0.029*

CA: catheter ablation; MIPI: minimal invasive thoracoscopic pulmonary vein isolation; TIA, Transient ischemic attack

* considered statistically significant

Safety

Procedure-related adverse events during follow-up occurred significantly more often in MIPI than in CA (37.5% versus 11.1%; difference, 26.4%; 95% CI, 3.2%–49.6%; $P=0.046$). This was mainly because of a difference in major complications (20.8% in MIPI versus 0%

in CA; difference, 20.8%; 95% CI, 4.8%–36.9%; $P=0.029$). Table 3 shows procedural and nonprocedural adverse events. All complications in the CA group were minor complications, whereas in the MIPI group, there were 5 major complications. In the MIPI group, 1 patient required an acute conversion to median sternotomy because of bleeding from a laceration of the left upper PV at the LA junction. One patient required pericardiocentesis for pericardial effusion with tamponade. Another patient in the MIPI group developed postoperative lung herniation through one of the right-sided surgical incisions for which reconstruction with a patch of marlex mesh was performed. One MIPI procedure was complicated by left phrenic nerve paralysis, and another patient developed a unilateral recurrent laryngeal nerve paralysis related to endotracheal intubation. One patient in the CA developed a ventilator-associated pneumonia, treated with antibiotics. One patient in the CA group developed a urosepsis because of an indwelling urinary catheter. Pericarditis without significant effusion was successfully treated with ibuprofen in both groups.

DISCUSSION

Main Findings

This is the first randomized controlled trial that randomized patients with symptomatic drug-refractory paroxysmal or early persistent AF to surgical or percutaneous ablation as a first invasive procedure. The follow-up strategy of this study comprised continuous rhythm monitoring with the use of an ILR in all patients. The main finding of this study is that PVI with percutaneous CA was noninferior to surgical MIPI in terms of arrhythmia-free survival after 2 years of follow-up. However, in the as-treated analysis, CA resulted in less atrial tachyarrhythmia recurrences, as compared with MIPI. Both ablation strategies reduced AF burden significantly. However, 2 years after ablation, a significant greater proportion of patients in the CA group had a low AF burden (<0.5%) compared with surgical MIPI. When assessing AF burden <0.5% in our study, which is only 0.8 hours per week, success rates would be 60% for CA and 27.3% for MIPI ($P=0.047$). Atrial arrhythmia-free outcome of CA in this study is in line with the results of a recent randomized study on percutaneous CA of AF.³

Of note, our findings are in contrast with results of earlier randomized trials comparing SA and CA.^{7,8} In these trials, however, a large proportion of patients with unsuccessful previous CA were included, resulting in importantly different study populations.

Head-to-head randomized comparison of primary SA versus CA has not been performed before. Previous randomized studies comparing SA and CA of AF always included patients with unsuccessful previous CA. The FAST trial (Atrial Fibrillation Catheter Ablation Versus Surgical Ablation Treatment) was a prospective randomized trial in 124 patients who had failed a previous CA procedure or had hypertension and an enlarged LA.⁷ In this latter study, patients were randomized in a 1:1 ratio to either CA or MIPI. Importantly, two-third of the patient

population had unsuccessful CA before randomization. In addition, cardiac rhythm follow-up method in the FAST trial did not consist of continuous monitoring with ILR. Therefore, shorter or asymptomatic episodes of AF can be easily missed in this way. The 12-month success rate, defined as freedom from atrial tachyarrhythmias >30 seconds in duration, measured by 7-day Holter monitoring, was significantly higher for the SA group compared with the CA group (65.6% versus 36.5%; $P=0.0022$). Similar efficacy results were seen in a trial by Pokushalov et al.⁸ They randomized 64 patients with paroxysmal and persistent AF after a failed initial transcatheter endocardial PV ablation to repeat CA ($n=32$) or SA ($n=32$).⁸ The follow-up method consisted of continuous monitoring with an ILR. The surgical procedure consisted of PVI, lines to create a posterior box lesion, and ablation of ganglionic plexi. At 12 months of follow-up, 81% of SA patients were free of atrial arrhythmias without AAD versus 47% in the CA group ($P=0.004$). The relatively poor efficacy in the catheter group was attributed to the fact that patients included in these studies were in an advanced stage of AF and might have required additional substrate ablation. Aging and associated disease promote development of elastic fibers, collagen, increase in fat content, and smooth muscle cell hyperplasia. This process results in an AF substrate that has a hindering effect on radiofrequency electrical current in penetrating the tissue and limits creation of transmural lesions. In vivo and in vitro studies demonstrated a large heterogeneity in thickness and composition of the atrial epicardium and myocardium.⁹ Traditionally, surgical epicardial approach is performed in patients with ≥ 1 failed endocardial ablation attempts. In these patients, it is more likely to create electrical PV disconnection with additional epicardial ablation than in patients without previous endocardial ablation(s). Therefore, performing surgical epicardial AF ablation after previous endocardial ablations increases the probability of creating durable transmural lesions without gaps and thus elimination of PV and non-PV triggers and effective modification of AF substrate.

In European and American guidelines, both surgical and percutaneous approach are recommended as first ablation treatment modality, although with different class and level of evidence (class 1, A class 2a, A for CA in paroxysmal and persistent AF and class 2b, B for SA).^{10,11}

CA is a commonly applied first-line treatment of symptomatic drug refractory paroxysmal and persistent AF, whereas surgical epicardial ablation is mostly performed in patients with previously failed CA procedures or evidence of advanced AF substrate.^{12,13} Minimally invasive surgery for AF showed a 12-month AAD-free success rate of 65% to 92% in different review studies.^{14,15} Based on the current evidence, especially regarding the safety aspect, we would recommend not to perform first-line stand-alone SA of paroxysmal and early persistent AF. The future guideline committee should, therefore, consider a class III (level of evidence B) recommendation for primary stand-alone SA of paroxysmal AF.

Safety

In the present study, CA had a better safety profile than SA (MIPI). Procedure-related complications occurred significantly more often in MIPI than in CA, which is largely explained by occurrence of major complications (20.8% in MIPI versus 0% in CA; $P=0.029$). This finding is in line with findings of the FAST trial, in which major early complication rate was significantly higher for the SA group compared with CA (23.0% versus 3.2%).⁷ Pokushalov et al⁸ also reported a much higher major complication rate after surgical procedures compared with CA (22% versus 3.2%; $P=0.02$). SA and CA of AF are highly complex procedures. The most recent worldwide survey of CA reported a 4.5% complication rate.¹⁶ It has to be recognized that the data were from voluntary surveys and likely underestimate the true complication rates. In our present study, most complications were general surgery-related complications, like bleeding and damage to organs or the nervous system. The high complication rate with surgical AF ablation was observed in many studies involving highly experienced surgeons, possibly highlighting the need for cardiac electrophysiological surgery as a subspecialty to reduce complication rates.

Cardiac Rhythm Monitoring

The present study is the first to randomize patients to MIPI or CA only in patients undergoing a first invasive treatment for AF with continuous rhythm monitoring with ILR to assess outcome. It has been shown that monitoring of symptoms in patients with AF is unreliable. Only 52% of symptoms correlate with documented measures of AF, and nearly half of AF episodes are asymptomatic.¹⁷ The Heart Rhythm Society task force recommend 24-hour Holter monitoring as an acceptable monitoring strategy for patients enrolled in a clinical trial. Hanke et al¹⁸ demonstrated that intermittent monitoring dramatically overestimates the success rate of ablation procedures. Another study in 647 AF patients with a mean AF burden of 0.12% showed that even with intensive intermittent monitoring, at least 30 days of Holter monitoring would be required to reach a sensitivity of 82% in detection of AF.¹⁹ For scientific and for AF patient management decisions, continuous monitoring after ablation procedures is strongly recommended.

Limitations

The main limitation of our study is the small sample size. Therefore, results of this trial should be interpreted as a pilot study. Absolute numbers in efficacy are similar in intention-to-treat and as-treated analyses, although even low crossover rates resulted in no significant differences in efficacy in the first and a significant difference in the latter. A larger than expected proportion of patients did not meet the requirement of AF burden $>10\%$, which was originally set as inclusion criterion. Highly symptomatic episodes of AF required electrical cardioversion before patients could reach the required 10% burden within 1 week of loop recorder monitoring. Later, we changed this inclusion criterion to 2% AF burden. We did not

systematically perform an electrophysiological study in patients with recurrent AF after MIPI. The current study shows a relatively high rate of postoperative recurrent atrial arrhythmias. However, AF burden data obtained with an ILR demonstrates that the mean AF burden was significantly reduced after surgery. The results of a previous study demonstrated that symptomatic atrial arrhythmias after minimally invasive epicardial PVI were predominantly because of reconnection of epicardial ablation lines.²⁰ Possibly, additional epicardial surgical radiofrequency applications or more extensive testing for PVI could have resulted in better outcome. Third, this trial was conducted in a single center. Pooling of randomized data from different centers and new, larger multicenter randomized studies are mandatory.

CONCLUSIONS

In patients with paroxysmal and early persistent AF without structural heart disease, percutaneous CA was noninferior to minimally invasive SA in long-term follow-up. However, CA was considerably safer than SA.

Sources of Funding

This study was supported by Medtronic External Research Programme (Medtronic, Inc, Minneapolis, MN) and Medtronic Bakken Research Center (the Netherlands). Medtronic External Research Program has provided funds to conduct this study. Medtronic Bakken Research Center (the Netherlands) provided case report forms, data monitoring, and data processing services. Medtronic was not involved in the design of the study, patient recruitment, or reviewing the article. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Disclosures

None.

The Data Supplement is available at

<https://www.ahajournals.org/doi/suppl/10.1161/CIRCEP.118.006182>.

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6 | Quality of life after catheter and minimal invasive surgical ablation of paroxysmal and early persistent atrial fibrillation. Results from the SCALAF trial.

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Clinical Research in Cardiology. 2020;109(2):215–224.

ABSTRACT

Aims: In the SCALAF trial, catheter-based pulmonary vein isolation (PVI) was as effective in long-term prevention of atrial fibrillation (AF) as minimally invasive thoracoscopic PVI and left atrial appendage ligation (MIPI). Catheter ablation (CA) resulted in significantly less major complications as compare to MIPI. We report quality of life (QOL) outcome in these patients.

Methods: In this study, 52 patients with symptomatic paroxysmal or early persistent AF were randomized to either MIPI or CA. QOL was assessed at baseline, 3, 6, and 12 months follow-up using the SF-36 Health Survey Questionnaire. AF-related symptoms were quantified at each follow-up visit using the European Heart Rhythm Association (EHRA) score.

Results: Median age was 57 years and 78% was male. Paroxysmal AF was present in 74%. At 3 months follow-up, physical role limitations (88.2 ± 29.5 ; versus 40.9 ± 44.0 ; $P = 0.001$, respectively) and bodily pain scores (95.5 ± 8.7 ; versus 76.0 ± 27.8 ; $P = 0.021$, respectively) were significantly higher after CA compared to MIPI, indicating less limitation in daily activity caused by physical problems and less pain after CA than after MIPI. AF symptoms assessed by the EHRA scores improved significantly at 3, 6, 12, and 24 months compared to baseline in both treatment groups ($P < 0.001$), with no significant differences between treatment groups.

Conclusions: CA and MIPI ablation of AF both resulted in an improvement in several QOL measurements, although CA resulted in significantly less physical problems and bodily pain 3 months after treatment compared to MIPI.

Clinical trial number: ClinicalTrials.gov identifier: NCT00703157.

Keywords: Atrial fibrillation; Catheter ablation; Minimally invasive surgery; Quality of life.

INTRODUCTION

Atrial fibrillation (AF) has a major impact on cardiovascular morbidity and mortality. Quality of life (QOL) is often significantly impaired in AF patients due to AF symptoms, underlying heart disease symptoms, and treatment related factors (e.g. side effects, hospitalization, interventions).¹ Both pharmacological and interventional therapies have shown to improve QOL.^{2,3} Percutaneous electrical isolation of the pulmonary veins (PV) by catheter ablation (CA) is a common and effective AF treatment modality to restore and maintain sinus rhythm, and is indicated in drug refractory paroxysmal and persistent AF.¹ The surgical Cox-Maze III procedure is recognized as a very effective treatment of AF but due to its invasiveness and complexity, it is not widely used as a stand-alone procedure. As an alternative, minimally invasive thoracoscopic pulmonary vein isolation (MIPI) was introduced in 1999 by Wolf et al. which allows an epicardial approach for pulmonary vein isolation (PVI) on a beating heart through less invasive incisions.⁴ Current guideline indications for AF ablation are mainly based on QOL and symptom improvement.¹ QOL, therefore, is increasingly recognized as an important clinical outcome measure in AF ablations. A variety of tools can be used to assess QOL.^{1,5} The SF-36 questionnaire is a widely validated generic instrument to assess QOL, which has been extensively used in AF studies.⁵ The SCALAF (Surgical versus Catheter Ablation for “Lone” Atrial Fibrillation) trial is the first randomized controlled trial to compare the efficacy and safety of catheter ablation (CA) versus minimally invasive thoracoscopic PVI and left atrial appendage ligation (MIPI) in the treatment of paroxysmal and early-persistent AF.⁶ In this study, CA was as effective as MIPI during long-term follow-up; however, CA resulted in less major complications. In the present analysis, we aimed to assess QOL in patients undergoing catheter or surgical ablation for the treatment of symptomatic paroxysmal or early-persistent AF, in context of the SCALAF trial.

METHODS

Purpose

The purpose of this study is to report data of the SCALAF trial on QOL after transcutaneous CA and surgical MIPI ablation for AF.

Study population

The SCALAF trial was a single-center randomized controlled trial on CA and surgical MIPI ablation of AF. The study group consisted of 52 consecutive patients who underwent percutaneous radiofrequency catheter ablation or surgical MIPI ablation for treatment after randomization in a 1:1 ratio from 2007 to 2013. Inclusion and exclusion criteria are described in an earlier publication of this trial.⁶ In short, patients with drug refractory (i.e. at least

1 failed class I or III AAD) symptomatic paroxysmal or early persistent AF (continuous AF duration < 3 months) were included and implanted a continuous loop recorder. Patients with symptomatic AF and a $\geq 2\%$ AF burden were included in the study. Patients with structural heart disease (e.g. coronary ischemia, cardiomyopathy, more than mild valvular heart disease) were excluded. Furthermore, patients with left atrial size > 50mm (parasternal long axis), ejection fraction <40%, and previous left atrial ablation were excluded. The study was approved by the local medical ethical committee and registered (ClinicalTrials.gov identifier: NCT00703157). All patients provided written informed consent.

Quality of life assessment

QOL was assessed at baseline and follow-up visits using the SF-36 Health Survey Questionnaire. The SF-36 includes eight health sections: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social functioning, and mental health. Scores can be calculated ranging along a 100-point scale, with higher scores indicating better perceived health status. AF related symptoms were quantified using the European Heart Rhythm Association (EHRA) score at baseline and follow-up visits. The EHRA classification contains four categories based on the impact of (presumed) AF related symptoms on daily activity; 'no symptoms' (category I), 'mild symptoms' (category II), 'severe symptoms' (category III), and 'disabling symptoms' (category IV).

Implantable loop recorder

After enrollment, patients were implanted a continuous loop recorder (Reveal® XT, Medtronic, USA). This implantable loop recorder (ILR) is a single lead electrocardiographic (ECG) subcutaneous monitoring device able to monitor atrial tachyarrhythmia occurrence and burden.

Ablation protocol

Further details of the ablation protocols are described in an earlier report of the SCALAF trial.⁶ Both catheter and surgical procedures were performed under general anesthesia supervised by a cardiovascular anesthesiologist.

Catheter ablation

Transesophageal echocardiography was performed directly pre-ablation procedure to assess interatrial septum and to exclude left atrial thrombus or other significant structural heart disease. Venous access was obtained through the femoral vein. A 6F deflectable quadripolar catheter (Bard, Lowell, Massachusetts, USA) was positioned in the coronary sinus. Transseptal access to the left atrium was achieved guided by fluoroscopy and pressure with a Brockenbrough needle, transseptal sheath (SL1, St Jude) and a guidewire. An initial bolus of 10.000 units of heparin was given and additional administration to achieve an activated

clotting time between 300 and 350 seconds. All sheaths were continuously flushed with saline containing 2500 IU heparin per 500 mL saline. Pulmonary vein angiography was performed for ipsilateral PV ostia to provide a geometric reference for catheter navigation and localization of the antrum. A three-dimensional electroanatomic map of the left atrium (LA) was constructed (CARTO, Biosense Webster). Isolation of all PVs was performed using circumferential periosteal applications of radiofrequency energy, with a power limit of 40 Watt on the anterior LA and 30 Watt on the posterior LA, and verified with a decapolar circular mapping catheter (Lasso, Biosense Webster). The ablation was performed with a 3.5-mm irrigated tip catheter (Thermocool, Biosense Webster). RF energy was applied for 20-60 seconds until the local electrogram amplitude was eliminated. The endpoint of the ablation procedure was defined as the absence or dissociation of PV potentials documented with a circular decapolar mapping catheter within the PVs ≥ 30 minutes post-ablation.

Surgical ablation

In supine position, a double-lumen tracheal tube was introduced. In the right hemithorax, a 5-10-cm incision in the fourth intercostal space in the anterior axillary line was placed. A soft tissue retractor was used to introduce the scope through the sixth intercostal space (submammary). The pericardium was opened anterior to the phrenic nerve. Two stay sutures were placed in the pericardium. Blunt dissection of Waterston's Groove was performed followed by a blunt dissection and opening of the oblique sinus (OS) caudal to the right inferior pulmonary vein (RIPV). Then blunt dissection and opening of the OS cranial of the right superior pulmonary vein (RSPV) between RSPV and right pulmonary artery were performed. Hereafter, a silastic tape was placed around the right-sided PVs in order to facilitate proper positioning of the device.

An irrigated bipolar clamp device (Cardioblate, Medtronic, USA) was introduced for PV isolation. This device has a self-regulating ablation protocol based on an impedance feedback system. Transmurality feedback is indicated based on a steady-state plateau in tissue impedance. After introduction of the device, antral tissue around the right sided PVs was clamped after gentle traction of the tape and RF energy was applied to ablate the left atrial wall adjacent to the junction with the right-sided PVs. After RF energy application, the clamp was repositioned approaching the antrum of the pulmonary vein pair from 180° and then a second RF application was performed. Isolation of the PVs was confirmed with pacing manoeuvres at the left atrium-PV junction. After 30 minutes, pacing maneuvers were repeated to check for electrical reconnection. The left hemithorax was opened similar to the right hemithorax, except for the incision of the pericardium that was incised posterior to the phrenic nerve.

Additional left atrial appendage occlusion with endoloop was performed. Ganglionated plexi ablation and additional ablation lines were not performed.

Endpoints

Efficacy and safety

The primary endpoint was defined as freedom from atrial tachyarrhythmias with a duration of ≥ 30 seconds during follow-up, without the use of anti-arrhythmic drugs. A 3-month blanking period was initiated. The safety endpoint was the absence of procedure related complications. Complications were regarded as major if it resulted in death, irreversible damage to structures or organs, stroke, atrio-esophageal fistula, conversion to sternotomy or need for re-operation. Mild or moderate pericardial effusion not necessitating intervention and managed conservatively, small groin hematoma not requiring blood transfusion and without significant drop in hemoglobin, and procedure related mild infection (such as urinary tract infection or respiratory tract infection) were regarded as minor complications.

Quality of life

The predefined primary QOL outcome measures used for this analysis were mean SF-36 and EHRA scores 3 months after procedure. Other secondary outcome measures were mean SF-36 scores at 6 and 12 months after procedure, median EHRA scores 6, 12, and 24 months after procedure, and change in SF-36 and EHRA scores as compared to baseline.

Post-procedural care

Anticoagulation was re-initiated as soon as possible, after control of bleeding, and was continued at least 3 months after the procedure. When CHADS₂VASC-score score was ≥ 1 , patients were kept on anticoagulation. During the blanking period of 3 months the AAD were tapered off.

Follow-up

Follow-up consisted of outpatient clinic visits at 3, 6, 12, and 24 months after the ablation procedure or at the emergency department when patients had symptoms. QOL was assessed using the SF-36 questionnaire at baseline, 3, 6, and 12 months follow-up. AF-related symptoms were quantified at baseline and each outpatient clinic visit using the EHRA score. Furthermore, a 12-channel ECG and ILR device download were performed to assess any recurrences of arrhythmias.

Statistical analysis

All statistical analyses were performed using the Statistical package for the social sciences (SPSS) version 22 (IBM Nederland B.V., Amsterdam, The Netherlands). A two-sided P value of <0.05 was considered statistically significant. To assess the primary efficacy endpoint, we performed both intention-to-treat-analysis (ITT) and as-treated patient analysis because of the small sample size. As-treated analysis was performed to assess the safety endpoint.

Categorical variables are reported as frequencies and percentages with 95% confidence interval (95% CI) where appropriate. Continuous variables are described using the mean and standard deviation (SD) when normally distributed or using the median with the interquartile range (IQR) when not normally distributed. The Mann-Whitney U test or Wilcoxon signed rank test was used for the continuous variables. The Chi-square test was used for the comparison of categorical variables. Time to first documented recurrence was analyzed by the log-rank statistic and plotted using Kaplan-Meier survival curve. Correlations between variables were evaluated using Spearman's rho.

RESULTS

Patient characteristics

A total of 52 patients met inclusion criteria and were randomized: 26 to catheter ablation and 26 to surgical ablation. All patients in the catheter group received catheter ablation. In the surgical group, 23 patients underwent MIPI and 2 patients received CA because after randomization these patients refused surgical ablation. One patient in the surgical group was excluded because of significant coronary artery disease necessitating coronary artery bypass surgery combined with PVI. In the CA group, one patient was excluded from analyses after ablation because on the pre-procedural TTE and TEE, a much larger left atrium was seen than expected (LA volume index $>50 \text{ ml/m}^2$). Figure 1 shows the patient distribution. Baseline characteristics are summarized in Table 1.

Procedural characteristics

The total median procedure time was not significantly different ($P = 0.14$) between CA (168 min ranging 124-195) and MIPI (176 min, range 155-221). In the CA group complete electrical isolation was achieved in all PVs (100%). In the MIPI group, PVI and left atrial appendage ablation ligation were successful in all patients. Hospitalization duration was significantly longer ($P < 0.001$) in MIPI with a median of 9 days (range 8-10) versus a median of 3 days (2-3) after CA. More details on procedural characteristics are described in an earlier publication of this trial.⁶

Efficacy and safety endpoint

Primary endpoint results of the SCALAF are described in detail in a previous report.⁶ In short, in ITT analysis of the primary endpoint, CA single-procedure arrhythmia-free survival without the use of AAD after 2 years of follow-up was noninferior compared to MIPI (2-year Kaplan-Meier event-rate estimates, 56.0% and 29.2%, respectively; log-rank $P = 0.059$; hazard ratio [HR], 0.56; 95% CI, 0.26 - 1.20).

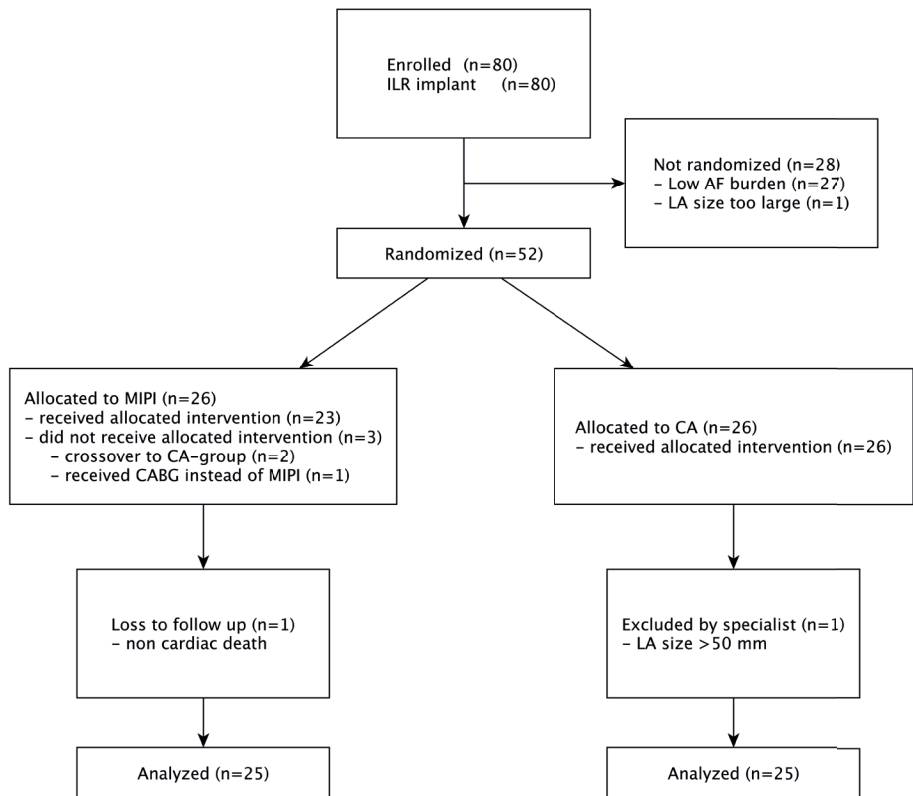


Figure 1. Patient distribution

Study design and patient distribution. AF: atrial fibrillation; CA: catheter ablation; CABG: coronary artery bypass grafting; ILR: implantable looprecorder; LA: left atrium; MIPI: minimal invasive thoracoscopic pulmonary vein isolation.

Procedure-related adverse events during follow-up occurred significantly more often in MIPI than CA (37.5% versus 11.1%; difference 26.4%; 95% CI 3.2% - 49.6%; $P = 0.046$). This was mainly due to a difference in major complications (20.8% in MIPI versus 0% in CA, difference 20.8%; 95% CI 4.8% - 36.9%; $P = 0.029$). All complications in the CA group were minor complications, whereas in the MIPI group there were five major complications.

SF-36 questionnaire

Primary QOL endpoint

The SF-36 questionnaire scores are presented in table 2 and illustrated in figure 2. At baseline, mean SF-36 scores for all health segments were not significantly different between CA and MIPI. Three months after ablation, physical role limitation score was significantly higher after CA compared to MIPI (88.2 ± 29.5 ; versus 40.9 ± 44.0 ; $P = 0.001$; respectively). This means that 3 months after CA, patients experienced less limitation in their daily activity

Table 1 Baseline characteristics

	Catheter ablation (N=25)	MIPI (N=25)
Age	59 (55-66)	55 (47-62)
Male	19 (76%)	20 (80%)
AF duration (years)	4.0 (1.7-7.9)	3.6 (1.5-8.8)
LVEF (%)	55 (50-60)	55 (53-60)
LA size, PLAX(mm)	41 (38-44)	39 (37-42)
Failed AAD prior to randomization		
Flecainide	16 (64%)	18 (72%)
Propafenone	0	2 (8%)
Sotalolol	14 (51.9%)	14 (60.9%)
Amiodarone	3 (12%)	2 (8%)
Beta-blocker	13 (52%)	15 (60%)
Verapamil/diltiazem	6 (24%)	1 (4%)
Digoxine	4 (16%)	2 (8%)
CHADS ₂ VASC score		
0	9 (36%)	9 (36%)
1	8 (32%)	11 (44%)
2	5 (20%)	4 (16%)
3	3 (12%)	1 (4%)
AF burden pre-ablation	35% (13-86)	25% (15-64)
Diabetes mellitus	2 (8%)	2 (8%)
Hypertension	10 (40%)	12 (48%)

Baseline characteristics (intention-to-treat analysis). Values are mean (\pm SD); median (interquartile range); number (%). CHADS₂VASC: congestive heart failure, 1; hypertension, 1; age, ($\geq 65=1$ point, $\geq 75=2$ points); diabetes mellitus, 1; stroke/TIA/systemic embolism, 2; vascular disease (peripheral arterial disease, previous myocardial infarction, aortic plaque), 1; and female gender, 1.

AAD, antiarrhythmic drugs; AF, atrial fibrillation; CA, catheter ablation; LA, left atrium; LVEF, left ventricular ejection fraction; MIPI, minimal invasive thoracoscopic pulmonary vein isolation; PLAX, parasternal long axis; and TIA, transient ischemic attack.

caused by physical problems than after surgical ablation. Bodily pain scores at 3 months after ablation were significantly higher after CA compared to MIPI (95.5 ± 8.7 ; versus 76.0 ± 27.8 ; $P = 0.021$; respectively), indicating less experienced pain 3 months after CA compared to MIPI. These differences were diminished 6 months after ablation. Median EHRA scores for AF symptoms at 3 months follow-up were not significantly different between CA and MIPI (1.5; interquartile range [IQR], 1-2; versus 2; IQR, 1-2; $P = 0.35$). None of the SF-36 measures were correlated to AF burden at baseline or follow-up.

Table 2. SF-36 questionnaire health sections

	CA (N=25)	MIPI (N=25)	P-value*
Physical functioning			
Baseline	72.3 (±19.8)	63.8 (±23.5)	0.200
3 months	82.4 (±21.7)	73.4 (±24.3)	0.200
6 months	85.3 (±22.3)	75.5 (±20.5)	0.055
Social functioning			
Baseline	71.0 (±24.6)	64.3 (±31.9)	0.521
3 months	86.9 (±25.9)	78.1 (±24.5)	0.210
6 months	86.9 (±21.8)	81.4 (±24.4)	0.380
Role limitations (physical problem)			
Baseline	43.8 (±42.5)	45.8 (±48.2)	0.956
3 months	88.2 (±29.5)	40.9 (±44.0)	0.001
6 months	81.9 (±38.2)	59.2 (±44.3)	0.142
Role limitations (emotional problem)			
Baseline	65.3 (±42.3)	70.8 (±44.3)	0.572
3 months	96.1 (±11.0)	75.7 (±41.4)	0.333
6 months	85.9 (±33.9)	85.9 (±33.9)	1.000
Mental health			
Baseline	71.3 (±17.1)	75.2 (±19.1)	0.374
3 months	80.2 (±16.3)	80.9 (±16.5)	0.967
6 months	78.7 (±18.9)	80.2 (±16.3)	0.784
Vitality			
Baseline	51.9 (±22.4)	44.4 (±21.5)	0.239
3 months	70.9 (±15.0)	59.8 (±21.6)	0.117
6 months	72.5 (±20.2)	62.3 (±19.5)	0.141
Pain			
Baseline	84.5 (±16.0)	68.4 (±28.3)	0.052
3 months	95.5 (±8.7)	76.0 (±27.8)	0.021
6 months	92.6 (±10.9)	83.0 (±21.3)	0.258
General health perception			
Baseline	56.0 (±17.1)	51.3 (±19.4)	0.155
3 months	73.8 (±16.4)	64.1 (±22.3)	0.211
6 months	73.2 (±20.8)	64.7 (±22.5)	0.284

* P-value based on intention-to-treat analysis. Data are displayed as mean (±SD)

Secondary endpoints

Significant higher SF-36 scores were found 3 months after treatment compared to baseline in both CA and MIPI groups regarding physical functioning, social functioning, physical role functioning, vitality, and general health perceptions, indicating better perceived health status

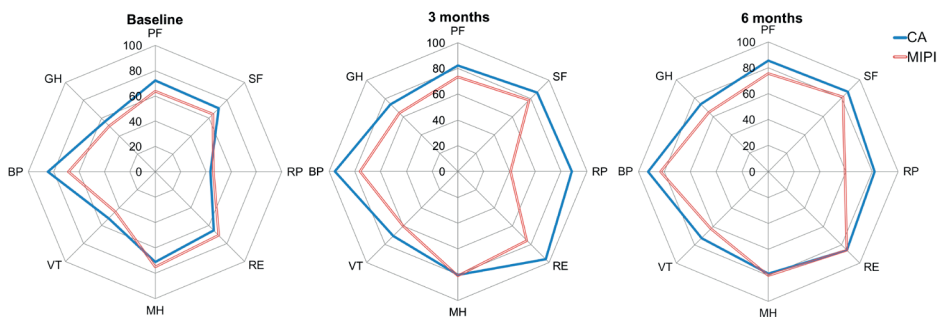


Figure 2. SF-36 Health Survey Questionnaire Scores

Radar chart showing SF-36 Health Survey Questionnaire scores at baseline, 3, and 6 months post CA and MIPI. BP: bodily pain; CA: catheter ablation; GH: general health perceptions; MH: mental health; MIPI: minimal invasive thoracoscopic pulmonary vein isolation; PF: physical functioning; RP: physical role functioning; RE: emotional role functioning; SF: social functioning; VT: vitality.

on these health sections compared to before ablation, as shown in figure 3. After 6 months, all health segments were significantly improved compared to baseline. Due to low response rate at 12 months, data are inconclusive and not presented (see table 3).

AF burden was not correlated to any of the SF-36 scores (Supplementary Table S1). Higher CHADS₂VASC-score scores were correlated with lower scores at baseline regarding physical functioning ($r = -0.36$, $p = 0.012$), social functioning ($r = -0.36$, $p = 0.011$), physical role functioning ($r = -0.31$, $p = 0.030$), emotional role functioning ($r = -0.41$, $p < 0.01$), MH ($r = -0.39$, $p < 0.01$), VT ($r = -0.36$, $p = 0.012$), BP ($r = -0.41$, $p < 0.001$), and at 6 months follow-up regarding SF ($r = -0.42$, $p < 0.01$), RE ($r = -0.34$, $p = 0.039$), and mental health ($r = -0.36$, $p = 0.026$). AF symptoms assessed by EHRA score improved significantly at 3, 6, 12, and 24 months compared to baseline for both treatment groups ($P < 0.001$) (Supplementary Table S2). EHRA score differences as compared to baseline were not different between treatment groups (Supplementary Table S3). There was no correlation between EHRA score improvement and AF burden decrease ($r = -0.22$, $p = 0.16$).

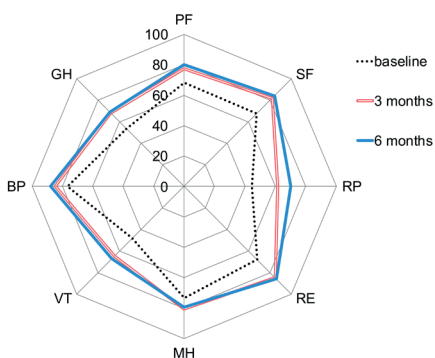


Figure 3. SF-36 Health Survey Questionnaire Scores

Radar chart showing SF-36 Health Survey Questionnaire scores at baseline, 3, and 6 months post ablation. BP: bodily pain; GH: general health perceptions; MH: mental health; PF: physical functioning; RP: physical role functioning; RE: emotional role functioning; SF: social functioning; VT: vitality.

Table 3 SF-36 scores changes

	CA (N=25)	MIPI (N=25)	P-value*
Physical functioning			
Change 3 months	6.47 (\pm 14.44)	6.67 (\pm 20.27)	0.331
Change 6 months	12.78 (\pm 13.85)	13.25 (\pm 19.21)	0.311
Social functioning			
Change 3 months	9.59 (\pm 27.35)	12.57 (\pm 35.30)	0.393
Change 6 months	13.11 (\pm 24.74)	20.00 (\pm 31.89)	0.496
Role limitations (physical problem)			
Change 3 months	35.29 (\pm 39.59)	-9.52 (\pm 49.67)	0.002
Change 6 months	40.28 (\pm 42.99)	17.11 (\pm 52.74)	0.159
Role limitations (emotional problem)			
Change 3 months	21.59 (\pm 37.20)	3.14 (\pm 43.33)	0.112
Change 6 months	17.53 (\pm 34.02)	22.79 (\pm 43.08)	0.762
Mental health			
Change 3 months	4.47 (\pm 13.33)	4.00 (\pm 21.09)	0.613
Change 6 months	7.79 (\pm 13.61)	6.00 (\pm 23.01)	0.931
Vitality			
Change 3 months	15.00 (\pm 15.71)	14.29 (\pm 25.11)	0.942
Change 6 months	20.00 (\pm 20.22)	19.75 (\pm 25.83)	0.931
Pain			
Change 3 months	9.00 (\pm 12.13)	6.81 (\pm 31.43)	0.303
Change 6 months	8.11 (\pm 13.54)	14.95 (\pm 28.23)	0.857
General health perception			
Change 3 months	13.82 (\pm 14.31)	11.67 (\pm 22.15)	0.276
Change 6 months	15.79 (\pm 15.21)	16.05 (\pm 20.92)	0.74

* P-value based on intention-to-treat analysis. Change as compared to baseline. Data is displayed as mean (\pm SD)

DISCUSSION

Main findings

This is the first randomized study comparing QOL outcome of catheter and minimally invasive surgical ablation as primary ablative treatment of paroxysmal and early persistent AF. In the present analysis, both ablation techniques resulted in improved QOL measures regarding physical functioning, social functioning, physical role functioning, and vitality at 3 months follow-up and for all health segments at 6 months follow-up. The only QOL measures that were significantly better after CA compared to SA were role limitations due to physical problems and bodily pain, at 3 months follow-up. These results might indicate that MIPI,

although using less invasive incisions, still leads to greater bodily discomfort compared to CA, up to 3 months after surgical treatment. After 6 months, these differences were diminished.

It is known that AF ablation can reduce AF occurrence and improve AF-related symptoms. According to current guidelines, the primary indication for CA is symptom reduction and QOL improvement.¹ Multiple studies have shown that CA is associated with improved QOL. In a meta-analysis of data from randomized controlled trials comparing CA and antiarrhythmic drug therapy for AF, CA was superior to antiarrhythmic drug therapy for improvement of QOL.^{3,7} Another meta-analysis showed CA of AF is associated with increased QOL; however, patients without AF recurrence after treatment had a better improvement than patients with AF recurrence.⁸ Although successful AF ablation results in higher QOL improvement in patients without AF recurrence, patients with recurrence also benefit from ablation.⁹ Limited data exist on QOL after thoracoscopic surgical ablation of AF. In a study by Bagge and colleagues, thoracoscopic PVI and ganglionated plexi ablation improved QOL, symptoms, and exercise capacity.¹⁰ In the AFACT study, patients with persistent AF undergoing thoracoscopic PVI with additional ablation lines showed improved QOL 12 months after ablation; however, patients with multiple AF recurrences after treatment did not benefit from ablation. Likewise, patients with permanent consequences of surgical procedural complications did not show QOL improvement.¹¹ Previous studies have shown that surgical ablation of AF is associated with more adverse events and longer hospital stay.^{4,12-13} Although the majority of the complications in our study was of a temporary nature, the higher complication rate after MIPI as compared to CA probably resulted in lower QOL scores on physical problems and pain experienced 3 months after MIPI.

AF burden and quality of life

In this trial, CA was noninferior to surgical MIPI in terms of arrhythmia-free survival after 2 years of follow-up. Both ablation strategies reduced AF burden significantly. The correlation between AF burden and SF-36 QOL measurements was poor in our study. Data on association between SF-36 scores and AF burden measured by ILR are scarce. In a subanalysis of the STAR AF 1 study, QOL improved after AF ablation regardless of treatment success, except in patients with very high AF burden assessed by external loop recorders.¹⁴ Furthermore, studies have shown that SF-36 scores after AF ablation are strongly related to AF recurrence within 30 days prior to the QOL assessment.³ The widely used SF-36 survey is influenced by a broad range of diseases and might lack sensitivity to changes with reductions in AF burden.¹ This is supported by our data showing increased CHADS₂VASC-score is well correlated with different QOL measures at baseline and 1 year follow-up.

Additional to impaired QOL, AF is associated with an increased risk of heart failure and mortality.^{15,16} Recent data showed that persistent forms of AF are associated with significant increase in thromboembolism and death, highlighting the need for therapies to prevent AF progression.¹⁷ Our data show a poor correlation between AF burden and perceived AF

symptoms after ablation, which highlights that asymptomatic AF is common, especially after ablation. This finding supports the guideline recommendation that discontinuation of anticoagulation after ablation should be based on patient's stroke risk profile and not on a supposedly successful ablation.¹

There is more evidence emerging suggesting AF ablation can also improve morbidity and mortality. The AATAC study comparing CA with amiodarone showed reduction in hospitalization and mortality in persistent AF patients with heart failure.¹⁸ The CASTLE-AF trial comparing ablation with pharmacological therapy showed similar results with reduction in hospitalization and mortality in patients with AF and heart failure.¹⁹ Furthermore, data suggest CA of AF is associated with a decreased risk of stroke and mortality.²⁰ Recent results from the CABANA trial, however, showed no significant benefit of CA over medical therapy in reduction of the composite end point of death, disabling stroke, serious bleeding, or cardiac arrest.²¹ In this trial, CA, compared with medical therapy, did lead to more favorable improved QOL outcomes at 12 months measured by Atrial Fibrillation Effect on Quality of Life (AFEQT) summary score and Mayo AF-Specific Symptom Inventory (MAFSI) frequency score.²² Future long-term follow-up studies are needed to assess whether AF ablation can reduce mortality and morbidity. Meanwhile, symptom reduction and QOL improvement remain the primary indication for catheter ablation.

Limitations

The main limitation of our study is the small sample size. A larger-than-expected proportion of patients did not meet the requirement of AF burden >10%, which was originally set as the inclusion criterion. Highly symptomatic episodes of AF required electrical cardioversion before patients could reach the required 10% burden within one week of loop recorder monitoring. Later, we changed this inclusion criterion to 2% AF burden. Furthermore, at 1 year follow-up the questionnaire response rate was too low for analysis to avoid nonresponse bias. The secondary outcome results should be interpreted with caution due to low study power.

In this study, the less AF-specific SF-36 Health Survey Questionnaire was used to assess QOL. The SF-36 scale is commonly used in medical studies and allows comparison with other medical interventions; however, it might lack the sensitivity to detect AF-specific changes.¹ Furthermore, post-procedural QOL assessment was first measured 3 months after treatment, while earlier assessment might have provided more insight into early procedural morbidity such as pain and physical role limitation.

Future perspectives

QOL should remain an important outcome in clinical research on AF ablation. To detect AF-specific QOL changes we recommend to use an AF-specific QOL scale (e.g. Atrial Fibrillation Effect on Quality-of-Life (AFEQT), University of Toronto Atrial Fibrillation Severity Scale, Mayo AF-Specific Symptom Inventory, or Symptom Severity Scale), especially in trials comparing

treatment strategies.¹ More data on QOL after minimally invasive survival ablation of AF are warranted. Upcoming are the results of the currently ongoing CASA-AF trial, which is a multi-center randomized controlled study comparing CA with MIPI in patients with long-standing persistent atrial fibrillation. We expectantly await the results concerning freedom from atrial arrhythmias (primary endpoint) and different QOL measures.

CONCLUSION

CA and MIPI ablation of AF both result in an improvement in several QOL measurements, although CA resulted in significantly less physical problems and bodily pain 3 months after treatment compared to MIPI. There was no significant correlation between AF burden, perceived AF symptoms, and QOL assessed by the SF-36 survey both before and after treatment.

Funding: This study was sponsored by Medtronic.

Conflict of interest: The authors declare that they have no competing interest.

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PART II

Novel ablation
technologies and future
perspectives

7 | Efficacy of multi-electrode linear irreversible electroporation

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EP Europace, euaa280, <https://doi.org/10.1093/europace/euaa280>

ABSTRACT

Aims

We investigated the efficacy of linear multi-electrode irreversible electroporation (IRE) ablation in a porcine model.

Methods and results

The study was performed in six pigs (weight 60–75 kg). After median sternotomy and opening of the pericardium, a pericardial cradle was formed and filled with blood. A linear seven polar 7-Fr electrode catheter with 2.5 mm electrodes and 2.5 mm inter-electrode spacing was placed in good contact with epicardial tissue. A single IRE application was delivered using 50 J at one site and 100 J at two other sites, in random sequence, using a standard monophasic defibrillator connected to all seven electrodes connected in parallel. The pericardium and thorax were closed and after 3 weeks survival animals were euthanized. A total of 82 histological sections from all 18 electroporation lesions were analysed. A total of seven 50 J and fourteen 100 J epicardial IRE applications were performed. Mean peak voltages at 50 and 100 J were $1079.2\text{V} \pm 81.1$ and $1609.5\text{V} \pm 56.8$, with a mean peak current of $15.4\text{A} \pm 2.3$ and $20.2\text{A} \pm 1.7$, respectively. Median depth of the 50 and 100 J lesions were 3.2 mm [interquartile range (IQR) 3.1–3.6] and 5.5 mm (IQR 4.6–6.6) ($P < 0.001$), respectively. Median lesion width of the 50 and 100 J lesions was 3.9 mm (IQR 3.7–4.8) and 5.4 mm (IQR 5.0–6.3), respectively ($P < 0.001$). Longitudinal sections showed continuous lesions for 100 J applications.

Conclusion

Epicardial multi-electrode linear application of IRE pulses is effective in creating continuous deep lesions.

Key Words: Linear Multi-electrode Epicardial Irreversible Electroporation Ablation

INTRODUCTION

Irreversible electroporation (IRE) is a promising ablation modality for catheter based therapy of cardiac arrhythmias.¹⁻⁴ Earlier studies showed that electroporation can create transmural epicardial lesions, and deep continuous circular lesions in the pulmonary veins.^{3,5} Furthermore, animal data suggests electroporation can be a safe treatment modality in the pulmonary veins, in the vicinity of important structures such as the coronary arteries, the right phrenic nerve, and the oesophagus.⁵⁻⁹ In addition, preliminary results of the first clinical studies suggest that electroporation is a safe and effective method for pulmonary vein isolation.¹⁰⁻¹² While the first in human study on pulmonary vein isolation with single pulse IRE ablation using a circular catheter is completed¹², additional animal data is needed to assess whether use of the technique outside the PVs, e.g. ablation of ventricular arrhythmias or extensive atrial substrate ablation, is also safe and feasible. The aim of this study was to assess feasibility of creating linear ablation lesions with linear multi-electrode electroporation, and to assess the relation between the magnitude of epicardially applied linear multi-electrode single pulse IRE pulses and lesion size.

METHODS

This study was approved by the Animal Experiments Committee of the University Medical Center Utrecht, Utrecht, The Netherlands and conducted in accordance with the Guide for The Care and Use of Laboratory Animals.

Study protocol

The study was performed in 6 pigs (weight 60-75kg). All pigs received Amiodarone (1200mg/d) 1 week prior to procedure and continued 800mg/d post-ablation to prevent procedure-related arrhythmias until euthanasia.¹³ Procedures were performed under general anaesthesia according to standard protocol.

Epicardial ablation

The thorax was opened via a median sternotomy. After opening the anterior pericardium, the pericardial edges were lifted and fixated creating an approachable pericardial cavity. Epicardial ablations were performed using a custom 7 French, 7-electrode linear catheter with 2.5 mm long electrodes with 2.5 mm spacing (figure 1). The catheter was placed at 3 different locations on the left ventricle using a passive placement and spacing device (figure 1). The pericardial cavity was then filled with blood to mimic endocardial conditions as demonstrated previously.² Using a Lifepak 9 (Physio-Control, Redmond, WA) defibrillator, monophasic IRE pulses were applied in a randomly assigned sequence, 1 pulse with 50 J and two pulses with

100 J. The catheter was connected to the cathode while a skin patch on the lower back was connected to the anode. Voltage and current waveforms of all IRE pulses were recorded with an oscilloscope (Tektronix TDS 2002b, Beaverton, OR) and analyzed for the occurrence of arcing.^{2,14} After each IRE application the catheter was removed from the epicardium. Ablation sites were marked with sutures. After completion of the ablation protocol the pericardium and thorax were closed in layers.

The animal was allowed to recover and was daily observed for symptoms of discomfort. After a 3-week survival period, the animals were euthanized by administration of intravenous potassium chloride. After sternotomy the heart was removed and the ablation sites were excised and fixated in formalin for histological analysis.

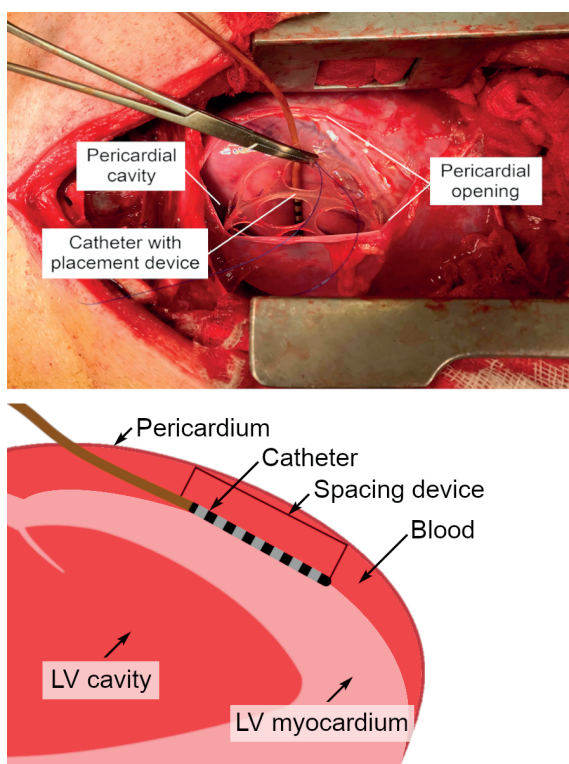


Figure 1. Pericardial Ablation Setup

Panel A shows the epicardial placed custom 7 French 7 electrode linear catheter with 2.5 mm electrodes with 2.5 mm spacing fixed to a plastic placement device, prior to filling of the pericardial cavity with blood to mimic endocardial conditions. Panel B shows a schematic drawing of catheter setup.

Histological evaluation

After fixation, 4 mm thick segments were taken from each lesion perpendicular to the catheter position during ablation. In 2 animals additional longitudinal sections were taken to as-

sess lesion continuity. The segments were embedded into paraffin blocks, sliced, and stained with hematoxylin-eosin and Elastic van Gieson stain. All histological slices were scanned and digitized to measure lesion width and depth. Measurements were performed blinded for the magnitude of applied IRE energy.

Statistical analysis

Generalized linear mixed model design was used to assess differences in lesion dimensions and to account for repeated measures. Continuous data are mentioned as mean ± standard deviation (SD) and median (interquartile range) when appropriate. A P-value of ≤ 0.05 was considered statistically significant. Statistical analysis was conducted using IBM statistics version 24.0 (IBM SPSS Statistics for Macintosh, 2016: IBM Corp., Armonk, New York, USA).

Results

A catheter placement device (figure 1) was used to ensure good epicardial contact. There were no signs of catheter failure during the IRE energy applications and no periprocedural complications were observed. All 6 animals survived the 3-week survival period uneventful.

Epicardial ablation

Energy application

A total of 18 epicardial IRE energy applications were performed in 6 animals, six 50 J and twelve 100 J applications. Mean peak voltage at 50 J and 100 J was 1079.2 ± 81.1V and 1609.5 ± 56.8V, with a mean peak current of 15.4 ± 2.3A and 20.2 ± 1.7A, respectively. Details of IRE energy applications are summarized in table 1. Additional resistors (10 – 25 Ω) were used in nine of the twelve 100 J applications to reduce peak current to prevent arcing, nevertheless pulse voltage and current waveforms showed distortions (implicating arcing) in all of the 100 J applications and in none of the 50 J applications.

Table 1 Magnitude of application, output, and lesion size

	Peak voltage V	Peak current A	Peak resistance Ω	Slices N	Depth mm	Width mm
50 J	1079.2 ± 81.1	14.5 ± 2.3	71.8 ± 15.6	26	3.2 (3.1 – 3.6)	3.9 (3.7 – 4.8)
100J	1609.5 ± 56.8	20.2 ± 1.7	80.0 ± 9.5	56	5.5 (4.6 – 6.6)	5.4 (5.0 – 6.3)
P-value †					<0.001*	<0.001*

Data is displayed as mean±SD or median (interquartile range) where appropriate.

* considered statistical significant

† assessed by general linear mixed models

Macroscopic Findings

Sutures placed at both ends of the linear lesion allowed lesion identification after the 3-week survival period. On visual inspection of the heart after termination, myocardial discoloration of the 100J ablation lesions appeared more distinct compared to 50 J lesions.

Histological Analysis

Lesion dimensions

In 6 animals, 82 histological slides from 18 electroporation lesions were assessed for lesion dimensions. In total 56 slides from twelve 100J lesions, and 26 tissue slices from six 50J lesions were analyzed. Median depth of the 50J and 100J lesions were 3.2 mm (IQR, 3.2 – 3.6) and 5.5 mm (IQR, 4.6 – 6.6), respectively. 100 J lesions were significantly deeper compared to 50 J lesions ($\Delta 2.3$ mm; 95% CI, 1.4 – 3.0; $P < 0.001$). Median lesion width of the 50J and 100J lesions were 3.9 mm (IQR, 3.7 – 4.8) and 5.4 mm (IQR, 5.0 – 6.3), $P < 0.001$ (figure 2). Longitudinal sections taken from four 100 J lesions and two 50 J lesions, showed continuous lesions of all four 100 J sections and partially separate (non-continuous) lesions in both 50 J sections (figure 3). Histological evaluation of coronary vessel branches that were by chance located in vicinity of the ablation lesions showed no signs of intimal hyperplasia for

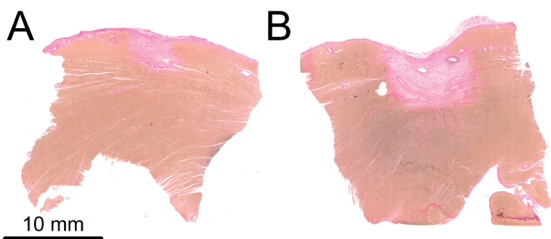


Figure 2. Transversal histological sections
Histological elastic van Gieson–stained perpendicular sections of linear lesions created with 50J (A) and 100J(B). The endocardial side is at the bottom and the epicardial side is at the top of the picture. Note tissue shrinkage difference (panels A and B) and unaffected blood vessels within the lesion (panel B).

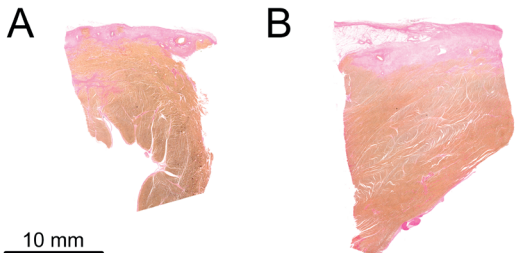


Figure 3. Longitudinal histological sections
Histological elastic van Gieson–stained longitudinal sections of linear lesions created with 50J (A) and 100J(B). The endocardial side is at the bottom and the epicardial side is at the top of the picture.

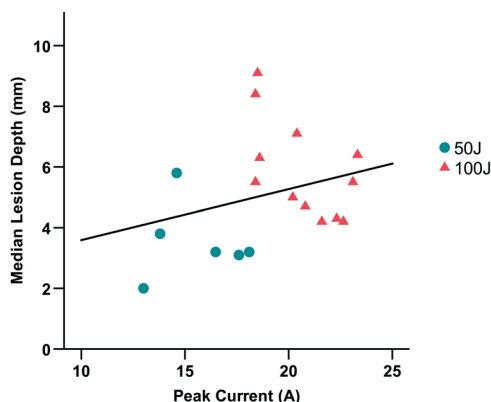


Figure 4. Peak Current and Lesion Depth Relationship between peak ablation current and median lesion depth. Symbols indicate median lesion depths for 50 and 100 Joule applications. The relationship between peak current and median lesion depth (line) assessed by linear regression was non-significant, with a slope of 0.17 mm/A (95% CI, -0.13 to 0.47 mm/A; $P=0.26$).

vessels located both within and outside the lesion. The relationship between peak current and median lesion depth, assessed by linear regression was non-significant, with a slope of 0.17 mm/A (95% CI, -0.13 to 0.47 mm/A; $P=0.26$), as displayed in figure 4.

DISCUSSION

The main finding of this study is that creation of deep and continuous myocardial ablation lesions using a linear multi-electrode electroporation catheter is feasible. All animals survived the study period and no complications were observed. With 50 J applications, myocardial lesions were 3.2 mm deep and 3.9 mm wide and with 100 J applications significant larger lesions were produced (5.5 mm deep and 5.4 mm wide). Histological evaluation of the ablation lesions showed no effect of electroporation on coronary vessels within the lesions, as was shown in previous animal studies.^{6,7}

Irreversible Electroporation (IRE)

Direct current (DC) ablation was routinely used to create myocardial lesions prior to the development of RF ablation technology in the late 1980s. In contrast to thermal ablation with RF energy, DC ablation is not heat mediated, but is caused by a strong electrical field that disrupts the lipid structure of the cell membrane leading to apoptosis.¹⁵ Even though DC ablation was effective in the 1980s, it had important disadvantages because it required general anaesthesia and was associated with potentially serious complications due to electrolysis and explosive evaporation and a pressure wave.¹⁴ Novel catheters and DC generators have been designed that addressed the issues of arcing and vapor formation. However, in the present study, we observed arcing with 100J IRE applications. This indicates that the applied peak current at the 100J setting was too large for the used catheter design, that is, a too small total electrode surface for the applied current.¹⁴ Furthermore, suboptimal submersion

of one or several electrodes might have contributed to arcing. An optimized electrode design or reduction in applied current with the present design will be required to prevent arcing. On the other hand, lesion depth with 100J applications is more than enough for atrial applications, thus slightly lowering the applied energy in combination with the current catheter design is a viable option. In the present study, the median lesion depths at 100J is 5.5 mm, that is 1 mm smaller than the mean lesion depth of 6.4 mm reported in a previous study of Neven *et al.*³ In that study, after sternotomy, a single 35-mm long and 6-mm wide linear electrode was placed on the epicardium using a suction device, ensuring optimal electrode-tissue contact and preventing current leakage to surrounding tissue. Even though the layer of blood used in our study simulating endocardial conditions intentionally led to energy leakage, as will happen during endocardial ablation, median lesion depth is adequate, suggesting endocardial linear multi-electrode IRE might be feasible. In another study of Neven *et al.*⁶ a 7-Fr deflectable octopolar circular catheter with eight 2-mm ring electrodes was epicardially placed through a surgical subxiphoidal approach. The 200J applications resulted in a median lesion depth of 6.4 mm showing feasibility of this epicardial approach.

Clinical implications

IRE may overcome the disadvantages of RF ablation. Recent studies investigated the potential of using the circular IRE ablation technique for pulmonary vein isolation in patients with atrial fibrillation.^{10,12} Circumferential isolation of pulmonary veins has become the standard ablation technique for paroxysmal AF. However, additional linear ablation lesions are commonly created (e.g. left atrial posterior wall, left atrial roof line) in an attempt to reduce AF recurrences after ablation in patients with persistent and long-standing persistent AF.¹⁶ Furthermore, linear lesions are used to target epicardial and endocardial substrate for ventricular arrhythmias, for example epi-/endocardial ablation of scar tissue after myocardial infarction or myocarditis and targeted ablation at the epicardium of the right ventricular outflow tract for the treatment of VT/VF in patients with Brugada syndrome.¹⁷ As mean left atrial wall thickness in commonly targeted regions for linear left atrial ablation vary between 1.1 and 2.9 mm, all 100 J and 83% of the 50 J lesions in our study can be considered transmural.^{18,19} Our study results demonstrate the feasibility of IRE using a linear multi-electrode catheter design.

Future perspectives

These preliminary data warrant further development of a multi-electrode linear electroporation catheter for creating linear ablation lesions targeting epicardial and endocardial substrates of ventricular arrhythmias in selected patient populations such as patients with ischemic heart disease, arrhythmogenic right ventricular cardiomyopathy or Brugada syndrome. Furthermore, linear IRE may become an effective tool in ablation of AF triggers and

substrate located outside the pulmonary veins (e.g. cavotricuspid isthmus, left atrial posterior wall, left atrial roof line).

Limitations

In order to mimic endocardial conditions, the epicardial IRE ablations were performed in a porcine heart submerged under blood. Therefore, differences with endocardial conditions should be considered regarding interpretation of our results. Factors that might have influenced lesions formation include the absence of blood flow and the presence of coronaries and epicardial fat. Although similar ablation results regarding lesion dimensions might be expected in true endocardial linear multi-electrode IRE, this remains to be investigated.

Optimal electrode-tissue contact is of great importance in creation of ablation lesions and clinical outcome.^{20,21} In our study, set-up effective electrode-tissue contact was achieved using a catheter placement device. For future development of multi-electrode IRE ablation catheters, electrode-tissue contact measurement should be incorporated into the design. Of note, due to tissue shrinkage at the ablation site, lesions depth measurements might be underestimated.

CONCLUSIONS

The results of our experiments demonstrate that IRE ablation is technically feasible for linear ablation of porcine myocardium.

Conflict of interest: Authors F.W. and R.v.E. have filed patents on irreversible electroporation technology. The other authors have no conflicts of interest to disclose.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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8

Feasibility of Irreversible Electroporation Ablation in the Coronary Sinus

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Submitted

ABSTRACT

Introduction: Previous studies demonstrated that the coronary sinus (CS) is an important target for ablation in persistent atrial fibrillation. However, radiofrequency ablation in the CS is associated with coronary vessel damage and tamponade. Animal data suggest irreversible electroporation (IRE) ablation can be a safe ablation modality in vicinity of coronary arteries. We investigated the feasibility of IRE in the CS in a porcine model.

Methods: Ablation and pacing was performed in the CS in 6 pigs (weight 60-75kg) using a modified 9-French steerable linear hexapolar Tip-Versatile Ablation Catheter (T-VAC). Pacing maneuvers were performed from distal to proximal segments of the CS to assess atrial capture thresholds before and after IRE application. IRE ablations were performed with 100 J IRE pulses. After 3-week survival animals were euthanized and histological sections from the CS were analyzed.

Results: A total of 27 IRE applications in 6 animals were performed. Mean peak voltage was 1509 ± 36 V, with a mean peak current of 22.9 ± 1.0 A. No complications occurred during procedure and 3-week survival. At 30 minutes post ablation 100% isolation was achieved in all animals. At 3 weeks follow-up pacing thresholds were significant higher as compared to baseline. Histological analysis showed transmural ablation lesions in muscular sleeves surrounding the CS.

Conclusion: IRE ablation of the musculature along the CS using a multi-electrode catheter is feasible in a porcine model.

Keywords: Coronary Sinus Irreversible Electroporation Ablation

INTRODUCTION

Irreversible electroporation (IRE) is a promising ablation modality for catheter based therapy of cardiac arrhythmias.¹⁻³ Studies have shown that IRE can create transmural epicardial lesions, and deep continuous circular lesions in the pulmonary veins.^{4,5} Moreover, animal data suggest IRE can be a safe ablation modality in the vicinity of important structures such as the coronary arteries, the phrenic nerve, and the oesophagus.⁴⁻⁸ The first clinical experience suggests pulmonary vein isolation (PVI) can be safely and effectively achieved using IRE.^{9,10}

From a cardiac electrophysiological perspective, the coronary sinus (CS) and the surrounding muscular sleeves may provide triggers and substrate for atrial arrhythmias.¹¹ Of note, in addition to epicardial accessory pathways, atrial and ventricular arrhythmias may originate from the CS. Therefore, the CS is a potential target for ablation in persistent atrial fibrillation (AF), atrial tachycardias and atypical atrial flutters. Ablation of the CS is associated with improved ablation outcome in persistent AF after failed PVI.¹²⁻¹⁴ However, radiofrequency (RF) ablation within the CS is associated with coronary vessel damage and tamponade.¹⁵⁻¹⁷

Although experimental data demonstrated that IRE ablation is a safe ablation modality in vicinity of the coronary arteries, additional animal data is needed to assess whether the use of IRE inside the CS is also safe and feasible. Therefore, the aim of this study was to assess feasibility of IRE ablation of the musculature along the CS using a multi-electrode catheter.

METHODS

This study was approved by the Animal Experiments Committee of the University Medical Center Utrecht, Utrecht, The Netherlands, and was performed in accordance with the Guide for The Care and Use of Laboratory Animals.

Study protocol

The study was performed in 6 female pigs (weight 60-75 kg). All animals received Amiodaron (1200mg/d) 1 week prior to the procedure and continued 800mg/d to prevent procedure-related arrhythmias. Procedures were performed under general anaesthesia according to local standard operating procedures.

Coronary sinus ablation

An electrode patch (7506, Valleylab Inc, Boulder, CO) was placed on the lower back of the animal. Access to the right atrium was obtained via the right internal jugular vein. Intravenous heparin was administered. CS angiography was performed to assess anatomy, using contrast injection with a 5-French diagnostic catheter (Inquiry™, St Jude, USA). Then, a modified Tip-Versatile Ablation Catheter (T-VAC; Medtronic Ablation Frontiers, CA, USA) was

introduced in the CS through a 9-French sheath. The T-VAC is a 9-French steerable hexa-polar ablation catheter, designed to create linear lesion e.g. roof lines, cavotricuspid isthmus lines and mitral isthmus lines, using radiofrequency energy (figure 1A). The catheter connection cable was customized to enable both cardiac pacing and delivery of IRE pulses. Electrograms were recorded using the EP-Workmate™ Recording System, (St Jude Medical, MN, USA).

Baseline pacing thresholds were assessed before performing the ablation protocol. First, the ablation catheter was positioned distally in the CS and bipolar pacing thresholds were consecutively measured at electrode pairs 1-2, 3-4, and 5-6, starting with a pacing output of 10 mA, pulse width 2 ms and a cycle length of approximately 60% of the RR interval. Pacing output was decreased with 0.2 mA steps until loss of atrial capture was observed on the surface ECG. Subsequently, the catheter was repositioned from distal to more ostial direction under fluoroscopic guidance to maintain an overlap of 3 electrodes with the preceding position (figure 1B). Pacing threshold measurement and catheter repositioning were repeated until electrode pair 5-6 reached the CS ostium. The catheter was then again repositioned distally in the CS for IRE energy applications. Prior to and after each IRE application, bipolar stimulation thresholds were reassessed. A synchronized monophasic 100 J IRE pulse was applied between the T-VAC catheter (cathode) and the indifferent electrode pad on the lower back (anode), using a Lifepak 9 defibrillator (Physio-Control, Redmond, WA). Thereafter, the catheter was repositioned in ostial direction maintaining an overlap of 3 electrodes with the preceding position.

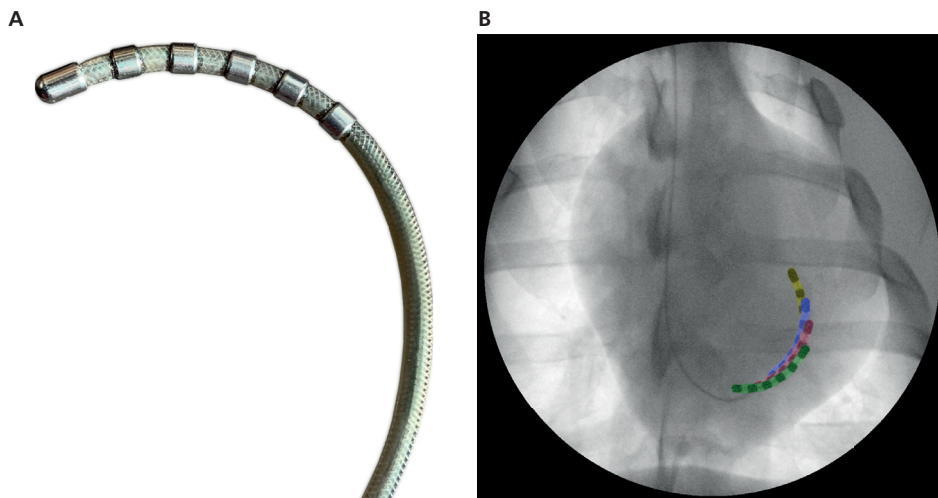


Figure 1. A Customized 9F steerable ablation catheter (T-VAC; Medtronic Ablation Frontiers, CA, USA) consisting of five 2 mm long ring electrodes and a 4 mm tip electrode with 3 mm spacing. **B** Fluoroscopy image of catheter positions within the CS. Colored overlays show an example of the different catheter positions during ablation.

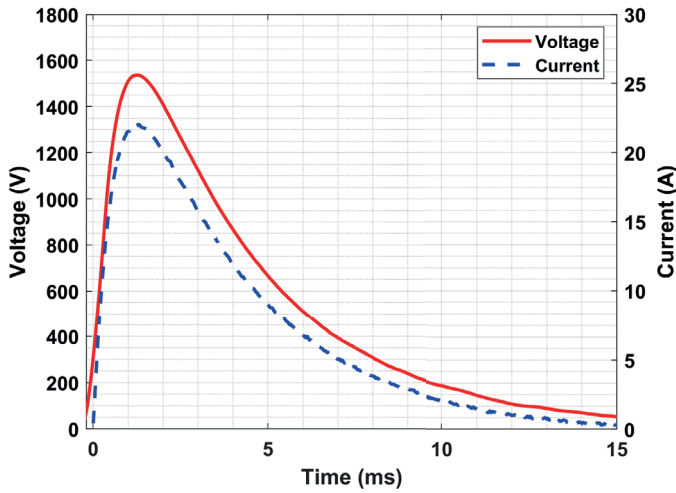


Figure 2. Voltage and current waveforms

Voltage and current waveforms of all IRE pulses were recorded with an oscilloscope (Tektronix TDS 2002b, Beaverton, OR, USA) and analyzed for the occurrence of arcing (figure 2).^{2,18} Additional resistance of 10 or 15 ohms was added to the circuit when deemed necessary to prevent arcing. After each IRE application the catheter position was checked using fluoroscopy, and stimulation thresholds were reassessed. After a 30 minute waiting period, bipolar stimulation thresholds were reassessed at each IRE application position under fluoroscopic guidance. CS angiography was repeated.

Thereafter, the catheter was removed. The animal was allowed to recover and was observed daily for symptoms of discomfort. After a 3-week survival period, angiography and stimulation threshold tests were repeated under general anesthesia. Subsequently, the animals were euthanized by administration of intravenous potassium chloride. After sternotomy the heart was removed and the CS was excised and fixated in formalin for histological analysis.

Histological evaluation

The heart was excised and opened along the right atrium. The CS was identified and excised with a margin of the left atrium and left ventricular myocardium. After fixation, 4.0 mm thick segments were taken from each lesion perpendicular to the long axis of the CS. The segments were embedded in paraffin blocks, sliced, and stained with hematoxylin-eosin and Elastic van Gieson. All histological slices were scanned and digitized (IntelliSite Ultra Fast Scanner; Philips Electronics Nederland BV, The Netherlands) to assess the CS and ablation lesions.

Statistical analysis

Pacing threshold differences were assessed by generalized linear mixed models design to account for repeated measures. Continuous data are listed as mean \pm standard deviation (SD) and median (interquartile range [IQR]) when appropriate. A P-value of ≤ 0.05 was considered statistically significant. Statistical analysis was conducted using IBM statistics version 24.0 (IBM SPSS Statistics for Macintosh, 2016: IBM Corp., Armonk, New York, USA).

RESULTS

There were no signs of catheter failure during the IRE energy applications and no periprocedural complications were observed. All 6 animals survived the 3-week survival period uneventful.

IRE application and electrophysiological analysis

A total of twenty-seven 100 J IRE energy applications were performed in the CS of 6 animals. Mean peak voltage was 1509 ± 36 V, with a mean peak current of 22.9 ± 1.0 A. Six IRE applications showed signs of arcing. In 5/6 animals an additional resistance of 10 or 15 ohms was added to the circuit. Acute isolation, defined as absence of capture with high-output pacing (> 10 mA), was found at all (100%) stimulation positions within the CS of all animals at 30 minutes post-ablation. At 3-week follow-up pacing thresholds > 10 mA were found at 64 of the 102 (63%) pacing positions, compared to 11 of the 90 (12%) pacing positions at baseline ($P < 0.001$).

Angiography

On angiography there were no signs of CS stenosis or thrombosis before and after the IRE applications, and also not after 3-weeks follow-up.

Macroscopic and histological findings

A total of 33 histological sections from the CS were taken from 6 animals. On histological evaluation, ablation lesions were identified in 26 (79%) sections. Lesions in the cuff of atrial myocardium surrounding the CS were found in 19 (58%) sections (figure 3). Of these lesions 18 (95%) were transmural, with a mean atrial wall thickness of $3.4 \text{ mm} \pm 1.4 \text{ mm}$. In 12 sections (36%), lesions extending towards the ventricular wall were identified, with a mean lesion depth of $6.4 \text{ mm} \pm 1.3 \text{ mm}$. In 7 sections (21%) of 4 animals there were no lesions identified.

Table 1 Magnitude of application, output, and pacing thresholds

Animal No	Peak voltage V	Peak current A	Peak resistance Ω	Pacing thresholds - absence of capture (%)			P-value [†]
				Pre-ablation	30 min post-ablation	3 weeks post-ablation	
1	1474±25	23.7±1.3	62±4	6 / 12 (50.0%)	12 / 12 (100%)	5 / 18 (27.8%)	
2	1541±17	22.3±0.6	69±2	2 / 12 (16.7%)	15 / 15 (100%)	5 / 18 (27.8%)	
3	1493±27	23.8±0.9	63±4	0 / 12 (0%)	15 / 15 (100%)	13 / 18 (72.2%)	
4	1511±21	23.0±0.4	66±2	1 / 18 (5.5%)	15 / 15 (100%)	11 / 15 (73.3%)	
5	1558±15	21.6±0.5	72±2	0 / 15 (0%)	15 / 15 (100%)	17 / 18 (94.4%)	
6	1479±19	23.7±0.6	63±2	2 / 21 (9.5%)	15 / 15 (100%)	13 / 15 (86.7%)	
All	1509±36	23.0±1.0	66±4	11 / 90 (12.2%)	87 / 87 (100%)	64 / 102 (62.7%)	<0.001*

Data is displayed as mean±SD or median (interquartile range) where appropriate.

* considered statistical significant

† assessed by general linear mixed models

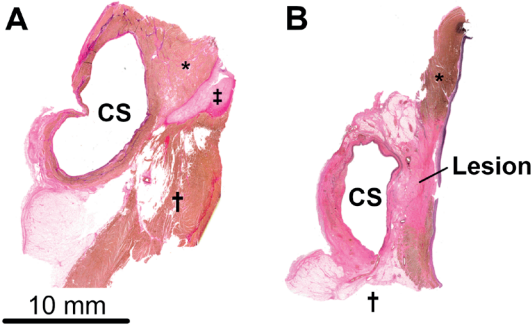


Figure 3. Transversal histological sections of the coronary sinus.

Histological elastic van Gieson–stained perpendicular sections of the coronary sinus without ablation lesions (panel A) and with ablation lesion (panel B). The epicardium is at the left side of each panel and the atrium is on the top side of each panel. CS: coronary sinus. * indicates atrial myocardium. † indicates ventricular myocardium. ‡ indicates fibrous annulus of the mitral valve. Note transmural lesion formation between the left atrium and the CS.

DISCUSSION

This study demonstrates that creation of transmural ablation lesions in atrial myocardium surrounding the CS is feasible with IRE energy applications within the CS using a linear multi-electrode catheter. No complications were observed during the procedures and follow-up. Angiography showed that structural integrity of the CS was preserved 3 weeks after IRE ablations. Acute electrical isolation of the CS was achieved in all animals.

Coronary sinus ablation

Radiofrequency catheter ablation from the CS has been performed for the ablation of accessory pathways^{19,20}, ventricular tachycardias^{21–23}, and atrial fibrillation^{14,24,25}. CS ablation is associated with improved ablation outcome in persistent AF after failed PVI.^{13,14,26} It is known that an envelope of muscular fibers around the CS connecting both atria plays an important role in the genesis and perpetuation of atrial arrhythmias.^{12–14} However, several studies reported major complications associated with radiofrequency ablation within the CS. Reported complications include major coronary vessel damage^{15–17}, and cardio-esophageal fistula²⁷.

Irreversible Electroporation

IRE ablation lesions are created by application of a short (<10 ms) electrical pulse to target tissue, which disrupts the lipid structure of the cell membrane resulting in cell death.²⁸ Tissues exhibit different thresholds to electrical field strengths that induce cell death by electroporation.²⁹ Among tissue types, cardiomyocytes appear to be most sensitive for IRE ablation.³⁰ Therefore, it is hypothesized that IRE spares structures such as the esophagus, coronary arteries, and nerves while effectively ablating myocardial tissue. This is supported by data derived from animal studies that perform ablation of myocardial substrate in the vicinity of important structures such as the coronary arteries, the right phrenic nerve, and the oesophagus.^{5–8,31}

In the 1980s, direct current ablation was associated with major complications that were related to barotrauma. Barotrauma can be the result of a shock-wave caused by arcing and vapor formation at the ablation electrode, since high energy levels were applied on a small electrode surface.¹⁸ Novel catheter designs and lower energy levels are now used to overcome the issues of arcing and vapor formation. In the present study, we did not observe any signs of barotrauma after IRE ablation within the CS of 6 pigs. Furthermore, angiography performed directly after energy application and at 3 weeks follow-up showed no signs of structural damage to the CS.

Clinical implications

Myocardial tissue selectivity of IRE might minimize the risk of damage to coronary vessels and esophagus during ablations within the CS. In the present study, feasibility of creating IRE ablations in the CS is shown, without occurrence of complications and signs of structural damage to the CS. These findings are in line with previous studies showing that blood vessels are not damaged by IRE.^{6,31} Although studies suggest that IRE can be safely applied in the CS, the available data is limited to experimental studies, and therefore should be interpreted with caution. The results of the present study contribute to further development of a safe IRE ablation modality in the treatment of cardiac arrhythmias involving substrate in the CS.

Limitations

In this study, positioning of the steerable catheter in the CS was guided by fluoroscopy and recorded intracardiac signals. While electrode-tissue contact was checked by assessing pacing thresholds, the exact position in the CS (e.g. endocardial versus epicardial side), and optimal electrode-tissue contact could not be determined. The difference between CS caliber and catheter diameter might have led to suboptimal electrode-tissue contact. Of note, it should be considered that the CS in pigs exhibit a greater caliber as compared to man.^{32,33} This might have resulted in suboptimal or loss of IRE energy transfer to the tissue, and possibly compromised lesion formation. Therefore, electrode-tissue contact measurements should be incorporated in future multi-electrode IRE ablation catheter design.³⁴

In the present study, we showed the feasibility of creating ablation lesions with 100 J IRE applications within the CS. We did not assess the effect of different energy applications on lesion size, as it is very difficult to establish the link between exact location of the application and the corresponding lesion at histological assessment. Moreover, other factors like electrode-tissue contact greatly influence lesion formation.³⁴

We demonstrated complete CS pacing conduction block 30 minutes after ablation, and significant more locations with loss capture in the ablated area at 3 weeks follow-up. It should be considered that myocardial stunning induced by the energy applications might produce block on testing shortly after ablation, but some areas might have recovered later. On the other hand, far-field left atrial capture with high output pacing might have occurred at the border zones of the ablated areas during pacing tests 3 weeks post ablation, masking a true conduction block. Furthermore, the complex anatomy of myocardial sleeves within the CS should be taken into consideration when interpreting these pacing threshold data.

Future perspectives

IRE might be applicable for the use in ablation of atrial arrhythmias from the CS, however more experimental and clinical data are needed to assess safety and efficacy.

CONCLUSIONS

IRE ablation of the musculature along the CS using a multi-electrode catheter is feasible in this porcine model. The results might contribute to development of IRE ablation in treatment of CS dependent atrial tachyarrhythmias including persistent AF.

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9 | General discussion

GENERAL DISCUSSION

Atrial fibrillation

Atrial fibrillation (AF) is the most frequently encountered sustained cardiac arrhythmia that is associated with reduced quality of life (QoL) and increased risk of heart failure, cognitive impairment, stroke, and death.¹ Management of AF is based on four pillars; (1) management of risk factors for AF development, (2) stroke prevention, (3) rate control and (4) rhythm control. State-of-the art AF care should include all these pillars in order to improve AF-related health outcome measures and patient satisfaction. Among the modifiable risk factors to reduce AF burden are; hypertension, obesity, obstructive sleep apnea, thyroid disease, and alcohol consumption.² Oral anticoagulation has reduced stroke and mortality risk. Treatment strategies to improve AF-related symptoms can be classified as 'rhythm control', aimed at restoration and maintenance of sinus rhythm, and 'rate control', aimed at controlling ventricular rate while presence of AF continues. These interventions have shown to improve AF-related symptoms and preservation of left ventricular function. Advances in pharmacological and catheter based AF rhythm control have led to significant reductions in AF burden while improving QoL of these patients. Recently, the EAST trial, an international multi-centre randomized trial that compared early rhythm control strategy with usual care, demonstrated that early rhythm control therapy reduced the risk of AF-related adverse events such as death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome.³ Of note, comprehensive management of AF and related co-morbidities may explain the low clinical adverse cardiovascular event rates and underline the importance of treatment of underlying causes of this complex arrhythmia.

Catheter ablation

Catheter ablation constitutes, along with anti-arrhythmic drugs, an important element in contemporary AF rhythm control strategy. Over the past decades catheter ablation has become an established treatment option for AF, in which electrical isolation of the pulmonary veins became the gold standard in the treatment of patients with paroxysmal and early persistent AF. Since the introduction of catheter ablation major advances have been made, however, AF recurrence after catheter ablation remains an important clinical problem. Electrical reconnection and conduction from the pulmonary veins is the dominant mechanism of recurrences of AF after pulmonary vein isolation, especially in patients with paroxysmal AF. Efforts have been made to improve lesion quality and durability, aimed at improving ablation safety and clinical outcome. These include development of different ablation technologies, ablation strategies, and energy sources, which are outlined in chapter 1. In this thesis, the effectivity and safety of existing and upcoming ablation strategies for AF ablation were assessed and compared. Furthermore, factors associated with AF ablation outcome were explored.

Anatomical factors

Understanding of the cardiac anatomy is important in catheter ablation of AF and other atrial arrhythmias. The targeted tissue in AF ablation is mainly located in the left atrium. Among observed complications of left atrial ablation are damage to the esophagus and phrenic nerve, which can be explained by the close anatomical relationship between the posterior wall of the left atrium and the esophagus, and the right upper pulmonary vein and the right phrenic nerve. Great variation in anatomy of targeted ablation sites can be found, including the frequently targeted antral tissue surrounding the pulmonary veins. In most patients four distinct pulmonary vein ostia can be found, however a variety of pulmonary vein anatomies can be seen. The most common anatomical variant is a common trunk of the pulmonary veins and accessory right sided pulmonary veins. Considering these anatomical variations, CT or MRI imaging of the left atrium is often performed prior to ablation to get a detailed understanding of the left atrial and pulmonary vein anatomy. In this thesis (chapter 2) it was shown that pulmonary vein orientation had a significant impact on ablation outcome after pulmonary vein isolation with a multi-electrode radiofrequency catheter for treatment of AF. Earlier studies have shown that pulmonary vein orientation significantly influences ablation outcome in laser balloon ablation of the antral tissue of the PVs⁴, but not in 3D mapping guided point by point contact force sensing ablation of the PVs⁵. Pulmonary vein orientation might be of influence on catheter positioning in the pulmonary vein, especially in single shot devices, which potentially can lead to less durable lesions and electrical reconnection. This hypothesis is supported by findings showing that pulmonary vein orientation was significantly associated with outcome in single shot laser balloon ablation, while PV orientation had no influence on arrhythmia free survival after contact-force point-by-point radiofrequency ablation of AF.

Energy sources

Since the introduction of catheter ablation for treatment of AF, different 'single shot' devices have been developed, including the cryothermal balloon, laser balloon, and multi-electrode radiofrequency catheters. The design of these catheters allow circumferential pulmonary vein ablation without the need for extensive catheter manipulation at the ostia of the pulmonary veins. Potential benefits, therefore, include easier catheter handling and reduced procedure time. In chapter 4 of this thesis we describe results of head to head comparison of the second-generation cryoballoon versus contact-force radiofrequency point-by-point pulmonary vein isolation in AF patients. Indeed, we observed a shorter procedure duration in the cryoballoon group, as was found in the randomized multicenter Fire&Ice trial.⁶ In that trial the reduced procedure time in cryoballoon ablation came at the expense of increased radiation dose, a trend which we also observed in our study, although it did not reach statistical significance. In contrast with the Fire&Ice trial, we found a significant higher arrhythmia-free survival in the cryoballoon group compared to the radiofrequency group 2 years after abla-

tion. Whether this is due to easier catheter handling resulting in more durable lesions, or other factors, such as the energy source itself, remains unclear. However, we did observe a lower rate of electrical reconnected pulmonary veins per patient at repeat ablation in the cryoballoon group, indicating more durable lesions compared to the radiofrequency group. Interestingly, the right-sided pulmonary veins were more likely to exhibit electrical reconnection after radiofrequency ablation compared to cryoballoon ablation. This might be explained by a more challenging catheter approach to the right-sided pulmonary veins, which might be easier with the cryoballoon due to its design, that allows a relative simple positioning and alignment of the catheter. However, limitations of a balloon based catheter should be considered in case of increased pulmonary vein diameter or left common pulmonary veins. At present, studies comparing radiofrequency and cryoballoon ablation have shown comparable efficacy and safety of PVI in treatment of paroxysmal AF. Multiple randomized studies have shown radiofrequency ablation to be more effective than medical therapy as treatment of paroxysmal AF in patients with no previous AF ablation or antiarrhythmic drug usage (first-line treatment).⁷⁻¹⁰ This has led to the ESC, EHRA and HRS recommendation that catheter ablation as first-line treatment is reasonable in patients with paroxysmal and persistent AF.² Whether cryoballoon PVI can be applied as first-line therapy in symptomatic patients with paroxysmal AF, remains to be answered, as results of the Cryo-FIRST trial are awaited.¹¹

Electrode-tissue contact

It is widely recognized that achieving permanent PVI is dependent on transmuralty and continuity of the ablation lesions. To date, no techniques are available to assess actual ablation lesion depth during procedure, so true transmuralty of the lesion cannot be determined. Several techniques have been developed that serve as a surrogate marker for transmuralty of the ablation lesions. It is known that, among other, electrode-tissue contact is a vital factor that affects lesion size in radiofrequency ablation.^{12,13} Without adequate contact, no ablation lesion will be formed. Previously used surrogate measures of contact, such as intracardiac electrogram amplitude, and impedance, have been shown to poorly predict contact-force.¹⁴ Therefore, techniques have been developed to measure actual electrode-tissue contact-force in radiofrequency ablation.^{15,16} Integration of force and time serves as an surrogate for lesion transmuralty. It is shown that optimal contact-force is associated with improved effectiveness of AF ablation.^{16,17} Surrogate markers for cryoballoon ablation include freezing temperature and duration of the thawing phase.^{18,19}

For circumferential multi-electrode ablation, a surrogate marker for transmuralty was suggested based on animal data. Lesion transmuralty could be assumed with more than 30 seconds of effective catheter-tissue contact, defined as electrodes with a temperature of $\geq 50^{\circ}\text{C}$ and a power of $\geq 30\text{ W}$.²⁰ This assumption is supported by findings described in this thesis in chapter 3. This is the first described clinical data on effective contact and ablation outcome after circumferential multi-electrode radiofrequency ablation of AF. Effective contact

could be useful as surrogate marker for lesion transmuralità in circumferential multi-electrode radiofrequency PVI, however more clinical studies are needed to assess the optimal number of lesions with effective contact to achieve durable PVI.

Electrode-tissue contact can be measured with mechanical contact force sensors, which is currently applied in single electrode ablation catheters. However, application of this technique in multi-electrode catheters requires the incorporation of multiple pressure sensors, which proves to be impossible with currently available technology. A novel method to measure electrode-tissue contact specifically for multi-electrode catheters is recently developed and studied. The so-called multi electrode impedance system (MEIS) method uses an electrical current between a target electrode and a neighboring electrode to measure the amount of electrode surface that is in contact with tissue. This method allows electrode-tissue contact measurements without the need for contact force sensors.²¹ The usefulness of the MEIS to measure electrode contact was assessed in the first-in-human study on pulmonary vein isolation with irreversible electroporation.²² The MEIS values appeared to correlate with the operator's interpretation of electrode contact, assessed by mapping, fluoroscopy, and local electrogram morphology. However, more data on this subject is needed for future utilization of the technique in ablation procedures.

Surgical and hybrid ablation

Reaching complete tissue transmuralità in PVI lesions remains challenging, as is illustrated by frequently found electrical reconnection of the pulmonary veins described in chapter 3. Historically, the surgical Cox-Maze III procedure is recognized as a very effective treatment of AF, with up to 95% AF freedom after 5 years follow-up.²³ However, despite its efficacy, the procedure is not widely used as a stand-alone procedure for treatment of AF because of its invasiveness and complexity. As an alternative, minimally invasive thoracoscopic PVI (MIPV) was introduced in 1999 by Wolf et al²⁴, which allows an epicardial approach for PVI on a beating heart through less invasive incisions. In this procedure a bipolar clamp ablation device containing two jaws is placed around the pulmonary veins. The ablation energy is delivered between the jaws of the clamp device aimed at creating transmural lesions and achieving PVI without creating collateral damage to surrounding structures. A limitation of the device is that only tissue clamped between the jaws can be ablated. This limits the creation of additional lesion sets in the left atrium. Nevertheless, the procedure is less complex and time consuming than the Cox-Maze III procedure, and is therefore often performed as concomitant AF surgery in patients undergoing open-heart surgery for other indications. In current practice, stand-alone surgical ablation of AF is mainly performed in patients with previous failed catheter ablations or patients with evidence of advanced AF substrate. In chapter 5 of this thesis results are described of the first randomized controlled trial that randomized patients with symptomatic drug-refractory paroxysmal or early persistent AF to MIPV or percutaneous catheter ablation as a first invasive procedure. The main finding is that PVI with

percutaneous ablation was noninferior to surgical MIPI in terms of arrhythmia-free survival after 2 years of follow-up. The relatively poor efficacy in both treatment groups illustrates the difficulty to create durable ablation lesions. In the catheter group patients had an advanced stage of AF. In more advanced stages of AF development of more elastic fibers, collagen, increase in fat content, and smooth muscle cell hyperplasia can hinder transfer of radiofrequency energy into the tissue and negatively influence lesion formation.²⁵ Tissue changes secondary to underlying disease process that may prevent creating transmural lesions (and impact final efficacy of the procedure), have also been observed after surgical radiofrequency ablation.²⁶ The high success rates of the classic cut-and-sew Cox Maze procedure are likely due to true transmural lesions, which might also explain less favorable efficacy of radiofrequency surgical ablation.²⁷ As in epicardial surgical ablation lesion formation can fail to reach the endocardium, and in percutaneous endocardial catheter ablation lesions may not extend to the epicardium, it is reasoned that both ablation strategies can be complementary to each other. Combining these endocardial and epicardial approaches might, therefore, increase the probability of creating durable transmural lesions without gaps. These so called 'hybrid' procedures can be performed during the same procedure or in a staged setting. The surgical procedure is performed with a thoracoscopic approach, and is followed by catheter ablation to complete gaps in the surgical lesions.²⁸ Early results of observational studies on hybrid ablation are promising^{29,30}, and have led to the European Heart Rhythm Association (EHRA) and Heart Rhythm Society (HRS) expert consensus statement recommendation that indications for stand-alone surgical ablation can also be considered for hybrid ablation (class IIb, level C) for the treatment of drug refractory AF.² In chapter 5 we discussed that based on the current evidence, especially regarding the safety aspect, we would recommend not to perform first-line stand-alone surgical ablation of paroxysmal and early persistent AF. However, it is reasonable to view catheter and minimally invasive surgical ablation as complementary strategies, which might in the future result in improved success rate of AF ablation, especially in more persistent forms of AF. Meanwhile, the results of randomized studies on hybrid ablations are awaited.

Quality of life

Efforts have been made to effectively restore and maintain sinus rhythm using ablation strategies. It is attempted to reduce the impact of AF on cardiovascular morbidity and mortality. There are conflicting data on the question whether AF ablation with restoration of sinus rhythm can improve morbidity and mortality. According to current guidelines, the primary indication for CA is symptom reduction and quality of life (QOL) improvement.² Therefore, it is important to include QOL endpoints in AF ablation studies. The impact of catheter ablation on QOL in AF treatment is well described. However, data on QOL of life after thoracoscopic surgical ablation of AF is limited. In chapter 6 QOL outcomes are described from the randomized study on catheter and minimally invasive surgical ablation as primary ablative treatment

of paroxysmal and early persistent AF. In line with previous studies, a QOL increase was found after ablation in both treatment groups. Remarkably, the correlation between AF burden and SF-36 QOL measures was poor in that study. Although data on association between SF-36 scores and AF burden measured by an implantable loop recorder are scarce, the SF-36 survey might lack sensitivity to changes with reductions in AF burden. The benefit of a generalized QOL scale, like the SF-36 survey, is that it is commonly used in medical studies and allows comparison with other medical interventions. However, to detect AF specific QOL changes we recommend to use an AF-specific QOL scale (e.g. Atrial Fibrillation Effect on Quality-of-Life (AFEQT), University of Toronto Atrial Fibrillation Severity Scale, Mayo AF-Specific Symptom Inventory, or Symptom Severity Scale) in future research, especially in trials comparing treatment strategies.

Irreversible Electroporation

While development of different AF ablation strategies are aimed at modification of the arrhythmogenic substrate, the development of novel ablation technologies and energy sources is mainly aimed at improving lesions quality and durability, while reducing procedure-related complications. In thermal ablation methods, lesion formation can be negatively influenced by loss of energy due to local blood flow, and tissue properties, such as tissue thickness and fibrosis. On the other hand, application of excessive energy in thermal catheter ablation of AF is associated with procedure-related complications. It proves to be difficult to deliver sufficient ablation energy to create transmural lesions, while preventing excessive amounts of energy, resulting in collateral damage outside the heart. In this light, researchers have reinvented the use of direct current ablation in AF ablation, nowadays known as irreversible electroporation (IRE). The major challenge was to overcome important issues such as arcing and barotrauma, while creating sufficient deep ablation lesions. Extensive pre-clinical research has led to the first in human studies on PVI using IRE for treatment of AF.^{22,31}

Preceding on this research, we assessed the potential benefits of IRE applied in linear ablation, that is commonly used for modification of arrhythmogenic substrate in cardiac ablation. In chapter 7 feasibility is shown of creating linear ablation lesions with IRE using a linear multi-electrode ablation catheter. Continuous myocardial lesions with sufficient depth can be created using a linear multi-electrode catheter design. Moreover, no periprocedural complications were observed. In line with earlier studies on IRE, we found coronary vessels located in the ablation lesion were intact. Tissue selectivity is one of the potential benefits of IRE in cardiac ablation. Previous animal research has shown that IRE can be a safe ablation method in the vicinity of important structures such as the coronary arteries, the right phrenic nerve, and the esophagus. However, in IRE ablation the energy application is limited due to occurrence of arcing and risk of barotrauma with increased energy levels. With arcing small amounts of gas, formed by electrolysis, builds up around the electrode forming a vapor bubble that insulates the electrode leading to a rapid rise in impedance. The continuing

current flow increases the electrical field between the insulated electrode and surrounding blood, to a point that an eruption of electrons from electrode to bubble surface occurs. This causes arcing, followed by a sudden temperature rise and rapid gas expansion, resulting in shockwave generation.³² The shockwave can lead to barotrauma to the surrounding tissue. Arcing can be avoided by lowering the energy of IRE applications to minimize the generation of electrolysis gas, thereby preventing bubble formation. Furthermore, arcing can be prevented by reducing peak current, which can be achieved by increasing the total impedance of the circuit. Finally, increasing electrode size reduces current density at the electrode surface and prevents arcing.³³ In our study, we did observe distortions in the voltage and current waveforms of the 100 J lesions, implicating the occurrence of arcing. No signs of barotrauma or any complication during the 3 week follow-up were observed. Moreover, the lesion depth reached with the 100 J applications was more than enough for atrial applications, thus slightly lowering the applied energy in combination with the current catheter design is a viable option. It should be noted that these ablation lesions were created on the epicardial side of the porcine myocardium. Previous animal studies had shown that with endocardial application of IRE it is difficult to precisely localize and match the ablation lesions to the IRE application, and therefore IRE was performed on the epicardial side. Although similar ablation results regarding lesion dimensions might be expected in endocardial linear multi-electrode IRE, differences with endocardial conditions should be considered regarding interpretation these results.

The findings described in chapter 7 can aid in further development of a multi-electrode linear electroporation catheter for creating linear ablation lesions. The clinical relevance of such a catheter lies in modification of arrhythmogenic substrate. Among these are AF substrate ablation in more progressive forms of AF with triggers and substrate located outside the pulmonary veins (e.g. cavotricuspid isthmus, left atrial posterior wall, left atrial roof line). Furthermore, IRE might be used in epicardial and endocardial substrates of ventricular arrhythmias in selected patient populations, such as patients with ischemic heart disease, arrhythmogenic right ventricular cardiomyopathy, or Brugada syndrome.

Coronary sinus irreversible electroporation

It is known that triggers that initiate and maintain AF frequently originate outside the pulmonary veins, especially in persistent forms of AF. Among the frequently targeted areas of interest, is an envelope of muscular fibers around the coronary sinus (CS) connecting both atria, which plays an important role in the genesis and perpetuation of atrial arrhythmias. CS isolation with radiofrequency ablation is associated with improved ablation outcome after failed PVI in persistent AF patients. However, serious concerns about the safety of CS ablation exist, due to major complications that are related to radiofrequency ablation of the CS. These complications are related to collateral damage to surrounding structures, including coronary vessel injury resulting in myocardial infarction, and development of a

cardio-esophageal fistula which can be life-threatening. A potentially major benefit of IRE, discussed earlier, is its tissue selectivity property, which is supported by findings of previous animal studies and results of our study on linear IRE described in chapter 7. Of special interest are animal studies that show IRE directly applied at the coronary arteries³⁴ and esophagus³⁵ resulted in no significant damage to these structures. Therefore, we hypothesized that IRE might be useful in CS ablation. In chapter 8 results are described of IRE in the CS of a porcine model using a multi-electrode catheter. The study shows that transmural ablation lesions can be created in atrial myocardium surrounding the CS using IRE. Electrical isolation of the CS was confirmed by assessing an exit block with pacing. Moreover, no complications occurred and the structural integrity of the CS was preserved. Although feasibility of creating ablation lesions with IRE from the CS is shown, it should be noted that these are the first results of IRE in the CS performed in an experimental setting. An important issue that should be addressed in further research is the assessment of optimal electrode-tissue contact during IRE ablation procedures. Electrode-tissue contact is important for effective energy transfer to the tissue, to minimize the risk of insufficient lesion depth or gaps within the ablation line. Results of *in vitro* and animal experiments on a method for electrode-tissue contact measurements with circular multi-electrode IRE catheters are very promising.²¹ This method uses an electrical drive current between neighboring electrodes to assess electrode-tissue contact, without the need for complex contact-force measurement technology. The technique can be applied in any multi-electrode catheter, and might therefore greatly contribute to further development of multi-electrode IRE ablation catheters.

Future perspectives

In this thesis different factors related to AF ablation technology and strategy that influence success of AF ablation are discussed. Although advances have been made in the field of AF ablation, limitations of the treatment should also be recognized, especially in patients with more progressive forms of AF. Appropriate patient selection remains important, thereby considering comorbidity and lifestyle. Imaging modalities might aid, by assessing the extent and localization of the underlying arrhythmogenic substrate. There is much more to learn about AF itself, the mechanisms of ablation and AF recurrence, and the impact of ablation on morbidity and mortality. Meanwhile, symptom reduction and QOL improvement remain the primary indication for catheter ablation.

Future research on AF ablation should consider anatomical factors and the influence on catheter placement and effective device-tissue contact. Better understanding of mechanisms behind electrical reconnection of the pulmonary veins, and the formation continuous transmural lesions might contribute to further improvement of treatment success. Challenges lay ahead in the appropriate selection of the widely available ablation techniques and strategies. Novel ablation technologies and energy sources might overcome limitations of the existing ones, while a combination of existing catheter and surgical modalities might potentially

result in higher treatment success. With challenges and opportunities lying ahead, the field of AF ablation continues to evolve rapidly, paving the path for enhanced patient satisfaction and improved clinical outcomes.

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10 | Nederlandse samenvatting

NEDERLANDSE SAMENVATTING | DUTCH SUMMARY

Atriumfibrilleren is een veel voorkomende hartritmestoornis gekenmerkt door een onregelmatige en vaak versnelde hartslag. Atriumfibrilleren is geassocieerd met een verhoogd risico op een herseninfarct en overlijden. Daarnaast kan atriumfibrilleren een grote impact hebben op kwaliteit van leven door aanwezigheid van invaliderende symptomen en door behandeling gerelateerde factoren, zoals ziekenhuisopnames, interventies en bijwerkingen van medicatie. De behandeling bestaat uit bloedverdunners om het risico op herseninfarcten te verlagen en medicatie om het hartritme te reguleren. Bij de behandeling van het hartritme kan er kozen worden om de hartritmestoornis te laten bestaan en een adequate regulatie van de hartfrequentie te verkrijgen (frequentie-controle) of het normale hartritme (sinus-ritme) te herstellen en dit pogen te behouden met anti-aritmica (ritme-controle). Catheter ablatie is een behandeloptie die tot de ritme-controle strategie behoort en die meestal wordt toegepast na het falen van een of meerdere anti-aritmica (door bijwerkingen of onvoldoende effect). In dit proefschrift worden studies beschreven naar verschillende ablatie technieken voor de behandeling van atriumfibrilleren. Bestaande ablatie technieken worden onderling vergeleken en nieuwe technieken worden onderzocht op de toepasbaarheid in atriumfibrilleren ablatie. De resultaten geven inzicht in de effectiviteit en veiligheid van verschillende ablatie technieken. Verder worden er factoren geïdentificeerd die van invloed zijn op succes van de behandeling. Tot slot worden resultaten beschreven van een nieuwe experimentele ablatie techniek voor de toepassing in atriumfibrilleren ablatie.

In **hoofdstuk 1** wordt er een introductie gegeven op atriumfibrilleren ablaties. De geschiedenis over het ontstaan en de ontwikkeling van catheter ablatie wordt beschreven. Er wordt een overzicht gegeven van de bestaande ablatie technieken en technieken die nog in ontwikkeling zijn. Sinds de ontdekking dat een belangrijke bron voor het initiëren van atriumfibrilleren in de pulmonaal venen gelegen is, is een groot deel van de ablatie technieken gericht op het elektrisch isoleren van die 'triggers' die afkomstig zijn uit de pulmonaal venen. Aanvankelijk werd dit gedaan met catheters die punt-voor-punt een aaneensluitende isolerende laesie creëerde bij de inmonding van de pulmonaal venen in het linker atrium, de zogenaamde pulmonaal venen isolatie (PVI). Over de loop van tijd zijn er catheters specifiek ontworpen voor het verkrijgen van PVI en daarnaast zijn er verschillende soorten ablatie technieken en strategieën ontwikkelt met het doel sneller, veiliger en effectiever ablaties te verrichten. Verschillende bestaande catheters en nieuwe experimentele technieken worden besproken.

In **hoofdstuk 2** wordt een observationele studie beschreven van 120 patiënten met symptomatisch atriumfibrilleren die een PVI kregen met een circulaire multi-electrode catheter. In de studie werd er gekeken naar de invloed van pulmonaal venen oriëntatie op de effectiviteit van de behandeling. Resultaten laten zien dat de oriëntatie van de linker pulmonaal venen

een significante invloed heeft op het succes van de behandeling. Uit eerdere studies was al gebleken dat pulmonaal venen oriëntatie van invloed is op de uitkomst van de behandeling met een laser ballon catheter, maar niet op punt-voor-punt ablatie PVI. De hypothese is dat pulmonaal venen oriëntatie van invloed kan zijn op de plaatsing van de catheter in het ostium van de pulmonaal vene met potentieel een verminderde aansluiting op het weefsel als gevolg. Hierdoor vermindert de kwaliteit van de ablatie laesies en wordt de uitkomst van de behandeling negatief beïnvloedt.

In **hoofdstuk 3** evalueren we de invloed van effectief elektrode-weefsel contact tijdens PVI met een circulaire multi-electrode catheter (PVAC GOLD™) op de uitkomst van de behandeling. De studie werd verricht in 50 patiënten met symptomatisch atriumfibrilleren die een PVI ondergingen. Er werd onderzocht of tijdens de procedure gemeten elektrode-weefsel contact als surrogaat marker voor voldoende diepte van de ablatie laesie (transmuraliteit) kan dienen en gerelateerd kan worden aan de uitkomst van de ablatie. De definitie voor transmuraliteit van een laesie was elk ablatiepunt met een temperatuur $>50^{\circ}\text{C}$ en een vermogen $>3\text{ W}$ gedurende minstens 30 seconden. We vonden een associatie tussen het aantal transmurale laesies en succes van de behandeling na 1 jaar follow-up. Bij een hoger aantal transmurale laesies blijkt de ablatie effectief en bovendien ook veilig te zijn. Alhoewel de studie niet ontworpen is om het optimale aantal transmurale laesies te bepalen, suggereren de resultaten dat het gebruik van effectief elektrode-weefsel contact metingen de uitkomst van de ablatie zouden kunnen verbeteren.

In **hoofdstuk 4** wordt een prospectieve studie beschreven waarin PVI met behulp van de tweede generatie cryoballoon wordt vergeleken met een punt-voor-punt radiofrequente ablatie catheter met druksensor voor de behandeling van atriumfibrilleren. Er werden 269 opeenvolgende patiënten geïnccludeerd die een eerste ablatie ondergingen, waarvan 136 cryoballoon en 133 radiofrequente ablatie kregen. Na een mediane follow-up duur van ruim 1 jaar was in de cryoballoon groep een groter deel (75%) van de patiënten vrij van atriale tachyarritmieën zonder het gebruik van anti-aritmica vergeleken met de radiofrequente groep (57%). Het aantal opgetreden complicaties was niet verschillend voor de behandelgroepen en in lijn met voorgaande studies. Bij patiënten die gedurende follow-up een herhaalde ablatie procedure ondergingen vanwege recidief atriumfibrilleren werd er in 92% van de patiënten elektrische reconnectie van een of meerdere pulmonaal venen gezien. Het aantal pulmonaal venen dat elektrische reconnectie liet zien was hoger in de radiofrequente groep vergeleken met de cryoballoon. Met name elektrische reconnectie van de rechter pulmonaal venen was hoger in de radiofrequente groep.

In **hoofdstuk 5** zijn de resultaten beschreven van de SCALAF studie waarin patiënten met paroxysmaal atriumfibrilleren gerandomiseerd zijn naar behandeling met radiofrequente

catheter ablatie of minimaal invasieve chirurgische ablatie met exclusie van het linker hartoor. Er werden 52 patiënten gerandomiseerd, 26 naar de radiofrequente ablatie en 26 naar de minimaal invasieve chirurgische ablatie groep. Patiënten kregen voor controle op het voorkomen van atriale tachyarritmieën een loop recorder geïmplant. Na een follow-up duur van meer dan 2 jaar was catheter ablatie in effectiviteit niet-inferieur aan de chirurgische groep. Er werden significant meer majeure complicaties gezien in de chirurgische groep. Beide behandelingen gaven een significante verlaging van atriumfibrilleren burden, waarbij er na catheter ablatie significant meer patiënten een lage atriumfibrilleren burden (<0.5%) hadden vergeleken met chirurgische ablatie. Dit is het eerste gerandomiseerde onderzoek dat deze behandelstrategieën als eerste invasieve behandeling voor atriumfibrilleren direct met elkaar heeft vergeleken.

In **hoofdstuk 6** wordt de kwaliteit van leven uitkomsten beschreven van de SCALAF studie, waarin 52 patiënten met paroxysmaal atriumfibrilleren gerandomiseerd zijn naar behandeling met radiofrequente catheter ablatie of minimaal invasieve chirurgische ablatie met exclusie van het linker hartoor. Kwaliteit van leven werd beoordeeld met de SF-36 gezondheidstoestand vragenlijst op 3, 6 en 12 maanden na de ablatie. Atriumfibrilleren gerelateerd symptomen werden beoordeeld met de European Heart Rhythm Association (EHRA) score. Patiënten in de catheter ablatie groep ervoeren minder beperkingen van dagelijkse activiteiten door fysieke problemen drie maanden na ablatie vergeleken met de chirurgische ablatie groep. Pijnscores waren 3 maanden na ablatie significant hoger in de catheter ablatie groep, wijzend op minder ervaren pijn vergeleken met de chirurgische groep. Na 6 maanden waren deze verschillen niet meer aanwezig. EHRA scores waren niet verschillend tussen de behandelgroepen gedurende follow-up. In beide behandelgroepen waren na 6 maanden follow-up alle SF-36 schalen significant beter vergeleken met baseline.

In **hoofdstuk 7** onderzoeken we in een diermodel de haalbaarheid van het creëren van ablatie lijnen met behulp van irreversibele electroporatie. De studie werd verricht in 6 varkens die onder algehele narcose een sternotomie ondergingen. Er werd een 7-polige multi-electrode catheter op het epicardium geplaatst. Vervolgens werd er een 50 Joule (J) en twee 100 J electroporatie applicaties toegediend. Het pericard en sternum werden gesloten en na 3 weken overleving werd het dier geëuthanaseerd. Het hart werd vervolgens uitgenomen en de ablatie laesies werden histologisch geanalyseerd. De mediane diepte van de 100 J laesies was met 5.5 mm significant dieper dan de 50 J laesies met 3.2 mm. Ook de mediane breedte van de 100 J laesies was met 5.4 mm significant breder dan de 50 J laesies met 3.9 mm. Histologische analyse liet continuïteit van de 100 J laesies zien. Er traden tijdens de procedure en gedurende follow-up geen complicaties op. Er was geen schade aan coronair arteriën die binnen de laesies vielen. De resultaten tonen aan dat het haalbaar is diepe en

continue myocardiale ablatie lijnen te maken met electroporatie met het gebruik van een multi-electrode catheter.

In **hoofdstuk 8** wordt voortgebouwd op de resultaten van het voorgaand hoofdstuk met een experimenteel onderzoek naar de haalbaarheid van het creëren van ablatie laesies in de sinus coronarius door irreversibele electroporatie toe te passen met behulp van een multi-electrode catheter. Het onderzoek werd uitgevoerd in 6 varkens onder algehele narcose, met behulp van een multi-electrode catheter met 6 electrodes. Ablaties werden verricht met 100 J energie toedieningen in de sinus coronarius. Elektrische geleiding tussen de atria en sinus coronarius werd voor, aansluitend aan en 3 weken na de ablatie gecontroleerd middels elektrische stimulatie over de ablatie catheter in de sinus coronarius. Succesvolle isolatie werd gedefinieerd als stimulatie drempel ≥ 10 mA. Na 3 weken overleving werd het dier geëuthanaseerd en werden er histologische coupes van de sinus coronarius genomen en geanalyseerd op aanwezigheid van ablatie laesies. In alle dieren werd er acute elektrische isolatie van de sinus coronarius bereikt. De stimulatie drempels waren significant hoger 3 weken na ablatie vergeleken met voor de ablatie. Histologische analyse liet transmurale laesies zien van myocard rond de sinus coronarius. Dit onderzoek toont de haalbaarheid het creëren van ablatie laesies in de sinus coronarius met behulp van electroporatie over een multi-electrode catheter. De potentiële toepassing van deze resultaten in de klinische praktijk wordt besproken.

In **hoofdstuk 9** volgt de algemene discussie waarin de resultaten van hoofdstuk 2 t/m 8 in perspectief worden gezet. Voorspellers voor en mechanismen van recidief atriumfibrilleren na een atriumfibrilleren ablatie worden geëvalueerd. Anatomische factoren, ablatie strategieën en toegepaste energie bronnen voor ablatie worden besproken. De uitkomsten van ablatie procedures op effectiviteit, veiligheid en kwaliteit van leven komen aan bod. Tot slot wordt er een blik op de toekomst van atriumfibrilleren ablatie geworpen, waarbij suggesties worden gedaan voor toekomstig onderzoek.

A



List of publications
Dankwoord
Curriculum Vitae

LIST OF PUBLICATIONS

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DANKWOORD

Bij het doen van wetenschappelijk onderzoek en het doorlopen van een promotietraject zijn veel mensen betrokken die, ieder op een eigen manier, hebben bijgedragen aan de totstandkoming van dit proefschrift. Graag wil ik iedereen die op enige wijze heeft bijgedragen bedanken. Met de voltooiing van dit proefschrift wil ik de kans niet onbenut laten een aantal mensen in het bijzonder te bedanken, want zonder de steun van hen had ik het promotietraject niet succesvol kunnen afronden.

Geachte *promotor, prof. dr. Doevendans*, bedankt voor de mogelijkheid die ik heb gekregen om mijn promotietraject onder uw leiding in Utrecht te mogen afronden. Bedankt voor uw begeleiding en enthousiasme. Het is een eer dat ik mijn verdediging in Utrecht mag voeren.

Geachte *leden van de leescommissie, prof. dr. P. van der Harst, prof. dr. I.C. van Gelder, prof. dr. B.K. Velthuis, prof. dr. M.A. Vos en prof. dr. K. Vernooy*, graag wil ik u hartelijk danken voor uw bereidheid om zitting te nemen in de beoordelingscommissie en voor de tijd en moeite die jullie hebben gestopt in de beoordeling van dit proefschrift.

Geachte *leden van de promotiecommissie*, veel dank voor de tijd en moeite die u neemt om met mij over dit proefschrift van gedachten te wisselen.

Geachte copromotor *dr. Elvan, beste Arif*, tijdens mijn wetenschapsstage in 2014 wist je mij te motiveren om onderzoek te gaan doen bij de cardiologie in Zwolle. Na het afronden van de stage begon ik aan mijn eerste jaar als arts op de cardiologie en daarnaast zette ik ook de eerste stappen binnen het doen van wetenschappelijk onderzoek. Het zou de basis vormen van wat nu dit proefschrift is geworden. We delen de interesse in technische aspecten van de cardiologie en zo kwam het promotietraject over atriumfibrilleren ablaties tot stand. Je gaf me de kans om mee te kijken met ablatie procedures en zelf onderzoeksvragen te bedenken. Uit al mijn enthousiaste voorstellen wist jij altijd wel de belangrijke te selecteren om mee verder te gaan. Je leerde mij daarbij resultaten van onderzoeken op de juiste manier te interpreteren en de kern van de boodschap goed te formuleren. En dat werkte motiverend! Daarnaast ben jij degene geweest die de samenwerking met Utrecht tot stand heeft gebracht. Ik ontdekte pas later in mijn promotietraject dat jij als jonge onderzoeker met jouw experimenten destijds zelf aan de wieg stond van catheter ablatie van atriumfibrilleren. Het maakt me trots dat jij mijn copromotor bent. Bedankt voor de hulp, het vertrouwen en de kansen die ik van je heb gekregen!

Beste copromotor *dr. van Es, beste René*, wij hebben elkaar leren kennen toen ik in Utrecht mocht deelnemen aan experimenteel onderzoek als onderdeel van het electroporatie

project. Met jouw ruime ervaring in dit onderzoeksgebied heb jij mij uitstekend begeleid en daarmee is een belangrijk onderdeel van mijn proefschrift tot stand gekomen. De overgang van onderzoek in de klinische naar de experimentele cardiologie was voor mij spannend en uitdagend. Jij liet mij het onderzoekslab zien en de projecten waar jullie mee bezig waren. Ik was erg onder de indruk van de technische en soms ingenieuze onderzoeksmogelijkheden die je me liet zien. Daarnaast heb jij een aanstekelijk enthousiasme en energie, waardoor ik al gauw gewend was aan de nieuwe onderzoek setting. We hebben samen experimenten verricht, waarin jij een ontzettend grote rol hebt gespeeld. Bedankt voor je hulp bij de praktische kant van het onderzoek in Utrecht, maar ook voor je enthousiasmerende en motiverende instelling.

Geachte *dr. Ramdat Misier*, bedankt voor de kans die ik heb gekregen om de opleiding tot cardioloog met een promotietraject te kunnen combineren. Als polikliniek supervisor bood u mij de ruimte voor het ontwikkelen van zelfstandigheid. Ik ontwikkelde mij als arts en daarnaast kreeg ik veel tijd voor onderzoek. Na het opstarten van het onderzoekstraject gaf u aan dat de opleiding voor mij in het verschiet lag. En na enig beraad met dr. Elvan ging ik al vlot in opleiding tot cardioloog. U stimuleerde mij vanaf het begin een duidelijk plan te trekken en bood mij dan vervolgens ook de kansen om dit plan waar te maken. Met wat flexibiliteit en creativiteit lukte het vervolgens om het promotietraject voort te zetten en daarnaast ook de opleiding tot cardioloog te volgen. Van u heb ik geleerd dat je met concrete plannen en wat doorzettingsvermogen heel ver kunt komen. Dank voor het vertrouwen en de kansen die ik heb gekregen.

Dr. Adiyaman, beste Ahmet, al vanaf het moment dat ik je leerde kennen ben ik onder de indruk van je ogenschijnlijk oneindige kennis van de cardiologie op zowel klinisch als wetenschappelijk gebied. Zonder moeite weet jij in een discussie altijd wel relevant en recent wetenschappelijk onderzoek te citeren, waarbij ook de exacte getallen en de klinische relevantie benoemd kunnen worden. Ik kan gerust zeggen dat jij mijn voorbeeld bent in mijn vorming als cardioloog. Ik hoop in de toekomst nog veel van je te kunnen leren op het gebied van ablaties, klinisch en wetenschappelijk werk. Daarnaast heb je ontzettend veel geholpen met het ontwerpen van onderzoeken en het schrijven van papers. Veel dank voor je scherpzinnige opmerkingen en de grote bijdrage die je hebt geleverd aan dit proefschrift.

Dr. Smit, beste Jaap Jan, bedankt voor je enthousiasme die je regelmatig hebt laten zien (en horen!) de afgelopen jaren, het werkt motiverend. Je hebt me veel geleerd over de verschillende theorieën over pathofysiologie van atriumfibrilleren. Daarmee leer je me ook als onderzoeker kritisch te blijven kijken naar algemeen geaccepteerde ideeën binnen de wetenschap. Ik neem deze kritische blik mee in mijn verdere carrière. Veel dank voor je bijdrage aan dit proefschrift.

De *overige stafleden* cardiologie ben ik ook dankbaar. Inmiddels werken we al enkele jaren samen en ik heb die tijd altijd als prettig ervaren. Iedereen draagt bij aan mijn ontwikkeling als cardioloog, zowel op klinisch als wetenschappelijk vlak. Ik weet nog goed hoe een van de stafleden op de zomerbarbecue, vlak nadat ik in opleiding tot cardioloog was gekomen, lachend grapte: "Thomas, je hebt mijn steun.. maar vergeet niet dat je opleiding altijd aan een zijden draadje hangt." Met die motiverende woorden ben ik inmiddels toch al best ver gekomen. Het kenmerkt de verhouding tussen ontspanning op zijn tijd, inspanning waar nodig en af en toe een prikkelende opmerking waar mogelijk. Velen van jullie zijn betrokken geweest bij mijn onderzoek en hebben bruikbare feedback geleverd. Uiteraard was ik zonder jullie steun niet gekomen waar ik nu ben. Dank voor de betrokkenheid en de mogelijkheden die ik van jullie heb gekregen.

Beste *dr. Fred Wittkamp* en *drs. Marijn Groen*, ik heb met jullie experimenteel onderzoek in Utrecht mogen doen. Ik heb daarbij veel geleerd van jullie technische achtergrond en vindingrijkheid. Ik herinner me nog goed dat Fred op een middag op een kladpapiertje schetste hoe hij vond dat een ablatie catheter eruit moest zien die we zouden gebruiken voor de experimenten. Nog geen twee weken later was de catheter ook daadwerkelijk geproduceerd door de technische dienst en klaar voor gebruik. Jullie weten van doorpakken en zien mogelijkheden, dat heeft mij geïnspireerd. Daarnaast veel dank aan de medewerkers van het dierenlaboratorium van het UMC Utrecht, zonder jullie was het niet mogelijk geweest de experimenten te verrichten.

Beste paranimfen, Jos de Jong en Chris Lakenvelt. We trekken als sinds de middelbare school als hechte vrienden met elkaar op. Toen al waren we bezig met observeren en analyseren. We hebben mooie momenten met elkaar beleefd en ik kan altijd op jullie vertrouwen. Ik ben blij dat de vriendschap ook na onze studententijd in Groningen sterk is gebleven ondanks onze verschillende woonplaatsen. Ik hoop ook in de toekomst nog vaak momenten met jullie te beleven waarin we van gedachten wisselen over de belangrijke en minder belangrijke zaken in dit leven.

Beste *Vera Derks*, veel dank voor alles wat je voor mij hebt betekend gedurende het promoveren, maar ook bij de opleiding tot cardioloog. Ik kreeg veel hulp bij de administratieve kant van het onderzoek. Daarnaast was je de steun en toeverlaat voor alle opleidingszaken. Je wees mij er ruim van te voren op als er belangrijke zaken geregeld moesten worden. En ook was je altijd wel bereikbaar voor een praatje.

Beste *dr. Pim Gal*, inmiddels ben je al even niet meer werkzaam in Zwolle. Samen met dr. Elvan betrok jij mij bij jouw onderzoek en leerde je mij hoe je snel en effectief databases opstelt en analyseert. Ik vind het nog altijd ongelooflijk hoe snel jij was in het analyseren

van data en het schrijven van een paper. Je hebt me daarin veel geleerd. Ik hoop dat op het gebied van onderzoek onze paden in de toekomst nog eens mogen kruisen.

Medewerkers van *Diagram*, jullie hebben veel op de achtergrond geregeld. We hebben als onderzoekers van de cardiologie in Zwolle het ontzettend getroffen dat we gebruik kunnen maken van jullie expertise, dank daarvoor.

Beste collega *onderzoek arts-assistenten*, dank voor de prettige samenwerking die ik met jullie heb gehad. In het bijzonder *dr. Annemiek Hoogerwaard*, we hebben elkaar leren kennen toen we onze studies geneeskunde aan het afronden waren. Sindsdien zijn onze trajecten bij de cardiologie eigenlijk synchroon aan elkaar. We zijn beide gestart met een promotietraject en daarnaast de opleiding tot cardioloog. Ik weet hoeveel tijd dat kost en ik heb daarom ontzettend veel respect voor je dat je naast het moederschap recent ook nog eens je promotie hebt afgerond! Maar zo ken ik je; vol discipline, doorzettingsvermogen en ambitie. Verder *dr. Mark Roland de Jong*, bedankt voor het begeleiden van mijn eerste meters in het doen van onderzoek. En alle huidige researchers; veel succes met jullie onderzoek!

Lieve ouders, vanzelfsprekend zijn jullie van onschatbare waarde geweest op de weg die mij tot dit punt geleid heeft. Jullie hebben mij altijd gestimuleerd om te doen wat ik leuk vind en de dromen na te jagen die ik heb. Ook als ik door mijn werk soms minder tijd had voor familie. Dank voor die onvoorwaardelijke steun en liefde! Mijn lieve broers, *Merijn, Ruben en Steffan*, ook jullie zijn heel belangrijk voor mij. Ik kan altijd wel bij jullie terecht om even een potje mentaal dan wel fysiek te sparren. Dankbaar ben ik voor jullie aanwezigheid in mijn leven!

Lieve *schoonfamilie*, door Annie zijn jullie onderdeel van mijn leven geworden en gelukkig heb ik het met jullie getroffen. Jullie enthousiasme, openheid en interesse waardeer ik altijd enorm. Dank daarvoor!

Tot slot mijn *liefste Annie*, jij bent degene die altijd achter mij staat bij het maken van keuzes in dit leven en ook in mijn carrière. Niemand heeft zoveel persoonlijke tijd in mijn promotietraject geïnvesteerd als jij. Je bent geduldig geweest en je hebt mij alle ruimte geboden om dit project af te ronden. Bij jou kan ik alles kwijt en ik kan volledig op je vertrouwen. Je oneindige enthousiasme geeft mij energie. Ik had deze reis niet zonder jou willen maken. Dank voor de liefde en steun die je mij geeft. Ik hou van je!

CURRICULUM VITAE

Thomas Jelmer Buist is geboren op 4 juli 1990 in Groningen. Na het behalen van zijn middelbare school diploma in 2008 (Gomarus College Groningen), ging hij geneeskunde studeren aan de Rijksuniversiteit te Groningen (2008 - 2014). Zijn co-schappen liep hij in het Universitair Medisch Centrum Groningen en Isala Zwolle. Tijdens de stages raakte hij geïnteresseerd in de cardiologie. Hij behaalde zijn artsenbul in 2014 en ging vervolgens werken als arts-assistent (ANIOS) op de cardiologie in Isala Zwolle. In 2015 begon hij aan zijn PhD traject op het gebied van atriumfibrilleren ablaties onder supervisie van dr. Elvan. Thomas startte met zijn specialisatie tot cardioloog in 2016 in Isala Zwolle. Tijdens zijn opleiding werkte hij aan het onderzoek dat heeft geresulteerd in dit proefschrift. Verder was hij actief als bestuurslid van het KNMG district Flevoland / Zwolle (2017-2020). De voltooiing van zijn specialisatie tot cardioloog staat gepland in 2022.

Thomas Jelmer Buist was born on the 4th of July 1990 in Groningen (The Netherlands). After graduating from his pre-university education in 2008 (Gomarus College Groningen), he attended medical school at the University of Groningen. Internships were followed at the University Medical Center Groningen and Isala Zwolle. During his internships he became interested in cardiology. He obtained his medical degree in 2014 and started working as a resident (ANIOS) cardiology at Isala Zwolle. In 2015 he started with his PhD candidacy in atrial fibrillation ablation research under supervision of dr. Elvan. Thomas started his specialization in cardiology in 2016 in Isala Zwolle. During his training he continued working on research which resulted in this thesis. Furthermore, he was a board member of The Royal Dutch Medical Association (KNMG) district Flevoland / Zwolle (2017-2020) in Zwolle. His specialization cardiology is planned to be finished in 2022.