Comparison of irrigated multi-electrode radiofrequency ablation and point-by-point ablation for pulmonary vein isolation in patients with persistent atrial fibrillation with persistent atrial fibrillation

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DISSERTATION

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Dissertation was done on Department of Cardiology, University Hospital Center Sestre milosrdnice Zagreb, Croatia and Department of Cardiology, University Hospital Basel, Basel, Switzerland.

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LIST OF ABBREVIATIONS

AF – atrial fibrillation

BMI - body mass index

CBA – cryoballoon ablation

CI – confidence interval

CK – creatin kinase

CS – coronary sinus

CRP – C reactive protein

DAP - dose area product

EHRA – European Heart Rhythm Association

ESC – European Society of Cardiology

FAM - fast anatomical mapping

HRS -Heart Rhythm Society

INR – international normalized ratio

LA – left atrium

LVEF – left ventricular ejection fraction

NS – not significant

PV - pulmonary vein

PVI - pulmonary vein isolation

IMEA - irrigated multi-electrode ablation

IMEA-PVI – irrigated multi-electrode ablation pulmonary vein isolation

NOAC – novel oral anticoagulant

RF - radiofrequency

RF-PVI – radiofrequency pulmonary vein isolation

RFA – radiofrequency ablation

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1. INTRODUCTION

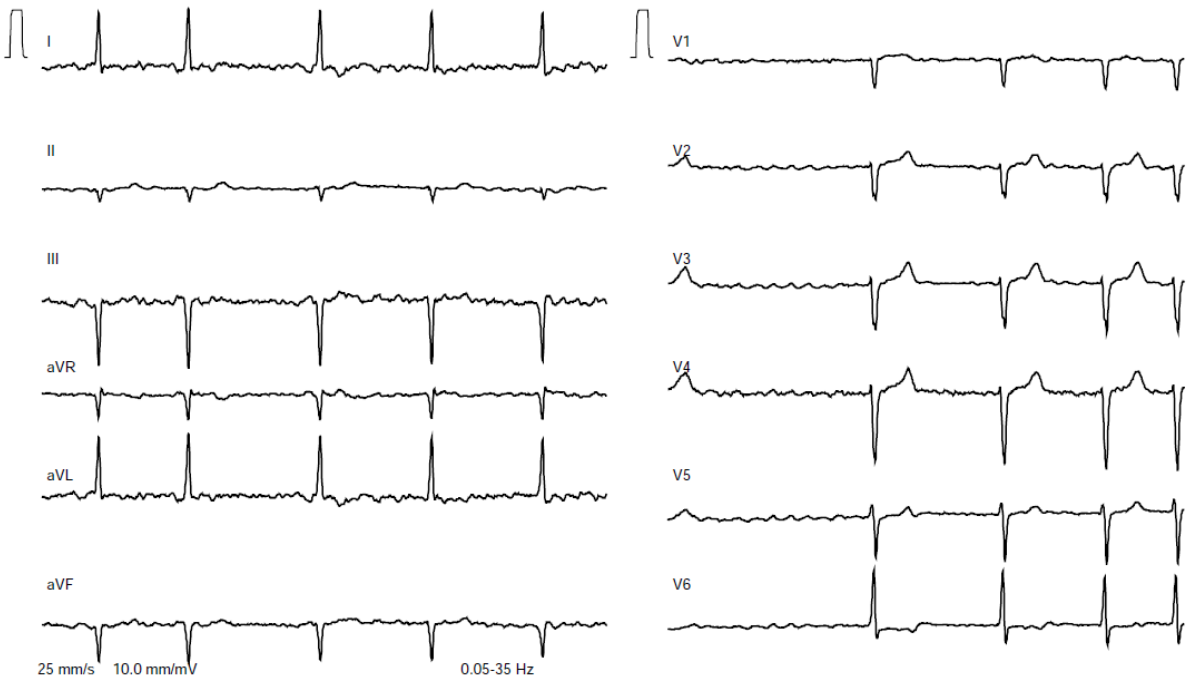
1.1 Atrial fibrillation

1.1.1. Definition and diagnosis

Atrial fibrillation (AF) is a supraventricular arrhythmia characterized by fast and irregular electrical activation of the atria and loss of mechanical function. 12 lead ECG should be used to diagnose AF and any AF episode lasting long enough to be recorded on 12 lead ECG should be diagnosed as AF (1,2) . If cardiac rhythm monitoring or strips are used, arrhythmia should last at least 30 seconds to be defined as AF. Three criteria should be met on 12 lead ECG to diagnose AF: 1. absolutely irregular R-R intervals; 2. No visible P waves and 3. If visible, atrial cycle length of less than 200 ms (**Figure 1.1**).

Atrial fibrillation is easily diagnosed in symptomatic patients by simple 12 lead ECG recording, however it may be difficult to diagnose atrial fibrillation in patient with self terminating paroxysmal AF and especially in asymptomatic patients (2). Therefore, guidelines recommend opportunistic screening for AF in patients older than 65 years with pulse taking or ECG recording, and systematic prolonged screening for AF in patients with previous stroke or transient ischaemic attack and patients with cardiac implantable devices (2). These approaches have been proven cost effective in mentioned populations at risk (2–5).

Figure 1.1 shows 12 lead ECG of atrial fibrillation. Absolutely irregular R-R intervals are seen and there are no visible P waves.



1.1.2. Types and classification of atrial fibrillation

Atrial fibrillation can present as overt, symptomatic arrhythmia or as silent, asymptomatic arrhythmia. Both symptomatic and asymptomatic AF can occur in the same patient (2).

Atrial fibrillation can be divided in five major types based on the presentation pattern and these are: 1. Paroxysmal AF is a self terminating episode of AF lasting less than 7 days (most often less than 48 h). Also, episodes cardioverted in the first 7 days should be considered as paroxysmal AF; 2. Persistent AF is episode of AF lasting more than 7 days, either self terminating or cardioverted after 7 days; 3. Long standing persistent AF is continuous AF that lasts more than one year; 4. Permanent AF is AF that lasts

more than one year and when rhythm control strategies were abandoned and the atrial fibrillation has been accepted by the patient and the physician. 5. First diagnosed atrial fibrillation is an episode that has never been diagnosed before, irrespective of duration or symptoms. Definitions of types of atrial fibrillation are given in **Table 1.1.2.**

Table 1.1.2 Definitions for different types of atrial fibrillation. Adapted from ESC Guidelines on management of atrial fibrillation. AF – atrial fibrillation.

Type of AF	Definition
Paroxysmal AF	Self terminating episode of AF lasting less than 7 days (most often less than 48 h). Also, episodes cardioverted in the first 7 days should be considered as paroxysmal AF
Persistent AF	Episode of AF lasting more than 7 days, either self terminating or cardioverted after 7 days
Long standing persistent AF	AF that lasts more than one year, however rhythm control strategy has been adopted
Permanent AF	AF that lasts more than one year and when rhythm control strategies were abandoned and the atrial fibrillation has been accepted by the patient and the physician
First diagnosed AF	Episode that has never been diagnosed before, irrespective of duration or symptoms

Several other, clinical definitions such atrial fibrillation in structural heart disease, atrial fibrillation in athletes, focal atrial fibrillation, polygenic atrial fibrillation, postoperative atrial fibrillation etc are given by the 2016 ESC Guidelines (2) for management of patients with AF.

It is clear that these definitions are arbitrary and are used mainly for patient selection and treatment approach. However, based on the current data, types of atrial fibrillation have impact on treatment success rates (6,7). Also, depending on clinical types of atrial fibrillation, treatment of underlying

disease such as valvular heart disease, hypertension, heart failure, renal failure, obesity, diabetes mellitus etc. may be required in selected patients.

In this research and document, definitions of persistent atrial fibrillation from HRS/EHRA/ECAS Expert consensus from 2012 were used (8) which are now consistent with the ESC Guidelines for the management of atrial fibrillation and the new HRS/EHRA/ECAS/APHRS/SOLEACE consensus statement on catheter and surgical ablation of atrial fibrillation (1,2).

1.1.3. Epidemiology

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population (1,2) with a marked increase in incidence with age (9). It is estimated that AF occurs in 1-2% of the general population (10) (11). It has been strongly associated with increased age, hypertension, ischemic heart disease and heart failure (12). In 2010 it was estimated that more than 30 million people had atrial fibrillation (13) . The prevalence of AF is predicted to increase significantly in the years to come (14) (15) and could even double in the next 50 years (10) (16). There are, among others, three important reasons for this increase. First, the population in developed countries is aging with more people at risk for AF (17). Second, treatments of confounding factors for AF are leading to increased survival (hypertension, heart failure, valvular heart disease, diabetes mellitus, renal failure) of patients (17). Third, there is better detection of atrial fibrillation with ECG screening, Holter monitors, implantable devices and event recorders (18). Assuming that the prevalence of AF is 1% in the general population, it affects more than 5 million people in the European Union. These numbers are calculated conservatively for the general population, not taking into account differences in age distribution between countries and with the lowest described prevalence of 1%. Since many patients with AF are asymptomatic (up to one third) and many of patients actually never present to hospital for diagnosis

these numbers could actually represent underestimation (19) (5). However, although these numbers are high, they are lower than prevalence of other ‘’modern epidemics’’ such as hypertension or diabetes.

The prevalence of AF is higher in men and it significantly increases with age. AF prevalence is <0.5% in people younger than 40 and reaches up to 15% in people older than 80 years (14) (20).

AF is associated with a decrease in functional status, quality of life and an increase in heart failure, stroke and mortality (10). AF has been shown to be an independent predictor of mortality with a 1.5 to 2.5 fold increase and these results are consistent in different trials (21). However, the increase in mortality is independent of commonly measured confounders such as hypertension, diabetes, obstructive sleep apnea and obesity. Since the mortality risk can only partially be explained by AF itself (tachycardia, irregular heart rhythm, loss of atrial systole, thromboembolism), other potential confounding factors likely coexist (myocardial fibrosis, systemic inflammation, endothelial dysfunction) which are not routinely measured.

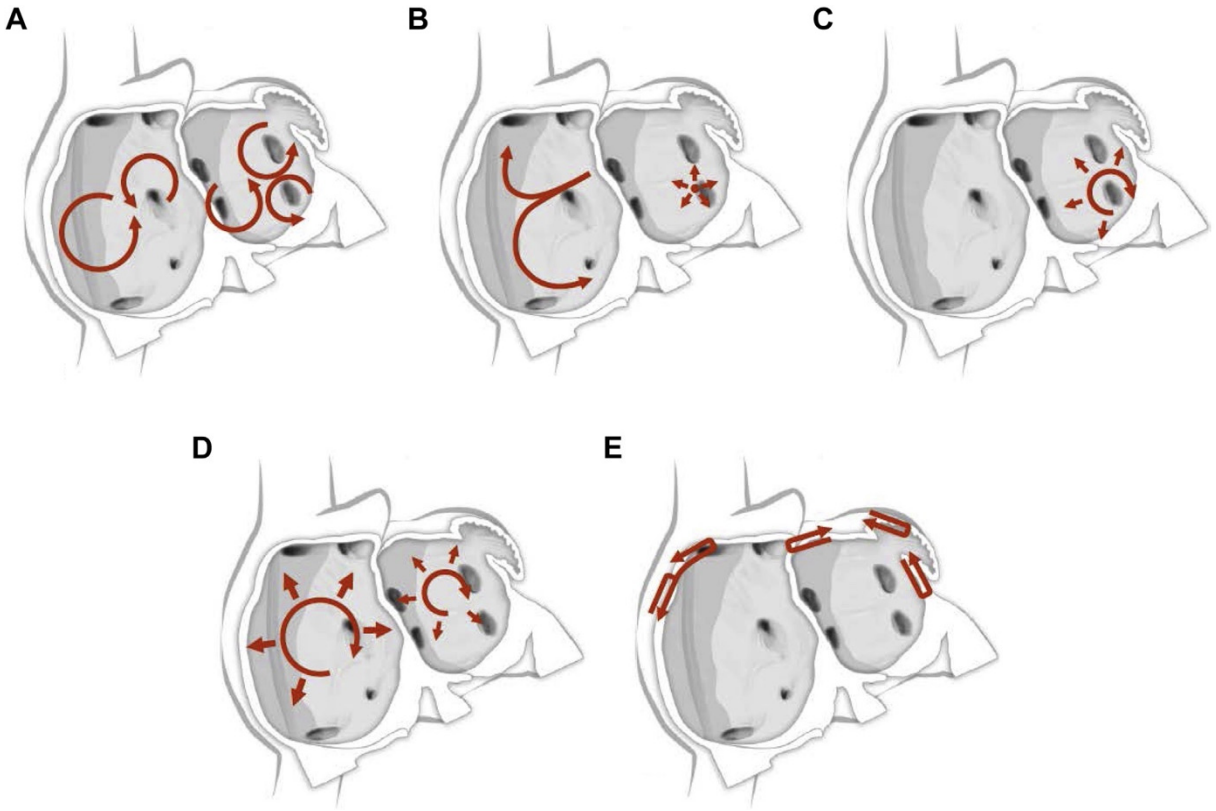
Risk for stroke is also increased significantly in patients with AF. It is estimated that 20% strokes are due to AF and patients with AF tend to have more severe strokes (10). There are many confounding factors for development of atrial fibrillation (22) (23) such as hypertension, valvular heart disease, obesity, thyroid dysfunction, atrial septal defect and other congenital heart disease, renal disease, obstructive sleep apnoea, chronic obstructive pulmonary disease, alcohol consumption, smoking (24–26). These conditions are all independent signs and markers of cardiovascular disease and also have role in initiation and perpetuation of atrial fibrillation by different mechanisms.

AF should be recognized as an independent predictor of mortality and management should be driven towards both treatment of AF as well as predisposing factors of AF.

1.1.4. Electrophysiological mechanisms

Two major factors were long thought to be necessary for atrial fibrillation. First is focal trigger that initiates atrial fibrillation and second anatomical and electrical substrate in the atria that supports further fibrillatory activity (27) (28). There were three main theories which tried to explain the mechanism of atrial fibrillation: multiple wavelet hypothesis, focal discharges, mainly from the pulmonary veins and localized reentry with fibrillatory conduction (1,29,30). Recent research based on computer models and experiments have lead to several more theories. One is functional reentry resulting from rotors and spiral waves. Rotor is an organizing center of the reentrant excitation which spins at exceedingly high frequencies, radiating spiral wavefronts and maintaining atrial fibrillation (1,31). Also recent research has shown that atrial fibrillation is maintained by dissociation between epicardial and endocardial layers, with production of multiplying activity that sustains the atrial fibrillation (1,32). Different mechanisms are shown on **Figure 1.1.4**

Figure 1.1.4 Different AF mechanisms. From Calkins et al Catheter and Surgical Ablation of Atrial Fibrillation, Heart Rhythm, Vol 14, No 10, October 2017



As stated above, although there are several theories on atrial fibrillation mechanisms, it is clear that both focal triggers and reentry play a role in initiating and maintaining atrial fibrillation.

Regardless of the mechanism of AF, it is certain that sustained AF (even after 24 h), leads to complex electrical and anatomical remodelling of the atria, including changes in refractory periods of atrial cells, changes in ion channels and changes in conduction times (33). These changes further promote continuation of AF and lead to concept ‚‘ atrial fibrillation begets atrial fibrillation‘‘ (34).

First theory regarding AF mechanism was described and developed by Moe and associates (35). According to this hypothesis, multiple, random wavelets exist and propagate through the atria maintaining AF. And while this was the first and for a long time dominant theory, today other theories both clinical and experimental have been developed which probably better describe AF mechanism.

Focal discharges theory was described by Haissaguerre and associates as they found that the AF was often triggered by focal activity origination in the pulmonary veins (36). These foci could in theory be amenable for ablation which could lead to elimination of AF. Further research confirmed these findings, and based on these data ablation of atrial fibrillation targeting pulmonary veins developed in subsequent years.

After initial trigger from the pulmonary veins or anywhere in the atria, fibrillatory activity and reentry occur throughout the atria. In experimental models and in human atria, it was shown that atial remodelling leads to development of additional triggers and localized reentry in different parts of atria (27) (29). The longer the AF lasts, changes in the atria are more substantial. Changes in action potential duration, refractoriness, conduction velocity and frequency gradients promote reentry and perpetuation of AF (37). These changes are the reason that in paroxysmal AF PVs are the sites of triggering and high frequency activity and in persistent and long standing persistent, multiple triggers are present and dominant fibrillatory activity shifts from PV ostia to other parts of the both atria. Based on current knowledge and understanding of atrial fibrillation initiation and maintenance, elimination of triggers and modification of substrate present around the pulmonary vein ostia is the potential target for ablation. These mechanisms also explain why, paroxysmal AF is relatively easily targeted for ablation with better results than persistent AF (1,7).

1.2. Treatment options

Major impacts of AF are increase in mortality, stroke and the reduction of quality of life. Therefore, the goal in treatment of any patient with AF should be mortality and stroke reduction and improvement in quality of life. And while some of these goals have been achieved, others, such as mortality reduction is still not completely achieved or proven in current practice.

There are three major treatment "arms" in patients with atrial fibrillation and include rate control, rhythm control and prevention of stroke and systemic thromboembolism. Other are treatment of concomitant disease and confounding factors and upstream therapy (1,2).

1.2.1. Rate control

Rate control is often the first therapy of choice for atrial fibrillation. Before the development of antiarrhythmics and catheter ablation it was the most common prescribed therapy. Rate control therapy is part of AF management both in the acute phase and in long-term. In part of patient population with AF, rate control is sufficient to control symptoms(2).

Rate control can be achieved with beta blockers, digoxin, calcium channel blockers (verapamil and diltiazem) and also some antiarrhythmic drugs (amiodarone, dronedarone, sotalol).

In the acute phase, depending on strategy (rate vs. rhythm control), patients frequently require rate control due to symptoms related to heart rate.

Beta blockers and calcium channel blockers are preferred drugs in the acute phase because of their rapid onset of action. However, patient characteristics, as well as concomitant diseases should be evaluated and taken into account. For instance, calcium channel blockers should be avoided in heart failure and non selective beta blockers in patients with severe asthma. Frequently combination therapy will be required adding digoxin or amiodarone, where amiodarone can be added as rate control drug, particularly in patients with acute heart failure with reduced LVEF.

In long term rate control therapy, same drugs as for acute phase can be administered. Doses should be titrated to maximal tolerated dose with the goal of heart rate <100 bpm, avoiding bradycardia. To achieve these goals, usually combination therapy will be required. There are no universal guidelines for choice

of rate control therapy, rather, drugs and doses should be chosen on individual basis after considering patient characteristics and comorbidities.

In selected patients, permanent pacemaker implantation and AV node ablation can be considered when drug therapy fails to control the heart rate and symptoms. It is a procedure with low complication rates and high rate of long term success in controlling heart rate and symptoms. However, this procedure makes patients pacemaker dependant lifelong, and should be performed in carefully selected patients. In a proportion of patients with heart failure and reduced LVEF, biventricular pacing should be considered since the patients will be paced from the ventricle lifelong (38).

Although the guidelines recommend relatively strict rate control (heart rate <100/min), there is little scientific data to support this guideline(2). Therefore, Race II Trial (Lenient versus Strict Rate Control in Patients with Atrial Fibrillation) was conducted (39). In this study, 614 patients were randomized to either strict (<80/min) or lenient (<110/min) rate control strategy. After a follow up of 3 years, there was no difference between the two groups in primary outcome (composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events). Also, lenient rate control was easier to achieve. Based on these data, more lenient rate control strategy seems to be safe and effective for most of the patients with AF.

1.2.2. Rhythm control

Acute restoration of sinus rhythm and maintaining of sinus rhythm are part of the rhythm control strategy. Restoration and maintenance of sinus rhythm significantly improve symptoms in patients with AF, however although it may seem that sinus rhythm improves outcomes, all the studies so far have resulted in neutral results (40,41).

1.2.2.1 Acute rhythm control

Acute restoration of sinus rhythm can be achieved with almost all antiarrhythmic drugs in recent onset AF. AADs restore sinus rhythm in approximately 50% of patients (42). Most widely used drugs in Europe are Class Ic (flecainide and propafenone) and Class III drug amiodarone. The choice of AAD, same as drugs for rate control, depends on patients' characteristics, underlying disease and patients choice. Other option for restoring sinus rhythm in recent onset AF is electrical cardioversion. It is always first choice of treatment in patients with recent onset AF and haemodynamic instability (2)

Synchronized direct current cardioversion restores sinus rhythm more effectively and faster than medical treatment with AADs (43). The use of electrical cardioversion is associated with shorter hospital stay, however, it requires sedation/anesthesia and fasting.

1.2.2.2. Maintenance of sinus rhythm

After acute restoration of sinus rhythm, long term maintenance of sinus rhythm can be achieved with long term AAD treatment or catheter ablation.

1.2.2.2.1 Antiarrhythmic drugs

The goal of AF treatment with AADs is mainly to reduce the symptom burden. According to available data, the use of AADs doubles the sinus rhythm maintenance when compared to no treatment. Also the use of AADs is increases adverse events and some of the AADs potentially increase mortality (44). It should be noted that AADs improve symptoms and reduce the AF recurrence rates rather than completely eliminate the recurrence of AF (2,44). The choice of AAD is driven by patient's characteristics and underlying disease. Generally, safety rather than efficacy of each AAD should primarily be considered when choosing the AAD for prevention of AF recurrence.

1.2.2.2.2. Catheter ablation

Catheter ablation has evolved as a common treatment method for selected patients with paroxysmal, persistent and long-standing persistent atrial fibrillation. When performed in experienced, high volume centers, it is more effective than AADs in maintenance if sinus rhythm (45). Regardless on type of atrial fibrillation catheter ablation is more effective in maintaining sinus rhythm than AADs in patients who have recurrent AF on antiarrhythmic drugs (46). As a first line treatment (patients who were not taking AADs), catheter ablation also improves outcomes compared to AADs in patients with paroxysmal AF (45,47). It is significantly more effective as a first line treatment in younger and otherwise healthy patients (47).

Current guidelines indicate catheter ablation for prevention of AF recurrence and symptom control. Currently there are no indications for mortality reduction or withdrawal of anticoagulation treatment in patients in AF (2). Indications for catheter ablation of AF in patients with different types of AF according to current ESC guidelines are shown in **Tables 1.2.2.2.2.-1.2.2.2.4,** while techniques and technologies are discussed in detail later.

Table 1.2.2.2.2. Indications for catheter ablation in patients with paroxysmal AF

Paroxysmal AF	**Recommendation**	**Class**	**Level of evidence**
Symptomatic AF refractory to at least one antiarrhythmic drug	Catheter ablation is recommended	I	A
Symptomatic AF prior to initiation of antiarrhythmic therapy	Catheter ablation is reasonable	IIa	B

Table 1.2.2.2.3. Indications for catheter ablation in patients with persistent AF

Persistent AF	Recommendation	Class	Level of evidence
Symptomatic AF refractory to at least one antiarrhythmic drug	Catheter ablation is reasonable	IIa	B
Symptomatic AF prior to initiation of antiarrhythmic therapy	Catheter ablation is reasonable	IIa	C

Table 1.2.2.2.4. Indications for catheter ablation in patients with long standing persistent AF

Long standing Persistent AF	Recommendation	Class	Level of evidence
Symptomatic AF refractory to at least one antiarrhythmic drug	Catheter ablation may be considered	IIb	C
Symptomatic AF prior to initiation of antiarrhythmic therapy	Catheter ablation may be considered	IIb	C

1.2.3 Rate vs. rhythm control

Although it seems as common sense that maintenance of sinus rhythm improves outcomes, many trials that have compared rate versus rhythm control strategies have failed to prove that rhythm control strategy is superior to rate control (40,48). One of the pivotal randomized controlled trials that compared these two strategies was AFFIRM study (41). AFFIRM study compared rate control to rhythm control strategies and found that the rates of complications and death were similar between two strategies.

However, subsequent subanalyses of AFFIRM trial have shown that rhythm control strategy (maintaining sinus rhythm) could be superior to rate control strategy. In the rhythm control group, adverse outcomes were mainly driven by AAD adverse events and discontinuation of anticoagulation therapy in patients in sinus rhythm (49). Further studies and registries have found no difference in outcomes (50,51), however one meta analysis of more than 7000 patients by Chatterjee et al in 2013 (48) reported lower all cause mortality with rhythm control in patients younger than 65 years. In the ablation era, large, multicentric randomized controlled trial CABANA was published in 2018. The trial randomized patients to ablation or antiarrhythmic drugs. The trial included 5 years follow up. At 5 years, there was no difference in the primary outcome (death, disabling stroke, serious bleeding, or cardiac arrest) - 8% vs. 9.2% (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.65-1.15, p = 0.3). However, there were significant number of crossovers between the arms (ablation to drug: 9.2%, drug to ablation: 27.5%) and when analyzed per treatment received, there was a significant reduction in death or CV hospitalization with ablation (52,53).

In selected group of patients with persistent AF and symptomatic heart failure, who were implanted with cardioverter defibrillator or cardiac resynchronization therapy, catheter ablation was with a significantly lower rate of a composite end point of death from any cause or hospitalization for worsening heart failure than medical therapy (54,55).

Although there is emerging evidence that maintenance of sinus rhythm, especially with catheter ablation improves patients' outcomes, until further evidence is available, current AF treatment practice is mainly symptom driven.

1.2.4. Stroke and thromboembolism prevention

Population based studies, cohorts and clinical trials have shown that AF carries an increased risk for thromboembolism and stroke. Also, during the years, risk factors for stroke in patients with AF have been identified (56).

Patients with AF and highest risk for stroke are those with "valvular AF" (patients with some types of valvular heart disease-mitral valve stenosis, heart valve prosthesis and after surgical repair of the mitral valve), patients with previous stroke or TIA, presence of left atrial appendage (LAA) thrombus or spontaneous echo contrast in LA and older age (>75 years).

And while in patients with valvular AF the indication for anticoagulation therapy is clear and driven by highest risk, several clinical risk calculators have been developed to evaluate risk of patients with "non valvular "AF and guide antithrombotic therapy.

Stroke risk has previously been assessed using the CHADS2 score which was developed Stroke Prevention in Atrial Fibrillation (SPAF) investigators and assigns 1 point for presence of cardiac failure, hypertension, age > 75y, diabetes and two points for history of stroke. Score of "0" was considered low risk, "1-2" moderate risk and >2 high risk for stroke (57). However, CHADS2 score did not include all clinically relevant stroke risks in population of patients with AF. Therefore, novel risk assessment scheme was developed, with CHA2DS2VASc which assigns 2 points for age >75y and previous stroke/TIA/peripheral thromboembolism and 1 point for each: congestive heart failure, hypertension, age 65-74, diabetes, vascular disease (myocardial infarction, prior revascularization, peripheral artery disease) and female sex(57)(58). Table shows CHA2DS2VASc risk factors and stroke risk depending on presence of these factors.

Anticoagulant therapy was shown to decrease the stroke risk in patients with AF (59). Also, until now, anticoagulant therapy is the only therapy proven to reduce mortality in patients with AF (60). There are several drugs drug groups and methods used for achieving anticoagulation and reducing the stroke risk

in patients with atrial fibrillation. First are vitamin K antagonists with most often used warfarin. Novel group of drugs called novel oral anticoagulants or non vitamin K oral anticoagulants (NOACs) or direct oral anticoagulants (DOACs). Interventional method used for stroke prevention in patients with high bleeding risk is occlusion of the left atrial appendage.

1.2.4.1. Vitamin K antagonists

This group of drugs, with warfarin being most widely used, were the first drugs used for reduction of thromboembolism and stroke in patients with atrial fibrillation (2). Warfarin reduces the risk of stroke by 60% compared to aspirin or no therapy showed a meta-analysis of 29 randomized controlled trials including more than 28000 patients(59) . These drugs have narrow therapeutic interval, and the quality of anticoagulation control is a major determinant of efficacy and safety of vitamin K antagonists (61). The quality of anticoagulation is measured with time in therapeutic range (TTR), and when TTR is in adequate range, these drugs are effective in stroke prevention. Of note, these drugs are currently the only group of drugs used for stroke prevention in patients with atrial fibrillation and rheumatic heart disease, moderate and severe mitral stenosis and in patients with mechanical heart valves (2,62).

1.2.4.2. Novel anticoagulants

Novel anticoagulants – non vitamin K antagonist oral anticuagulants (NOAC) have emerged as an alternative to warfarin and other vitamin K antagonists for prevention of thromboembolism and stroke in patients with atrial fibrillation (63,64). NOACs include dabigatran as a direct thrombin inhibitor and apixaban, edoxaban and rivaroxaban as factor Xa inhibitors. These drugs have predictable effect, shorter plasma half lives, less food and drug interactions and there is no need for monitoring. Randomized

controlled trials were conducted with these drugs where they proved to be non-inferior or superior to warfarin with regards to stroke reduction and risk of major bleeding reduction (65–68). These results were more or less confirmed in several population based registries and retrospective analyses (real world data) (69–71).

The use of NOACs is increasing rapidly in the western countries while the use of warfarin has significantly declined. The use of NOACs has surpassed the use of vitamin K antagonists in patients with non-valvular atrial fibrillation (72,73).

Although novel anticoagulants have been compared in different studies, they have never been compared head to head in randomized controlled trials. Currently, one randomized controlled trial ‘’Comparison of Efficacy and Safety Among Dabigatran, Rivaroxaban, and Apixaban in Non-Valvular Atrial Fibrillation’’ (DARING-AF) comparing NOACs is currently enrolling patients (ClinicalTrials.gov Identifier: NCT02666157). The results are expected in 2019.

1.2.4.3. Left atrial appendage occlusion

Interventional left atrial appendage occlusion emerged as an alternative to anticoagulation in highly selected patients with atrial fibrillation, high risk of stroke and risk of or repetitive bleeding. The majority of data is derived from single center studies and registries. There are only few randomized trials with single device comparing left atrial appendage occlusion to anticoagulation with warfarin. These trials have shown that occlusion with WATCHMAN device is non inferior to warfarin in stroke prevention in patients with atrial fibrillation with lower risk of bleeding in long term (74,75). Although the use of LAA occlusion devices is on the rise especially in the patients with high risk of bleeding there are some concerns regarding this treatment – first of all, there is no clear evidence between left atrial appendage and stroke (76), the devices have been compared to warfarin (while there are new anticoagulant drugs with better safety and efficacy profile), the devices have not been compared to no

therapy at all, there are risks of serious complications of the procedure (77) etc. True efficacy and safety, as well as the use of these devices need to be confirmed in future and larger randomized controlled trials. LAA occlusion should be offered as a treatment option in patients with high risk of stroke who have reccurent, not controllable bleeding while on anticoagulant treatment.

1.2.5. Treatment of underlying disease

There are many diseases and conditions that increase the risk of AF and of AF related complications. Some of those are hypertension, heart failure, valvular heart disease, obesity, diabetes mellitus, chronic obstructive pulmonary disease, obstructive sleep apnoea, renal disease and smoking. These risk factors increase the risk of AF by increasing the left atrial pressure and diastolic dysfunction (mitral stenosis or hypertension) or by systemic inflammation, increased systolic activity and increased fatty infiltration of the atria (2).

Aggressive treatment of these confounding factors in patients with AF has been shown to reduce the risk and incidence of AF, reduce symptoms, increase the success rates of AF ablation and improves maintenance of sinus rhythm after cardioversion (78–80).

Recently published RACE 3 trial randomized patients to standard heart failure and AF treatment or standard treatment plus additional four therapies: statins, mineralocorticoid receptor antagonists, angiotensin converting enzyme inhibitors and cardiac rehabilitation with physical activity and dietary restrictions(81). After 12 months follow up, 75% of patients who underwent targeted therapy of underlying conditions were free from AF compared to 63% of patients with conventional treatment (P=0.042). Australian LEGACY trial evaluated long-term impact of weight loss and weight fluctuation on rhythm control in obese individuals with AF (82). It included 355 obese patients with atrial fibrillation who were offered weight management. Weight loss ≥ 10% resulted in a 6-fold (95% confidence interval: 3.4 to 10.3; $p < 0.001$) greater probability of arrhythmia-free survival compared

with the other 2 groups. These studies have proven that today, except for classic treatment arms (anticoagulation, antiarrhythmics, ablation), more effort should be made in treatment of risk factors, weight loss and lifestyle changes in patients with atrial fibrillation.

1.3. CONCEPT OF PULMONARY VEIN ISOLATION

As described, one of the mechanisms for development of atrial fibrillation is automaticity, triggered activity or localized reentry originating from pulmonary veins. Anatomically, muscular sleeves extending from the atrial myocardium have been found in the pulmonary veins. These muscular bands are situated on epicardial surface of the ostium and are of different length (up to 25 mm from the ostium), width, arrangement and orientation. Also, different amount of gaps and fibrosis are found between the muscular fibbers. This provides the substrate for automaticity, triggered activity (potentially by dilatation and stretch) and localized reentry.

It was the pivotal work by Haissaguerre et al (83) in 1998 that described focal discharges from the pulmonary veins initiating atrial fibrillation. This study in 45 patients with drug refractory atrial fibrillation has identified the pulmonary veins as major sources of ectopic foci triggering AF. Also, it the same study the authors found that these respond to treatment with radiofrequency ablation. Although this pivotal research set grounds for ablation of atrial fibrillation, this procedure was associated with high incidence of pulmonary vein stenosis since the ablation was performed in the pulmonary veins (84). As a result, further research has lead to strategies for electrical or anatomical isolation of arrhythmogenic tissue around the pulmonary veins by ablation outside the ostia of the vein (85,86). Initially, segmental ostial ablation was developed, where ablation was performed at the ostium of each pulmonary vein. Electrical isolation could be achieved in almost all patients, however long term success rates were modest (86). Next was circumferential PVI which includes circular ablation at the antra of ipsilateral veins. This method is similar to the procedure most widely used today – wide antral circumferential

ablation (WACA). Circumferential PVI and WACA have increased success rates of ablation of AF (87). Better success rates of circumferential PVI can be explained by several mechanisms: wider area of ablation may not only affect triggers in the pulmonary veins but also triggers in the PV antra, posterior wall and ligament of Marshall. It may also affect part of the arrhythmogenic substrate required for AF maintenance, not only the PV triggers (88). Antral isolation also affects the autonomic ganglia around the PVs, which have been shown to play a role in AF initiation and maintenance (89). Also, reduction of the atrial muscle mass may make multiple re-entries impossible.

And while PVI was and still is the cornerstone of AF ablation, especially paroxysmal atrial fibrillation, additional, more extensive ablation strategies have been developed during history for ablation of persistent atrial fibrillation. These included linear lesions such as roof line, mitral isthmus line or cavotricuspid isthmus line (90). Other were ‚'box isolation'' of the PVs and the posterior wall, left atrial appendage isolation or ablation of complex fractionated atrial electrograms (91–93). One of the proposed strategies was ‚'stepwise approach'' used by Bordeaux and Hamburg groups where different lesion sets are used in addition to PVI until sinus rhythm is achieved in patients with persistent atrial fibrillation (94). All these methods had promising results; however, they were usually reported by single centers with limited number of patients. When these results and outcomes were tested in larger studies, recurrence rates were usually higher. Other, novel strategies continue to emerge. These include ablation of potential areas that are critical for maintenance of atrial fibrillation (so called rotos). These are mapped with the use of multielectrode catheter or non-invasively by using body surface potential mapping (95,96). One of the most important trials in ablation of persistent AF was STAR AF 2 trial (97). In this trial, 589 patients were randomized to PVI alone, PVI plus linear lesions or PVI plus CFAE ablation. After 18 months of follow up there was no difference in success rates between three different strategies. Groups who underwent additional ablation lesions had higher fluoroscopy and procedure times and possibly higher complication rates. Star AF 2 trial has shown that PVI also remains the cornerstone of persistent AF ablation. All novel and experimental methods described will have to be compared head to head with PVI alone in multicentre, randomized manner to be validated and possibly accepted as widely used ablation methods.

Except for different "anatomical" approaches, different ablation targets and lesion sets, several different technologies have been developed to achieve PVI. These include different catheters, mapping systems and different energy sources that can be used for ablation of AF.

1.4. Techniques and technologies for pulmonary vein isolation

1.4.1 Point-by-point techniques

1.4.1.1. Radiofrequency ablation

Radiofrequency catheter ablation for cardiac arrhythmias was introduced by Huang et al in 1985 (98). Since then, it has become the most widely used energy source for treatment of cardiac arrhythmias. Development and improvement of catheters made radiofrequency ablation treatment with high safety and efficacy profile. RF ablation uses electromagnetic energy that is effectively transformed into thermal energy with the goal of irreversibly destroying arrhythmogenic substrate by heating. The mode of heating in RF energy is resistive. When the current passes the myocardium, heat is produced. Typical, frequency of 500 Hz is produced for RF ablation. RF energy is typically applied in a unipolar fashion (where RF energy is applied between the ablation electrode and an indifferent electrode applied to the skin). From the tip of the catheter, current flows radially from the source, and resistive heating occurs mostly at the tissue electrode surface. From there, resistive heating decreases proportionally depending on distance. Deeper tissues are heated by the means of thermal conduction and follow general thermodynamic principles. For irreversible damage to the tissue, temperatures higher than 50 C are required. Histologically, RF energy lesions, typically show coagulation necrosis.

RF energy lesion size is proportional and dependant on achieved electrode-tissue contact, electrode-tissue temperature, delivered power and electrode size(99). Other factors influencing lesion size are electrode orientation, electrode material, tissue composition (lesions are smaller in dense scar or in epicardium due to presence of fat), ablation duration etc (100). The lesion size is however, also limited by the tissue electrode temperature that limits adequate power delivery and deeper lesion formation. With increase in power, temperature at the electrode tip rises and when it reaches 100 C impedance rise occurs with coagulum formation, steam pops and tissue desiccation.

RF ablation became a standard for treatment of majority of cardiac arrhythmias. Standard 7F catheters with 4 mm tip have become the most widely used ablation catheters. However, their ability for creating lesions is limited to few millimetres from the electrode-tissue interference. To overcome these limitations, cooled tip catheters have been developed. Catheter tip is irrigated with saline (**Figure1.4.1.1-1**) to reduce the electrode-tissue temperature and allow for higher power delivery. Compared with non irrigated RF delivery, cooled (irrigated) ablation allows delivery of higher powers and longer durations of RF ablation (101).

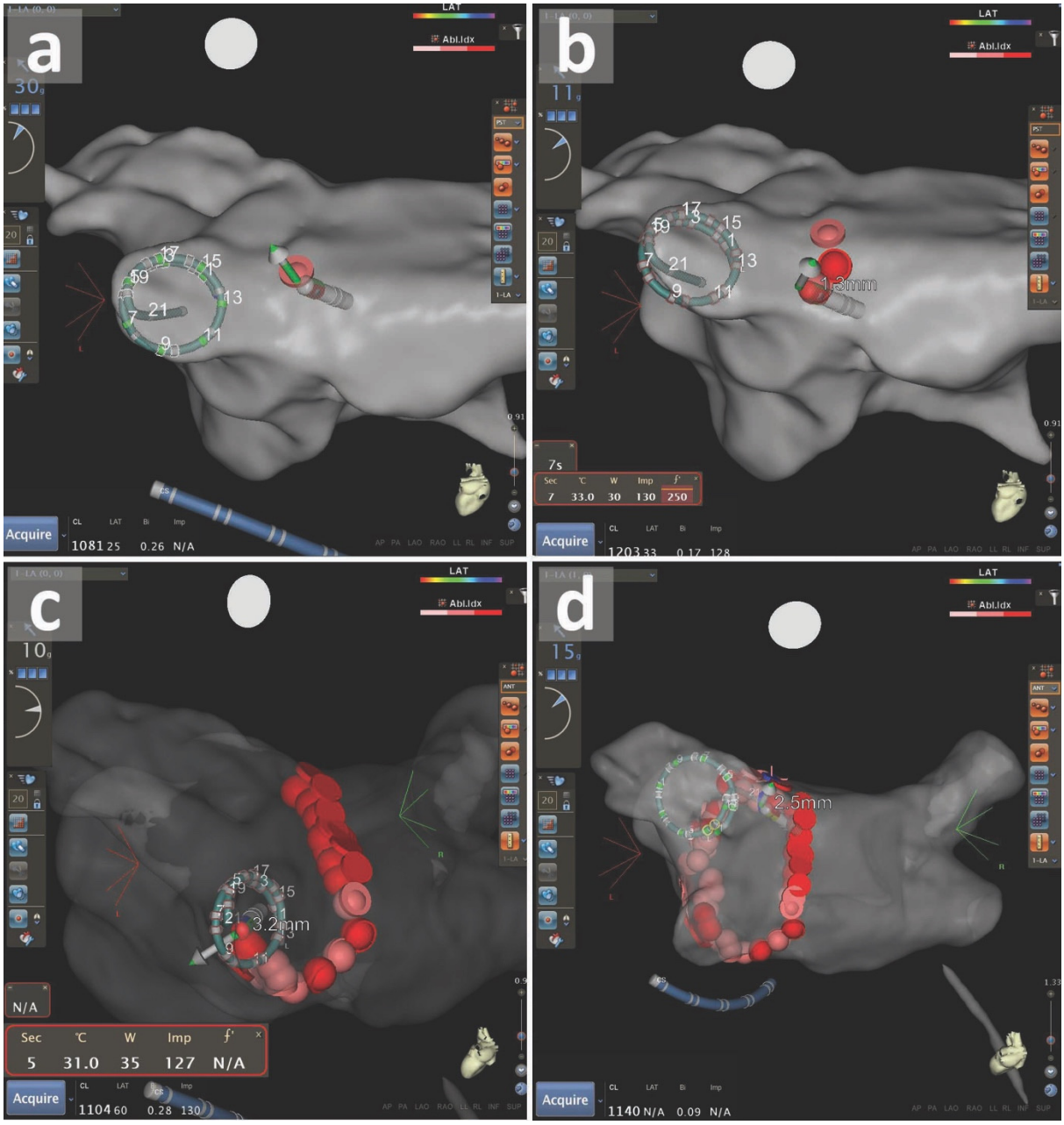
For atrial fibrillation, non irrigated 4 and 8 mm tip catheters have been used initially for either ectopic foci ablation and for pulmonary vein isolation (102). Theoretical advantages of irrigated tip catheters, primarily ability to produce transmural lesions, have been proven in clinical trials (102,103). Today, irrigated tip catheters have completely replaced standard non irrigated catheters for AF ablation, mostly due to lower risk of steam pops, char and coagulum formation and lower thromboembolic risk (104).

In addition to different electrode sizes and open irrigation, contact force sensors have been incorporated in novel generation ablation catheters which provides operator with live tissue-electrode contact feedback. With the use of these catheters, outcomes of ablation have been further improved….

Point-by-point irrigated tip catheter RF ablation has become the gold standard for PVI. It requires deployment of RF lesions with the catheter tip one point at the time and creates a continuous circumferential line around the ipsilateral pulmonary veins as described previously (**Figure 1.4.1.1-2)**. To achieve durable isolation, each lesion, ideally has to be transmural and continuous with previous lesions. This can be time consuming, requires operator experience and volume.

Figure 1.4.1.1.-1 4 mm tip open irrigated catheter

Figure 1.4.1.1.-2 Point-by-point radiofrequency pulmonary vein isolation. Left atrium is shown from posterior view. Left sided veins are isolated by application of ablation points one at the time until full circle around the PV antrum is achieved (A-D).



1.4.1.2 Cryoablation

First application of cryoenergy on myocardial tissue was described in 1948 (105) and the first application on conduction system ablation was performed in 1964 (106). Since then, focal cryoablation technology improved and cryoablation is more widely used in cardiac electrophysiology for various clinical indications (107).

Lesion formation with cryoablation relies on freezing and thawing the tissue in contact with the catheter. Mechanisms of tissue injury can be divided in three phases: the freeze–thaw phase, the hemorrhage and inflammation phase, and the fibrosis phase (108).

Similar to RF ablation, lesions formed with cryoablation are dependent on electrode size, electrode tissue contact, duration of ablation, electrode temperature.

The potential advantages of cryoablation include better catheter stability, potential reversibility of initial lesions, less thromboembolic complications due to less tissue disruption and less pain during the procedure (108). This is why cryoablation is widely used in children and in critical locations like para Hisian accessory pathways (108,109).

Regarding PVI, point-by-point cryoablation was proven to have similar success rates compared to RF point-by-point ablation, however with significantly longer procedure and fluoroscopy times, rendering cryoablation impractical (108,110,111). There are also concerns regarding nontransmurality of lesions with cryoablation particularly for endocardial ablation of epicardial autonomic ganglia. This is why, for atrial fibrillation ablation, point-by-point cryoablation is abandoned, especially after development of ‘’single shot’’ cryoballoon.

1.4.2 ‚Single shot' technologies

With the goal to produce more predictable and continuous lesions and potentially shorten the PVI procedures, catheters that create circumferential lesions with single or only several applications have been developed. As for point-by-point ablation, these catheters are different in design and use different energy sources.

1.4.2.1 Multielectrode circumferential catheters

There are two multielctrode ablation catheters in clinical use. The first one is PV ablation catheter (PVAC, Medtronic) and the other one is irrigated multielectrode ablation catheter nMarq (Biosense Webster, Diamond Bar, CA, USA).
The PVAC catheter consists of 10 platinum iridium electrodes that deliver duty-cycled bipolar or unipolar RF energy (temperature controlled and power limited) (1). Initial experience with the catheter has shown it has good clinical efficacy (112), however, it showed to have higher incidence of asymptomatic cerebral embolism and stroke (104). After catheter and protocol modifications these complications were significantly reduced while efficacy remained comparable to standard point-by-point ablation (113,114).

Irrigated multielectrode ablation catheter (nMarq) consists of 10 platinum-coated electrodes. Electrodes are 3 mm and have 4 mm interelectrode distance. It is irrigated through 10 holes in each electrode **(Figure 1.4.2.1-1)**. Radiofrequency ablation is performed via all 10 electrodes simultaneously or by selecting only some of the electrodes. RF energy delivery can be up to 25 W in unipolar mode or up to 15 W in bipolar mode. Energy delivery can be tailored and controlled on the nMarq console **(Figure 1.4.2.1-2)**

This circular catheter can be used both for mapping, creating 3D map in conjunction with the CARTO mapping system, and ablation.

Initial single and multicenter studies have shown it to be highly effective in achieving acute pulmonary vein isolation with 12 months success rates similar to point- by-point radiofrequency ablation (115–119). However, at that time there was almost no experience with this catheter in patients with persistent atrial fibrillation. Also, there were some concerns in initial reports regarding complication rates such as atrio-esophageal fistula or silent cerebral embolism (120–122).

Figure 1.4.2.1-1 shows the ablation electrodes of the nMarq catheter. Electrodes are 3 mm long with 4 mm interelectrode distance. Irrigation holes are seen on each of the electrodes.

Figure 1.4.2.1-2 the control panel of the nMarq console. Temperature and power can be selected and controlled for each of the 10 ablation electrodes. During the ablation one or more electrodes can be turned on or off.

1.4.2.2 Cryoballoon ablation

Most widely used balloon based system for pulmonary vein isolation is the cryoballoon ablation system (1). Today it has proven to be a valid alternative to standard radiofrequency point-by-point ablation. The system consists of noncompliant balloon in two sizes and has an injection and exhaust lumen for nitrous oxide injection, a central lumen for guide wire or circular catheter

positioning and contrast injection (123). The first generation catheter was introduced more than a decade ago, while second generation was introduced in 2012(1). Second generation balloon distributes the coolant (nitrous oxide, N2O) more homogenously and thereby increases the effective surface area of the

balloon (123). Pivotal trial which lead to FDA approval of cryoballoon was STOP AF randomized controlled trial which compared PVI with cryoballoon and antiarrhythmic drugs in patients with paroxysmal AF. It showed significantly higher freedom from atrial fibrillation after 12 months in patients treated with ablation (69.9% vs. 7.3%) (124). After that, numerous single center, non randomized trials showed similar efficacy of cryoballoon ablation and standard radiofrequency ablation for paroxysmal atrial fibrillation (125–127) . FIRE AND ICE, one of the largest randomized controlled trials in atrial fibrillation ablation compared cryoballoon ablation versus standard point-by-point radiofrequency ablation in 762 patients (128). The trial showed that cryoballoon ablation was non-inferior to radiofrequency ablation. However, secondary endpoints, rates of rehospitalisation and need for additional ablations were in favor of cryoballoon (129). Several single center, non-randomized studies have also shown similar efficacy of cryoballoon ablation vs. radiofrequency ablation in patients with persistent atrial fibrillation(130,131) .

1.4.2.3 Laser and ultrasound

Laser balloon system uses light energy to achieve pulmonary vein isolation. The balloon itself is compliant, allowing for different sizes and can adopt for different pulmonary vein sizes. It also has an endoscope allowing for ablation under direct visualization. Although it was constructed as a potential single shot device, it usually requires additional balloon rotations and repositioning for achieving pulmonary vein isolation. A prospective, multicenter randomized trial compared the efficacy and safety of visually guided laser balloon with standard point-by-point irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation (132). After 12 months follow up, there was no difference in efficacy (61% vs. 61.7% freedom from symptomatic atrial fibrillation). Phrenic nerve palsy occurred more often in laser balloon ablation patients (3.5% vs. 0.6%; P 0.05), but PV stenosis was less common (0.0% vs. 2.9%; P 0.03) (132). This technology has been approved in Europe and in United States for

treating patients with drug refractory paroxysmal atrial fibrillation. It has not been tested in patients with persistent atrial fibrillation.

Ultrasound ablation was first developed as a balloon based system called high intensity focused ultrasound (HAIFA) ablation system (133). Although this system has been found to be effective in patients with paroxysmal atrial fibrillation (134), it was withdrawn from the market due to high incidence of severe complications including death (135).

New low-intensity collimated ultrasound ablation system is being developed, which automatically creates a map of the left atrium, and then the operator defines the ablation lines which are then created automatically. This system has been shown effective in a procine model, while clinical trials are ongoing.

1.4.2.4 Other technologies

Novel technologies are constantly being developed with the goal of improving success rates or shortening and simplifying the AF ablation procedures. These include imaging guided ablation (MRI), mapping the AF drivers in the form of the form of high-frequency reentrant sources (rotors) either by intracardiac or body surface mapping or development of novel ablation catheters as radiofrequency balloon or new catheter (Globe®) with a distal multielectrode array consisting of 16 ribs with 122 gold-plated electrodes (136). And while all the novel technologies show promising results, they all still lack multicentric data as well as data derived from randomized controlled trials.

1.4.3 Role of mapping systems in pulmonary vein isolation

Mapping and ablation in the left or right atria require adequate navigation and creating ablation lines with different technologies and energy sources. Historically, first procedures were performed using fluoroscopy solely. Electro anatomical mapping systems combine anatomical and electrical data and allow for accurate 3D reconstruction of the cardiac chambers, in the case of PVI, of atria and pulmonary veins. Currently there are several electro anatomical mapping systems used in clinical practice and several of them under development. Most widely used is CARTO system from Biosense Webster (CARTO 3; Biosense Webster, Diamond Bar, CA, USA) which has magnetic and impedance (current) based catheter localization (1,137). The NavX Ensite Precision system from St. Jude Medical (St. Jude, St. Paul, MN, USA) is based on impedance-based catheter visualization (1,137). It has recently been modified to also provide magnetic based navigation, which has improved the precision of the system. The third mapping system is the magnetic electrical Rhythmia mapping system (Boston Scientific, Marlborough, MA, USA) which has been used only for several years so the experience so far is limited (1). 3D images obtained with mapping systems can be combined with intracardiac ultrasound images, CT or MRI which further improves accuracy of these maps (138,139).

The routine use of electroanatomical mapping systems has proven to significantly reduce fluoroscopy use (137,140,141) or even bring it to zero (142), reduce procedure duration and improve safety of the procedure (1,137). In addition to anatomical reconstruction, novel generations of mapping systems allow for intracardiac electrogram analysis and creation of voltage maps which allow for understanding and ablation of AF substrate (137). In addition to that, high density mapping is achievable with use of multielectrode catheters and mapping systems software. With the contact force catheters and mapping systems, real time catheter tissue contact is available, further improving efficacy and safety of ablation procedures (143,144). Combination of contact force sensing catheters and mapping systems allows for application of RF energy at desired location and formation of continuous lesions. Also, different mathematical models have been developed to assess lesion quality, size and depth to predict and improve

outcomes. With the use of strict protocols regarding lesion depth and contiguity used by the mapping system results in durable PVI and improved patient outcomes (145)

Use of the mapping systems increases the cost of the procedure, however majority of PVI procedures today are performed in conjunction with some of these three mapping systems (1).

2. HYPOTHESIS:

Acute success rates defined as electrical isolation of the pulmonary veins using Irrigated Multi-Electrode Radiofrequency Ablation compared to current standard point-by-point ablation are similar in patients with persistent atrial fibrillation.

One year outcomes of pulmonary vein isolation using Irrigated Multi-Electrode Radiofrequency Ablation is comparable to current standard point-by-point ablation are similar in patients with persistent atrial fibrillation.

Procedural parameters and complication rates are similar between two methods.

3. AIMS:

Primary aims of the study are:

1. To evaluate acute efficacy of irrigated multielectrode ablation in achieving pulmonary vein isolation in comparison to standard point-by-point radiofrequency ablation in patients with persistent atrial fibrillation
2. To evaluate 12 months success rate of irrigated multielectrode ablation in comparison to standard point-by-point radiofrequency ablation (defined as freedom from AF or atrial tachycardia in patients persistent atrial fibrillation)

Secondary aims of the study are:

1. To evaluate procedural details: procedure duration (defined as vascular access to sheath removal), radiofrequency ablation time (total net ablation time with each of the catheters and cumulative ablation time for the IMEA catheter), fluoroscopy time, and total radiation dose.
2. To evaluate and compare procedure-related complications.

4. PATIENTS AND METHODS

4.1. Patients

The study population consisted of 49 consecutive patients with symptomatic persistent AF from the prospective "Basel Atrial Fibrillation Pulmonary Vein Isolation" (BEAT-AF-PVI) cohort study. Persistent AF was defined according to current guidelines (1,2). Pulmonary vein isolation is a standard first time procedure for patients with persistent AF at our institution. Additional substrate modification in the atria is not performed in the first procedure in patients with no documented atrial tachycardia or atrial flutter. Twenty-four patients underwent PVI using the IMEA catheter, and twenty five patients undergoing PVI using a 3.5 mm irrigated tip catheter served as a control group. Patients were included consecutively in both groups, and the IMEA-PVI group patients were included consecutively after the IMEA catheter became available.

Patients with paroxysmal or long-standing persistent AF, history of any previous left atrial procedure (surgical or percutaneous), with documented left atrial tachycardia or atrial flutter requiring additional ablation lines were excluded from the study. Also, patients with contraindication for pulmonary vein isolation (mainly left atrial appendage thrombus) or those not able to provide informed consent were excluded from the study.

Inclusion and exclusion criteria are shown in **Table 4.1**.

All patients provided informed consent and the study was approved by local Ethics committee.

Table 4.1 inclusion and exclusion criteria for the current study

Inclusion criteria

- Symptomatic persistent atrial fibrillation (defined as AF episode lasting more than 7 days and less than one year. Also, any episode that was cardioverted to sinus rhythm after 7 days was defined as persistent AF)
- Scheduled for first ablation procedure
- Age 18-80 years
- Signed informed consent

Exclusion criteria

- Inability to provide informed consent
- Asymptomatic patients
- Paroxysmal or long standing persistent AF
- Any previous left atrial ablation procedure (percutaneous or surgical)
- Documented atrial tachycardia or flutter
- Left atrial thrombus
- Severe bleeding diathesis

4.2. Methods:

4.2.1. Pre-procedural management

The study was approved by the local ethics committee, and all patients provided informed consent both for the procedure and participation in the study. Atrial fibrillation was verified in a 12 lead ECG in all patients. Standard laboratory testing was performed in all patients and included full blood count, BUN, serum creatinine level, serum electrolytes, CRP and coagulogram including INR.

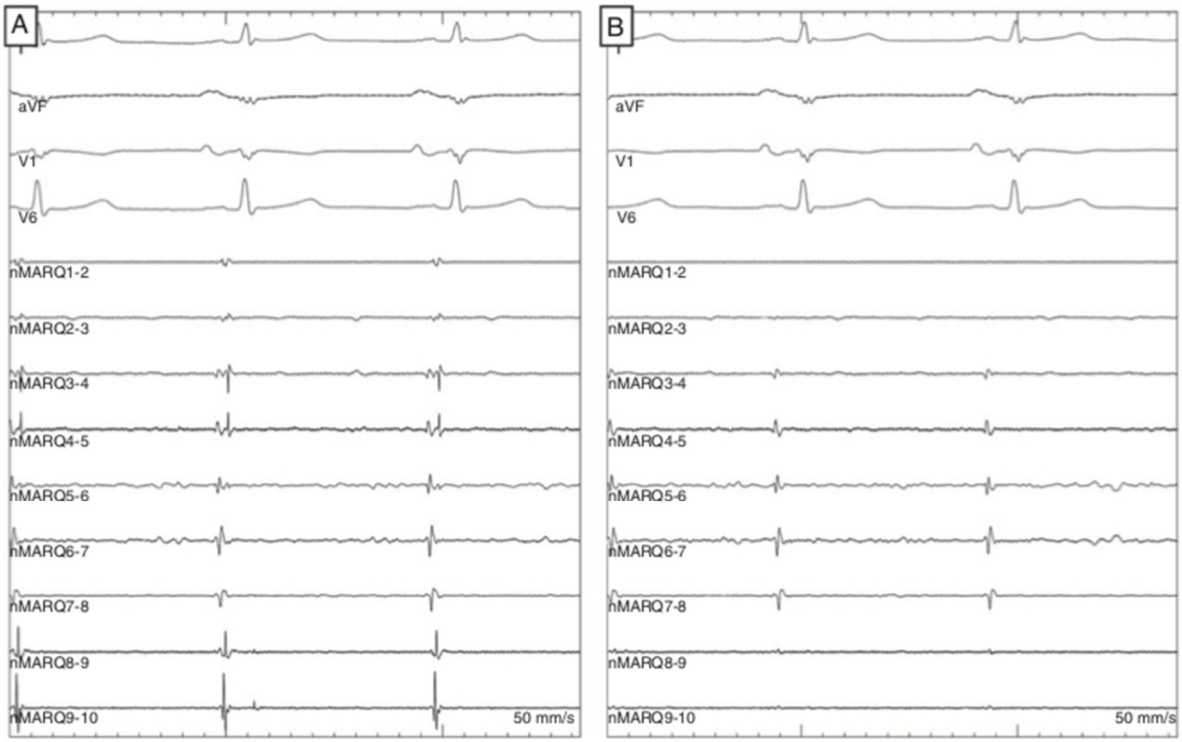
All subjects underwent transthoracic electrocardiography where standard preprocedural measures were taken (left ventricular ejection fraction, left atrial diameter from parasternal long axis, left atrial volume, valvular function). Also transesophageal echocardiography was performed to rule out left atrial thrombus before the procedure in all patients. Left atrial anatomy was assessed in all patients using cardiac magnetic resonance imaging prior to the procedure. Oral anticoagulation was not interrupted for the procedure according to current recommendations. In patients on warfarin, INR 2-3 was targeted before the ablation, and the drug was withheld on the morning of the procedure. In patients on dabigatran and apixaban, last dose was given the night before the procedure and withheld one the morning of the procedure. Patients on rivaroxaban taking the drug in the morning were switched to take the last dose of rivaroxaban the night before the procedure. First dose of NOACs was given 4-6 hours after pulling the sheaths and achieving hemostasis.

4.2.2. Electrophysiological procedure

All PVI procedures were performed under conscious sedation using fentanyl, midazolam and propofol according to local protocol. The right femoral vein was used for vascular access in all cases. Two sheaths were positioned in patients undergoing irrigated multielectrode ablation (one short 8F sheath and one long 8.5 F transseptal sheath) and three sheaths in patients undergoing standard point-by-point

radiofrequency ablation (one short 8F sheath and two long 8.5F transseptal sheaths). A 7F, decapolar, deflectable diagnostic catheter (EZSteer, Biosense Webster, Diamond Bar, CA) was positioned in the coronary sinus as a reference and for pacing. Transseptal puncture was performed under fluoroscopic guidance with standardized protocol (146). Coronary sinus catheter was used for anatomic orientation, and transseptal puncture was performed using contrast injection and pressure control. After transseptal puncture, intravenous heparin was administered to achieve and maintain an activated clotting time (ACT) >350 seconds and ACT was monitored every 15 minutes during the procedure. Additional heparin doses were administered depending of ACT values. The sheaths were continuously flushed with heparinized saline. Intracardiac electrograms and surface electrograms were recorded and displayed at a speed of 100 mm/s. The endpoint was entrance block in all patients (elimination of all PV potentials on the circumferential mapping catheter – **Figure 4.2.2**) according to the current consensus (1,8). Pacing manoeuvres were used to differentiate far-field signals from pulmonary vein potentials. All procedures were performed in conjunction with an electroanatomical mapping system (Carto3, Biosense Webster, Diamond Bar, CA, USA) and the reconstructions from magnetic resonance imaging were imported and used for guidance for mapping of the left atrium and the pulmonary veins.

Figure 4.2.2. Endpoint of pulmonary vein isolation – entrance block. Catheter is positioned in the right inferior pulmonary vein. A before ablation, far-field atrial and PV potentials are seen. B after the ablation, only far-field atrial signals are seen.

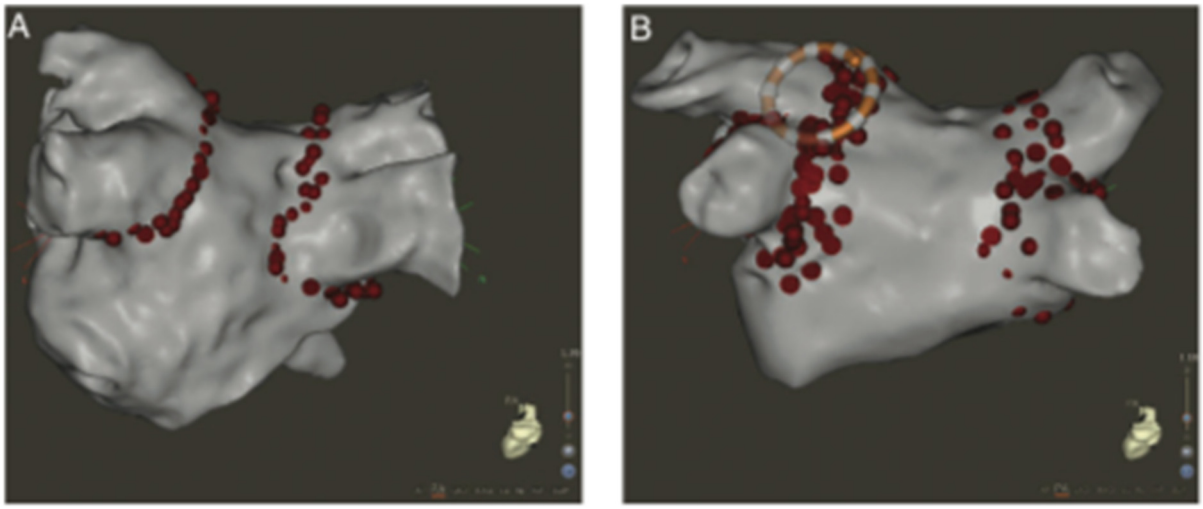


4.2.2.1. Irrigated multi-electrode ablation (IMEA-PVI group)

An esophageal temperature probe with 3 poles was positioned in all patients (Sensitherm, St. Jude, MN, USA) and the alert limit was set to 38°C. Single transseptal puncture was performed using the SL1 sheath (St. Jude Medical) which was then and replaced for a steerable sheath (Agilis Nxt, St. Jude Medical). A 20-pole circumferential mapping catheter (Lasso 2515, Biosense Webster, Diamond Bar, CA, USA) was used to create the 3D-electroanatomic map of the left atrium using the "fast anatomical mapping" (FAM) feature of Carto3mapping system. After connecting the deflectable and adjustable decapolar IMEA catheter (nMARQ, Biosense Webster, Diamond Bar, CA, USA), an idle flow rate of 4 ml/min. was chosen for irrigation. After positioning the catheter at the antrum of each PV, ablation was performed. All ablations were performed in a unipolar mode for 30-40 seconds and a starting power of

15 Watts (flow rate 60 ml/min.) per lesion on all 10 electrodes with presumed tissue contact. The assessment of tissue contact was based on signal quality, electrode position, the “tissues connect” feature of the Carto3 system and tactile feedback. If no signals were recorded on an electrode or one part of the catheter was within the PV, RF delivery was disabled on selected electrodes. Power was titrated up to a maximum of 18 Watts at the posterior wall and 20 Watts at the anterior wall if needed. Temperature, power and impedance were closely monitored throughout the energy application on the nMARQ generator. Total catheter ablation time and cumulative ablation times were recorded for the IMEA catheter. Total catheter ablation time was defined as the total time that IMEA catheter was used for RF ablation, regardless of the number of electrodes used, as reported by the nMARQ generator. Cumulative ablation time for the IMEA catheter was defined as the sum of all RF ablations by all electrodes delivering RF energy. This time represents the total delivered RF energy in the left atrium. Points were taken on the mapping system to locate each energy application for both technologies, and each was taken after achieving 10 s of ablation (**Figure 4.2.2.1**)**.** Ablation was stopped if one of the three temperature sensors reached the pre-defined threshold of 38°C. If a PV could not be isolated using the IMEA catheter, a standard focal irrigated-tip ablation catheter (Thermocool SF, Biosense Webster) was used to complete PVI. PV isolation was confirmed using the standard 20-pole circumferential mapping catheter in all patients. All complications were classified according to the HRS/EHRA/ECAS expert consensus statement on AF ablation.(8) All catheter-related technical issues were documented and collected.

Figure 4.2.2.1 ablation points with different technologies – A RV PVI; B IMEA PVI. Both figures show postero-anterior view of the left atrium. The number and distribution of ablation tags represent cumulative energy delivered for ablation and could potentially have clinical implications.



4.2.2.2. Point-by-point radiofrequency ablation (RF-PVI group)

Double transseptal puncture was performed in all patients using SL-1 sheaths (St. Jude Medical). A 20-pole circumferential mapping catheter (Lasso 2515, Biosense Webster) was advanced into the left atrium and mapping of the left atrium was performed using FAM. RF-PVI was performed using a 3.5 mm open irrigated-tip catheter (Thermocool SF, Biosense Webster). The 3D-reconstruction of the left atrium was used to guide the continuous circumferential antral ablation around the ipsilateral PVs. RF energy was delivered using the EP Shuttle RF generator (Stockert, Freiburg, Germany) with a power of up to 30 Watts and a maximum temperature of 50°C. Power at the posterior wall was limited to 25 Watts. Total ablation time was recorded. With the standard 3.5 mm irrigated tip catheter, cumulative RF time is equal to total catheter ablation time.

4.2.3. Post-ablation management

After sheath removal all patients were monitored overnight. Transthoracic echocardiography was performed in all patients after the procedure to rule out pericardial effusion. The first dose of NOACs was given four hours after achieving hemostasis and Vitamin-K antagonists were resumed the night of the procedure (147) (148). Oral anticoagulation was continued for at least 3 months after the procedure in all patients and after that according to CHA_2DS_2VASC score criteria (8). 12 lead ECG was performed the next day. Patients were discharged the day after the procedure if no complications occurred.

4.2.4. Follow-up

Follow-up was performed at 3, 6, 9 and 12 months. Every follow up included patient history, physical examination, 12 lead ECG recording and 24 hour Holter ECG. After 12 months, 7 day Holter ECG was performed. Episodes of AF lasting more than 30 seconds or atrial tachycardia were counted as recurrences (8). Recurrence rates were analyzed without a blanking period.

4.2.5. Statistical analysis

Continuous variables are presented as mean ± one standard deviation or as median and interquartile range (IQR) in case of skewed distribution. For continuous variables, comparisons were made using Student's T-test, or Mann-Whitney U test, as appropriate. Discrete variables were compared using Fisher's exact test. A p-value <0.05 was considered to indicate statistical significance. Calculations were made using SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA).

5. RESULTS:

5.1. Baseline data:

A total of 49 patients were included in our study. Patients had a mean age of 60+9 years and 82% were men. The mean left atrial size in the parasternal long axis was 43+5 mm with no significant difference between groups.

Left ventricular ejection fraction was 55% (47–60%). Atypical PV anatomy (left common ostium or three separate right PVs) was identified in four patients (17%) in the IMEA-PVI group and in five patients (20%) in the RF-PVI group. There were no significant differences Baseline characteristics of the patients are shown in Table. No significant differences were found between the two groups in general patient characteristics.

Table 5.1-1 baseline demographic data of patients included in this study.

	Total, N=49	RF-PVI, N=25	IMEA-PVI, N=24	P value
Age (years)	60±9	60±7	59±10	0.69
Male (n)	40 (82)	22(88)	18(75)	0.42
BMI				
Hypertension	37(75)	17(68)	20(83)	0.37
Diabetes	5(10)	2(8)	3(13)	0.91
CAD	7(14)	3(12)	4(17)	0.92
AADs				
Amiodarone	26(53)	14(56)	12(50)	0.89
Dronedarone	2(4)	2(8)	0(0)	0.49
Flecainide	8(16)	3(12)	5(21)	0.64
Sotalol	1(2)	0(0)	1(4)	0.98
OAC				
Vit K antagonists	29(59)	15(60)	14(58)	0.88
NOAC	20(41)	10(40)	10(42)	0.96
EHRA scoreI-IV	0/24/25/0	0/14/11/0	0/10/14/0	0.49
CHA2DS2VASc score	1.7±1.1	1.6±1.2	1.9±1.0	0.34
HAS BLED score	1 (0.75-1)	1 (0-1)	1 (1-1.5)	0.15

AAD – antiarrhythmic drug; BMI body mass index; CAD coronary artery disease; OAC oral anticoagulation; NOAC. Novel oral anticoagulant; EHRA – European heart rhythm association. RF-PVI, point-by-point radiofrequency ablation group; IMEA-PVI irrigated multielectrode ablation pulmonary vein isolation group;

5.2. Procedural characteristics:

Acute isolation of all PVs using the IMEA catheter was achieved in 22 of 24 (92%) patients and 92 of 94 (98%) PVs compared with 25 of 25 patients (100%) in the RF-PVI group. In 2 (8%) patients and 2 (2%) PVs in the IMEA group, additional ablation with a standard 3.5 mm irrigated-tip catheter was required. In one patient, after a total catheter ablation time of 29.4 min and a cumulative ablation time of 140.5 min, additional point-by-point ablation was needed to achieve isolation of the right inferior PV.

In a second patient, after a total catheter ablation time of 15.1 min and a cumulative ablation time of 88.5 min, additional ablation was needed for isolation of the left inferior PV.

Procedure duration, fluoroscopy time, and dose area product (DAP) in the IMEA group were 125+23 min, 12.2 (11–16.1) min, and 3163 (1738–4865) μGy m2, respectively. Procedure duration did not differ between the two groups; however, fluoroscopy duration and radiation dose were significantly higher in the IMEA-PVI group. Total net catheter ablation time with IMEA catheter was 11.8 (10.2–15.4) min. This was markedly shorter compared with the ablation time with the 3.5 mm tip catheter. However, cumulative ablation time with the IMEA catheter was much higher with 75.1 (63.2–113.5) min (P = 0.001). Procedural details for both groups are given in **Tables 5.2-1-4.** Difference between net and cumulative ablation times are shown in the **graph 5.2**.

Table. 5.2-1 Procedural parameters - procedure duration, fluoroscopy duration and dose

	Total, N=49	RF-PVI, N=25	IMEA-PVI, N=24	P value
Procedure duration (min)	127±27	127±31	125±23	0.79
Fluoroscopy time (min)	9.9 (4.9-14.5)	5.2 (4.1-9.3)	12.2 (11-16.1)	**<0.001**
DAP (mcGym2)	1924 (1087-3612)	1337 (944-1989)	3163 (1738-4865)	**<0.001**

DAP dose area product. RF-PVI, point- by-point radiofrequency ablation group; IMEA-PVI irrigated multielectrode ablation pulmonary vein isolation group;

Table 5.2-2. Procedural data. Baseline anatomical data and rhythm characteristics during the ablation.

	Total, N=49	RF-PVI, N=25	IMEA-PVI, N=24	P value
Number of PVs	193	99	94	
PV anatomy				
3 PVs (left common)	6(12)	3(12)	3(13)	1
4 PVs	40(82)	20 (80)	20 (83)	0.92
5 PVs	3(6)	2(8)	1(4)	0.99
Ablation in AF (%)	31 (63)	17(68)	14(58)	0.56
Conversion to sinus with RFA (%)	7 (14)	5(29)	2(14)	0.42
Cardioversion (%)	24 (49)	12(71)	12(86)	1

AF, atrial fibrillation; RF-PVI, point-by-point radiofrequency ablation group; IMEA-PVI irrigated multielectrode ablation pulmonary vein isolation group; RFA radiofrequency ablation; PV pulmonary vein

Table 5.2-3. Ablation times between the groups.

Ablation times (min)	**Total, N=49**	**RF-PVI, N=25**	**IMEA-PVI, N=24**	**P value**
Total/Net (min)	23.9(11.8-34.4)	33.6 (30.3-40.1)	11.8(10.2-15.4)	**<0.001**
Cumulative	51.1(33.6-75.1)	33.6(30.3-40.1)	75.1(63.2-113.5)	**<0.001**

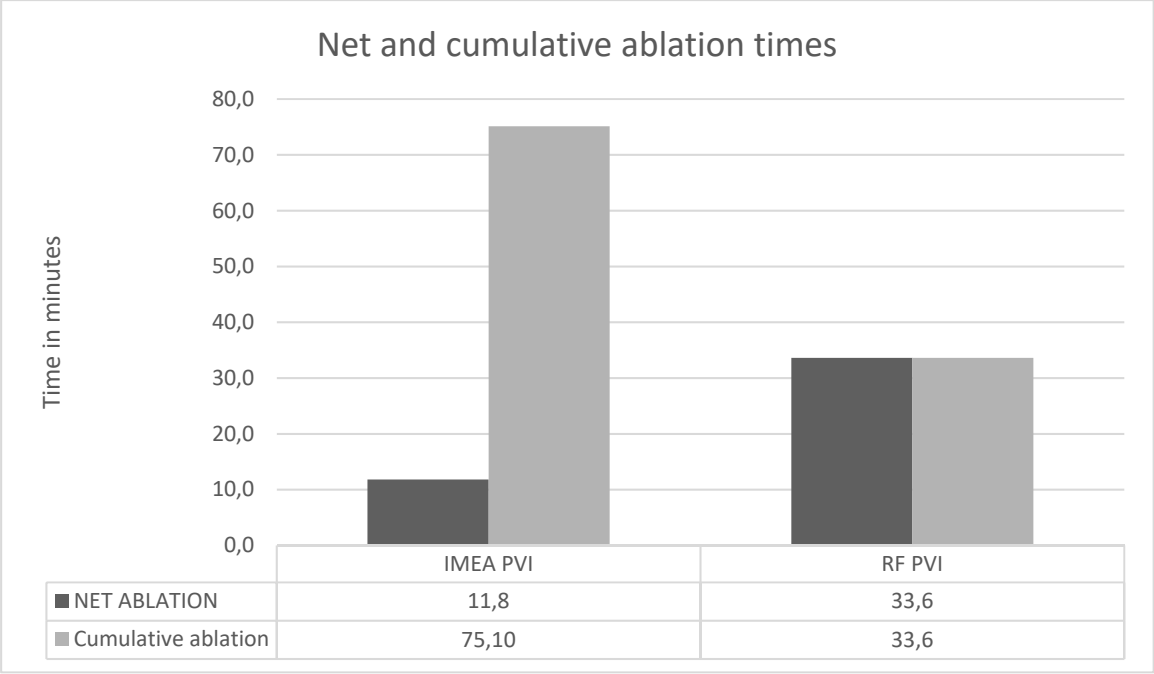
RF-PVI, point-by-point radiofrequency ablation group; IMEA-PVI irrigated multielectrode ablation pulmonary vein isolation group;

Table 5.2-4. Procedural parameters. Successful ablation achieved with the primary catheter.

Successful ablation with primary catheter	**Total, N=49**	**RF-PVI, N=25**	**IMEA-PVI, N=24**	**P value**
Per patient	47 (96)	25(100)	22(92)	0.24
Per PV	191(99)	99(100)	92(98)	0.24

RF-PVI, point-by-point radiofrequency ablation group; IMEA-PVI irrigated multielectrode ablation pulmonary vein isolation group;

Graph 5.2 Difference in net and cumulative ablation times with the same catheter. Note that these values are the same for the RF-PVI group, however, significantly different for IMEA PVI group.



RF-PVI, point-by-point radiofrequency ablation group; IMEA-PVI irrigated multielectrode ablation pulmonary vein isolation group;

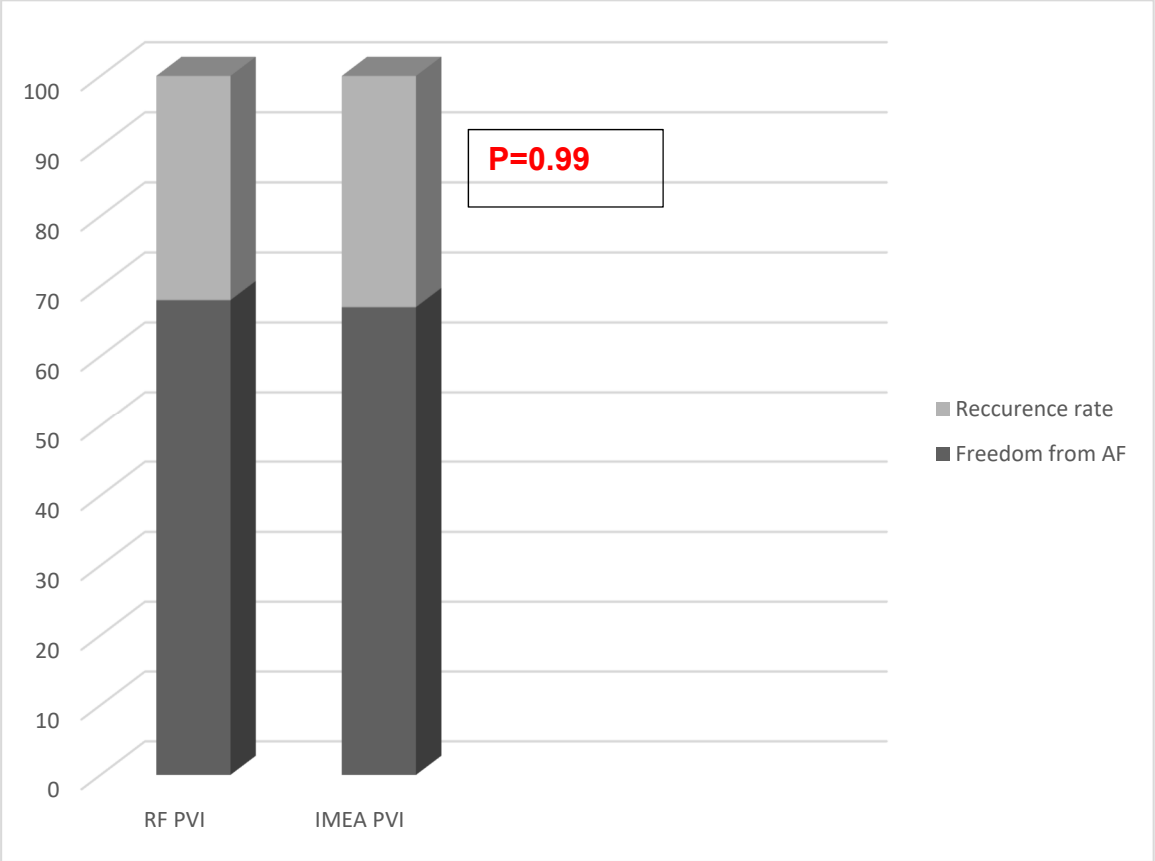
5.3. Validation of pulmonary vein isolation:

Of 94 PVs presumed to be isolated after ablation using the IMEA catheter, validation using a standard circular mapping catheter (Lasso 2515, Biosense Webster) showed persistent PV potentials in 33 PVs (35%). Ablation using the IMEA catheter was continued until all PV potentials were eliminated based on the recordings from the circular mapping catheter. On a per PV basis, persistent PV conduction despite presumed isolation based on the IMEA catheter was found in 7 of 21 (33%) LSPVs, in 9 of 21 (43%) LIPVs, in 6 of 24 (25%) RSPVs, in 11 of 24 (46%) RIPVs, in 0 of 1 RMPV, and in none of the 3 left common PVs. Presumed isolation was found numerically more often in the inferior PVs (44%) compared with the superior PVs (29%), but this difference was not statistically significant (P =0.19).

5.4. Efficacy and safety:

During a follow-up of 12 months (including a standard blanking period of 3 months as recommended in the guidelines), 16 of 24 patients (67%) in the IMEA group compared with 17 of 25 patients (68%) in the RF-PVI group were free from AF after a single procedure (P . 0.99). There were no periprocedural complications. In the IMEA group, a total of 5 catheters in 4 of 24 procedures (17%) had to be replaced due to a technical issue. One catheter had a faulty magnetic sensor, one had a defective puller wire preventing deflection of the catheter, two showed wrong temperature measurements at baseline (beginning of the procedure), and one showed a wrong impedance measurement at baseline. There were no catheter related technical issues in the RF-PVI group. No complications have occurred due to catheter related technical issues.

Graph 5.4. 12 months success rates between the two groups



5.5. Repeat procedures:

Six of 24 patients in the IMEA group (25%) and 4 of 25 patients in the RF-PVI group (16%) underwent a repeat left atrial procedure (P = 0.50). All patients undergoing a repeat procedure underwent repeat left atrial imaging with no evidence of PV stenosis. At least one PV with reconnection was found in all patients undergoing repeat ablation. Per patient, the mean number of PVs with reconnection was 2.3+1.2 in the IMEA group compared with 2.8+1.5 in the RF-PVI group (P = 0.64). Of the 14 PVs with reconnection in the 6 patients in the IMEA group, there were 8 left-sided (3 in LSPV; 5 in LIPV) and 6 right-sided (3 in RSPV; 3 in RIPV) reconnections, whereas of the 11 PVs with reconnection in the RF-PVI group, there were 3 left-sided (2 in LSPV; 1 in LIPV) and 8 right-sided (4 in RSPV; 3 in RIPV; 1

in RMPV) reconnections (P = 0.28). Of the 20 reconnection sites (in 14 PVs) in the IMEA group, 13 sites (65%) were left sided (6 in LSPV; 7 in LIPV) and 7 (35%) were right sided (3 in RSPV; 4 in RIPV). In contrast, of the 15 reconnection sites (in 11 PVs) in the RF-PVI group, 4 (27%) sites were left sided (3 in LSPV, 1 in LIPV) and 11 (73%) were right sided (5 in RSPV; 1 in RMPV, 5 in RIPV) (P = 0.04).

6. DISCUSSION

Since the introduction of the IMEA (nMarq) catheter into clinical practice, and until this research has been published three single-centre studies were recently published (116,119,149) showing comparable acute success rates compared with reported acute success rates of point-by-point RF ablation and other 'single-shot' devices for PVI (150,151). However, to the best of our knowledge, this is the first study reporting 1-year follow-up after PVI using the IMEA catheter. The main findings of our study are: (1) Acute PVI can be achieved in almost all patients and PVs using solely the IMEA catheter. However, the recordings from the IMEA catheter were not sufficient to confirm isolation in 35% of PVs (requiring additional IMEA ablation in these PVs to achieve isolation). (2) Procedure duration is similar between ablation using the IMEA catheter and standard point-by-point ablation, while fluoroscopy times and radiation doses are higher in the IMEA-PVI group. (3) Net catheter ablation times are lower with the IMEA catheter than with the 3.5 mm irrigated-tip catheter, but cumulative RF time with the IMEA catheter is significantly higher. (4) There was no significant difference in freedom from AF after a follow-up of 1 year.

6.1. Acute success and validation of pulmonary vein isolation

In our study, the procedural endpoint of PVI confirmed by a standard 20-pole circular mapping catheter was reached in all patients. In the IMEA group, PVI was achieved using solely the IMEA catheter in 22 out of 24 patients (92%) and 92 out of 94 PVs (98%). The median number of RF applications with the IMEA catheter was 24 (22–32) and comparable with previously reported studies (116,119,149). In the RF-PVI group, acute PVI could be achieved in all patients. In the study by Deneke et al. (116), mapping

and confirmation of PVI (by abatement of electrograms and exit block confirmation if the IMEA catheter could be advanced into the PV) were performed using the IMEA catheter only. With this method they could achieve and verify isolation in 160 of 163 targeted veins which is similar to our finding. Shin et al.(149) could confirm exit block in 93% of the PVs and 72% of patients with the IMEA catheter. In the cases where the IMEA catheter could not be advanced into the PV, confirmation of isolation was performed using a standard circular mapping catheter. This was required in total of 28% patients, and in all of them it was required for right inferior pulmonary vein. In our study, however, we performed confirmation of PVI with a standard circular mapping catheter in all our patients (both in the IMEA-PVI and RF-PVI groups) for two reasons: first, PV signals or their disappearance cannot always be verified on the IMEA catheter, especially after ablation, as recently shown by Rosso et al (152). Second, current recommendations for the verification of PVI require at least demonstration of entrance block and not only voltage abatement on the antral ablation line (1,8). However, due to the higher stiffness of the 8.4 French distal circular part of the IMEA catheter and its minimal diameter of 20 mm, it cannot be advanced into smaller PVs. Rosso et al. (152) found that the recordings of the potentials at the antrum of the pulmonary veins in both catheters (standard diagnostic circular catheter and IMEA catheter) were concordant in 92% of cases before the ablation. However, after the ablation in 30% of veins (12 of 39) after the ablation, presumably disappeared pulmonary vein potentials on IMEA catheter were clearly seen on standard circular diagnostic catheter. On the other hand, in 28% of veins (11 of 39) fragmentation of signals which were not seen on standard diagnostic catheter.

Although, in contrast to Rosso et al., we did not use the standard circular mapping catheter for real-time recordings from the PVs during energy application (because of possible contact issues at the antrum with the IMEA catheter), our results are in line with the findings of Rosso et al. With 35% of all PVs presumed to be isolated based on IMEA recordings showing persistent PV potentials on the standard circular mapping catheter, our results also suggest that the IMEA catheter is insufficient to accurately confirm PVI.

This was the first report evaluating the acute efficacy and signal verification in patients with persistent atrial fibrillation. In the previous studies it was used solely in the patients with paroxysmal atrial

fibrillation. Patients with persistent atrial fibrillation tend to have larger atria with more pronounced fibrosis and frequently require additional substrate ablation. However, pulmonary vein isolation was used in our center as the first procedure in all patients with persistent atrial fibrillation. In achieving acute pulmonary vein isolation, our study showed comparable results to those of previous IMEA catheter studies in patients with paroxysmal atrial fibrillation.

Further studies, including patients with paroxysmal and persistent atrial fibrillation were published afterwards with larger number of patients from prospective registries have reported successful isolation of pulmonary veins in both group of patients in 99.6% (153) and up to 100% (117)of pulmonary veins, not requiring additional ‚touch up'' ablations. In a multicenter study by Mahida et al. (153) 374 patients were included, among which 111 patients with persistent atrial fibrillation. A total of 1,468 of 1,474 veins (99.6%) were isolated with the nMARQ catheter alone. Another prospective registry by Vurma et al. (122) included 327 patients with paroxysmal and persistent atrial fibrillation. And while they report procedural data and success rates after 12 months, rate of acute PV isolation is nor reported.

6.2 Procedural characteristics

Procedure duration was not different between the two study groups, whereas fluoroscopy duration and DAP were significantly higher in the IMEA-PVI group (P = 0.001). Procedure times in our study are longer compared with one previous study (119) and similar to the other two previously reported studies with IMEA catheter (116,149) and are also similar to other ablation methods (112,132,150).

Although shorter procedure times are a potential advantage of single-shot technologies, this was not achieved in this study. One of the reasons for this might be the relatively high rate of technical failures with the IMEA catheter leading to delays during procedures. Increased reliability of future generation IMEA catheters may overcome this problem. Also, in theory larger experience and overcoming the learning curve with the new catheter could reduce the procedure times.

Study by Vurma et al. (122) published afterwards, with 327 patients included, reported shorter procedural times both for paroxysmal and persistent atrial fibrillation. There was a difference, with shorter procedural times in patients with paroxysmal atrial fibrillation (68.6+22.5 min vs. 75.0+22.7 min, p=0.023). In this study, longer procedural times could in part be explained by longer ablation times in patients with persistent atrial fibrillation due to larger atrial area and wider antral ablation in these patients (122).

In a study by Mahida et al (153), with 374 patients included reported similar procedural times to our and other previous studies.

However, in our study, the procedure duration did not change with increasing experience with the IMEA catheter.

Fluoroscopy times and DAP in our study were significantly higher in the IMEA group, however both groups in our study had lower fluoroscopy times and DAP than previously reported. (116,119,154). Fluoroscopy times in studies that followed were also higher than reported in our study, both in patients with paroxysmal and persistent atrial fibrillation (122,153).

One of the reasons for consistently lower fluoroscopy times when compared to all other studies is following ALARA (as low as reasonably achievable) principle by our group. Due to risks from exposure to radiation for patients and operators, every effort should be made to reduce the fluoroscopy use to a minimum (155). With the advent of mapping systems, radiation burden has been decreased (142). Additionally, by using standardized protocols, radiation could be decreased to minimum or even zero during the procedures with electroanatomical mapping systems. We have demonstrated that during RF point-by-point ablation, PVI could be performed without fluoroscopy after achieving transseptal access (140,141). Previous groups have reported that PVI could be performed with no use of fluoroscopy, however with the additional use of intracardiac or transesophageal echocardiography (156). In patients with patent foramen ovale, our group has shown that PVI could be performed with no use of fluoroscopy, using only mapping system (142). In a patient with a PFO, IMEA catheter ablation could also be performed with no use of fluoroscopy as reported by Mühl et al (157).

Applying standardized protocols when using mapping systems, led to reduced fluoroscopy times reported in our study (total 9.9 (4.9–14.5)min, RF group 5.2 (4.1–9.3) min vs. IMEA group 12.2 (11–16.1) min). Also, in our study, with increasing experience with the IMEA catheter, fluoroscopy duration was decreased between the first and the last five procedures in the IMEA-PVI group.

6.3 Delivery of radiofrequency energy

The total net ablation time was lower in the IMEA-PVI group [11.8 (10.2–15.4) min] than that in the RF-PVI group [33.6 (30.3–40.1) min]. This was similar compared with previously reported studies (19 and 15 min) (116,154). When comparing our study in patients with persistent atrial fibrillation with those previously reported studies in patients with paroxysmal atrial fibrillation, ablation times were similar. Mahida et al (153) reported very similar ablation times to our results (13.5 ± 6.4 min). In study by Vurma et al (122) ablation times were higher than reported in our study (18.9+6.4 min in paroxysmal and 22.1+6.1 min in persistent). The difference between ablation times was significant ($P<0.001$). The 13% longer ablation times were explained with larger atrial area and wider antral ablation in these patients.

However, these reported RF times do not adequately represent the total amount of RF energy delivered with multi-electrode ablation. With the IMEA catheter, RF energy is applied over a pre-selectable number of electrodes (1–10) simultaneously. However, the ablation system counts and reports only the duration of energy delivery for every energy application, independent of the number of selected electrodes. These times are reported and compared in all reports on IMEA catheter ablation (116,119,122,153,154).

Consequently, in our study, the effective, cumulative RF time was calculated by adding the ablation time for every ablation multiplied by the number of selected electrodes. The resulting median cumulative time of RF ablation was 75.1 (63.2–113.5) min, which is significantly higher compared with point-by-

point ablation in our study. In point-by-point ablation, RF net ablation time is equal to cumulative ablation time since only one ablation electrode is being used.

Some authors suggest that ablation times cannot be compared, since these ablation times do not adequately represent the amount of energy being delivered (122), this holds true only for reported net ablation time. This value, given by the system does not adequately represent total energy that was delivered. If cumulative ablation times were used, they would be comparable between the studies, regardless of protocols and number of electrodes used for every RF energy application. Although we reported no complications in our study, these cumulative ablation times which are significantly higher than all reported net ablation times and higher than cumulative ablation time in the RF PVI group in our study, could explain higher reported risks of complications with this technology (120,122). Even if cumulative ablation times would be used for reporting and comparing energy delivery this could still be misleading especially for predicting the risk of oesophageal injury since the applications are performed simultaneously on the anterior and posterior wall from several electrodes. Also, the potential for overlapping energy regions from two adjacent electrodes has to be taken into account.

6.4 Procedure related complications

In this study no procedural complications occurred. Pericardial effusions were excluded by transthoracic echocardiography and there were no clinical signs of access site complications nor manifest cerebral thromboembolism.

In a study by Shin et al. (154), with 25 patients, also no complications were reported. In their study they also performed pre and postprocedural cardiac MRI which no signs of acute PV stenosis. However, it is known that PV stenosis can occur delayed after the ablation (149,158).

In a study by Deneke et al. they routinely performed postprocedural brain MRI with the goal of detecting asymptomatic cerebral lesions (silent cerebral lesions). Although they did not report any symptomatic

cerebral events, they reported asymptomatic cerebral lesions detected by MRI in 17 of 43 (33%) patients. Incidence is slightly higher compared to single-tip irrigated RF (24%), laserballoon (24%), or cryoballoon (21%) ablations and lower compared to phased RF technology (37%) when using a comparable MRI protocol (116,159). Recent report of 2 IMEA catheter studies (160) have shown that adherence to strict anticoagulation protocols resulted in significant decrease in post procedural silent cerebral lesions. Clinical relevance of these silent cerebral lesions is still unclear.

Zellerhof et al. (119) reported one case of tamponade in 39 patients who underwent PVI with IMEA catheter. The tamponade was related to transseptal puncture and not the ablation and the patient fully recovered.

Other potential issue with radiofrequency ablation, especially with IMEA catheter are thermal lesions of the esophagus and devastating complication atrioesophageal fistula which has very high mortality rate. Reported rate of atrioesophageal fistula with standard point-by-point radiofrequency (RF) ablation ranges between 0.03 and 0.2% (161,162). Oesophageal thermal lesions have been reported in up to 20% of patients using standard point-by-point RF ablation (163).

Esophageal temperature monitoring is used to prevent thermal lesions. Esophageal temperature probe is placed and the goal is to keep the maximal luminal oesophageal temperature (LET) below a predefined cut-off value during ablation.

We had data from luminal esophageal temperature monitoring for 40 of total 49 patients (20 in RF PVI group and 20 in IMEA group).

Deneke reported temperature increase above 40.5 °C in 51% of patients undergoing ablation with IMEA catheter (116). Of those 22 patients, two thirds had mild thermal lesions of the oesophagus detected endoscopically.

With point-by-point ablations, esophageal lesions have been reported in up to 11% and thermal esophageal damage in 30–46% of patients using temperature monitoring (116). On the other hand, with cryoballoon ablation, esophageal damage has been identified in up to 17% (164).

Unfortunately, case of atrio-esophageal fistula was reported early with the use of the first generation IMEA catheter (120). Later, study by Vurma et al (122) reported 2 cases of atrio-esophageal fistula in series of 327 patients 0.6%, however both of them occurred consecutively with the use of second generation IMEA catheter in 39 patients (2/39, 5.4%) which is higher than in any other reports and studies regardless of technology used. Because of potential technical problems, the catheter was recalled by the manufacturer, and further results of the technical investigation are pending.

6.5. Freedom from atrial fibrillation

During a follow-up of 12 months (including a standard blanking period of 3 months), 16 of 24 patients (67%) in the IMEA group compared with 17 of 25 patients (68%) in the RF-PVI group were free from AF after a single procedure ($P > 0.99$). One previous study reported 4-month success rates of 80.9% in patients with paroxysmal AF, whereas another reported success rates of 77% after a follow-up of 140 days using IMEA ablation in patients with paroxysmal atrial fibrillation (119,149). However, both of these studies enrolled only patients with paroxysmal atrial fibrillation. Also maximal reported follow up was 4 months in these studies.

In our study, results of point-by-point ablation and IMEA catheter ablation for persistent AF were similar in approximately two-thirds of patients being free from AF after a follow-up of 1 year, the longest available follow-up data in patients undergoing PVI using IMEA regardless on type of atrial fibrillation at the time.

These success rates were consistent in studies that followed. In a study by Vurma et al (122). As stated before, total of 327 patients were included, among those 228 with paroxysmal atrial fibrillation and 97 with persistent. After a single procedure and after a median of 3.3 month follow up, 75% of patients with paroxysmal AF and 52% of patients with persistent AF were free from atrial fibrillation. It the patients who underwent redo procedures (5%) and those taking antiarrhythmic drugs the success rates rose to 90% and 83% respectfully. In our study, however, the follow up was longer and the patients were held off antiarrhythmic drugs with somewhat higher success rates. Looking at the patient population,

there were no obvious differences in the left atrial size or duration of atrial fibrillation. The patients in study by Vurma et la were slightly older than our study population (64.8±8.2 vs. 59±10).

In the largest study with IMEA catheter by Mahida et al. (153) Which included total of 374 patients among which 111 patients with persistent atrial fibrillation. This study reported the success rates at 12 months follow up. 65% of patients in both groups (paroxysmal and persistent atrial fibrillation) were free from atrial arrhythmias at 12 months follow up. However, of 374 patients, 12 months follow up data was available in total 85 patients (21%). In the persistent group follow up data were available in 20 of 97 patients. In this group, 65% of patients were free from atrial arrhythmia, 20% had AF recurrence and 15% had atrial tachycardia. In our study we had similar success rates after 12 months follow up. And while both studies by Vurma and Mahida report experience with IMEA catheter in a larger number of patients, only a small proportion of these patients, especially those with persistent atrial fibrillation have 12 month outcomes in a study by Mahida. Our study had fewer patients included, however available follow up after 12 months in higher number of patients with persistent atrial fibrillation. Also, in our study, safety and efficacy of IMEA catheter ablation were compared to standard point-by-point ablation with similar results.

Other studies using either point-by-point radiofrequency ablation or other technologies in patients with persistent atrial fibrillation reported similar success rates after 12 months (165–167). These trials were multicenter, randomize trials that compared ablation versus antiarrhythmic drugs and the success rates defined as freedom from AF after 12 months were 56%, 70% and 74% respectfully. However, only in the trial by Hummel et al (165) which used phased RF ablation was only pulmonary vein isolation performed. This trial had success rates of 56%. In other trials by Oral et al. (166) and Mont el al. (167) (both 146 patients), in addition to PVI, substrate modification was performed. In a trial by Oral, roof and mitral lines were performed and in the trial by Mont CFAEs and optional lines in the left atrium were performed. As stated before, different technologies exist for ablation of atrial fibrillation. And while it was and still is clear that the pulmonary vein isolation is the cornerstone for treating atrial fibrillation and is very efficient and usually only procedure that is needed in patients with paroxysmal atrial fibrillation, approach in patients with persistent atrial fibrillation differs. Some centers, as our two

centers do, used solely PVI as the first procedure, but as seen in studies by Oral and Mont, additional substrate modification as mitral and roof lines of ablation of CFAEs is used by some centers. This is why results and success rates differ among different studies.

In 2015 results of STAR AF II Trial were published. Study by Verma et al. (97) included 589 patients undergoing ablation for persistent atrial fibrillation and randomized them in 1:4:4 ratio to pulmonary-vein isolation alone (67 patients), pulmonary-vein isolation plus ablation of electrograms showing complex fractionated activity (263 patients), or pulmonary-vein isolation plus additional linear ablation across the left atrial roof and mitral valve isthmus (259 patients). After 18 months of follow up, there was no difference in success rates between groups (59% vs. 49% vs. 46%, p=0.15) with a trend for more complications in groups with additional ablation protocols. This study proved that pulmonary vein isolation alone is also the cornerstone of persistent atrial fibrillation.

In addition to first procedure, approximately 20% of patients in our study underwent a repeat left atrial procedure for recurrent AF (168). The number of reconnected pulmonary veins per patient was not different between the IMEA-PVI and RF-PVI groups, but there were significantly more reconnection sites at the left-sided PVs in the IMEA group. There were no differences in reconnection patterns at the right sided pulmonary veins. Zellerhoff et al. (119) also analysed PV reconnection patterns in patients undergoing a repeat ablation after IMEA-PVI. Although no comparison was made with standard RF-PVI, they also described reconnection in all PVs with a typical site being the antero-superior circumference of the left superior PV and the anterior circumference of the left inferior PV. On the right sided pulmonary veins, typical reconnection patterns were superior part of the right superior PV and inferior part of right inferior PV.

In a study by Mahida et al. (153) 17 of 374 patients underwent repeat procedures and reconnection patterns were reported in 16 of them. Like in the study by Zellerhof, there was no comparison with standard RF PVI. Distribution of reconnection patterns differed with most frequent reconnection areas being the anterior aspect of the RSPV, the inferior aspect of the RIPV and the superior aspect of the LSPV.

At the left sided veins, reconnection patterns in all three studies are similar and may be explained with the difficulty of adequate circumferential tissue contact when positioning the IMEA catheter at the left-sided PV ridge region. We reported no difference in reconnection patterns with RF PVI and IMEA catheter ablation at the right sided veins and in the other two studies patterns were slightly different – anterior vs. superior part of the right superior pulmonary veins and inferior part of the right inferior vein. Inferior part of the RIPV could reflect inadequate catheter-tissue contact in this region similar to other single shot technologies (123)

7. CONCLUSIONS

In patients undergoing ablation for persistent AF, IMEA-PVI resulted in shorter net ablation time but longer cumulative ablation duration compared to RF-PVI. Procedure times were similar between the two groups, while fluoroscopy time was significantly longer in IMEA-PVI group. Technical issues occurred in 5 IMEA catheters, while there were no technical issues with standard point-by-point catheters.

Success rates defined as freedom from AF after 12 months were similar in both groups. No complications occurred in both groups of patients.

It can be concluded that IMEA-PVI is as effective as point-by-point RF ablation in patients with persistent AF at the cost of longer fluoroscopy and longer cumulative ablation times. Whether the longer cumulative ablation duration has an impact on safety or on long-term efficacy needs to be investigated in future studies.

8. SAŽETAK

Fibrilacija atrija je najučestalija supraventrikulska aritmija u općoj populaciji. Povezana je s povišenom stopom morbiditeta i mortaliteta te sniženom kvalitetom života bolesnika. Kao opcija liječenja kob dijela bolesnika, razvijena je izolacija plućnih vena koje je i danas temelj ablacijskog liječenja fibrilacije atrija. Razvijeni su brojni kateteri i tehnologije za izolaciju plućnih vena, a jedna od novijih je i multielektrodna irigacijska ablacija. Dosad postoje istraživanja koja su ispitivala učinkovitost i sigurnost navedene tehnologije kod bolesnika s paroksizmalnom fibrilacijom atrija, međutim do sada nije korištena niti ispitana kod bolesnika s perzistentnom fibrilacijom atrija.

Cilj naše studije bio je usporediti novi multielektrodni irigacijski ablacijski kateter sa standardnom point-by-point radiofrekventnom ablacijom kod bolesnika s perzistentnom fibrilacijom atrija koji su podvrgnuti izolaciji plućnih vena.

U studiju je uključeno 49 bolesnika (60± 9 godina, 82% muškarci). Kod 24 bolesnika PVI je učinjena multielektrodnim irigacijskim ablacijskim kateterom (IMEA-PVI) uz korištenje maping sustava, a kod 25 bolesnika radiofrekventnom ‘’point-by-point’’ ablacijom standardnim 4 mm irigacijskim kateterom (RF-PVI). Bolesnici su praćeni 24h Holter EKGom tijekom 12 mjeseci svaka tri mjeseca, a u 12-om mjesecu učinjen je 7 dnevni Holter EKG.

Rezultati su pokazali da je vrijeme procedure usporedivo, ali vrijeme fluoroskopije kao i kumulativno vrijeme ablacije bili su znatno viši u IMEA grupi. Trajanje procedure bilo je 125 + 23 min u IMEA grupi i 127 + 31 min u RF-PVI grupi (P = 0.79). Vrijeme fluoroskopije bilo je 12.2 (11 – 16.1) min u IMEA grupi, a 5.2 (4.1 – 9.3) min u RF-PVI group (P = 0.001). Vrijeme ablacije kateterom bilo je 11.8 (10.2 – 15.4) min u IMEA grupi, a 33.6 (30.3 – 40.1) min u RF-PVI grupi (P= 0.001). Međutim, kumulativno vrijeme ablacije (vrijeme ablacije po RF elektrodi) bilo je značajno više u IMEA PVI grupi. I iako je incidencija komplikacija bila niska u ovom istraživanju, dulje kumulativno vrijeme ablacije bi moglo imati implikacije na incidenciju komplikacija koje su prijavljene u drugim studijama.

Rezultati su potvrdili našu hipotezu da nema značajne razlike u jednogodišnjoj uspješnosti (definirana kao odsutnost fibrilacije atrija) između dvije metode.16 of 24 bolesnika (67%) u IMEA grupi i 17 od 25 pacijenata (68%) iu RF-PVI grupi nisu imali fibrilaciju atrija nakon 12 mjeseci (P=0.99).

U zaključku, IMEA-PVI ablacija povezana je sa kraćom ablacijom kateterom, ali znatno duljom kumulativnom ablacijom. Također, procedura je slične duljine trajanja kao RF PVI, ali uz znatno dulje korištenje fluoroskopije. Uspješnost u održavanju sinusnog ritma nakon 12 mjeseci je jednaka u obje skupine.

9. SHORT SUMMARY

Atrial fibrillation is the most common supraventricular arrhythmia in the general population. It is related to increased morbidity and mortality and reduced quality of life. Pulmonary vein isolation has emerged and today remains the cornerstone of atrial fibrillation ablation. There are multiple different tools and technologies used to achieve pulmonary vein isolation, and irrigated multi-electrode ablation was a novel tool to perform pulmonary vein isolation. It has been evaluated in patients with paroxysmal atrial fibrillation; however there is no data on use of this technology in patients with persistent atrial fibrillation. The aim of our study was to compare irrigated multi-electrode ablation with point-by-point radiofrequency (RF) ablation in patients with persistent atrial fibrillation under-going PVI.

In this prospective study, we included forty-nine patients (age 60 + 9 years, 82% male). In 24 patients, the IMEA catheter was used in conjunction with an electroanatomic mapping system. Twenty-five patients undergoing RF point-by-point ablation (RF-PVI) served as a control group. Patients were followed for 12 months with 24 Holter ECG monitoring at 3, 6, and 9 months and 7 days Holter ECG at 12 months follow up.

Results have confirmed our hypothesis that procedural parameters are similar between irrigated multielectrode ablation and standard point-by-point radiofrequency ablation. Procedure time was 125 + 23 min in the IMEA group and 127 + 31 min in the RF-PVI group (P = 0.79). Fluoroscopy time was 12.2 (11 – 16.1) min with IMEA compared with 5.2 (4.1 – 9.3) min in the RF-PVI group (P, 0.001). Net ablation time was 11.8 (10.2 – 15.4) min in the IMEA group compared with 33.6 (30.3 – 40.1) min in the RF-PVI group (P, 0.001). However, cumulative ablation times were significantly longer in the IMEA group compared to RF PVI group. Although complication rates were low in our study, longer cumulative ablation times could have implications on complication rates, which needs to be verified in future studies.

Success rates, defined as freedom from any atrial fibrillation at 12 months were similar between the two groups. At 12 months, 16 of 24 patients (67%) in the IMEA group compared with 17 of 25 patients (68%) in RF-PVI group were free from AF (P. 0.99).

In conclusion, IMEA-PVI was associated with shorter net ablation time and longer fluoroscopy time with similar procedure duration. Irrigated multi-electrode ablation recordings were not sufficient to confirm isolation in 35% of PVs. Single procedure efficacy after 12 months was similar between the two groups.

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11. CV

Nikola Pavlović was born in 1981 in Zagreb where he finished primary school and high school. In 2005 he graduated from University of Zagreb Medical School. He finished his one year residency 2005 to 2006 at University Hospital ‚Sestre milosrdnice'' and passed medical license exam in 2006. From 2007 to 2011 he was Internal medicine fellow at University Hospital ‚Sestre milosrdnice''and in June 2011 he passed the Internal medicine exam. Since then he has been working on Cardiology department at University Hospital Centre ‚Sestre milosrdnice''. His primary interests are arythmonology, clinical electrophysiology, ablation and cardiac pacing. From September 2013 to September 2014 he was electrophysiology fellow in University Hospital Basel, Switzerland as part of European Heart Rhythm Association (EHRA) Fellowship in Advanced Electrophysiology where he was additionally trained in complex arrhythmia ablation and device implantations. He also received additional training during short visits in University Hospital Centre Ljubljana, Slovenia; Bratislava, Slovakia, Dresden and Frankfurt Germany;

In 2014 he completed the EHRA Electrophysiology exam, and achieved Level 1 EHRA certification in electrophysiology. After verifying prerequired number of different ablation procedures perfumed he achieved full Level 2 EHRA certification in cardiac electrophysiology.

Nikola Pavlović actively participated in several Croatian and international congresses as well as EHRA faculty for EHRA courses and during EHRA congresses.

He is a member of Croatian Medical Chamber, Croatian Society of Cardiology, European Society of Cardiology, European Heart Rhythm Association, and European Association of Percutaneous Cardiovascular Interventions. In 2018 he became an active member of EHRA Young electrophysiologists committee and served as a member of EHRA Certification Committee during two EHRA Boards. In 2018 he was appointed as a member of European Society of Cardiology Membership Committee. In 2017 he became a Fellow of the European Society of Cardiology.

Nikola Pavlović published more than 50 papers in indexed journals among which 20 are indexed in Current Contents. He is participating in several randomized controlled trials as co-investigator or principal investigator in Croatia. He is a reviewer for 8 international, peer reviewed journals and ESC reviewer for ESC guidelines on supraventricular tachycardia and ESC guidelines on atrial fibrillation. Also, he serves as a reviewer for EHRA consensus documents.