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Programvezető: Dr. Merkely Béla, egyetemi tanár

Témavezetők: Dr. Szegedi Nándor, egyetemi docens

ENHANCING CLINICAL OUTCOMES IN ATRIAL FIBRILLATION ABLATION: EVALUATION OF HIGH- AND VERY HIGH-POWER SHORT-DURATION TECHNIQUES AND THE ROLE OF LOCAL IMPEDANCE DROP IN GUIDING EFFECTIVE PULMONARY VEIN ISOLATION

PhD thesis

Zoltán Salló, MD

Semmelweis University Doctoral School

Cardiovascular Medicine and Research Division

Supervisor: Nándor Szegedi, MD, PhD

Official reviewers: Gábor Bencsik, MD, PhD
Zsolt Bári, MD, PhD

Head of the Complex Examination Committee: Tivadar Tulassay, MD, PhD, DSc

Members of the Complex Examination Committee: Henriette Farkas, MD, PhD, DSc
Charaf Hassan, MD, PhD, DSc

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LIST OF ABBREVIATIONS

Abbreviations	Meaning
AAD	antiarrhythmic drug
ACT	activated clotting time
AF	atrial fibrillation
AI	ablation index
AV	atrio-ventricular
CF	contact force
CHA_2DS_2-VA	congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age
CKD	chronic kidney disease
CT	computed tomography
DC	direct current
DOAC	direct oral anticoagulant
ECG	electrocardiogram
EHRA	European Heart Rhythm Association
EP	electrophysiology
ESC	European Society of Cardiology
FPI	first-pass isolation
FTI	force-time integral
GI	generator impedance
HPSD	high-power short-duration
ILD	interlesion distance
LA	left atrium
LAA	left atrial appendage
LI	local impedance
LPLD	low-power long-duration
OAC	oral anticoagulant
OR	odds ratio
PFA	pulsed field ablation
PV	pulmonary vein
PVI	pulmonary vein isolation

RF	radiofrequency
ROC	receiver operating characteristic
SD	standard deviation
TIA	transient ischemic attack
TOE	transoesophageal echocardiography
vHPSD	very high-power short-duration

1. INTRODUCTION

Cardiac arrhythmias represent a diverse group of electrical disturbances in the heart. Antiarrhythmic drugs (AADsa) were the primary treatment until the late 1960s, when surgical methods emerged as an invasive option. Eventually, clinical electrophysiology (EP) evolved into a specialized branch of cardiology, focusing on the invasive diagnosis and management of cardiac arrhythmias. Decades ago, this approach could address only a few basic arrhythmias, but today it enables us to treat even the most complex atrial and ventricular arrhythmias. Central to this evolution is the advancement of electroanatomical mapping. The ability to interpret high-fidelity intracardiac signals and translate them into multidimensional topographical maps is fundamental to guiding precise ablative therapies. As the field continues to experience rapid technological expansion, the refinement of catheter-based treatments remains a critical frontier for improving long-term clinical outcomes in patients with refractory arrhythmias.

Nowadays, atrial fibrillation (AF) is the most commonly treated arrhythmia in modern EP laboratories. As a result, numerous studies are being conducted in this field. Radiofrequency (RF) energy is the most commonly used energy source; however, recent technological advancements have focused on improving procedural efficiency and lesion durability. As the number of patients undergoing AF ablation continues to grow, the procedure needs to be accelerated as well. With the development of catheters capable of delivering high-power short-duration (HPSD) RF energy, significant progress has been made in this area. Nevertheless, the acceleration of procedural workflows must be balanced against clinical efficacy and safety profiles. Furthermore, the integration of local tissue impedance monitoring represents a critical advancement in assessing real-time lesion formation. Enhanced accuracy in measuring impedance drops provides essential feedback for ensuring effective lesion creation. The present research evaluates these emerging technologies within the context of optimizing AF ablation outcomes.

1.1. Atrial fibrillation

1.1.1. Definition and diagnosis

AF is a supraventricular arrhythmia with uncoordinated atrial activation, which results in a loss of effective atrial contraction. Diagnosis is confirmed by documenting an arrhythmia lasting more than 30 seconds, with an AF pattern characterized by completely irregular R-R intervals and an absence of distinct P waves, as seen on an electrocardiogram (ECG) (*Figure 1*).

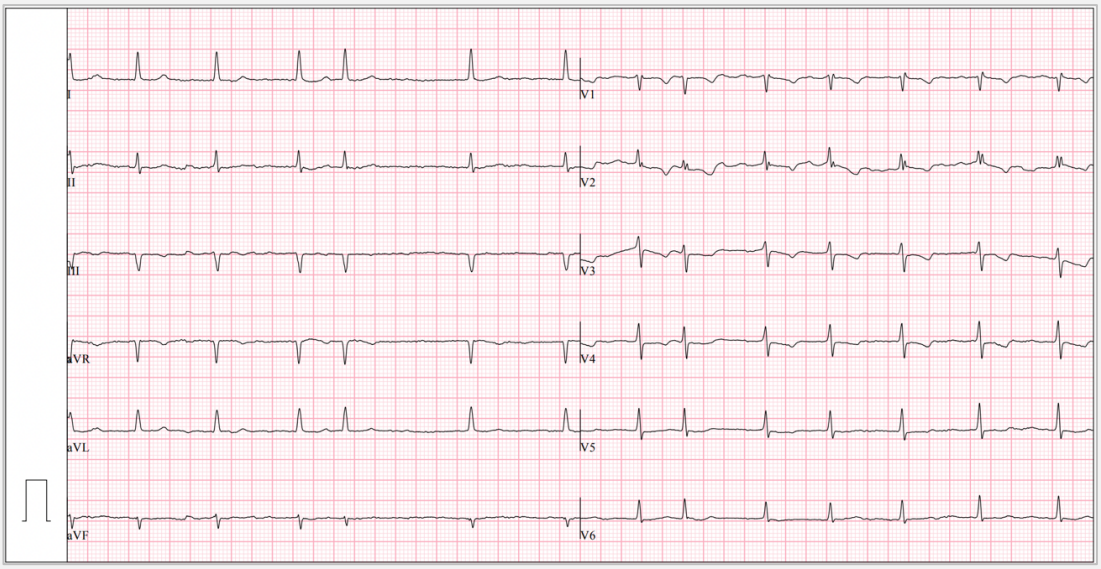

Figure 1. Twelve-lead ECG recording of AF (25mm/s, 10mm/mV; Heart and Vascular Center of Semmelweis University). ECG=electrocardiogram; AF=atrial fibrillation

AF is classified into five types based on the presentation, duration, and termination of episodes: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF (*Table 1*). These classifications help guide treatment and management strategies, including decisions on rhythm versus rate control, anticoagulation, and other therapeutic measures. Typically, AF progresses from short, infrequent episodes to longer, more frequent occurrences. Over time, many patients transition to more sustained forms of AF. This progression is driven by a gradual structural remodeling of the atria, influenced by various cardiac and non-cardiac factors, including structural heart disease, hypertension, and even AF itself. Structural remodeling causes electrical dissociation between muscle

bundles and creates local conduction heterogeneities, which promote re-entry and sustain arrhythmias (1, 7, 8).

Table 1. Classification of AF.
*Based on the classification used in the 2020 European Society of Cardiology Guidelines for the diagnosis and management of AF **(1)**. AF=atrial fibrillation*

First-diagnosed AF	AF not diagnosed before, irrespective of its duration or the presence/severity of AF-related symptoms.
Paroxysmal AF	AF that terminates spontaneously or with intervention within 7 days of onset
Persistent AF	AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after > 7 days
Long-standing persistent AF	Continuous AF of >12 months' duration when decided to adopt a rhythm control strategy.
Permanent AF	AF for which no further attempts at restoration of sinus rhythm are planned, after a shared decision between the patient and physician.

1.1.2. Epidemiology

AF is the most prevalent sustained cardiac arrhythmia among adults globally; therefore, the treatment of AF places a significant burden on the healthcare system. In the European Union there were approximately 8.8 million adults with AF in 2010 - if the prevalence estimates of AF remain stable, this number will more than double by the year 2060 (*Figure 2*) (2). In Hungary, AF affects an estimated 200,000 individuals, with an annual incidence of approximately 80 per 100,000 inhabitants, corresponding to about 8,000 new cases each year (9, 10). It is estimated that AF affects about 2-4% of adults, with higher prevalence observed in older individuals and those with conditions labeled on *Figure 3* (1, 11-13). AF is linked to higher mortality rates as an independent risk factor compared to the general population (1, 14). AF is a leading cause of stroke, heart failure, sudden death, and cardiovascular morbidity globally, making its proper management and the treatment of underlying conditions crucial (1).

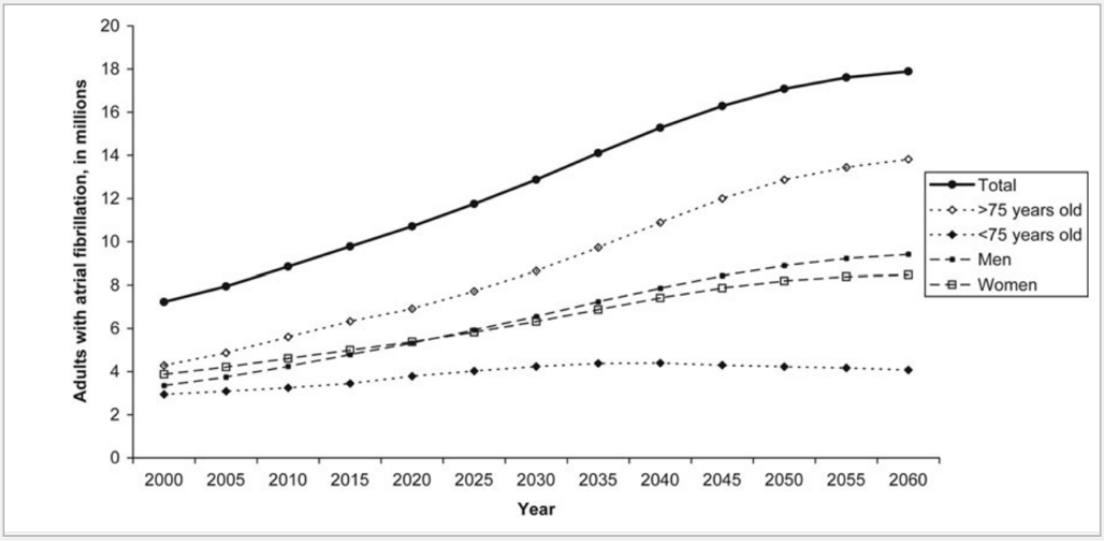

Figure 2. Projected number of adults with AF in the European Union between 2000 and 2060. Reproduced from Krijthe et al.(2), with permission from Oxford University Press. AF=atrial fibrillation

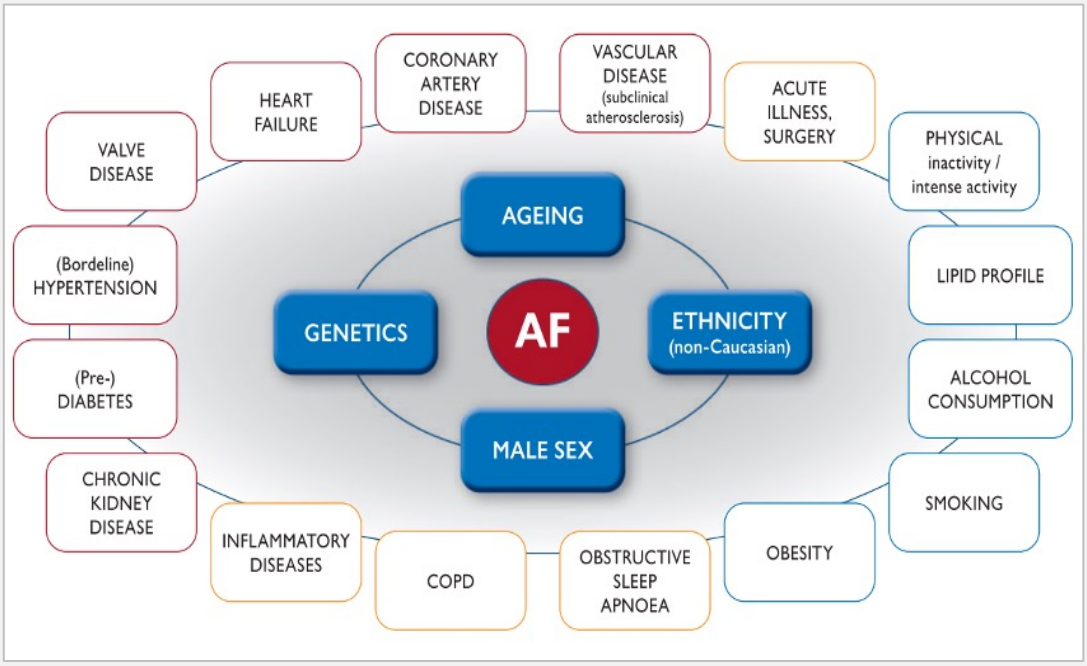

Figure 3. Risk factors and conditions associated with a higher prevalence of AF. Reproduced from Hindricks et al. (1) with permission by Oxford University Press. AF=atrial fibrillation; COPD=chronic obstructive pulmonary disease

1.1.3. Etiology

AF is a complex disease where both environmental and genetic factors contribute to disease pathogenesis (15). The development of AF is influenced by a combination of non-modifiable and modifiable risk factors, which interact with underlying structural and electrophysiological changes in the atria. Cardiovascular disorders such as chronic heart failure, coronary artery disease, valvular abnormalities, cardiomyopathies, myocarditis, and congenital defects including atrial septal defects represent important etiological contributors (16). In addition, systemic and lifestyle-related factors such as hypertension, obesity, diabetes mellitus, thyroid dysfunction, chronic kidney disease, obstructive sleep apnea, excessive alcohol intake, smoking, and high-level endurance sports are well-established determinants of AF. Among these, advancing age, hypertension, and obesity confer the greatest relative risk for the development of the arrhythmia (1, 16, 17). Elevated atrial pressure and wall stress promote fibrosis, inflammation, and fatty infiltration, creating a substrate for reentry. At the cellular level, altered expression and function of ion channels shorten atrial refractory periods and facilitate ectopic activity, most commonly originating from the pulmonary veins or other atrial sites. Autonomic imbalance, with both sympathetic and parasympathetic overactivity, further contributes to arrhythmia initiation and maintenance (15-17). Collectively, these processes establish a self-perpetuating cycle, in which atrial remodeling sustains and promotes progression from paroxysmal to persistent and permanent AF ("AF begets AF") (18).

1.1.4. Pathophysiology

AF is a multifactorial arrhythmia - AF mechanisms are conventionally divided into initiating factors, termed triggers, and perpetuating mechanisms that maintain the arrhythmia. The triggers are rapid ectopic activity and reentrant mechanisms (19). The mechanism maintaining AF is often called the driver. The initiation of AF is predominantly attributed to spontaneous ectopic electrical activity originating from atrial myocardial fibers that extend into the pulmonary vein (PV) orifices, while the arrhythmogenic substrate is represented by the structurally remodeled and fibrotic atrial tissue. In 1998, Haïssaguerre and colleagues demonstrated that, in the majority of cases,

the earliest electrical signals preceding the onset of AF episodes could be localized to the PV orifices, and targeting PV triggers has been shown to prevent the initiation of AF (20). Although the exact processes responsible for the perpetuation of AF are still controversial, multiple wavelet activity and localized drivers, whether focal or reentrant, are generally recognized as central mechanisms (*Figure 4*) (6).

In paroxysmal AF, we typically observe a driver mechanism. Histopathological studies have demonstrated that myocardial fibers adjacent to the PVs exhibit cellular features characteristic of specialized conduction tissue. Within this region, cells resembling those of the sinoatrial and atrioventricular nodes - including P cells, Purkinje-like cells, and transitional forms - have been identified, likely representing remnants of embryonic development (21). In addition, these cardiomyocytes exhibit electrophysiological features

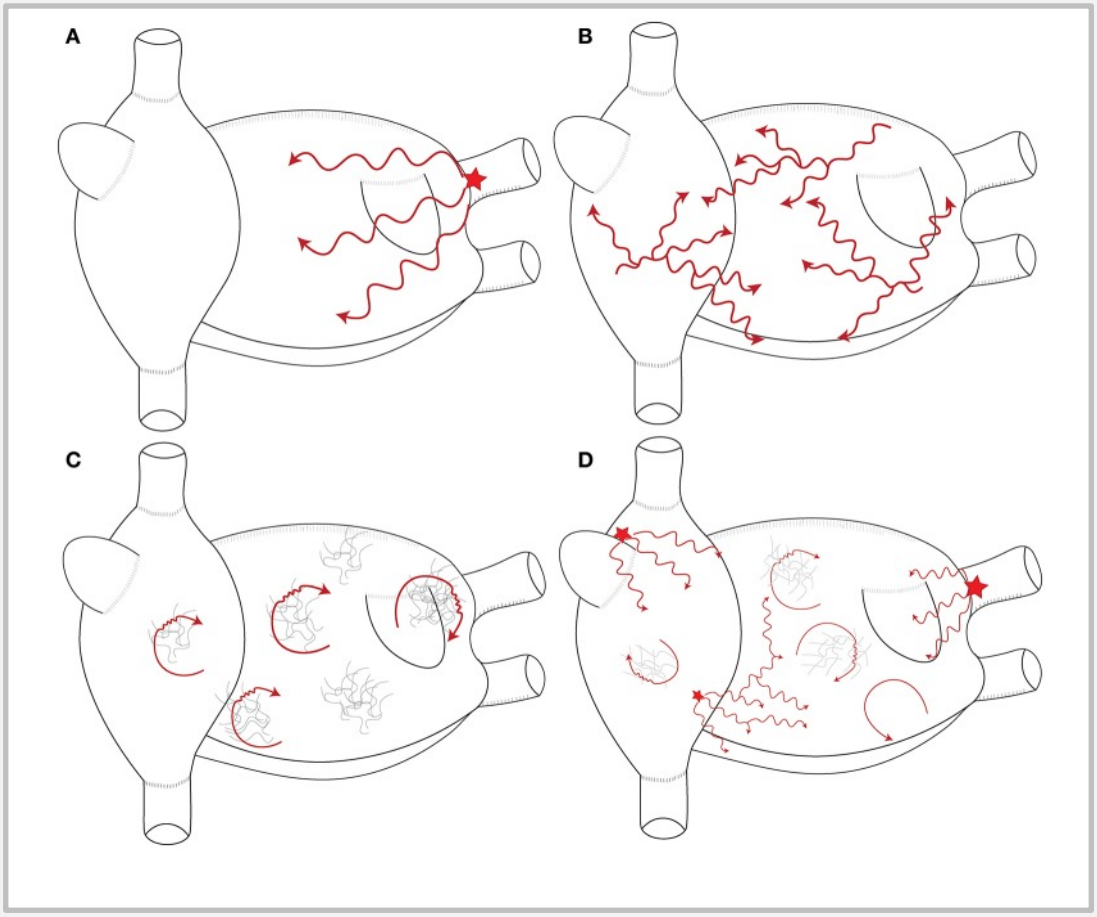

Figure 4. Principal AF maintaining mechanisms. ***A,*** *Single stable focal or reentrant source (star) with fibrillatory conduction.* ***B,*** *Multiple wavelets: multiple waves propagate randomly and give birth to new daughter wavelets.* ***C,*** *Multiple reentries (red arrows) around areas of scar and fibrosis.* ***D,*** *Combination of the different mechanisms that sustain AF in humans. Reproduced from Cheniti et al. (6) with permission from Frontiers in Physiology. AF=atrial fibrillation*

distinct from the adjacent atrial myocardium, characterized by unique ion channel expression, abbreviated action potential duration, and shortened refractory periods (22). Abrupt changes in myocardial fiber orientation and other structural discontinuities promote the formation of substrates that favor reentrant arrhythmias (23). The clinical course of AF often follows a trajectory from paroxysmal episodes to persistent forms, ultimately progressing to permanent AF. This transition is primarily driven by atrial remodeling, triggered by recurrent arrhythmic episodes, elevated left atrial pressure with wall strain, concomitant structural heart disease (24), or systemic conditions such as diabetes and obesity. These processes activate fibroblasts, leading to myocardial fibrosis, inflammation, and fatty infiltration, thereby establishing an arrhythmogenic substrate (25). In parallel, AF-induced electrical remodeling, mediated through altered expression and function of cardiac ion channels, facilitates functional reentry. Although these electrical changes are reversible through reverse remodeling upon rhythm restoration, they play a critical role in sustaining and advancing AF (26). Once atrial remodeling progresses to irreversible structural alterations, AF becomes permanent. The spectrum of AF subtypes and their proposed underlying mechanisms are summarized in *Figure 5* (3). PV sources account for approximately 90% of cases of paroxysmal AF. As AF progresses, atrial structural and functional remodeling becomes more pronounced, and even in paroxysmal AF, non-PV foci may contribute. The ligament of Marshall has been identified as a potential source of spontaneous ectopic activity; catheter-based studies have demonstrated that ablation of this structure can terminate AF when ectopic discharges from the myocardial bundle are documented (27). Additional non-PV trigger sites include the posterior left atrial wall, coronary sinus, superior vena cava, atrial septum, and left atrial appendage (LAA) (28). Autonomic influences further modulate arrhythmogenesis: vagal ganglia located adjacent to the PVs facilitate ectopic activity, and complete PV denervation has been associated with reduced AF recurrence (29). Both sympathetic and parasympathetic activation are recognized as key contributors to the initiation and maintenance of AF (30). Clinically, AF often begins as self-terminating paroxysmal episodes; however, over time, a significant proportion progress to a persistent form, with approximately 10-15% of paroxysmal AF patients transitioning within one year (24). This progression is driven by cumulative atrial remodeling - structural and electrophysiological - which creates a substrate increasingly capable of sustaining AF.

While paroxysmal AF is predominantly maintained by localized triggers and drivers, particularly from PVs, persistent and permanent AF are characterized by the predominance of reentrant substrates, initially functional and later structural in nature (3).

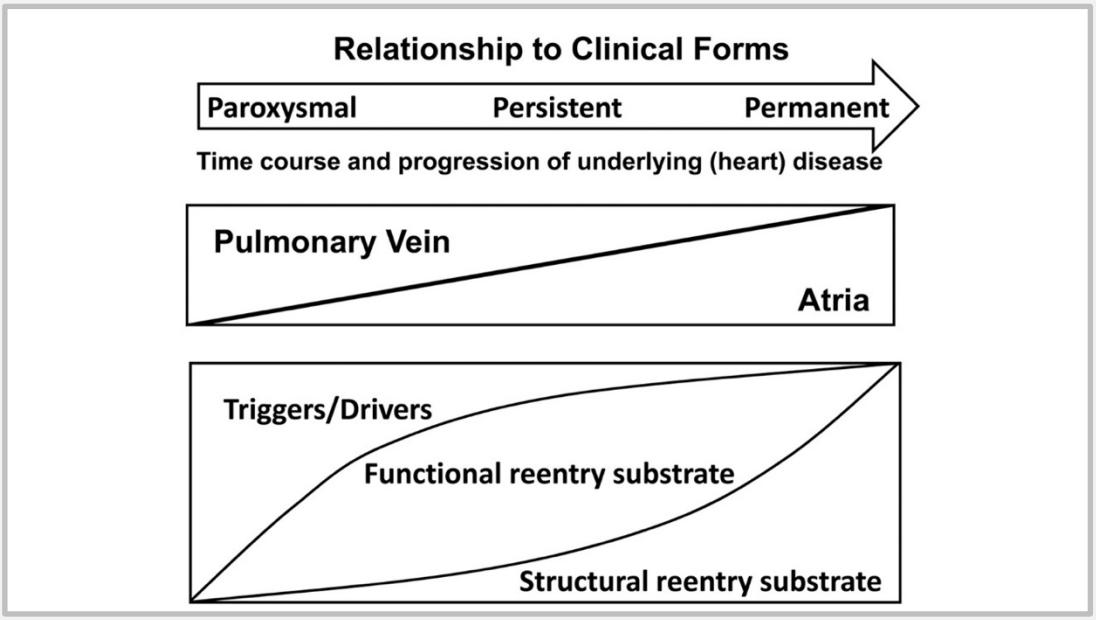

Figure 5. The spectrum of AF subtypes and their proposed underlying mechanisms. Adapted from Iwasaki et al. (3) with permission by Wolters Kluwer Health, Inc. AF=atrial fibrillation

1.1.5. Clinical presentation and importance

AF presents with a wide range of clinical manifestations, extending from asymptomatic cases to highly symptomatic disease. The severity and nature of symptoms are primarily determined by the ventricular response rate, which may cause bradycardia or tachycardia. Commonly reported complaints include palpitations, chest discomfort, dyspnea, dizziness, nausea, excessive sweating, reduced exercise tolerance, and sleep disturbances. In more severe cases, particularly when high ventricular rates occur, AF can lead to hemodynamic instability, resulting in syncope, pulmonary oedema, or acute heart failure (17). To standardize the evaluation of symptom burden, the modified European Heart Rhythm Association (mEHRA) score (*Table 2*) is employed (31), which parallels the New York Heart Association (NYHA) functional classification used in chronic heart failure.

Table 2. Symptom classification of AF according to the mEHRA score. mEHRA=modified European Heart Rhythm Association; AF=atrial fibrillation

mEHRA Class	Description	Typical Symptoms
1	No symptoms	Asymptomatic
2a	Mild	Symptoms present but not affecting daily activity
2b	Moderate	Symptoms affecting daily activity without discontinuation
3	Severe	Symptoms leading to limitation or discontinuation of daily activity
4	Disabling	Symptoms leading to complete inability to perform daily activity or requiring urgent medical care

The clinical significance of AF lies in its strong association with increased morbidity, mortality, impaired quality of life, and substantial healthcare resource utilization (17). The most important contributors to AF-related mortality are stroke and heart failure, both of which occur more frequently in persistent AF. Patients with AF have a fivefold higher risk of stroke, and AF-related strokes tend to be more severe than those of non-AF origin (32). Approximately 20-30% of all strokes are attributed to AF. The arrhythmia is responsible for around 10% of cryptogenic strokes, and heart failure develops in 20-30% of patients with AF (1, 17). AF is also associated with cognitive decline and dementia, likely mediated through overt strokes, silent cerebral embolization, and impaired cerebral perfusion related to irregular ventricular response (33). From a prognostic perspective, AF increases all-cause mortality by 1.5- to 3-fold and has also been linked to a higher incidence of sudden cardiac death (1). In addition, quality-of-life assessments consistently demonstrate a significant reduction in physical and social functioning, as well as in mental and general health, compared with healthy controls (34). The economic burden of AF has increased over time and is further amplified by its major complications. These costs include direct expenses related to treatment and hospitalization, as well as indirect costs resulting from productivity loss (35).

1.1.6. Management

Managing AF requires comprehensive patient care, which includes lifestyle modifications (such as weight loss, regular physical activity, reducing alcohol intake, and avoiding large meals), diagnosing and treating underlying conditions (like obstructive sleep apnea, valvular heart disease, uncontrolled hypertension, and thyroid dysfunction), anticoagulation, and arrhythmia treatment through rate and/or rhythm control.

1.1.6.1. Oral anticoagulation

Anticoagulation therapy in AF patients based upon the CHA_2DS_2-VASc score (*Table 3*) (1) system, which is a clinical prediction tool used to estimate the annual risk of stroke in patients with non-valvular AF. After the previously used CHA_2DS_2-VASc score the newest European Society of Cardiology (ESC) Guidelines for management of AF has introduced the reconsidered CHA_2DS_2-VA score (17), which is now a widely accepted tool for assessing thromboembolic risk in patients with non-valvular AF.

Table 3. CHA_2DS_2-VASc score system.
TIA=transient ischemic attack

CHA_2DS_2-VASc	**Meaning of abbreviation**	**Points**
C	Chronic heart failure	1
H	Hypertension	1
A	Age 75 years or above	2
D	Diabetes mellitus	1
S	Stroke / TIA / thromboembolism (prior)	2
V	Vascular disease	1
A	Age 65-74 years	1
Sc	Sex category (female)	1
Maximum score		9

Patients without clinical stroke risk factors do not require anticoagulant therapy. For those with one risk factor (excluding female gender), anticoagulation may be considered, but it

is not strictly recommended; decisions should be made after discussing the risks and benefits of oral anticoagulant (OAC) therapy with the patient. For patients with a higher CHA_2DS_2-VA score (≥2 both for men and women), anticoagulation is recommended, preferably with direct oral anticoagulants (DOAC) (17). The only group for whom DOACs are not recommended includes those with valvular AF, specifically patients with a mechanical heart valve or moderate/severe mitral stenosis (1). Percutaneous or stand-alone surgical closure of the LAA represents an alternative strategy for stroke prevention in AF patients with contraindications to long-term anticoagulation (17).

1.1.6.2. Pharmacological rate and rhythm control treatment of AF

1.1.6.2.1. Pharmacological rate control

Rate control is a key aspect of managing AF and is often sufficient for alleviating AF-related symptoms. Pharmacological rate control for tachyarrhythmia can typically be achieved both acutely and in the long term. Beta-blockers - such as metoprolol, bisoprolol, atenolol, esmolol, nebivolol, and carvedilol - are considered first-line agents for ventricular rate control in AF. In cases where beta-blockers are contraindicated or not tolerated, non-dihydropyridine calcium channel blockers (verapamil and diltiazem) may be employed as alternatives (1, 36, 37). Cardiac glycosides such as digoxin and digitoxin may be considered for patients with heart failure and reduced ejection fraction. However, several retrospective analyses have linked digoxin therapy to increased mortality in patients with AF (38, 39).

1.1.6.2.2. Pharmacological rhythm control

Rhythm control in AF management focuses on restoring and maintaining sinus rhythm. This is typically achieved using class IA, IC, or class III antiarrhythmic agents. These drugs roughly double the likelihood of maintaining sinus rhythm compared to placebo and may slightly reduce the risk of AF-related hospitalizations. Early rhythm control (by AADs or ablation) reduces cardiovascular mortality, as shown by the EAST-AFNET 4 study (40). AAD therapy can be used to maintain sinus rhythm and alleviate the symptom burden in AF, though its effectiveness is limited and adverse extracardiac effects are

common. The guiding principle in initiating or discontinuing AAD therapy is that patient safety must take precedence over potential efficacy. If a particular drug fails to achieve adequate rhythm control or produces intolerable side effects, switching to an alternative agent is appropriate. In contrast, concomitant use of multiple AADs is discouraged because of the increased risk of proarrhythmia and systemic toxicity (17).

1.1.6.3. Non-pharmacological rate and rhythm control treatment of AF

1.1.6.3.1. Non-pharmacological rate control

Atrio-ventricular (AV) nodal ablation combined with pacemaker implantation can effectively control high ventricular rates when medications fail to manage the rate and symptoms. However, since AV nodal ablation results in permanent pacemaker dependency, this approach is reserved for patients whose symptoms cannot be managed with rate-controlling medications or rhythm control strategies. In cases of bradyarrhythmia, heart rate control involves increasing the heart rate to the normal range using pacemaker implantation. For patients with permanent AF and severe symptoms, who have been hospitalized at least once for heart failure, AV node ablation combined with cardiac resynchronization therapy may be the preferred treatment strategy (1).

1.1.6.3.2. Non-pharmacological rhythm control

Synchronized direct current (DC) electrical cardioversion is a fast and effective method for converting AF to sinus rhythm and is the preferred treatment for patients with severe hemodynamic instability. It can also be used to restore sinus rhythm in cases of persistent or long-standing persistent AF to manage AF-related symptoms. Another non-pharmacological approach to rhythm control is catheter ablation, which currently represents the most effective therapeutic approach for both paroxysmal and persistent AF. In patients with symptomatic paroxysmal AF, it is recommended as a first-line strategy. For those with persistent AF, ablation is generally indicated following the failure of AAD therapy, although current guidelines also permit its consideration as a first-line option in selected cases (15, 17).

1.1.6.4. Catheter ablation

Pulmonary vein isolation (PVI) is the cornerstone of rhythm control therapy for AF (41, 42). Catheter ablation has been shown to reduce AF burden by decreasing both the frequency and duration of paroxysmal episodes, slowing progression to persistent AF, and attenuating symptom severity in recurrent cases. These benefits are associated with significant improvements in patient-reported quality of life (43, 44). In patients with heart failure with reduced ejection fraction and concomitant AF, catheter ablation improves left ventricular ejection fraction and functional status. Importantly, large randomized controlled trials including CASTLE-AF (45) and AATAC (46), have demonstrated reductions in mortality and heart failure hospitalizations in this patient population. The CABANA trial further supported ablation as superior to drug therapy in reducing AF recurrence and improving quality of life, although the trial did not show a statistically significant mortality benefit in the overall cohort (47). In recent years, contact force (CF)-sensing ablation catheters were introduced. Today, the use of these has become routine practice in most EP laboratories (48-52). A new era in catheter ablation therapy for cardiac arrhythmias is emerging with the advent of irreversible electroporation, commonly referred to as pulsed-field ablation. This new technology may open a new era in catheter ablation (53).

1.1.6.4.1. Theoretical background of PVI

The exact mechanism of AF in individual patients remains unclear and is a subject of ongoing research. However, the PVs and surrounding structures are known to play a significant role in the pathophysiology for most patients (see *Figure 6*) (20). Jais et al. identified distinct electrophysiological properties of PVs in patients with AF compared to those in healthy individuals. The primary difference observed was the short or extremely short refractory period of the PVs, which likely plays a significant role in arrhythmogenesis (23). Additionally, episodes of AF can shorten the effective refractory

period of both the atria and PVs, potentially promoting recurrent and prolonged AF episodes ("AF begets AF") (8, 54).

These findings are further supported by a study from De Ponti et al., which demonstrated through high-density mapping of the PVs that most ectopic beats exhibit a multifocal pattern and originate proximally (55). In addition to the PVs, several other

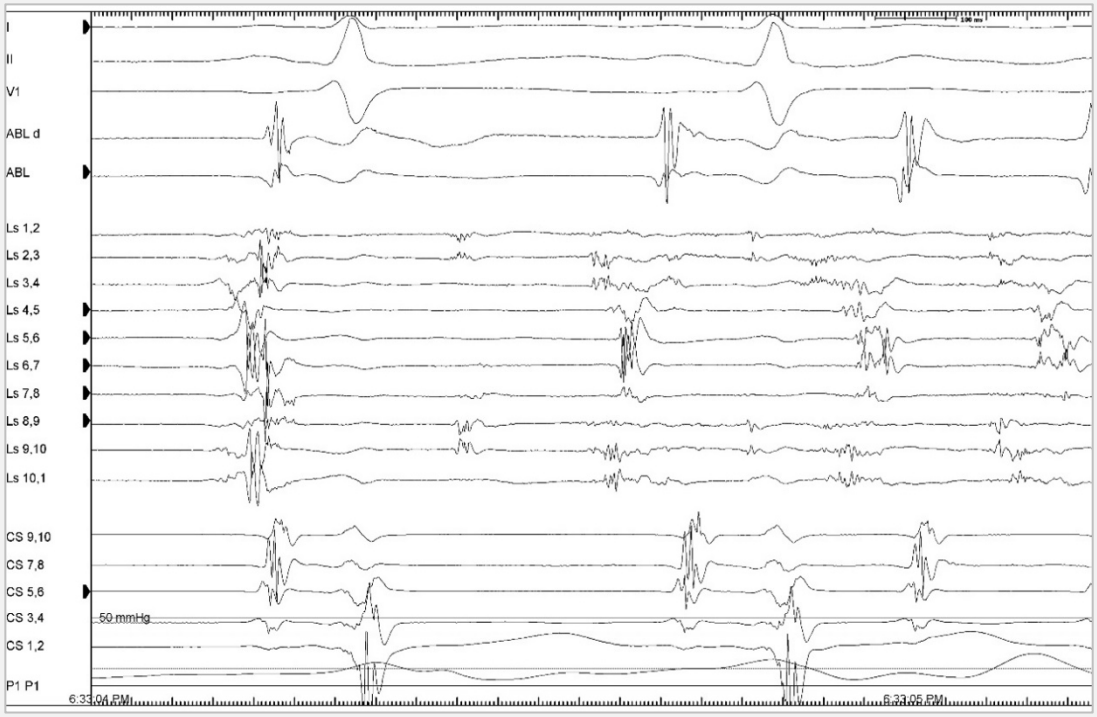

Figure 6. High-frequency electrical activity in the right superior PV registered by the Lasso catheter. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University. PV=pulmonary vein; ABL=ablation catheter; Ls=Lasso catheter; CS=coronary sinus catheter; P1 pressure curve

pathophysiological factors may contribute to the mechanism of AF, including the ligament of Marshall, vagal ganglia, micro-reentrant circuits, and spiral or rotational activities (27, 29, 56, 57). Circumferential ablation around the PVs may offer additional benefits beyond PVI, including ganglionated plexus modification and alteration of other substrates located near the PVs (58). The durability of PVI largely depends on the precision of lesion creation. Currently, the two most commonly used ablation techniques are point-by-point RF ablation and cryoballoon ablation.

1.1.6.4.2. RF point-by-point ablation

Circumferential antral PVI using RF energy was the first ablation technique demonstrated to be superior to AAD therapy (59). This technique requires minimal fluoroscopy, as catheter guidance is performed using an electroanatomical mapping system. However, a significant disadvantage is that it demands extensive training due to the need for precise catheter manipulation. It has been shown to be effective in both paroxysmal and persistent AF for reducing AF-related symptoms (60, 61). Moreover, it may have a positive impact on mortality in patients with heart failure (45, 46, 62). The clinical efficacy of catheter ablation for AF is often limited by challenges in achieving durable PVI. Insufficient catheter tip-to-tissue CF during lesion delivery can reduce efficacy. Although acute PVI is almost universally achieved, atrial arrhythmia recurrences are common, typically caused by PV reconnection. Using CF information during PVI leads to shorter procedure durations and lower rates of AF recurrence compared to conventional PVI without this data. Initial studies have established optimal minimum CF and force-time integral (FTI)

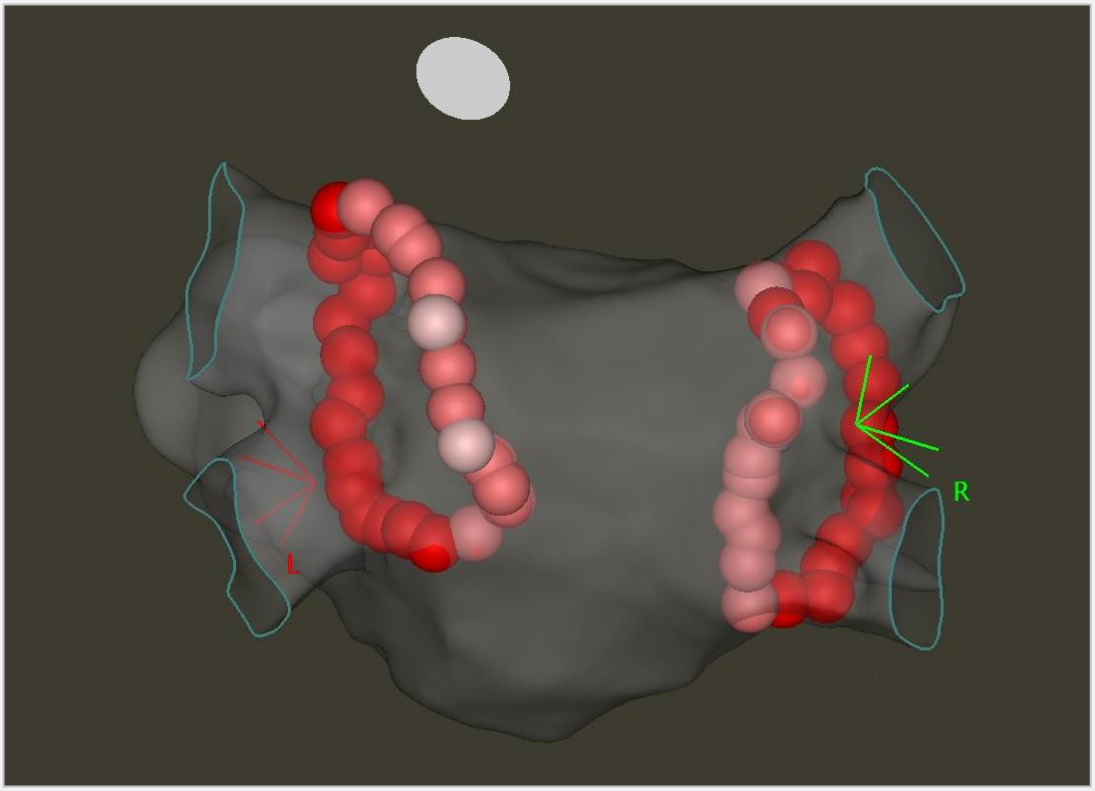

Figure 7. Pulmonary vein isolation performed with CARTO system using the CLOSE protocol. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University.

values for RF applications (48-52, 63, 64). The routine use of CF-sensing ablation catheters has improved arrhythmia-free survival following PVI. However, the rate of arrhythmia recurrence remains significant. Recently developed techniques, which are discussed later, such as the ablation index, CLOSE protocol, and lesion size index, have shown promise in achieving more durable PVI and have been confirmed to be superior to previously used methods (65-71). *Figure 7* illustrates an example of PVI performed using the CARTO system and the CLOSE protocol.

1.1.6.4.3. Cryoballoon ablation

PVI can be achieved using a balloon catheter by occluding the PVs and inducing tissue necrosis with cryothermal energy around the vessel orifice. The occlusion of the PV by the cryoballoon is confirmed using contrast injection and fluoroscopic imaging (*Figure 8*). Once proper occlusion of the PV orifice is verified, freezing can commence. However,

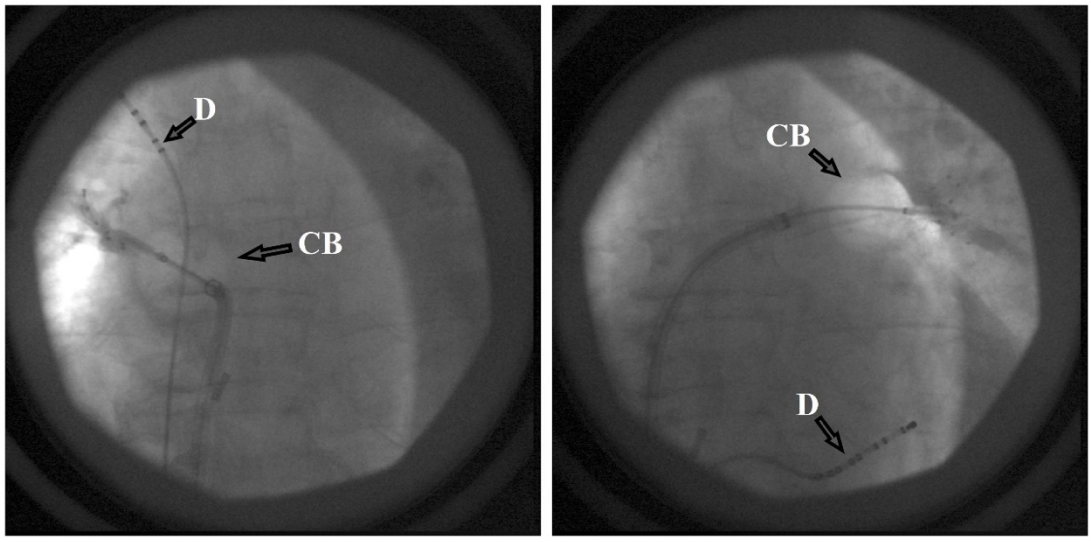

Figure 8. Left side: contrast injection into the right inferior PV, occluded by cryoballoon (CB, arrow); decapolar catheter (D, arrow) is placed in the superior vena cava to perform phrenic nerve pacing. Right side: contrast injection into the left superior PV occluded by cryoballoon; decapolar catheter is in the coronary sinus. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University. PV=pulmonary vein

the requirement for fluoroscopy for each PV may result in prolonged fluoroscopic time and increased radiation exposure. The first-generation cryoballoons delivered ablation only at the equator of the balloon. The Freeze AF randomized trial demonstrated that the

first-generation cryoballoon was noninferior to RF ablation in efficacy. However, it was associated with a higher incidence of (mostly transient) phrenic nerve palsy (72). The second-generation cryoballoon features double the number of injection ports, positioned more distally, resulting in a larger and more uniform freezing zone (73). This resulted in a higher rate of single-shot PVI and improved lesion durability, leading to better clinical outcomes (74). The second-generation cryoballoon was shown to be non-inferior to RF ablation in the Fire and Ice randomized trial in terms of efficacy and safety for treating drug-refractory paroxysmal AF. Phrenic nerve injury was the most common adverse event in the cryoballoon group (75). However, these events are transient in most cases (76, 77). The cryoballoon is also safe and effective for patients with persistent AF. Additionally, isolating the LAA alongside PVI may improve 1-year outcomes compared to a PVI-only approach (78-80). A disadvantage of the cryoballoon is that it may be less effective in certain anatomical variations of the PVs, such as a long left common trunk or additional PVs (81, 82).

1.1.6.4.4. Pulsed field ablation

In 1979, DC cardioversion during an EP study caused complete AV block, leading to the development of "closed-chest catheter ablation" for drug-resistant supraventricular tachycardias and other arrhythmias. However, DC ablation was abandoned in the 1990s due to severe complications like cardiac perforation and a high mortality rate of up to 25%, attributed to barotrauma from high-energy DC shocks. Modern catheter designs and technology have reignited interest in DC ablation, now termed "pulsed field ablation" (PFA). PFA uses ultra-rapid electric fields to create nanoscale pores in target tissues, causing cell death via irreversible electroporation. This nonthermal method avoids collateral damage to adjacent cardiac and extracardiac tissues while creating effective myocardial lesions. Advances in waveform and energy delivery help prevent complications such as barotrauma. Preclinical and clinical studies since 2011 have shown PFA to be safe and effective for PVI in paroxysmal AF. In 2021, the first endocardial ablation system for PFA received commercial approval, marking it as a promising alternative to traditional thermal ablation methods (*Figure 9, 10*).

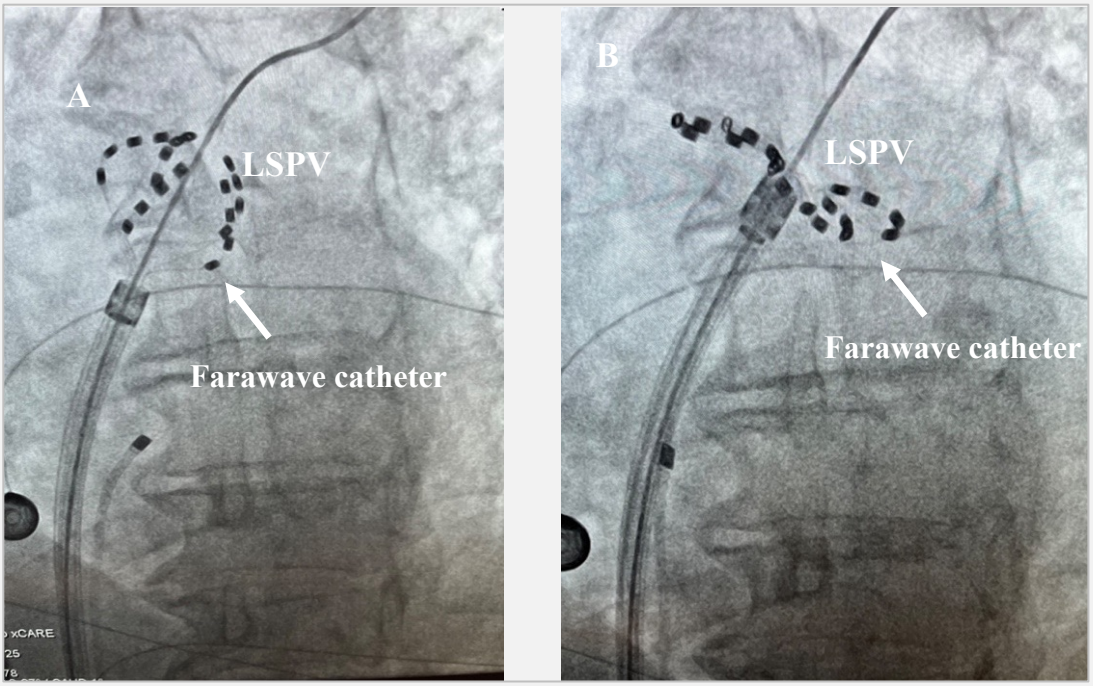

Figure 9. Pulsed field ablation with the Farapulse system. Panel A: Farawave catheter in basket configuration in the LSPV. Panel B: Farawave catheter in flower configuration at the ostium of the LSPV. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University. LSPV = left superior pulmonary vein

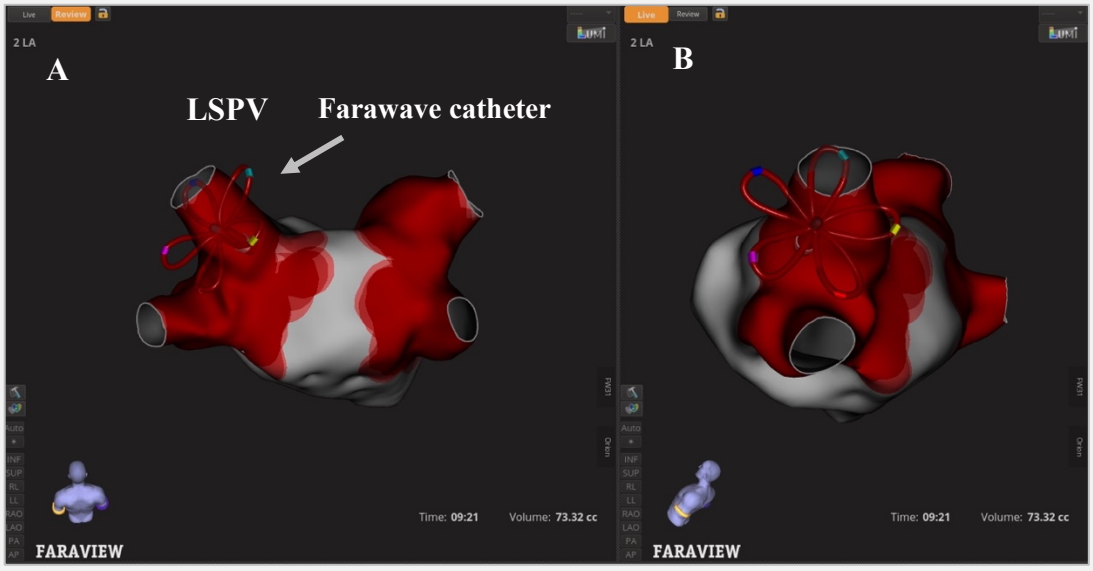

Figure 10. Pulsed field ablation with the Boston Scientific's Opal mapping system. Panel A: Farawave catheter in flower configuration in the LSPV, postero-anterior view. Panel B: Farawave catheter in flower configuration in the LSPV, left lateral view. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University. LSPV = left superior pulmonary vein

1.1.6.4.5. Complex left atrial ablation for persistent AF

Persistent AF is more challenging to treat than paroxysmal AF. In addition to the triggers initiating the arrhythmia, a complex substrate often develops due to atrial enlargement and fibrosis. Consequently, PVI alone is generally less effective for persistent AF compared to paroxysmal AF. The success rate of catheter ablation may be improved with substrate modification techniques, such as additional linear lines, ablation of complex fractionated atrial electrograms, or isolation of the LAA. However, the value of these techniques remains controversial. Notably, many studies reporting negative results for extensive ablation techniques were conducted before the CF era and in low-volume centers.

1.1.6.4.6. Complications of AF ablation

AF ablation procedures carry a significant risk of complications, occurring in 1% to 8% of cases. The most common adverse events include pericardial effusion and vascular access site complications. However, rarer but potentially life-threatening or severe complications, such as stroke, transient ischemic attack (TIA), atrio-esophageal fistula, phrenic nerve palsy, or PV stenosis, also require attention. The relatively high complication rate has fueled ongoing efforts to develop safer and more effective ablation techniques. Advances in technology and a deeper understanding of arrhythmia mechanisms have significantly improved both the efficacy and safety of ablation. While recent studies have investigated predictors of complications following AF ablation, most have focused on initial procedures. Limited data are available regarding complications in repeat catheter ablation procedures (83-90).

1.1.6.4.7. Use of ablation index, energy settings, first-pass isolation and local impedance drop during RF point-by-point ablation

Effective RF energy delivery during ablation relies on adequate catheter-tissue contact. Factors such as CF, the surface area of catheter-tissue interaction, RF power, RF application time, and the characteristics of the underlying tissue all play a role in

determining the efficiency of energy transfer. Over the last decade, catheter technologies have evolved dramatically, enabling more accurate lesion prediction. The ablation index (AI) is a marker of ablation lesion quality determined by a weighted formula that integrates CF, RF application time, and power. AI is typically integrated with the CLOSE protocol, a point-by-point RF ablation workflow that uses predefined AI targets and a maximum interlesion distance (ILD) of 6 mm to achieve contiguous, durable PVI. Higher power settings enable the target AI to be reached more rapidly. Despite elevated energy levels, lesion formation can still be effectively monitored in real time. The reduction in RF application duration associated with higher power delivery facilitates improved catheter stability, which may contribute to a more efficient creation of the circumferential lesion set encircling the PVs. Although AI was initially validated for use with power levels up to 45 W, subsequent studies have demonstrated that AI-guided ablation using 50 W is both safe and effective (91, 92).

In the conventional low-power long-duration (LPLD) protocol, ablation was performed using energy settings ranging from 20 to 35 W. Various power levels for high-power ablation protocols have been reported in the literature, typically ranging between 40 and 90 W. High-power short-duration (HPSD, 35-50W) and very high-power short-duration (vHPSD, 90 W) RF catheter ablation represent emerging approaches aimed at improving the safety and procedural efficiency of AF ablation, while also reducing overall intervention time, including the left atrial dwell time, which is the total duration a catheter remains inside the left atrium (LA). Shortening RF application time facilitates catheter stability, potentially expediting the creation of circumferential lesion sets around the PVs, which may improve the first-pass isolation (FPI) rate. FPI is the immediate, complete electrical isolation of PVs upon completion of the initial ablation set, without needing extra touch-up applications, and it is a key predictor of procedural success, resulting in lower arrhythmia recurrence rates and more durable PVI compared to cases requiring multiple additional RF applications (93, 94). High-power RF protocols are known to generate lesions with altered geometries compared to conventional low-power approaches. Nonetheless, the depth achieved with HPSD and vHPSD remains sufficient to ensure transmurality in atrial tissue (95, 96). HPSD and vHPSD approaches aim to create effective, transmural lesions with reduced collateral damage by limiting conductive heat spread to adjacent tissues. When RF energy enters into the tissue, heat is generated

because of tissue resistance, resulting in a narrow heated area, surrounding the ablation electrode; this process is referred as resistive heating. This heat is then passively transferred to the surrounding tissue through conductive heating, resulting in thermal injury and cellular necrosis at greater depths, continuing until tissue temperatures fall below 50 °C. Upon termination of the RF application, the initially heated resistive zone cools by dispersing residual thermal energy into adjacent tissues. This post-ablation heat transfer causes a delayed temperature increase in the surrounding area, further contributing to lesion growth. This delayed thermal effect is known as “thermal latency” (97). Currently, limited data exist on the cumulative energy delivery in LPLD, HPSD, and vHPSD ablation protocols. Nakagawa et al. reported that lesions generated via LPLD may exhibit the largest diameters, attributed to greater overall energy delivery (34). HPSD and specifically vHPSD lesions may have decreased lesion diameters. However, their experimental design did not incorporate AI-guided protocols, relying instead on fixed RF durations, thus limiting the applicability of their findings to clinical AI-guided workflows. Notably, the evaluation of AI is not possible during vHPSD power setting, because it is technically not available during vHPSD applications, as both time and power are set to 4 seconds and 90 W as baseline in this scenario. Emerging evidence suggests that both HPSD and vHPSD can shorten procedure times and improve lesion durability, while maintaining a favorable safety profile when guided by real-time biophysical markers and precise catheter control (4, 91, 92, 98).

Although AI is a clinically proven marker of RF lesion creation, it does not provide „real-time” feedback on lesion creation, but it is rather a statistical probability marker of lesion formation. Real-time changes of tissue properties can be better monitored by the changes in impedance. Traditionally, clinicians have used metrics like generator impedance (GI), CF, and catheter tip temperature to evaluate tissue contact and associated heating, though their reliability varies (99). Earlier investigations explored the decrease in GI during ablation as a potential surrogate marker for lesion formation (24, 25). However, the usefulness of GI is constrained by its measurement methodology, which goes from the catheter tip to a remote indifferent electrode on the patient's back. More recent evidence has shown that GI fluctuations exhibit only a weak correlation with the extent of lesion formation (26). During recent years, local impedance (LI), measured between the minielectrodes on the catheter tip and the proximal ring, has emerged as a

promising method for evaluating catheter-tissue contact. Studies have shown a correlation between a drop in LI and the formation of durable lesions, highlighting LI's sensitivity to localized volumetric tissue heating (100-102). Preclinical data with a new catheter were presented by Garrott et al., who showed that LI drop correlates with the lesion depth both in vitro and in vivo in a swine model. Thus, according to these animal data, an LI drop provides information on sufficient lesion creation (LI drop > 20 Ohms) and also indicates excessive heating that might increase the risk of steam pop (LI drop > 65 Ohms) (99). However, human studies did not verify these findings.

2. OBJECTIVES

The overarching objective of this doctoral research was to investigate new technologies that enhance the efficacy and safety of RF catheter ablation technologies for the management of AF. To achieve this, the thesis is conceptually divided into two primary avenues of investigation.

In the first part of the thesis, different RF power delivery strategies were compared during PVI, with particular focus on LPLD, HPSD, and vHPSD ablation. The aim of this analysis was to determine whether increasing power shortens procedural and left atrial dwell time and reduces RF application duration while maintaining procedural safety. In addition, acute procedural efficacy was assessed by evaluating the rate of FPI and the need for additional RF applications. Since FPI is a well-established determinant of durable PVI, its relationship with mid-term arrhythmia-free survival was also examined. Furthermore, biophysical parameters of lesion deployment, including the number of RF applications, total delivered energy, and AI-guided workflow characteristics, were analyzed to better understand the mechanistic basis of the observed procedural and clinical outcomes.

The second specific aim focuses on the clinical validation of LI monitoring as a marker of effective lesion formation during PVI with high-power RF energy ablation (40-50 W). Preclinical studies have provided data on a novel CF-sensing ablation catheter capable of measuring LI changes, but clinical validation remains pending. Therefore, this research sought to assess the significance of the LI drop in predicting lesion formation during RF ablation and to identify optimal LI drop thresholds to guide PVI.

3. METHODS

3.1. General study population

The overarching cohort for this research comprised individuals diagnosed with symptomatic, drug-refractory AF who were underwent their first PVI procedure at the Heart and Vascular Center of Semmelweis University.

In the first part of the research, which evaluated the use of high-power energy delivery, a total of 156 consecutive patients were prospectively enrolled between January 2019 and June 2021. The ablation protocols were implemented sequentially: initial procedures utilized the LPLD technique, followed by HPSD, and finally vHPSD ablation settings.

In the second phase, which focused on the clinical validation of LI monitoring, patients were scheduled for PVI due to symptomatic, drug-refractory AF, in accordance with current guidelines (1).

The investigations were conducted in strict accordance with the ethical principles delineated in the Declaration of Helsinki. The study protocols were approved by the Regional and Institutional Committee of Science and Research Ethics at Semmelweis University (Approval Reference Numbers: 134/2020 and 280/2020). Comprehensive written informed consent was systematically obtained from all participants prior to pre-procedural imaging and enrollment.

3.2. Standard patient preparation and periprocedural care

Periprocedural management was highly standardized across the entire cohort. AF ablation was conducted based on current guideline recommendations (1, 42). Patients on vitamin K antagonists continued their medication uninterrupted, targeting an INR of 2.0-2.5 on the day of the procedure. For those on DOACs, the morning dose was withheld, and medication was resumed 4 hours post-procedure if no major bleeding complications occurred. To rule out LAA thrombus, all patients underwent transoesophageal echocardiography (TOE) or computed tomography (CT) angiography within 48 hours prior to the procedure. All ablation procedures were performed under local anesthesia with conscious sedation, facilitated by a combination of midazolam, propofol, and fentanyl. Following the intervention, patients were observed overnight and discharged the

following day after checking vascular access sites, vital signs, and completing echocardiography. AADs were continued for at least 3 months. Long-term anticoagulation followed the ESC guidelines (1, 42). All patients also received proton-pump inhibitors for 4 weeks post-ablation.

3.3. General electrophysiological and mapping protocols

Experienced electrophysiologists (>100 PVIs/year) carried out the procedures. Vascular access was achieved via the right femoral vein. A 6 Fr steerable decapolar catheter (Inquiry™ by St. Jude Medical or Dynamic XT™ by Boston Scientific) was inserted into the coronary sinus. Transseptal puncture was performed using a Swartz™ SL0™ sheath and a BRK XS needle (Abbott) under fluoroscopy, pressure monitoring, and/or intracardiac echocardiography (ACUSON AcuNav™). A second steerable sheath (Agilis NxT, Abbott) was inserted through the initial puncture into the LA. Heparin was administered after transseptal puncture to maintain an activated clotting time (ACT) above 300 seconds. Depending on the specific research aim, three-dimensional electroanatomical mapping was performed using one of two advanced platforms.

3.4. Study-specific protocols

3.4.1. AF ablation with LPLD, HPSD, and vHPSD RF energy settings

A 3D electroanatomical map of the LA was created using the CARTO 3® system (Biosense Webster) via fast anatomical mapping with a multi-electrode catheter (Lasso™, Biosense Webster). PVI was achieved with point-by-point RF ablation. The Lasso™ catheter was positioned in the contralateral PVs during ablation to blind the operator to FPI status (*Figure 11*). In patients undergoing LPLD and HPSD ablation, AI-guided techniques were employed using a power-controlled, open-irrigated tip catheter (ThermoCool SmartTouch®, Biosense Webster). Ablation was performed using a slightly modified CLOSE protocol (67), maintaining an ILD of less than 6.0 mm. The target CF was set between 10 and 20 grams, with AI targets of 500 on the anterior and 400 on the posterior wall of the LA. VisiTag™ settings included a minimum stability time of 3 seconds, a location range of 2.5 mm, and a force-over-time threshold of 30%

with a minimum CF of 3 grams. The lesion tag radius was set at 3.0 mm. The RF power was set at 30 W for the LPLD group and 50 W for the HPSD group, with no adjustments based on atrial wall location. Irrigation flow rates were 17 mL/min for LPLD and 30 mL/min for HPSD ablation.

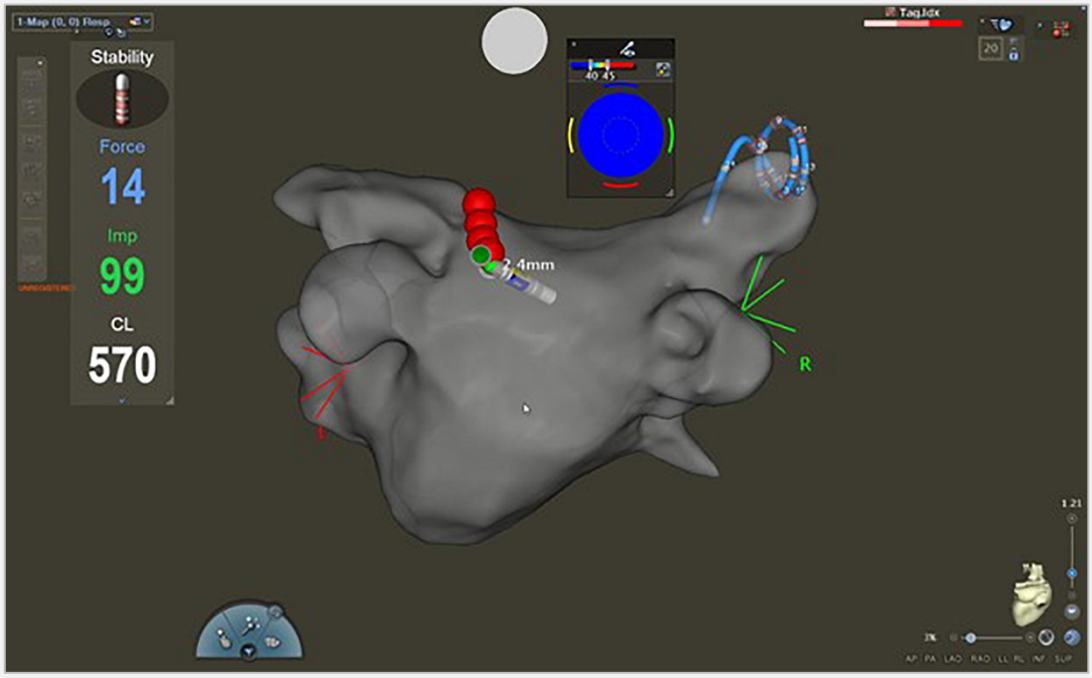

Figure 11. Fast anatomical map of the left atrium with CARTO system (postero-anterior view). During the ablation, the Lasso catheter was placed in the contralateral PVs to blind the operator to the presence or absence of first-pass isolation. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University. PV=pulmonary vein; Imp=impedance; CL=cycle length

In the vHPSD group, ablation was performed with the QDot Micro™ catheter (Biosense Webster) using QMODE+ settings: 90 W for 4 seconds, temperature-controlled (98). Target CF was 10–20 g with an ILD of <5.0 mm. After completing the circumferential PVI, the Lasso™ catheter was reinserted into the PVs to check for FPI (*Figure 12*). Entrance block was confirmed by the absence of PV potentials; exit block was verified by pacing at 20 mA and 2.0 ms pulse width from the ablation catheter at various ostial locations. FPI was defined by both entrance and exit block after initial lesion deployment. If any residual conduction remained, additional RF applications were performed. Lack of FPI was recorded in such cases. The procedural goal was to reach acutely durable PVI, verified after a 20-minute waiting period. Adenosine was not administered (103).

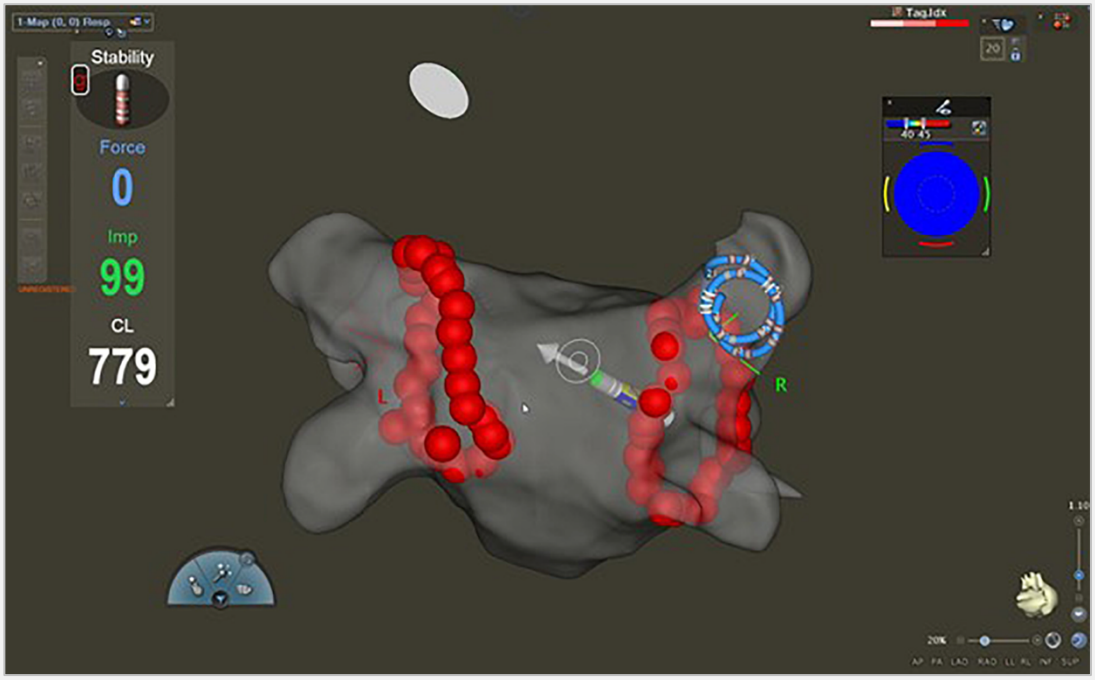

Figure 12. Fast anatomical map of the left atrium with CARTO system (postero-anterior view). After the completion of the circumferential PVI, the Lasso catheter was introduced into the ablated PVs to assess first-pass isolation. The Lasso catheter is in the right superior PV. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University. PVI=pulmonary vein; PVI=pulmonary vein isolation

After the procedure, patients underwent scheduled outpatient follow-up at 3, 6, and 9 months. Each visit included a clinical assessment and ECG evaluation with a 12-lead ECG and 24-hour Holter monitoring. Arrhythmia recurrence was defined as the documentation of any atrial tachyarrhythmia - including AF, atrial flutter, or atrial tachycardia - lasting for 30 seconds or longer after the 2-month blanking period.

3.4.2. Impact of LI drop on acute lesion formation during PVI using a novel CF-sensing catheter

Following femoral venous access and fluoroscopy-guided double transseptal puncture, a high-density anatomical map of the LA was created using the Rhythmia Mapping System (Boston Scientific, Marlborough, MA, USA) and a 64-electrode basket mapping catheter (Intellamap Orion, Boston Scientific, Marlborough, MA, USA). Point-by-point RF ablation was performed around the antra of the ipsilateral PVs using a 4 mm tip, irrigated, CF sensing ablation catheter (StablePoint catheter), in conjunction with a steerable sheath

(Agilis, S or M curve; Abbott). During ablation, the diagnostic basket catheter was placed in the contralateral PVs to prevent contact during RF delivery and avoid distortion of ablation parameters (e.g., CF, LI). RF energy was delivered in power control mode (40–50 W) with a maximum temperature of 43°C. The irrigation flow rate was set at 30 ml/min during ablation and 2 ml/min during mapping. Ablation points were automatically tagged with 6 mm diameter, numbered AutoTags. Ablation points were intentionally overlapped, ensuring that the distance between adjacent tags was less than 6 mm. AutoTag criteria included catheter stability (within 3 mm for > 3 seconds), minimum CF (≥ 3 g for at least 30% of the time), and a minimum LI drop > 3 Ohms. AutoTag color coding was based on LI drop: white for <10 Ohms, pink for 10–20 Ohms, and red for > 20 Ohms. LI drop was monitored in real-time to guide the duration of each ablation application, with a target LI drop of 20-30 Ohms, based on previous experimental findings (99). After completing the circumferential ablation line around the PVs, the success of the first-pass lesions was assessed using bipolar pacing at the distal electrode pairs of the ablation catheter along the full ablation line, with a 10 mA output and 2 ms pulse duration, as previously described (104-107). Successful RF applications were defined by the absence of tissue capture at the ablation site. In contrast, lesions were considered unsuccessful if local tissue capture persisted. AutoTag numbers corresponding to both successful and unsuccessful lesions were recorded. Additional RF applications were delivered at unsuccessful sites until unexcitability was achieved. Subsequently, the left and right ipsilateral PVs were mapped using the basket catheter to assess electrical conduction within the PVs. In cases where LA-to-PV conduction was present, further RF applications were performed at identified conduction gaps along the circumferential line to achieve complete PVI. Twenty minutes after the final RF application, entrance and exit block were confirmed by analyzing basket catheter signals within each PV and through pacing maneuvers with the ablation catheter. A three-dimensional, high-density voltage map of the LA was then constructed to confirm the completeness of the isolation line (*Figure 13*). The ablation catheter used in this study can measure real-time LI from a local electric field generated at the catheter tip. For each first-pass ablation point, the following data were collected: power, minimum CF, maximum CF, mean CF, application duration, baseline LI, and LI drop. Additionally, the CF range was calculated by subtracting the minimum CF from the maximum CF for each ablation point. The FTI was calculated by multiplying the average

CF with the duration of force application. All numbered AutoTag points were exported from the system for analysis conducted offline.

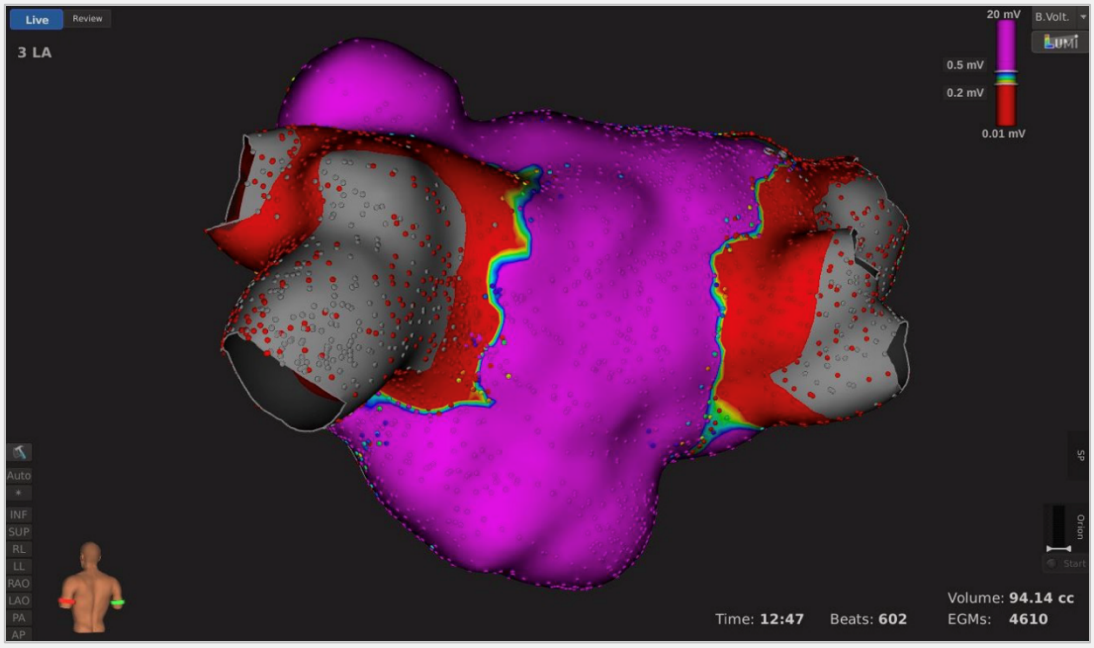

Figure 13. Left atrial bipolar voltage map created with Rhythmia electroanatomical mapping system after successful PVI. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University. PVI=pulmonary vein isolation

3.5. Statistical analysis

The distributions of most variables were non-parametric, as determined by the Shapiro-Wilk test. Continuous variables were presented as medians with interquartile ranges, while categorical variables were expressed as percentages accompanied by event counts. Comparisons between continuous variables were conducted using the Mann-Whitney U test or the Kruskal-Wallis test, as appropriate. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) analysis was employed to determine optimal cut-off values, which were then compared using the log-rank test. Univariate logistic regression analysis was performed to assess the association between ablation strategy and procedural endpoints, including first-pass isolation and long-term procedural success, and to evaluate the predictive value of LI drop cut-off points. All statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 7.1 and 8 (GraphPad

Software Inc., San Diego, CA, USA). A two-tailed p-value of less than 0.05 was considered indicative of statistical significance.

4. RESULTS

4.1. AF ablation with LPLD, HPSD, and vHPSD RF energy settings

4.1.1. Patient population

A total of 156 patients were included in the analysis. *Table 4* displays their baseline characteristics. Most patients had paroxysmal AF (n = 97, 62%), while the remainder had persistent AF.

Table 4. Baseline characteristics of the study patients.

AF=atrial fibrillation; LA=left atrium; LPLD=low-power long-duration; HPSD= high-power short-duration; vHPSD=very high-power short-duration; LVEF=left ventricular ejection fraction; TIA=transient ischemic attack; CHA_2-DS_2-VASc=congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age. The continuous variables were expressed as medians and interquartile ranges, while the categorical variables were expressed as percentages with absolute numbers. The bold variables are statistically significant.

Variable	LPLD (n = 53)	HPSD (n = 50)	vHPSD (n = 53)	P-value
Age (years)	60 (40-75)	58 (35-79)	68 (57-75)	0.3840
Sex (male)	32 (60%)	27 (54%)	33 (62%)	0.6732
Paroxysmal AF	29 (55%)	37 (74%)	31 (59%)	0.1037
Prior stroke or TIA	8 (15%)	0 (0 %)	1 (2%)	**0.0015**
Diabetes mellitus	8 (15%)	7 (14%)	8 (15%)	0.9839
Hypertension	33 (62%)	37 (74%)	35 (66%)	0.4340
Congestive heart failure	2 (4%)	6 (12%)	2 (4%)	0.1472
CHA_2-DS_2-VASc score	2 (1-3)	2 (1-3)	3 (2-4)	**0.0242**
LVEF (%)	60 (55-63)	55 (53-61)	56 (54-62)	0.1583

LA diameter (mm)	44 (39-48)	43 (38-46)	43 (41-46)	0.6935

The baseline characteristics were comparable between the groups. However, the incidence of prior stroke or TIA was higher in the LPLD group, and a significant difference was observed in the CHA_2DS_2-VASc scores between the HPSD and vHPSD ablation groups.

4.1.2. Ablation procedure

Bilateral PVI was successfully achieved in all patients. Procedural characteristics are detailed in *Table 5.*

Table 5. Procedure characteristics.

DAP=dose area product; LA=left atrial; LPLD=low-power long-duration; HPSD=high-power short-duration; vHPSD=very high-power short-duration; RF=radiofrequency; FPI=first-pass isolation; PV=pulmonary vein. The continuous variables were expressed as medians and interquartile ranges, while the categorical variables were expressed as percentages with absolute numbers. The bold variables are statistically significant.

Ablation characteristics	**LPLD (n = 53)**	**HPSD (n = 50)**	**vHPSD (n = 53)**	**P-value**
Procedure time (min)	85 (75-101)	79 (65-91)	70 (53-83)	**<0.0001**
LA dwell time (min)	61 (55–70)	53 (41–56)	45 (34–52)	**<0.0001**
DAP (mGym2)	0.16 (0.11–0.25)	0.1 (0.08–0.18)	0.17 (0.11–0.27)	**0.0014**
Ablation points	61 (52–69)	56 (44–65)	85 (63–99)	**<0.0001**
RF ablation time (s)	1,567 (1,366–1,761)	1,398 (1,021–1,711)	336 (247–386)	**<0.0001**
Total RF energy (J)	47,010 (40,980–52,830)	69,900 (51,050–85,538)	30,240 (22,095–34,875)	**<0.0001**
FPI both sides	30 (57%)	39 (78%)	43 (80%)	**0.0097**

FPI of the left PVs	35 (66%)	46 (92%)	46 (85%)	**0.0015**
FPI of the right PVs	38 (72%)	44 (88%)	48 (88%)	**0.0188**

The median procedure times were 85 minutes (75–101) for the LPLD group, 79 minutes (65–91) for the HPSD group, and 70 minutes (53–83) for the vHPSD group, with statistically significant differences among groups ($p < 0.0001$). Left atrial dwell time also significantly decreased with increasing RF power: 61 minutes (55–70) in the LPLD group, 53 minutes (41–56) in the HPSD group, and 45 minutes (34–52) in the vHPSD

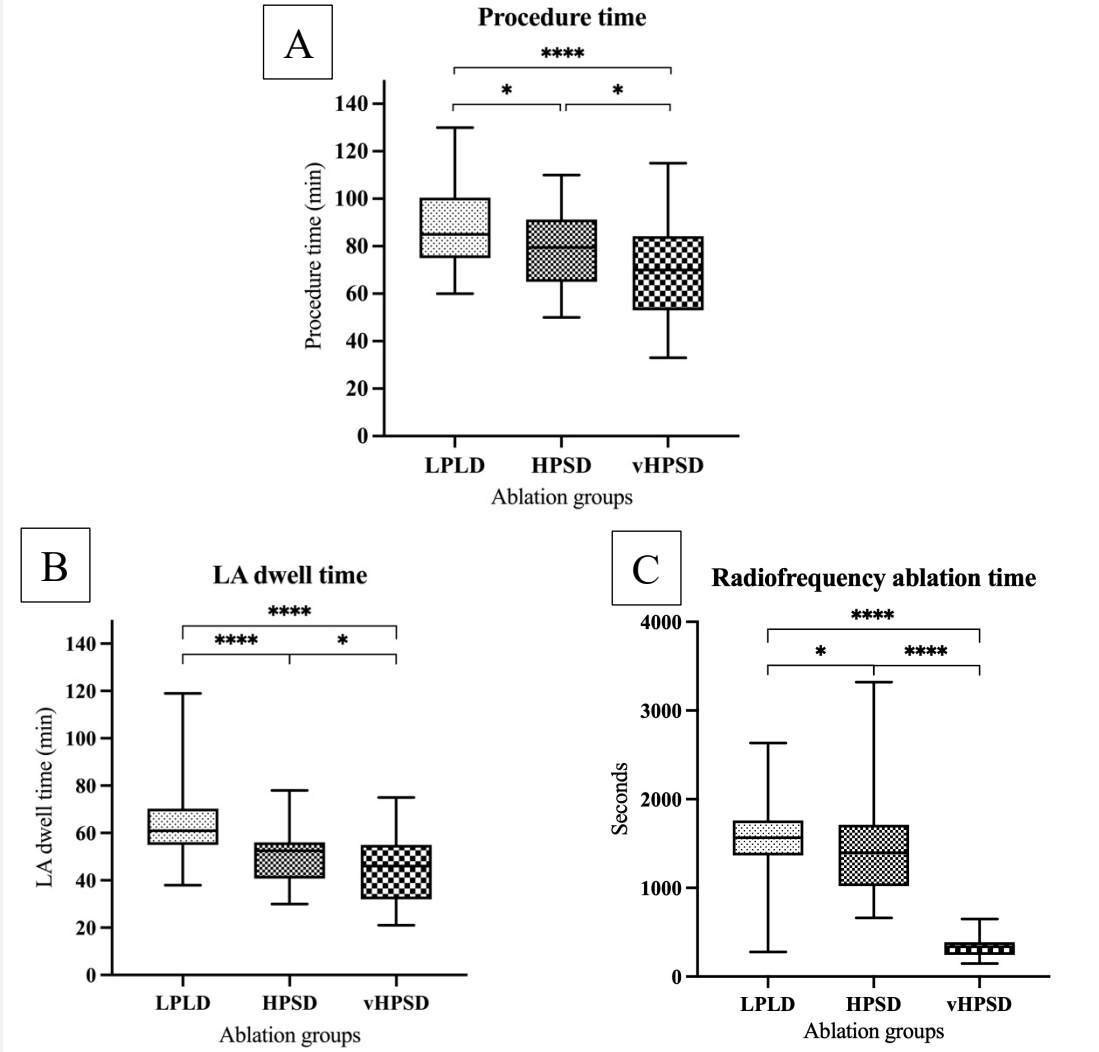

*Figure 14: Procedure time (A), left atrial dwell time (B), and radiofrequency ablation time (C) in the different ablation groups. LPLD=low-power long-duration; HPSD=high-power short-duration; vHPSD=very high-power short-duration; LA=left atrial; min=minutes; sec=seconds.*p < 0.05, ****p < 0.0001, $^{ns}p > 0.05$ (4).*

group ($p < 0.0001$). Total RF ablation times were 1,567 seconds (1,366–1,761) for LPLD, 1,398 seconds (1,021–1,711) for HPSD, and significantly shorter at 336 seconds (247–386) for vHPSD ($p < 0.0001$). Correspondingly, the total RF energy delivered was 47,010 Joules (40,980–52,830) for LPLD, 69,900 Joules (51,050–85,538) for HPSD, and 30,240 Joules (22,095–34,875) for vHPSD ($p < 0.0001$, see *Figure 14*). The number of RF applications was 61 (52–69) in the LPLD group, 56 (44–65) in HPSD, and 85 (63–99) in vHPSD ($p < 0.0001$).

Bilateral FPI was observed in 57% (n=30) of patients in the LPLD group, 78% (n=39) in HPSD, and 80% (n=43) in vHPSD ($p = 0.0097$). Left-sided FPI was achieved in 66%, 92%, and 85% of patients in the LPLD, HPSD, and vHPSD groups, respectively ($p =$

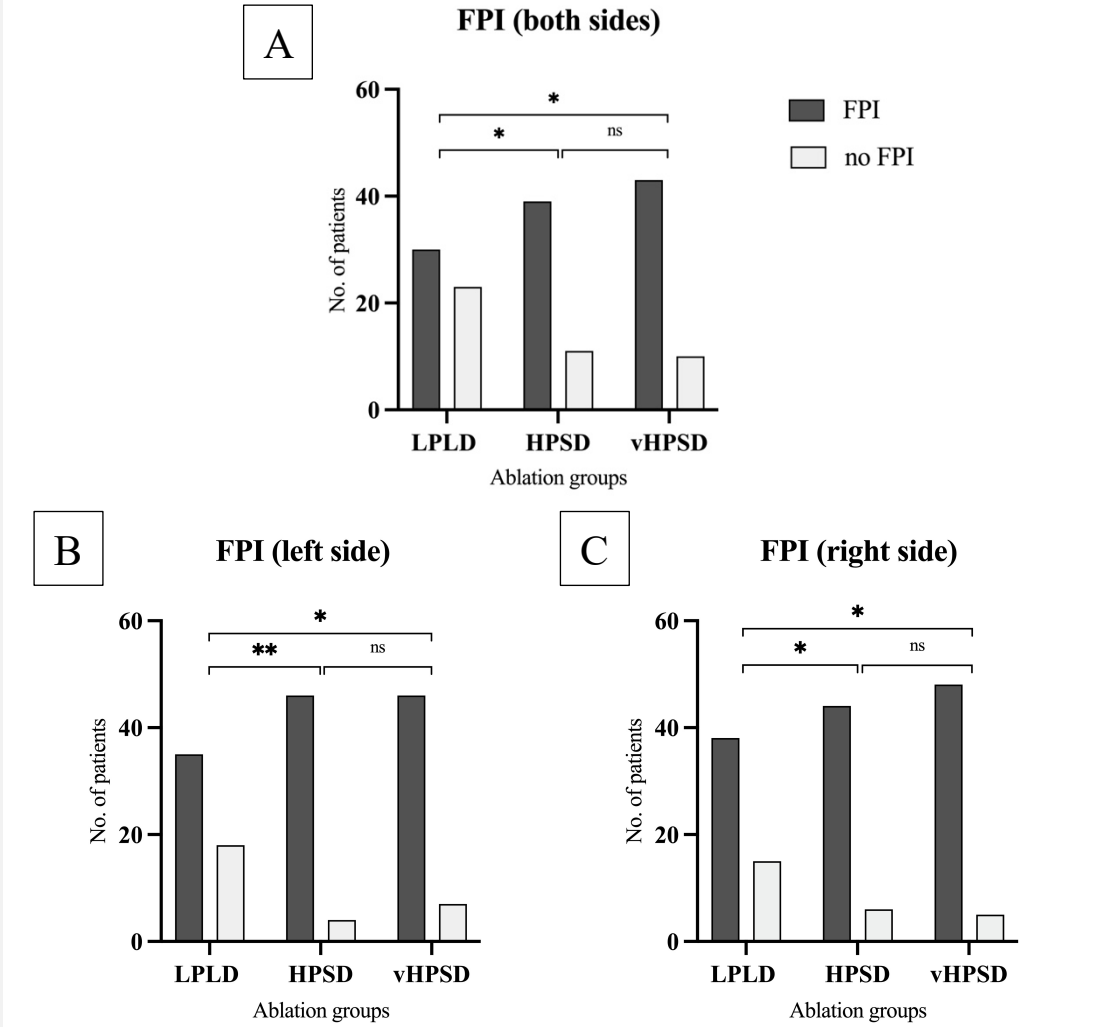

*Figure 15. First-pass isolation results in the different ablation groups (A: both sides; B: left side; C: right side). No.=number; FPI=first-pass isolation; LPLD=low-power long-duration; HPSD=high-power short-duration; vHPSD=very high-power short-duration. *p < 0.05, **p < 0.01, $^{ns}p > 0.05$ (4).*

0.0015). Right-sided FPI occurred in 72%, 88%, and 88% of patients, respectively (p = 0.0188). Comparisons revealed that HPSD significantly improved bilateral (p = 0.021), left-sided (p = 0.0015), and right-sided (p = 0.0401) FPI rates compared to LPLD. However, no significant additional benefit was observed when comparing vHPSD to HPSD for bilateral (p = 0.8080), left-sided (p = 0.5275), or right-sided FPI (p = 0.7561) (see *Figure 15*).

Univariate analysis showed that both HPSD (both sides: OR = 2.72, 95% CI 1.15–6.44, p = 0.023; right side: OR = 2.90, 95% CI 1.02–8.20, p = 0.045; left side: OR = 5.91, 95% CI 1.84–19.04, p = 0.003) and vHPSD (both sides: OR = 2.90, 95% CI 1.24–6.44, p = 0.014; right side: OR = 3.09, 95% CI 1.09–8.74, p = 0.045; left side: OR = 2.89, 95% CI 1.13–7.43, p = 0.027) ablation strategies were significantly associated with higher odds of achieving FPI.

4.1.3. Arrhythmia recurrence rate during the follow-up period

All patients in the study completed the 9-month follow-up period. At this time, a significant difference in AF recurrence rates was observed among the groups, with 36% in the LPLD group, 10% in the HPSD group, and 8% in the vHPSD group (p = 0.0001). According to the results of univariate analysis, both the HPSD and vHPSD ablation techniques were associated with a significantly lower risk of AF recurrence at 9 months. Specifically, the use of HPSD showed an odds ratio (OR) of 0.19 with a 95% confidence interval (CI) of 0.07 to 0.57 (p = 0.003), while vHPSD had an OR of 0.14 and a 95% CI of 0.04 to 0.46 (p = 0.001). Moreover, achieving FPI was strongly associated with reduced AF recurrence as it follows: bilateral FPI was linked to an OR of 0.09 (95% CI: 0.04–0.24, p < 0.0001), while right-sided and left-sided FPI were associated with ORs of 0.09 (95% CI: 0.04–0.23, p < 0.0001) and 0.11 (95% CI: 0.04–0.27, p < 0.0001), respectively.

4.2. Impact of LI drop on acute lesion formation during PVI using a novel CF-sensing catheter

4.2.1. Patient population, included applications

In total, 645 applications across eight subjects were analyzed. The baseline characteristics of the study population are detailed in *Table 6*. Of these applications, 561 were deemed successful, while 84 were classified as unsuccessful.

Table 6. Baseline characteristics.
AF=atrial fibrillation; TIA=transient ischemic attack; GERD=gastroesophageal reflux disease; CHA_2-DS_2-VASc=congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age; LVEF= left ventricular ejection fraction; LA=left atrial; DAP=dose area product. The continuous variables were expressed as medians and interquartile ranges, while the categorical variables were expressed as percentages with absolute numbers.

Patient characteristics (n=8)	
Age (years)	53 (43-59)
Sex (male)	8 (100%)
Type of AF	
Paroxysmal	6 (75%)
Persistent	2 (25%)
Prior stroke or TIA	0 (0%)
Diabetes	2 (25%)
Hypertension	7 (88%)
Congestive heart failure	1 (13%)
Ischaemic cardiomyopathy	1 (13%)
GERD	1 (13%)
CHA_2-DS_2-VASc score	1 (1-2)
LVEF (%)	65 (55-65)
Procedure characteristics	
Procedure time (min)	100 (83-118)
LA dwell time (min)	90 (67-98)
Absorbed fluoroscopy dose (mGy)	231 (11-26)
DAP (uGym2)	252 (109-302)
Fluoroscopy time (min)	7 (4-11)

4.2.2. Lesion parameters

Compared to the unsuccessful ablation points, successful applications were associated with significantly shorter durations ($p = 0.0429$) and a greater drop in LI ($p < 0.0001$). In contrast, no statistically significant differences were observed between successful and unsuccessful applications with respect to mean CF ($p = 0.8571$), minimum CF ($p = 0.7093$), maximum CF ($p = 0.1518$), CF range ($p = 0.0519$), or FTI ($p = 0.0699$). Notably, no steam pops were detected. A comprehensive summary of lesion parameters is provided in *Table 7* and visualized in *Figure 16*.

Table 7. Characteristics of the successful and unsuccessful lesions.

*CF=contact force; FTI=force time integral; g=grams; gs=gram*second; LI=local impedance; s=seconds; W=Watts. * %LI drop was calculated: impedance drop divided by the baseline impedance and multiplied by 100. The variables were expressed as medians and interquartile ranges. The bold variables are statistically significant.*

Parameter	**Successful lesions**	**Unsuccesful lesions**	**p value**
Application duration (s)	8.2 (5.8-11.4)	10.4 (5.9-13.4)	**0.0429**
Baseline impedance	164.7 (156.2-175.1)	155.5 (150.3-161.1)	**0.0001**
Impedance drop (Ohm)	23.1 (18.4-27.4)	16.7 (13.7-19.5)	**0.0001**
%LI drop* (%)	13.9 (11.6-16.1)	10.4 (8.6-12.3)	**0.0001**
No. of applications with 50W (vs. 40W)	485 (vs. 76)	68 (vs.16)	0.1823
Mean CF (g)	11.4 (8.3-16.7)	11.4 (7.6-17.3)	0.8571
Minimum CF (g)	6.0 (3.4-10.0)	6.5 (2.6-11.9)	0.7093
Maximum CF (g)	18.3 (12.5-26.1)	20.6 (13.9-27.4)	0.1518
CF range (g)	10.1 (6.3-17.4)	12.0 (7.4-20.0)	0.0519
FTI (gs)	96.3 (65.8-142.1)	113.0 (78.9-153.2)	0.0699

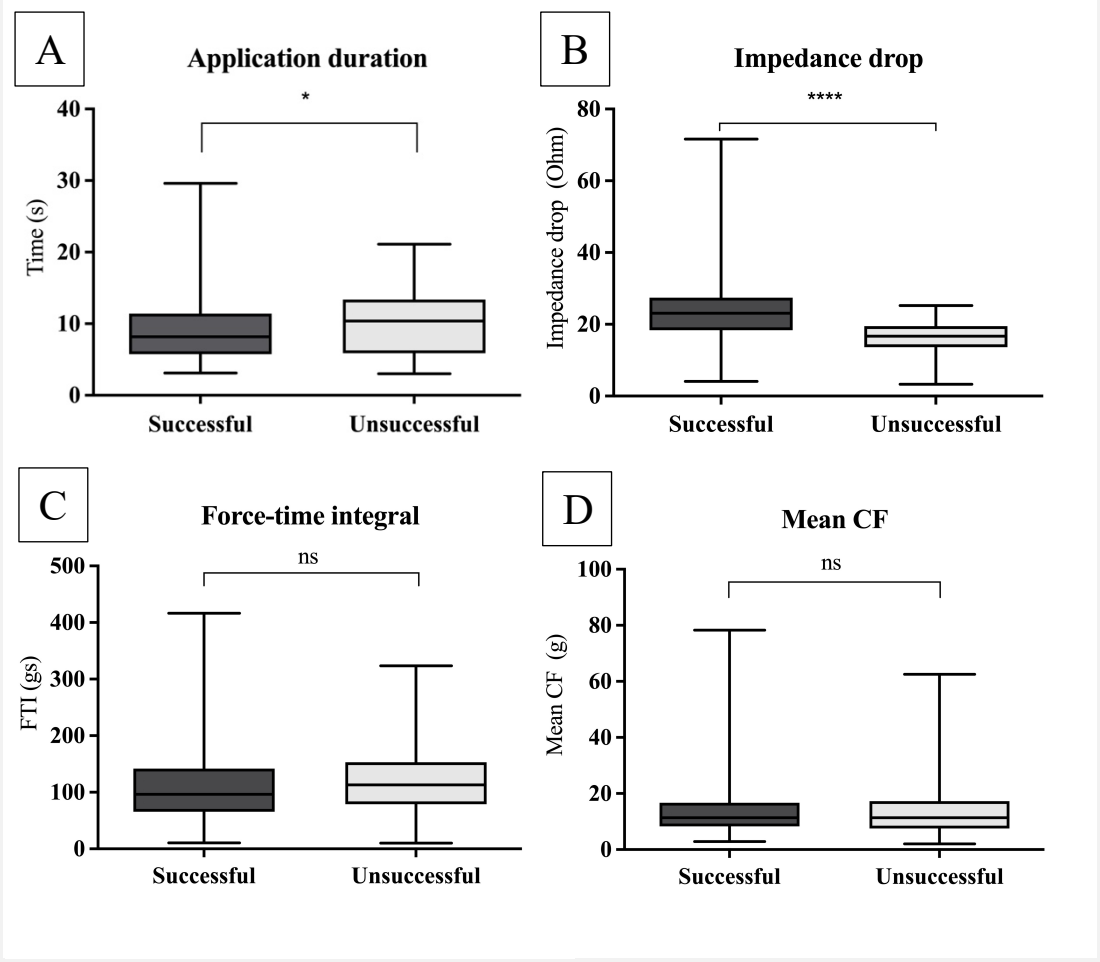

*Figure 16. Application duration, impedance drop, force-time integral and mean CF parameters of the successful and unsuccessful lesions. CF=contact force, FTI=force-time integral, *= $p<0.05$, ****$p<0.0001$, $^{ns}p > 0.05$ (5).*

A significant positive correlation was found between the LI drop and the baseline LI (Pearson's R = 0.68, $p < 0.0001$), as illustrated in *Figure 17*. Acute reconnection was observed in one instance, localized to the postero-inferior segment of the right superior PV following a 20-minute waiting period. The distribution of unsuccessful applications around the PVs was as follows: left anterior (n = 18), left posterior (n = 9), right anterior (n = 16), and right posterior (n = 41).

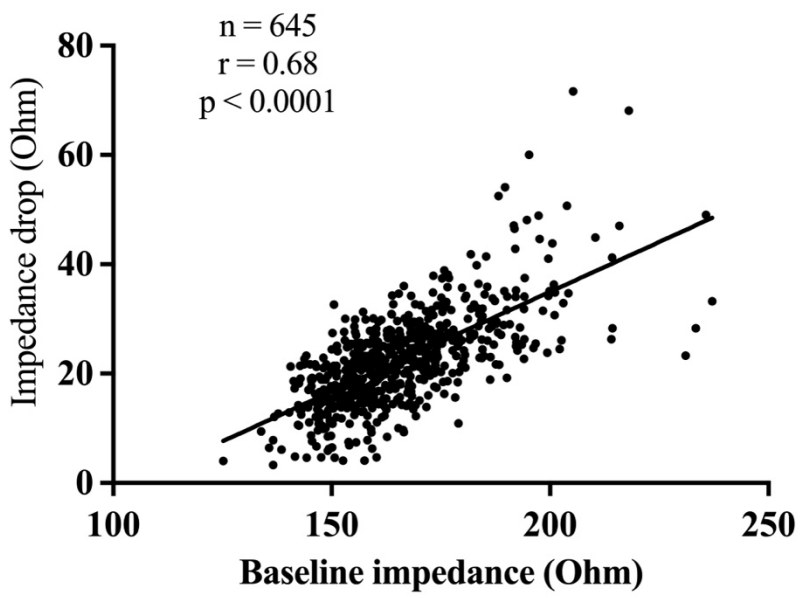

Figure 17. Scatter plot with the line of best fit demonstrating the correlations between starting local impedance and local impedance drop. n = number of applications, r = correlation coefficient (5).

4.2.3. Establishing the predictive cut-off value of LI drop for optimal lesion creation

The next step was the analysis of the data to identify the most appropriate cutoff value of LI drop associated with effective lesion creation. For this, a ROC curve analysis was performed. On the anterior wall, an LI drop exceeding 21.80 Ohms was identified as the optimal cut-off value [AUC = 0.80 (95% CI: 0.75–0.86), p < 0.0001], yielding a sensitivity of 66% (60–71), specificity of 85% (69–95), positive predictive value (PPV) of 98% (95–99), and negative predictive value (NPV) of 22% (18–26). For lesions on the posterior wall, an optimal cut-off was established at an LI drop greater than 18.30 Ohms [AUC = 0.77 (95% CI: 0.72–0.83), p < 0.0001], with a sensitivity of 66% (60–72), specificity of 80% (66–90), PPV of 94% (91–97), and NPV of 32% (27–37).

Subsequently, patient groups were stratified based on whether the LI drop was below or above the defined cut-points. The predictive value of the LI drop for lesion efficacy was further assessed using logistic regression. An LI drop exceeding 21.80 Ohms was significantly associated with a higher likelihood of effective lesion formation on the anterior wall (OR = 11.21, 95% CI: 4.22–29.81, p < 0.0001). Similarly, an LI drop above

18.30 Ohms on the posterior wall demonstrated a significant association with effective lesion formation (OR = 7.91, 95% CI: 3.77–16.57, p < 0.0001). These findings are summarized in *Table 8* and illustrated in *Figure 18.*

Table 8. The number of successful and unsuccessful lesions used for sensitivity, specificity, and predictive value calculation.
Applications below and above the LI cut-points are shown separately to enable the identification of true positive and negative, false positive and negative values. LI=local impedance.

Anterior wall	**Successful lesions**	**Unsuccessful lesions**
LI drop >21.80 Ohms	201	5
LI drop <21.80 Ohms	104	29
Posterior wall	**Successful lesions**	**Unsuccesful lesions**
LI drop >18.30 Ohms	170	10
LI drop <18.30 Ohms	86	40

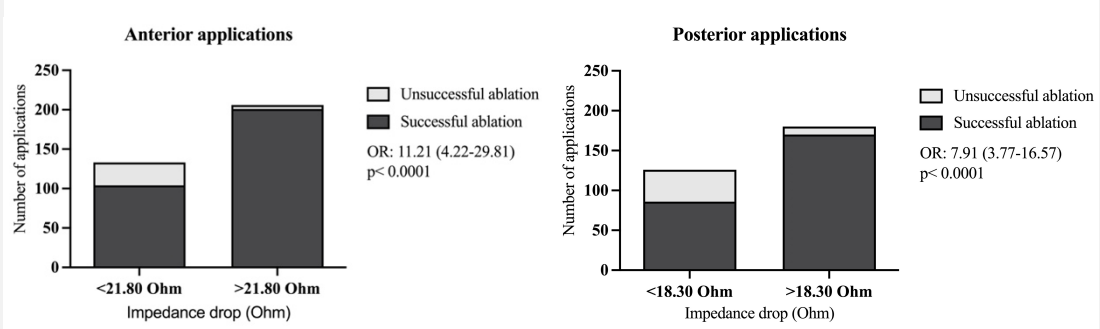

Figure 18. Logistic regression analysis of lesion efficacy on the anterior (left side) and posterior (right side) walls. Abbreviation: OR = odds ratio (5).

5. DISCUSSION

5.1. AF ablation with LPLD, HPSD, and vHPSD RF energy settings

This study demonstrates that increasing RF power substantially improves procedural efficiency while maintaining, and potentially enhancing, lesion durability. The reductions in left atrial dwell time, total procedure duration, and RF delivery time observed with HPSD and vHPSD settings can be mechanistically explained by the biophysics of resistive heating: higher power enables rapid attainment of therapeutic tissue temperatures, thereby shortening individual applications and improving catheter stability. More stable catheter-tissue contact facilitates the creation of contiguous, transmural lesion sets, which are a prerequisite for durable PVI. Importantly, the improved FPI rates and greater 9-month AF-free survival associated with high-power protocols confirm that procedural acceleration does not compromise lesion durability.

5.1.1. Procedure efficiency and safety in high-power ablation

Acute PVI was achieved in all patients without RF-related complications, supporting the safety of high-power strategies under controlled workflow conditions. Despite ongoing debate regarding the necessity of power reduction on the posterior wall, no power modulation was employed in this study. Importantly, no major complications were observed as a result (91, 108).

Our findings were similar to the QDOT-Fast and "Fast and Furious - AF" trials, which similarly demonstrated that vHPSD significantly reduces procedure and RF times compared to historical data without compromising safety profiles (98). In the latter trial, 28 patients undergoing vHPSD ablation were compared to 28 patients treated with conventional CF-sensing catheters guided by AI. All PVs were successfully isolated using vHPSD ablation technique. Median RF time was significantly reduced [338 (286–367) s vs. 1,580 (1,350–1,848) s; $p < 0.0001$], as was total procedure duration [55 (48–60) min vs. 105 (92–120) min; $p < 0.0001$], with no significant difference in periprocedural complications (98). In a separate study by Bunch et al. (109), PVI procedure time was significantly reduced using 50 W compared to conventional 30 W settings (104.3 ± 63.6

min vs. 170.8 ± 59.2 min; $p < 0.0001$). Wielandts et al. (110) randomized 96 patients to HPSD (45 W) or LPLD (35 W) ablation and reported no significant difference in fluoroscopy dose, although RF application time was markedly shorter in the HPSD group [16 (14–18) min vs. 26 (22–30) min; $p < 0.001$]. These results are consistent with our present findings. The progressive reduction in procedure time and left atrial dwell time with increasing power has important clinical implications, as shorter left atrial instrumentation may reduce thromboembolic risk, fluid load, and anaesthesia exposure.

In the HPSD group, both unilateral and bilateral FPI rates were significantly higher than in the LPLD group, though no significant differences were observed between the HPSD and vHPSD protocols. FPI might be regarded as an integrative procedural endpoint reflecting lesion depth, continuity, and transmurality. The significantly higher FPI rates observed with HPSD compared with LPLD therefore provide a mechanistic explanation for the lower AF recurrence during follow-up. Our results are in line with previous studies demonstrating improved FPI and long-term success with high-power protocols (93, 111, 112). Vassallo et al. (113) found that HPSD ablation (50 W anteriorly, 45 W posteriorly) significantly improved bilateral FPI compared to LPLD protocols (87.32% vs. 23.29%; $p < 0.00001$), alongside improved 12-month success rates (87.32% vs. 67.12%; $p < 0.0039$). However, in our cohort, the absence of a significant difference in FPI between HPSD and vHPSD ablation groups suggests that once a critical threshold for lesion contiguity is reached, further shortening of individual applications yields diminishing returns in terms of acute efficacy. In this setting, factors such as ILD and catheter stability may become more important than absolute power.

5.1.2. Lesion formation and AI dynamics

The faster attainment of target AI at higher power levels reflects the mathematical structure of the index: the AI is calculated using a weighted formula incorporating CF, RF time, and power. However, its clinical relevance lies in the improved catheter stability enabled by shorter applications. Stable catheter positioning is a key determinant of contiguous lesion formation and therefore of durable PVI. Various HPSD power settings have been reported, ranging from 40 to 90 W (114). Although the AI was initially validated for use at up to 45 W, recent studies using 50 W AI-guided ablation report

favorable safety and efficacy outcomes (91). Our findings, together with literature data (112, 115), suggest that higher power applications in the LA are more likely to result in successful ablation, in agreement with experimental data (95, 116). It is well-established that HPSD ablation produces a different lesion geometry - characterized by broader but shallower lesions - compared to conventional low-power strategies. Nonetheless, HPSD applications achieve sufficient lesion depth to ensure transmurality in atrial tissue (95, 117). Nakagawa et al. reported that LPLD ablations produced the largest lesion diameters, coinciding with higher energy delivery (96). However, their results stemmed from experimental setups lacking AI guidance, limiting direct applicability to clinical AI-guided ablation scenarios. Our comparison of LPLD (30 W) and HPSD (50 W) ablation aligns with the findings of Hoffmann et al., who explored the optimal ILD during CLOSE-protocol PVI using a consistent power setting of 30 W. Their data showed that an ILD of 3.0-4.0 mm resulted in a significantly higher 1-year success rate than ILD values of 5.0-6.0 mm (FPI: 90.9% vs. 35.0%; $p < 0.0001$) (118). In our study, an ILD of <6 mm was used for LPLD and HPSD groups. However, lesion size tends to be smaller with vHPSD ablation (96), therefore we used a tighter ILD (<5 mm) in the vHPSD group to maintain the continuity of the ablation line. This modification increased the number of RF applications relative to the HPSD group. The usefulness of this workflow was confirmed by our results, as the FPI rates were higher in both high power groups compared to LPLD group, but there was no difference between FPI in HPSD vs. vHPSD groups. The comparable FPI rates between HPSD and vHPSD, despite shorter RF delivery with vHPSD, suggest that lesion continuity rather than cumulative energy delivery is the dominant determinant of acute success.

Limited data exist on cumulative energy delivery for LPLD, HPSD, and vHPSD techniques. The observation that total RF energy was highest in the HPSD group highlights an important conceptual point: effective lesion formation is not solely dependent on energy magnitude but on the interaction between power, duration, CF, and catheter stability. The deliberately lower CF (10-20 g) applied during HPSD, compared to LPLD ablation, to enhance safety, likely contributed to this finding. This strategy may explain the minimal difference in overall RF energy between the 30 W and 50 W protocols, despite the power discrepancy. Importantly, the target AI remained constant across these groups.

5.2. Impact of LI drop on acute lesion formation during PVI using a novel CF-sensing catheter

The principal finding of this study is that LI drop provides a direct, real-time marker of effective lesion formation. Unlike composite indices, LI reflects the immediate electrical consequences of tissue heating and therefore offers a more physiologically relevant endpoint for RF delivery. Specifically, an LI drop exceeding 21.80 Ohms on the anterior PV wall and greater than 18.30 Ohms on the posterior wall was significantly associated with an increased likelihood of achieving a successful lesion.

5.2.1. Evaluation of lesion efficacy using the “Loss of Capture” technique

In the present study, lesion efficacy was assessed using the loss-of-local-capture method. This electrophysiological approach has been extensively investigated in prior research and is recognized as a reliable indicator of durable lesion formation. Steven et al. demonstrated that pace capture testing along the ablation line can effectively identify sites of conduction gaps (105). Similarly, two independent studies reported that pacing for unexcitability during PVI safely detects potential regions of dormant conduction, thereby supporting lesion completeness (104, 107). Furthermore, adopting loss of capture as an endpoint during PVI has been associated with improved long-term procedural outcomes, including enhanced 5-year success rates (106).

5.2.2. High-power ablation and lesion formation in the LA

Consistent with prior experimental data, our findings confirm that high-power delivery (40–50 W) safely produces effective continuous lesion sets in the LA (95, 116). When guided by real-time LI monitoring, operators can exploit this broader lesion geometry while precisely terminating energy delivery before excessive depth poses a safety risk.

5.2.3. The role of LI drop in predicting lesion formation

The superiority of LI over conventional generator impedance stems from its truly local measurement field. LI measurement offers a more precise real-time indicator of tissue

response during ablation compared to conventional GI monitoring (100). Supporting preclinical data from Garrott et al. further reinforces the clinical relevance of LI monitoring. Their in vitro and in vivo studies demonstrated that LI drop correlates with lesion depth and can be used to assess both efficacy and safety during ablation. Specifically, they proposed that an LI drop >20 Ohms is indicative of adequate lesion formation, whereas values exceeding 65 Ohms may suggest excessive heating and increased risk of steam pop. Their findings indicated a significant reduction in total RF application time when LI guidance was utilized. Additionally, they noted that baseline LI values may vary depending on catheter orientation relative to tissue (99).

Prior clinical investigations have primarily evaluated the utility and optimal LI drop thresholds using the IntellaNav MiFi OI catheter (Boston Scientific, Marlborough, MA, USA) (101, 119). In line with findings from the LOCALIZE clinical trial, the present study confirms that LI drop reliably predicts effective lesion formation. Our results demonstrated that higher baseline LI values correlate with greater impedance drops, and distinct LI cut-off values should be employed for the anterior and posterior walls of the PVs. However, methodological and technical differences exist between the LOCALIZE study and the present investigation. Notably, the LOCALIZE trial utilized a catheter equipped with microelectrodes embedded within the tip (between electrodes 1 and 4, measuring LI with microelectrodes and electrode 2) (101), whereas the catheter employed in the current study - the IntellaNav StablePoint - lacks microelectrodes and measures impedance across the distal electrode pair (electrodes 1 and 2). As a result, the absolute LI values reported in our study were higher than those in the LOCALIZE trial. The different absolute LI values observed with the StablePoint catheter highlight the system-specific nature of impedance measurements and explain why previously published cut-off values cannot be directly transferred between technologies. Further distinctions arise from procedural parameters. In the LOCALIZE trial, ablations were performed using a non-CF sensing catheter at power settings ranging from 25 to 40 W. Additionally, optimal ILD (≤ 6 mm) was achieved in only 53% of the ablation segments, potentially compromising lesion continuity. This is reflected in the reported acute reconnection rate of 16.8%, which is relatively high compared to outcomes associated with CF-sensing catheter use (68). In contrast, the very low rate of acute reconnection in our cohort - which occurred in only one PV (3.1%) - is most likely the result of the combined use of CF-

sensing catheter, strict interlesion spacing, and high-power (40-50 W) delivery. Another key methodological difference relates to data analysis. The LOCALIZE study analyzed mean LI parameters per segment and derived regional cut-off values only from segments with ILD ≤ 6 mm, resulting in a final dataset of 416 points (101). Conversely, our study evaluated each ablation point individually, generating a more granular dataset comprising 645 discrete LI values. This allowed the identification of wall-specific LI thresholds. Before our data, no clinical studies have established optimal LI drop thresholds for effective lesion creation using the StablePoint catheter. The current investigation addresses this gap, demonstrating that LI measurement is predictive of successful lesion formation. Moreover, we identified anterior and posterior wall-specific LI drop cut-off values associated with effective ablation outcomes. Importantly, our findings also indicate that LI guidance facilitates shorter RF application durations, further enhancing procedural efficiency.

5.2.4. Implications for clinical practice

The current study offers several important insights with potential implications for clinical practice. Our findings demonstrate that LI drop serves as a reliable real-time indicator of effective lesion formation during atrial ablation. The proposed LI drop cut-off values exhibited strong diagnostic performance, with notable sensitivity, specificity, and both positive and negative predictive values. Interestingly, no significant differences were observed in mean, minimum, or maximum CF, CF range, or FTI between successful and unsuccessful ablation points when LI drop guidance was applied. This suggests that optimal lesion formation may be more dependent on catheter stability than on absolute CF metrics alone. In particular, unstable catheter positioning may compromise lesion efficacy despite achieving seemingly adequate CF values.

Moreover, the significantly shorter RF application times observed at successful sites suggest that LI guidance may prevent unnecessary energy delivery, thereby improving safety. This is especially relevant in high-power ablation protocols where short-duration RF applications are preferable, particularly along the posterior wall, where the risk of collateral damage (e.g., esophageal injury) is heightened (110, 120, 121).

Based on our results, an LI drop exceeding 22 Ohms on the anterior wall and 18 Ohms on the posterior wall appears to represent a practical threshold for optimal lesion creation during PVI. These values may be integrated into clinical workflows to enhance both efficacy and safety during high-power ablation procedures. Nevertheless, larger-scale prospective studies with extended follow-up are warranted to validate these findings and to establish standardized LI-guided ablation protocols in diverse patient populations.

5.2.5. Limitations

This doctoral work has a few limitations that should be considered when interpreting the findings. First, the comparison of LPLD, HPSD, and vHPSD ablation strategies was performed as a prospective, observational study in a relatively small cohort and without randomization, which may introduce selection bias. In addition, repeat ablation procedures were not systematically performed during follow-up; therefore, PV reconnection could not be directly assessed as a mechanistic correlate of arrhythmia recurrence. Clinical efficacy was evaluated using scheduled outpatient visits with intermittent Holter ECG monitoring rather than continuous rhythm surveillance, raising the possibility that asymptomatic or transient atrial arrhythmia episodes may have been missed. Second, the LI analysis represents a pilot clinical investigation with a limited number of enrolled patients, despite the volume of individual ablation lesions analyzed being sufficient to achieve statistical significance and support the primary findings. The absence of long-term follow-up in this cohort precludes definitive conclusions regarding the clinical durability and relevance to outcomes of the identified LI drop thresholds. Finally, LI measurements are technology- and platform-specific and were assessed using a single proprietary catheter and its associated EP platform. Consequently, the identified cut-off values may not be directly transferable to other systems, and integration with alternative lesion quality metrics is limited. Larger prospective studies with extended follow-up, standardized monitoring, and broader representation of technologies are warranted to validate and generalize these findings.

6. CONCLUSION

PVI remains the cornerstone of rhythm control in AF; however, achieving durable, continuous lesion sets without compromising procedural efficiency or patient safety continues to challenge the field of EP. This work investigated two complementary aspects of contemporary RF catheter ablation for AF: the optimization of energy delivery and the real-time assessment of lesion formation. Although these were examined in separate clinical studies, their findings converge toward a common conceptual framework in which procedural efficiency and lesion durability are no longer competing objectives but interdependent components of a physiology-guided ablation strategy.

The comparison of LPLD, HPSD, and vHPSD ablation demonstrated that using high power significantly shortens LA dwell time and total procedure duration. This reduction in procedural duration not only contributes to improved workflow efficiency in the EP lab but may also minimize the duration of patient exposure to anesthesia and reduce overall procedural burden. Furthermore, the use of high-power ablation techniques correlated with improved FPI rates and acute and mid-term procedural success rates. These findings support the growing body of evidence indicating that optimized power delivery strategies can enhance lesion durability without compromising safety when ablation is performed within a controlled workflow that ensures catheter stability and lesion contiguity. FPI emerged as a central mechanistic link between acute procedural success and long-term rhythm outcome. Taken together, these findings support the concept that HPSD represents a balanced strategy that optimizes both procedural speed and lesion durability.

Reliable intra-procedural indicators of lesion quality are essential to ensure transmurality and continuity, both of which are critical for achieving long-term PVI and minimizing arrhythmia recurrence. The second major finding of this thesis is the clinical validation of LI drop as a real-time marker of effective lesion formation. In contrast to composite indices that estimate lesion quality based on delivered energy and contact parameters, local impedance directly reflects tissue response to RF application. In this study, we demonstrated that the magnitude of the LI drop during ablation is significantly associated with the likelihood of achieving a successful lesion. Our data provided exact cut-off values. The ability to quantify tissue response through LI drop measurement

allows operators to tailor energy delivery more precisely, potentially reducing the risk of under- or over-ablation. By adopting clearly defined LI drop targets, ablation procedures may be guided with greater consistency, ultimately improving procedural safety, efficiency, and outcomes. In clinical practice, the integration of LI guidance - particularly with clearly established regional cut-off values - has the potential to standardize lesion assessment and support real-time decision-making during high-power short-duration ablation strategies. Further large-scale, multicenter studies are warranted to confirm these findings and to explore the generalizability of these cut-offs across different catheter platforms and patient populations.

Taken together, these results support a paradigm shift in AF ablation from empiric, parameter-driven workflows toward an individualized, physiology-guided approach. In such a model, HPSD energy delivery improves procedural efficiency, while LI monitoring ensures lesion effectiveness and prevents unnecessary energy application. This combined strategy has the potential to increase procedural reproducibility, reduce operator dependence, and enhance both safety and long-term clinical outcomes.

7. SUMMARY

The aim of this doctoral thesis was to improve the efficacy, safety, and reproducibility of RF catheter ablation for AF by addressing two key determinants of lesion formation: the mode of energy delivery and the real-time assessment of tissue response.

In the first part, evaluation of characteristics of PVI procedures performed with different RF energy settings including the presence of FPI, and the long-term success of the ablation was assesed. Between 2019 and 2021 data of 156 patients were prospectively collected who underwent their first PVI due to paroxysmal or persistent AF. The procedures were performed using three different energy settings: 30W (LPLD ablation, n=53), 50W (HPSD ablation, n=50), and 90W (vHPSD ablation, n=53). The results demonstrated that increasing RF power to HPSD and vHPSD settings significantly reduced procedural and RF delivery times while increasing FPI and improving mid-term arrhythmia-free survival compared with conventional LPLD ablation. These findings demonstrate that accelerated workflows can enhance, rather than compromise lesion durability when lesion continuity and catheter stability are maintained.

In parallel, this work provides clinical validation of LI monitoring as a direct physiological marker of effective lesion formation. The role of LI drop in tissue lesion formation during PVI using a novel ablation catheter in patients with paroxysmal AF was investigated. Procedures followed a standardized protocol, and lesion characteristics were analyzed. The findings showed that LI drop reliably indicates successful lesion formation. This work was the first to clinically define threshold values for effective ablation with this technology: >21.80 Ohms on the anterior and >18.30 Ohms on the posterior wall of the PVs. Applying these targets reduced lesion formation time without significant differences in CF or force-time integral between successful and unsuccessful lesions.

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9. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

9.1. Publications related to the PhD thesis

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9.2. Publications not related to the PhD thesis

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