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CEREBRAL SAFETY AND LESION EFFICACY OF RADIOFREQUENCY ABLATION OF ATRIAL FIBRILLATION

PhD thesis

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List of Abbreviations

Abbreviations	Meaning
AF	atrial fibrillation
AAD	anti-arrhythmic drug
ACT	activated clotting time
ADC	apparent diffusion coefficient
AI	ablation index
AUC	area under curve
AV node	atrioventricular node
BGI	baseline generator impedance
BMI	body mass-index
bMRI	brain magnetic resonance imaging
CAD	coronary artery disease
CBA	cryoballoon ablation
CF	contact-force
CHA_2DS_2-VA	congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, age
CHF	chronic heart failure
CI	confidence-interval
CRT	cardiac resynchronization therapy
CT	computed tomography
DWI	diffusion-weighted imaging
ECG	electrocardiogram
ECV	electrical cardioversion
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
FPI	first-pass isolation
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HPSD	high power short duration
ILD	interlesion-distance
INR	international normalized ratio
LA	left atrium
LAA	left atrial appendage
LOC	loss of contact
LPLD	low-power long-duration
LVEF	left ventricular ejection fraction
NOAC	non-vitamin K oral anticoagulant
NYHA	New York Heart Association
OR	odds-ratio

PFA	pulsed-field ablation
PV	pulmonary vein
PVAC	pulmonary vein ablation catheter
PVI	pulmonary vein isolation
PVR	pulmonary vein reconnection
RCT	randomized controlled trial
rePVI	repeated pulmonary vein isolation
RFA	radiofrequency ablation
ROC	receiver operating characteristic
SCE	silent cerebral embolism
TEE	transesophageal echocardiography
TIA	transient ischemic attack
US	United States
vHPSD	very high-power short-duration
VIF	variation inflation factor
VKA	vitamin-K antagonist

1. Introduction

1.1. Atrial fibrillation

1.1.1. Definition and diagnosis

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia in which normal sinus rhythm is replaced by high-frequency chaotic electrical activity in the atria, resulting in ineffective atrial contractile function. The diagnosis of AF is based on a standard 12-lead electrocardiogram (ECG) recording or a single-lead ECG recording of at least 30 seconds duration with no detectable P waves and irregular RR intervals (in absence of atrioventricular block) [1]. The classification of AF is defined in terms of temporal AF patterns. Paroxysmal AF is defined as episodes of less than one week; persistent AF as the arrhythmia lasting longer than one week and less than one year; long-standing persistent AF as an episode lasting longer than one year while still aiming for rhythm control; and permanent AF is used when the restoration or maintenance of sinus rhythm is no longer an objective [1]. As a chronic disease, AF follows a progressive course with increasing AF burden and progression from paroxysmal episodes to persistent arrhythmia.

1.1.2. Epidemiology

AF is the most common clinically significant, sustained arrhythmia. Its prevalence increases with age, with an overall prevalence of 2% in the general population (based on

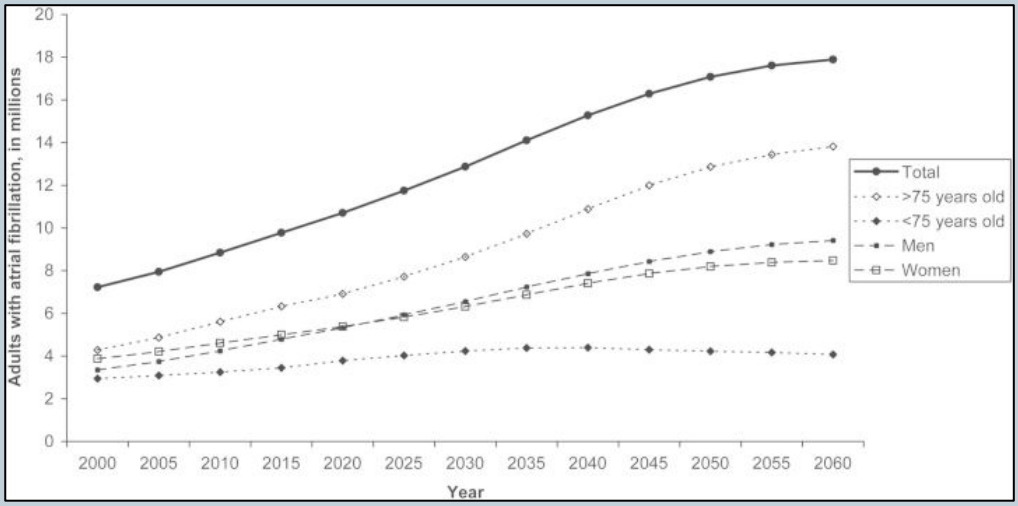

Figure 1. Number of adults with atrial fibrillation in the European Union between 2000 and 2060, adapted from Krijthe et al, with permission by Oxford University Press and the European Society of Cardiology [3].

2010 European Union data) and 10% above the age of 75 [2,3]. In Hungary, this represents a total of approximately 200 000 patients with AF. The annual incidence is around 80/100 000/year [4], which in our country means 8000 new cases per year. AF incidence is projected to increase several-fold in the near future as life expectancy and comorbidity rates increase and as screening becomes more widespread (Figure 1) [3,5].

1.1.3. Pathogenesis

AF requires a trigger that initiates the arrhythmia and a substrate that maintains it. The trigger is most often the spontaneous electrical activity of the atrial myocardial sleeves extending into the orifice of the pulmonary veins (PVs), and the substrate is the remodeled, scarred atrium. Haïssaguerre et al. described in 1998 that the earliest electrical activity recorded by a multielectrode catheter prior to the onset of AF episodes can be localized at the orifice of the PVs in the vast majority of cases (Figure 2) [6]. Focal PV activity may trigger AF or even provide a driver stimulus to maintain the arrhythmia. Histologic studies have shown that precursor cell markers common to the nodal tissues are found in these myocardial fibers [7], and that P cells, Purkinje cells and transitional cells forming the sinus node and AV node are also found in this region (probably as developmental remnants) [8]. In addition, myocardial cells at these sites have a different ion channel profile than normal myocardium [8]. In these regions, shorter action potential durations and shorter refractory periods have been observed [8,9], and abrupt shifts in the fiber-orientation of cardiomyocytes have been shown to play a role in promoting reentry [15]. The elimination of pulmonary triggers may prevent the onset of the arrhythmia [6]. Later studies have suggested that triggers other than pulmonary veins may play a role in the initiation of AF [10]. One of these non-trigger sites is the ligament of Marshall, which may be a source of spontaneous electrical potentials. This has been demonstrated by catheterization of the

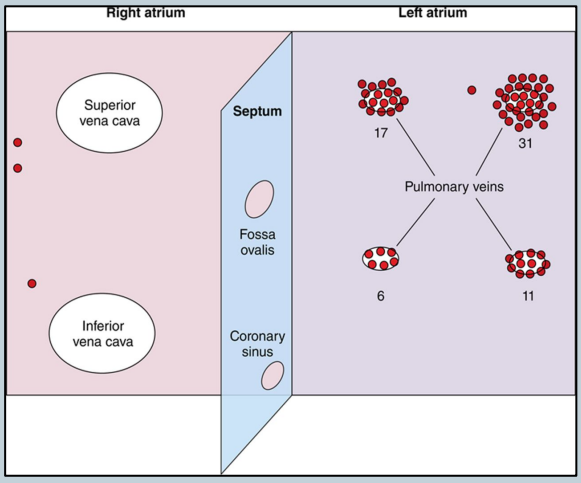

Figure 2. Drawing showing the localization of 69 ectopic triggers that initiate atrial fibrillation. Reproduced with permission from Haïssaguerre et al. Copyright Massachusetts Medical Society [6].

vein of Marshall in AF patients, whereby ablation of the vein terminated the arrhythmia in patients with documented ectopic activity from the myocardial bundle extending into the ligament [11]. Other possible non-PV trigger sites include the posterior left atrial wall, coronary sinus, superior vena cava, atrial septum, and left atrial appendage [10,12]. The vagal ganglia are also thought to play a role in driving trigger activity. Patients in whom complete denervation of the pulmonary veins was achieved were less likely to have AF recurrence [13]. Both sympathetic and parasympathetic activation may contribute to the initiation and maintenance of arrhythmias [14].

The substrate for AF is the structurally and electrically remodeled, fibrotic left atrium [12,15]. Various AF risk factors significantly contribute to fibrosis, and AF itself may be profibrotic [15]. Structural remodeling may be due to persistent AF episodes, elevated left atrial pressure and atrial strain, or other systemic effects such as diabetes or obesity. In the process, fibroblast activation results in myocardial scarring, inflammation and fatty infiltration [16,17]. In parallel, the atrium becomes enlarged and its function deteriorates. Fibrosis slows down the propagation of depolarization wavefronts and favours the development of microreentrant circuits [18,19], and fatty tissue deposition also has an arrhythmogenic effect [20]. In AF of long duration, disturbances in the calcium homeostasis of myocardial cells also play a role in maintaining the arrhythmia. Down-regulation of calcium-binding proteins and dysfunction of ion channels result in ectopic triggered activity [21,22]. Although AF usually starts with paroxysmal episodes, a significant proportion of patients progress to a persistent form. The transition is believed to reflect the progression of structural and electrical remodeling in the atria [12]. As AF progresses, PV sources become less dominant as AF becomes more persistent and remodeling continues. The transition from paroxysmal to persistent AF occurs in 10-15% of patients over 12 months [23].

The pattern and precise mechanism of atrial activation during AF has been the subject of several hypotheses (Figure 3) [12]. The multiple wavelet theory originally proposed by Garrey (Figure 3A), was the dominant model for explaining the mechanism of AF for decades [24,25]. Since then, several other theories have been proposed, such as the theory of rapid-firing automatic foci (3B), single reentry with circular fibrillatory conduction (3C), reentry of rotor or spiral waves (3D), and AF arising from dissociation between epicardial and endocardial layers (3E). However, there is still no consensus in the literature on this,

because no single mechanism can answer all the observations about AF mechanism in different patients. It is likely that both ectopic activity and reentry play a role in the mechanism of atrial fibrillation [12].

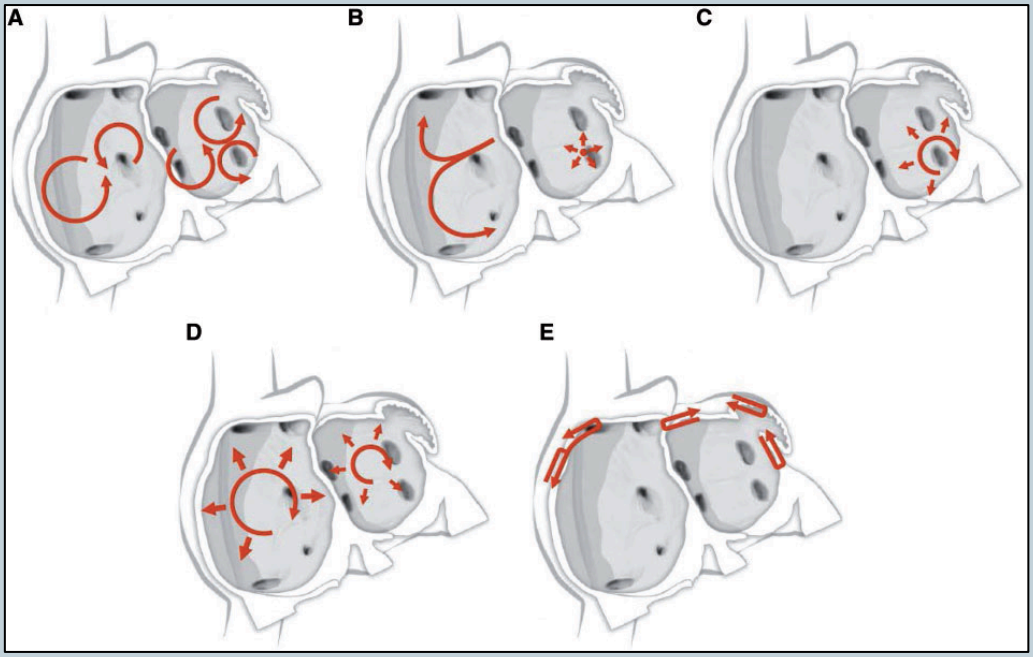

Figure 3. Schematic diagram showing different hypotheses on the mechanism of AF. (A) Multiple wavelets. (B) Rapidly firing automatic foci. (C) Single reentry with circular fibrillatory waves. (D) Reentry resulting from rotor or spiral waves. (E) AF resulting from dissociation between epicardial and endocardial layers. Adopted from Calkins et al. [12], with permission by Oxford University Press and the European society of cardiology.

One of the most important factors in the pathomechanism of AF is the hypercoagulable environment in the left atrium. Thrombus formation is favoured by stasis of blood due to ineffective atrial contraction and by damage to endothelial function as a result of fibrosis and local inflammation [26]. The predilection site for thrombus formation is the left atrial appendage, from where clot detachment can lead to arterial thromboembolism, resulting in stroke, and less commonly limb or mesenterial embolism. Another major consequence of AF is heart failure, which develops as a result of prolonged high ventricular frequency and irregular ventricular contractions, with the contribution of comorbidities underlying AF [27].

1.1.4. Etiology

A number of modifiable and non-modifiable risk factors can contribute to the development of AF. Non-modifiable factors include age, familial aggregation

(monogenic and polygenic inheritance), gender and height [12,27,28]. Modifiable factors include hypertension, obesity, diabetes mellitus, thyroid disease, chronic kidney disease, obstructive sleep apnoea, alcohol consumption, smoking, and endurance sports [29]. In addition, other cardiac diseases may be aetiological factors of AF, such as chronic heart failure (CHF), coronary artery disease (CAD), valvular diseases, cardiomyopathies, myocarditis and atrial septal defects [12,27]. The relative risk of developing AF in association with each of these factors is highest for obesity, hypertension and age [30]. Obesity contributes to atrial remodeling through fatty infiltration and diastolic dysfunction, hence a unit increase in body mass index (BMI) increases the risk of AF by 3-7%, and obesity is responsible for potentially one fifth of AF cases [31,32]. Elevated arterial blood pressure and impaired left ventricular systolic function both result in increased left atrial pressure, which contributes to atrial wall fibrosis and infiltration by inflammatory cells [33], making hypertension and heart failure significant risk factors for AF [34]. Among the Framingham Study participants with a diagnosis of both AF and CHF, the first diagnosis was AF in 38%, CHF in 41%, and 21% were diagnosed with both diseases at the same time [35]. These patients have a worse prognosis and higher mortality than those with AF alone. Similarly, diabetes promotes atrial remodeling, by contributing to fibrosis and conduction slowing [28,36], and is a significant independent risk factor of AF. Patients with diabetes have a significantly higher incidence of asymptomatic AF due to neuropathy [37], and therefore screening for AF is particularly important in these patients [27]. Finally, it is important to note that AF itself enhances remodeling and promotes the development and persistence of subsequent AF episodes ("AF begets AF"). The impact of risk factors and comorbidities on the risk of AF development suggests that early intervention and management of modifiable risk factors can reduce the incidence of AF and are key components of therapy [27,38].

1.1.5. Clinical presentation

Symptoms of AF vary widely; in some cases it can be asymptomatic, in other cases it manifests as highly symptomatic. It can result in both bradycardia and tachycardia, symptoms are usually determined by the ventricular rate [39]. Frequent complaints include palpitations, chest pain or discomfort, dyspnea, sweating, dizziness, and nausea. Decreased exercise capacity and sleep disorders are common. In severe cases with high ventricular rates, hemodynamic instability might result in syncope, lung edema, or acute

heart failure [27]. Symptom severity can be classified based on the modified European Heart Rhythm Association score (mEHRA) similarly to CHF functional classification of the New York Heart Association (NYHA) [1].

1.1.6. Importance

In addition to its prevalence, the importance of AF comes from the fact that it is associated with higher morbidity, mortality, and deterioration in the quality of life, and also places a heavy burden on the healthcare system economically and in terms of other resources [12,27]. The two most important consequences in terms of AF-associated mortality are stroke and heart failure, the risks of which are higher in persistent AF. AF is associated with a fivefold increase in stroke risk, and AF-related strokes are more severe than non-AF stroke cases [40,41]. AF is responsible for approximately 20-30% of all stroke cases, and 10% of cryptogenic strokes are AF-related [27]. Heart failure develops in 20-30% of AF patients, with a greater probability in persistent AF [35]. Patients with atrial fibrillation have an increased risk of dementia, which may be due to strokes, silent microembolizations, and abnormal cerebral perfusion caused by pulse variability [42]. In quality of life questionnaires, AF patients report significantly worse quality of life (with 20-30% lower scores) than healthy controls on measures of physical and social functioning, mental and general health [43]. It is important to highlight that AF increases all-cause mortality by 1.5-3 fold and has also been shown to be associated with an increased risk of sudden cardiac death [35,44]. AF is also a major issue in terms of healthcare costs. In the United States, it is reported to account for more than 450 000 hospitalisations per year, contribute to more than 99 000 deaths and increase annual healthcare costs by $8 700 per patient in a population of around 330 million [45,46].

1.1.7. Treatment

There are three main elements to the treatment of AF, anticoagulation therapy, treatment of the arrhythmia with rhythm or rate control, and treatment of the underlying diseases (comorbidities) [27].

1.1.7.1 Anticoagulation

The most effective treatment for the reduction of mortality and thromboembolic events is anticoagulation. The first step is to assess the risk of stroke in patients with AF. In clinical practice, the need for anticoagulation can be assessed by the CHA_2DS_2-VA score (Table 1), which is a scoring system estimating the annual risk of stroke in non-anticoagulated atrial fibrillation patients. Anticoagulation is not recommended for a score of 0, should be considered for a score of 1, and is recommended for a score of 2 or more for both men and women [27].

Table 1. Calculation of CHA_2DS_2-VA score. TIA = transient ischemic attack.

CHA_2DS_2-VA	Meaning of abbreviation	Points
C	**C**hronic heart failure	1
H	**H**ypertension	1
A	**A**ge 75 years or above	2
D	**D**iabetes	1
S	**S**troke / TIA / thromboembolism (prior)	2
V	**V**ascular disease	1
A	**A**ge 65-74 years	1
Maximum score		8

The CHA_2DS_2-VA score only takes a small portion –but the most relevant– of stroke risk factors into account, because it has to balance precision against practicality in clinical settings. Other risk factors for cardioembolic stroke include for example malignancies, chronic kidney disease, and smoking [27]. In certain cardiac diseases (e.g., hypertrophic cardiomyopathy or amyloidosis), anticoagulation is recommended irrespective of the CHA_2DS_2-VA score. It is important to note that non-paroxysmal (persistent and permanent) AF is associated with a higher risk of stroke than paroxysmal AF [12].

The two main groups of oral anticoagulants are vitamin K antagonists (VKAs: warfarin, acenocoumarol) and non-VKA oral anticoagulants (NOACs: dabigatran, rivaroxaban, apixaban, edoxaban). VKA treatment reduces the risk of stroke by 64% and mortality by 26% compared with placebo [47]. At present, VKAs are the only anticoagulant treatment option with proven safety in AF patients with rheumatic mitral valve disease or with mechanical prosthetic valves [27]. The use of VKAs is constrained by the narrow therapeutic range, which requires frequent INR (international normalized ratio, patient prothrombin time divided by control prothrombin time) monitoring and dose adjustment

on this basis [48]. NOACs have demonstrated significant benefits compared to VKAs, showing a 19% reduction in the risk of stroke and systemic thromboembolism, a 51% reduction in haemorrhagic stroke risk, and the use of NOACs was associated with a 10% improvement in all-cause mortality in a meta-analysis of pivotal randomized trials [49]. In terms of safety endpoints, there was a non-significant 14% reduction in the risk of major bleeding, a significant 52% reduction in intracranial bleeding, and a 25% increase in gastrointestinal bleeding with NOACs compared with warfarin [49]. NOACs are therefore the most used drugs today for anticoagulation in AF.

Percutaneous or stand-alone surgical closure of the left atrial appendage (LAA) may be considered in patients with contraindications to anticoagulation [1]. Randomized controlled trials (RCTs) comparing the Watchman occluder device with VKAs have found LAA occlusion to be non-inferior in AF patients at moderate risk of stroke who are also at moderate risk of bleeding [50]. However, in the NOAC era, further evidence is needed about the comparative efficacy and safety of percutaneous LAA occlusion against long-term anticoagulation with NOACs. The OPTION trial, which evaluated LAA occlusion compared to NOACs in patients undergoing atrial fibrillation ablation, demonstrated non-inferiority in terms of a composite outcome of all-cause mortality, stroke, or systemic embolism, and showed the superiority of LAA closure in terms of non-procedure-related bleeding [51].

1.1.7.3. Rate-control

Rate control is an essential part of AF management and can effectively reduce AF-associated symptoms. For this reason, it is the basic therapy of choice for all AF patients, the first-line treatment of choice for patients with asymptomatic or mild symptoms, and the remaining option for patients with permanent AF if rhythm control fails [27]. The RACE II and AFFIRM RCTs in permanent AF patients found no difference in the incidence of clinical events between strict (target heart rate <80/min at rest and <110/min during moderate exercise) and more permissive (target heart rate <110/min) frequency control [52,53]. For this reason, permissive rate control is an acceptable initial approach, regardless of heart failure status (apart from tachycardia-induced cardiomyopathy), unless symptoms require tighter rate control.

The first-line agents used for frequency control are beta-blockers (metoprolol, bisoprolol, atenolol, esmolol, nebivolol, carvediol), of which non-dihydropyridine calcium channel blockers (verapamil, diltiazem) may be substitutes. The use of digitalis (digoxin, digitoxin) can be considered in heart failure patients with reduced ejection fraction, but several retrospective studies have shown their mortality-increasing effect in AF patients [54,55].

In case of progression to permanent AF, the non-pharmacological rate control strategy is AV node ablation and pacemaker implantation. This option has a similar favourable mortality rate [56], and was shown to not reduce left ventricular ejection function (LVEF) [57]. In selected patients, the procedure may even improve LVEF [58]; while in other subgroups, conduction system pacing following AV-node ablation might become a frequently used method in the following years [59]. In patients with severe symptoms and persistent AF who have been hospitalised at least once for HF, AV ablation in combination with cardiac resynchronisation pacemaker therapy (CRT) may be preferred [27].

1.1.7.2. Rhythm-control

The rhythm control strategy is aimed at restoring and/or maintaining sinus rhythm and can be achieved by several methods, including electrical cardioversion (ECV), pharmacological cardioversion, anti-arrhythmic drug (AAD) therapy, or catheter ablation. Maintenance of sinus rhythm is justified based on current evidence to reduce symptoms, to improve ejection fraction and survival in heart failure patients, and to prevent/slow AF progression [60-63]. The benefit of early rhythm control (AAD or ablation) on cardiovascular mortality was demonstrated in the EAST-AFNET 4 study [64].

Acute rhythm control may be required in hemodynamically unstable AF patients. In such cases, synchronised ECV is the option of choice over pharmacological cardioversion [27]. In stable patients, pharmacological cardioversion can be performed (e.g., with flecainide, propafenone, amiodarone), which has the advantage of not requiring sedation. Cardioversion of AF patients with non-severe symptoms is usually performed electively. A known left atrial thrombus is an absolute contraindication of cardioversion. Oral anticoagulation is ideally required before and after cardioversion to reduce the risk of periprocedural thromboembolism, both in the case of ECV and pharmacological

cardioversion [27]. If the patient has not received anticoagulant treatment for at least 3 weeks prior to cardioversion, then exclusion of LAA thrombus by transesophageal echocardiography (TEE) or computed tomography angiography (CTA) is necessary [27]. In all cases, postprocedural anticoagulation of patients is recommended for at least 4 weeks, with continuation thereafter as required based on the CHA_2DS_2-VA score.

Long-term AAD treatment is an option to maintain sinus rhythm and reduce symptoms. However, the efficacy of these agents is moderate, and they have frequent extracardiac side effects. Safety, not efficacy, should be the main consideration for starting and stopping AAD treatment [27]. If treatment with one type of drug is unsuccessful or has intolerable side effects, another drug may still be effective, but a combination of AADs is not recommended [27]. Several AADs have been shown to reduce the incidence of AF episodes. The most commonly used agents are amiodarone, propafenone and sotalol. In structurally intact hearts, propafenone, flecainide, dronedarone, or sotalol can also be used [27]. In the case of CAD, valvular heart disease, or heart failure with preserved ejection fraction (HFpEF), the drugs of choice are amiodarone, dronedarone, and sotalol; while in heart failure with reduced ejection fraction (HFrEF), the single option is amiodarone [27]. Some non-antiarrhythmic drugs may also have antiarrhythmic properties (as upstream therapy). Drugs that slow the process of atrial remodeling may prevent new-onset AF by acting as non-traditional AADs. Such drugs include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, beta-blockers and statins [27].

Catheter ablation is the most effective treatment for both paroxysmal and persistent AF. For symptomatic paroxysmal AF it is recommended as a first-line treatment, while in persistent AF it is recommended after unsuccessful AAD therapy, but can also be considered as first-line treatment according to current guidelines. The cornerstone of ablation is pulmonary vein isolation (PVI), which can achieve freedom from arrhythmia in a large proportion of patients by eliminating pulmonary vein triggers [12]. It is also effective in reducing the time spent in AF (AF burden), reducing the frequency and duration of paroxysms, slowing the progression to persistent AF, and also the severity of AF-associated symptoms following recurrence, and therefore may also improve quality of life in these patients [60,61,65]. It is effective in improving ejection fraction in patients with HFrEF and AF, and has been described as having a mortality benefit in these patients in

several RCTs [62,63]. The techniques, effectiveness, and complications of AF ablation are discussed in detail in the following sections.

1.1.7.4. Treatment of comorbidities

Underlying diseases that are modifiable risk factors for AF (such as hypertension, obesity, diabetes, thyroid disease, OSAS, other heart diseases) contribute to atrial remodeling, thereby increasing the risk of AF and increasing the likelihood of recurrence after catheter ablation. For this reason, management of underlying diseases is a key part of therapy for AF patients. Lifestyle interventions can reduce the body weight of obese patients, which is also beneficial for hypertension and diabetes. Reducing BMI per unit reduces the risk of AF by 3-7% [31,32]. In hypertension, strict blood pressure control is a mandatory part of the management of AF patients, with a recommended target of <130/80 mmHg [27]. Metformin therapy for patients with diabetes has been shown to reduce AF-associated risks [66]. Rhythm control is improved in patients with sleep apnoea by continuous positive airway pressure therapy [67], abstinence of alcoholic patients [68], and correction of thyroid hormone levels even in subclinical hyperthyroidism (thyroid stimulating hormone level < 0.1 mU/L) [69].

1.2. Pulmonary vein isolation (PVI)

1.2.1. Techniques

The catheters for PVI are guided into the heart through the femoral vein and inferior vena cava and then inserted from the right into the left atrium through a transseptal puncture.

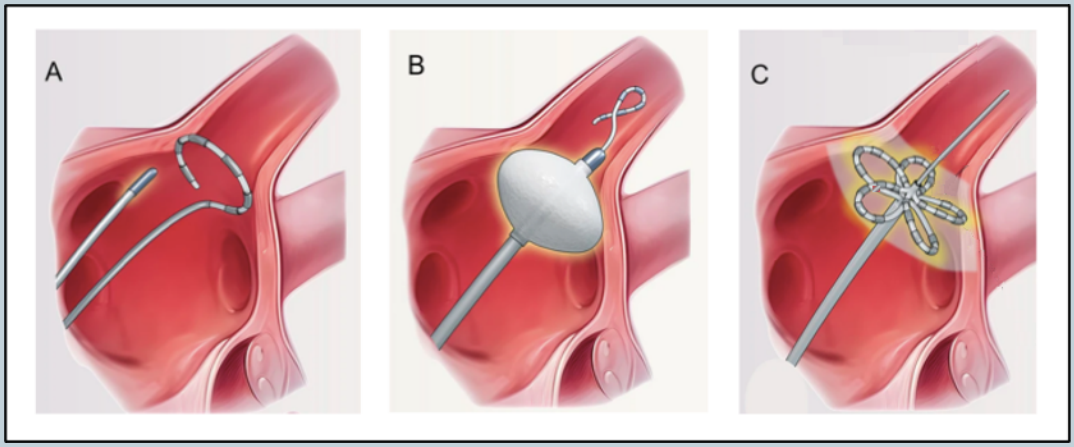

Figure 4. Images presenting ablation catheters using the three main technologies for cardiac ablation: radiofrequency (A), cryoballoon (B), and pulsed-field ablation (C). Reproduced with permission by Zhang et al. [70]

Several ablation technologies are available to create the myocardial lesions required for isolation. Today, the most widely used technologies are radiofrequency ablation (RFA, Figure 4A), cryoballoon ablation (CBA, Figure 4B), and pulsed-field ablation (PFA, Figure 4C) [70].

In addition to these, there are other technologies not used in everyday clinical practice, such as the multielectrode circular RF catheter (PVAC - pulmonary vein ablation catheter), RF balloon catheter, laser, ultrasound or microwave ablation systems. Surgical ablation for AF is also possible but rarely performed, mainly in AF patients requiring cardiac surgery for other indications, such as mitral valve replacement. RF point-by-point catheter ablation of AF requires precise navigation in the left atrium. Therefore, some form of real-time visualization of the anatomy and catheters is a requirement for PVI. This can be achieved with standard fluoroscopy, which is the old method, or with the more recent electroanatomical mapping systems. These systems use multielectrode catheter mapping to record anatomical and electrical information from intracardiac electrograms, allowing accurate anatomical reconstruction of the 3D inner surface of the left atrium, visualization of catheter movement, and electrical function (Figure 5) [71].

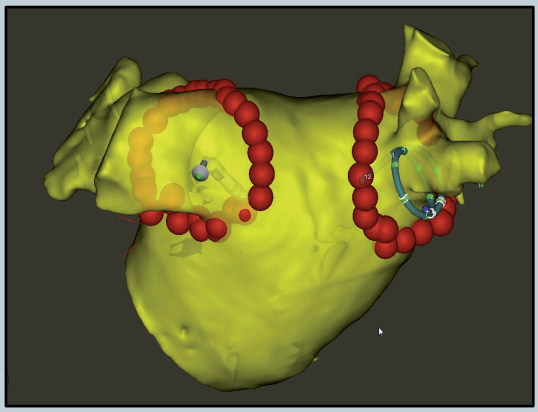

Figure 5. Left atrial CT angiography "merge" image on the mapping system after PVI [71]. CT = computed tomography, PVI = pulmonary vein isolation.

RFA is one of the most commonly used techniques for PVI (Fig. 4A), during which, ablation circles around the ipsilateral PVs are created in a point-by-point fashion (Fig. 6A) [12]. The RF energy is delivered in a unipolar way from the catheter end. The circuit is completed by a dispersive electrode placed on the back of the patient. During ablation, lesions are formed by the heating caused by the radiofrequency current passing through the tissue, resulting in myocardial cell damage and coagulation necrosis resulting in the loss of electrical conduction properties. The technique requires minimal fluoroscopy because catheter navigation is possible using the electroanatomical mapping system. The disadvantage is that it requires extensive training due to the need for precise catheter manipulation.

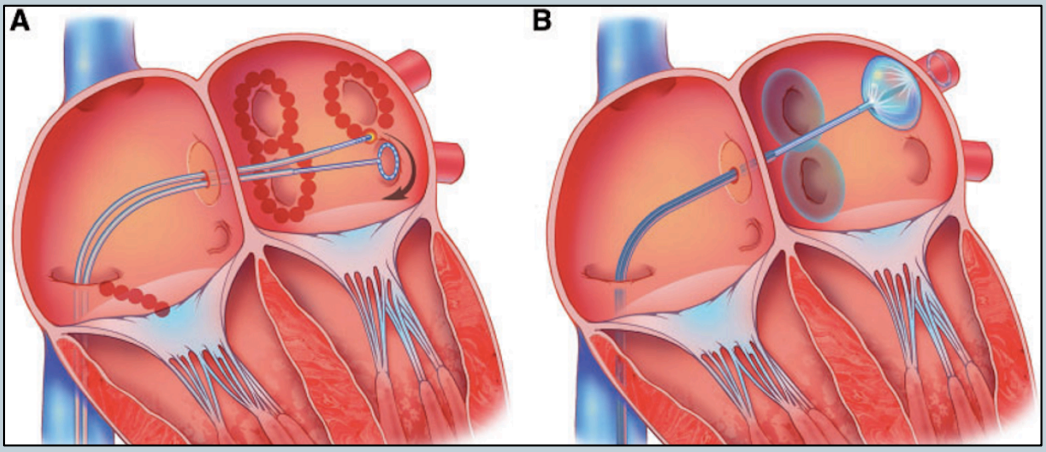

Figure 6. Drawings showing PVI lesion sets with radiofrequency (A) and cryoballoon (B) ablation. Adopted from Calkins et al [12], with permission by Oxford University Press and the ESC.

In the last decade, CBA (Fig. 4B) was the most commonly used alternative tool for PVI. In CBA, circular lesions are generated by a single-shot method (Fig. 6B). First, the balloon catheter is inflated in the PV orifice, and then cryothermal energy causes tissue death by freezing. The occlusion of the pulmonary vein by cryoballoon is monitored by contrast injection and fluoroscopy [72]. For this reason, one disadvantage of the technique is that it requires more fluoroscopy to position the balloon catheter in the PV orifice. One limiting factor of the technique can potentially be variational PV anatomy. The antrum of PVs with a common trunk is often oval in shape, which makes it difficult to fit the balloon properly, which resulted in reduced efficacy of PVI in some reports [73]. The advantage of this technique is that it is simpler, quicker to learn (shorter learning curve) [74], and less operator-dependent, and rapid procedures can be achieved even in less skilled hands[74].

PFA (5C.) is a promising new ablation technology. This form of energy is a series of microsecond-duration, high-amplitude electrical pulses that ablate the myocardium by electroporation of the cell membrane without significant tissue heating [75]. Unlike thermal forms of energy, the efficiency of PFA does not necessarily depend on the force of the catheter-tissue contact, but it does depend on the contact of the electrodes with the target tissue. A unique characteristic of PFA is its tissue selectivity. The myocardium is highly susceptible to irreversible injury by PFA, while smooth muscle tissue, nerve tissue, and blood vessels are relatively resistant, resulting in a better safety profile. Isolation of veins using a multielectrode single-shot device can be achieved very quickly (in seconds), which means that PFA can significantly reduce the duration of the procedure [76]. Data so far show that the technique is non-inferior in efficiency to those used previously [77,78]. Its

current disadvantage is the high costs, limiting its widespread use in electrophysiology laboratories. A further disadvantage is that the procedure often requires general anesthesia, which implies additional staffing requirements.

According to the most recent European survey available (published May 2025), RFA remains the most widely used energy source for AF ablation, with 68% of physicians reporting it as their primary modality [79]. The survey, which representatively included responses from a diverse range of hospital types and geographic regions, found that only 19% of physicians primarily use CBA, while 13% have adopted PFA as their main approach [79]. Notably, the report emphasizes a marked trend toward a transition to PFA from RFA and CBA across clinical practices.

1.2.2. Efficacy

The two main arguments for the effectiveness of AF ablation, supported by a large number of randomized trials, are that it significantly improves the quality of life of AF patients (to a greater extent than AAD treatment) [60,61]; and that it significantly improves ejection fraction and survival in HFrEF patients [62,63]. Due to the improvements seen in quality of life, ablation is justified mainly in cases of symptomatic AF [27]. A meta-analysis found that the left ventricular ejection fraction (LVEF) of HFrEF patients improved by 11% after ablation [80], and the CASTLE-AF and AATAC trials have shown that the intervention has a mortality benefit over AAD treatment in heart failure patients [62,63]. These findings suggest that ablation is benefitial in all patients with atrial fibrillation who are also diagnosed with HFrEF. RCTs in patients without heart failure have not yet demonstrated a benefit in terms of mortality or stroke. The largest RCT to date that has examined this question was CABANA, which found that ablation did not significantly reduce the composite endpoint of all cause death, stroke, and major bleeding compared with AAD treatment [81]. However, the outcome of the study was affected by lower than expected event rates and treatment cross-overs, which should be taken into account when evaluating the results of the study. Several large retrospective studies and meta-analyses of these studies have shown that catheter ablation compared with AADs is effective in reducing the risk of stroke [82,83], dementia [84,85], and mortality [83]. However, even despite careful propensity-score matching, these results cannot be taken as unquestionable hard evidence. The argument that a longer time spent in AF (longer-lasting paroxysms and

persistent AF) is associated with higher morbidity and mortality, also suggests that ablation may be beneficial not only for the treatment of symptoms, but also of AF-related morbidity and mortality. Since mortality and stroke are relatively rare endpoints in patients with preserved LVEF, addressing this question scientifically would require large randomized clinical trials with adequate sample sizes and long-term follow-up. However, such trials would face substantial feasibility and ethical challenges, as clinical equipoise no longer exists for withholding a treatment that has demonstrated significant benefits across multiple other outcomes.

In terms of sinus rhythm maintenance, AF ablation is clearly more effective than AAD treatment as a first-line therapy [86,87]. 12-month arrhythmia-free rates after RF PVI are 59-89%, 54-85% for CBA and 5-40% for AAD treatment [12]. The FIRE AND ICE trial randomizing 762 patients was the largest study demonstrating that the efficacy of CBA is non-inferior to RFA [88]. The long-term clinical efficacy of catheter ablation of AF remains limited by the insufficient durability of PVI. Despite the fact that acute PVI can be achieved in almost all cases, recurrence of atrial arrhythmias is common after AF ablation. Recurrence is usually due to reconnection of PVs, either as a consequence of ineffective lesion formation during ablation or inadequate continuity of the ablation line [72]. This is probably the reason why several studies have shown a correlation of first-pass isolation (FPI) with long-term success in RFA [89,90].

Among the factors limiting the efficacy of the intervention, comorbidities including hypertension, obesity and OSAS play a major role [12]. In addition, large LA size, MR-detected LA fibrosis, and age also negatively affect the efficacy. Furthermore, an important consideration is the duration of AF, as persistent and especially long-standing persistent AF have a significantly higher risk of recurrence. Therefore, diagnosis-to-ablation time might be an important factor to consider, and AF patients accepting catheter ablation treatment might benefit from undergoing the procedure as early as possible, even as first-line treatment [27]. Finally, the duration of ablation procedures is also an important factor in the effectiveness of AF management at the population level. The anticipated rise in atrial fibrillation prevalence underscores the importance of ensuring that the most effective therapies are accessible to as many patients as possible. This highlights the need for shorter procedure durations, which enable the most number of patients to receive treatment in a given unit of time.

1.2.3. Complications

PVI procedures are associated with a non-negligible risk of complications. The types of complications and their incidence are summarized in Table 2. Potential vascular complications resulting from femoral vein puncture are inguinal haematoma, femoral artery pseudoaneurysm, and arteriovenous fistula [12]. Retroperitoneal bleeding is extremely rare but may also occur as sheaths are guided up the inferior vena cava [12]. The overall incidence of major vascular complications is 0.2-1.5% [91,92].

Table 2. Complications of PVI procedures in the case of RFA, CBA, and PFA. CBA = cryoballoon ablation; RFA = radiofrequency ablation; SCE = silent cerebralis embolism; TIA = transient ischemic attack; PFA = pulsed field ablation, PV = pulmonary vein.

Complications	RFA	CBA	PFA
Vascular	0.2-1.5%		
Cardiac tamponade	1.3–2.4%	0.3–1.5%	0.97%
Atrio-esophageal fistula	0.03–0.04%		0%
Any esophageal damage	18%		0%
Phrenic nerve palsy (transient / permanent)	0.17–0.48%	3.5–11.2%	0.46%
PV stenosis	0–40%		0%
Stroke / TIA	0.5–0.9%		0.4%
SCE	5–16%	4–9%	3%
Coronary artery spasm	0%	0%	0.14%
Hemolysis	0%	0%	0.03%

A serious complication of the procedure is atrial wall perforation, which can result in pericardial tamponade and consequent cardiogenic shock. One cause may be incorrect transseptal puncture; which, if too posteriorly directed, may allow the needle to enter the pericardium directly from the right atrium; or it may puncture the left atrial wall after the needle has passed through the septum. It may also be caused by direct mechanical trauma during catheter manipulation or excessive thermal effect during RF or CB ablation. The incidence in RFA is 1.3-2.4% [88,93], with CBA at 0.3-1.5% [88,94] and PFA at 0.97% [95]. Periprocedural anticoagulation increases the risk of severe bleeding. The condition can be managed with pericardiocentesis, circulatory support and the suspension of the effect of heparin with protamine. The most dangerous complication is atrioesophageal fistula, a very rare form of perforation where the esophagus adjacent to the atrial wall is damaged and a communication is created between the atrium and the lumen of the esophagus. It

has been described in both RF and CB ablation, with an incidence of 0.03-0.04%, but an extremely high mortality rate of 83% [96,97].

Damage to the oesophagus may be caused by thermal effects during ablation, or may occur due to the use of transesophageal ultrasound or an esophageal temperature probe during the procedure [12]. Endoscopically, mucosal erythema, or in more severe cases erosion, ulceration can be seen. Erythema occurs in 29% and ulcerative complications in 18% of cases of conventional RFA [98]. No detectable oesophageal injury was found with PFA [77]. Symptoms may include dysphagia, regurgitation, or hoarseness, but minor injuries are often asymptomatic. In the long term, oesophageal stricture and dysmotility may develop.

Phrenic nerve palsy may also develop as a complication of the procedure. Mostly the right nerve is injured, especially during ablation of the right upper PV [12]. Incidence with RFA is 0.17-0.48%, but much higher with cryoablation, transient paresis occurs in 3.5-11.2%, but in 0.3% paralysis can be permanent with CBA [96]. The reason for the higher incidence is that the balloon stretches the pulmonary vein and presses it against the phrenic nerve when inflated. PFA does not cause permanent damage to the nerve tissue, but temporary n. phrenicus stunning may occur [99]. Possible symptoms include dyspnoea, tachypnoea, cough, hiccups and chest pain, with physical examination revealing a bilaterally elevated diaphragm, and lung base atelectasia.

A late complication is pulmonary vein stenosis, which may develop due to thermal injury to the intima, media and adventitia layers of the blood vessels and consequent scarring. Similar incidences have been described for CB and RF ablation, with a wide range of incidence from 0-40% [12]. A wider circular RFA around the pulmonary veins reduces the incidence. No lumen reduction occurs with PFA [100]. Symptoms may appear weeks or months after the procedure, and may include difficulty breathing, hemoptysis, coughing, chest pain, pneumonia. The complication is often asymptomatic. PV stenosis is significant at 70% lumen narrowing and can be treated by balloon dilatation or stent implantation [12].

Two rare complications specific to PFA are coronary artery spasm (0.14%) and hemolysis (0.03%) [101], which do not occur with thermal ablation modalities.

Thromboembolic events are one of the most serious complications of PVI. Stroke or transient ischaemic attack (TIA) occurs at an overall rate of 0.4-0.94% [95,102]. They typically occur in the first few days after the procedure and the high-risk period lasts until the end of the second week after the procedure [103]. Silent (asymptomatic) cerebral embolism (SCE), which can be detected by diffusion-weighted brain magnetic resonance imaging (bMRI) [104], is much more frequent [12,102,105]. There are several possible causes of embolism as a result of the procedure: 1) tissue debris from transseptal puncture, 2) coagulum from RF ablation that detaches from the catheter tip, 3) LA thrombus not detected by pre-procedural imaging, 4) thrombus formation on the sheath, 5) air embolism caused by air entering the sheath, 6) tissue debris resulting from steam-pop, 7) steam bubbles generated during ablation, 8) thrombus formation on ablated tissue surface (damaged endothelium acts as thrombogenic surface) [102]. The prevalence of SCE is a good indicator of the ablation technology in terms of embolic risk. For point-by-point RFA, the SCE rates described are 6-16%, while for CBA they are 4-9% [106-114]. For PFA, the first studies found an incidence of around 3% [115]. This low incidence is not a surprising result considering that lesion formation is non-thermal, tissue selective and does not damage the endocardium. Nevertheless, a small number of thrombi may form on the surface of the sheath, which is significantly larger with PFA than with RFA, and for the same reason the risk of air embolism is higher. Previous data indicate that SCEs may have meaningful long-term effects on brain function, potentially contributing to a higher risk of developing dementia [116]. Moreover, recent findings suggest that even in the short term, silent brain infarcts may lead to cognitive decline comparable to that caused by symptomatic strokes [117].

In order to prevent thromboembolic complications, a thorough preprocedural imaging examination is necessary, attention should be paid to sheath management during the procedure, and catheter exchange should be avoided if possible. In addition, the guideline recommended anticoagulation protocol should be followed [12]. One month prior to the procedure oral anticoagulation is recommended also for patients with a CHA_2DS_2-VA score of 0. On the day of ablation, some recommendations suggest uninterrupted oral anticoagulation, while others suggest skipping a single dose. The procedure is performed with intravenous Na-heparin, which should be dosed according to the activated clotting time (ACT). The recommended minimum target ACT is 300 seconds. After ablation, oral

anticoagulation should be continued for at least 2 months, after which its discontinuation depends on the patient's risk factors (i.e. CHA_2DS_2-VA score).

1.2.4. Technical aspects of RF ablation

Over the past decade, the development of contact force (CF) sensing technology has significantly improved the ability to monitor catheter tip–tissue contact, leading to the creation of more effective RF lesions. The EFFICAS I and II trials highlighted the critical role of maintaining appropriate CF during ablation procedures [118,119]. CF measurement has become a fundamental part of lesion quality indices, such as the Ablation Index (AI) used in the CARTO system, which integrates CF, power, and ablation duration into a weighted formula. AI plays a central role in the CLOSE protocol, which was developed based on findings from El Haddad et al., who analyzed characteristics of the weakest points in PVI lesion sets [120]. The CLOSE protocol is an RFA strategy aimed at achieving complete pulmonary vein encirclement through continuous and optimized lesion formation. It incorporates a target inter-lesion distance (ILD) of approximately 6 mm and applies an AI of at least 400 at the posterior wall and at least 550 at the anterior wall. Numerous subsequent studies have confirmed the protocol's clinical efficacy, demonstrating high first-pass isolation rates (82–98%) and 12-month atrial tachyarrhythmia freedom rates between 78–91% [121,122]. Furthermore, two comparative studies have reported superior clinical outcomes for PVI performed with the CLOSE approach compared to conventional methods (94% vs. 84% and 79% vs. 64%) [123,124]. Collectively, these findings suggest that the CLOSE protocol currently represents the most effective RF ablation strategy for treating atrial fibrillation. The shortcoming of using RF power to predict lesion sizes is that the actual local current, charge density and tissue heating is influenced by many factors. One biophysical parameter that directly impacts RF current is the generator impedance, which incorporates the resistance of all tissues between the catheter tip and the dispersive patch, including subcutaneous fat. Therefore it is influenced by body composition and dispersive electrode placement, and shows variability among patients. Previous experimental studies showed that it is an important factor determining the actual lesion size when RF power is delivered at a fixed level [125-127]. As generator impedance values slightly drop during RF delivery, ablation systems measure the starting value, called baseline generator impedance (BGI).

The goal of PVI is to achieve a permanent exit block, i.e. to prevent the PV from conducting impulses to the left atrium. Demonstration of an entrance block (no conduction from the atrium to the vein) is usually considered sufficient, as unidirectional blocks are rare. Still, the most reliable endpoint of PVI is the verification of both entrance and exit blocks. Entrance block can be verified by observing the electrogram leads of the catheter inserted into the PV, while exit block requires stimulation of the PVs, usually with the ablation catheter. In the case of RFA, we define first-pass isolation (FPI) as the achievement of bidirectional block after finishing the initial point-by-point circle without touch-up applications (at the time of the first evaluation of PVI blocks). If this is not achieved, additional ablation points (touch-up applications) are required to fill isolation gaps (holes in the isolation chain).

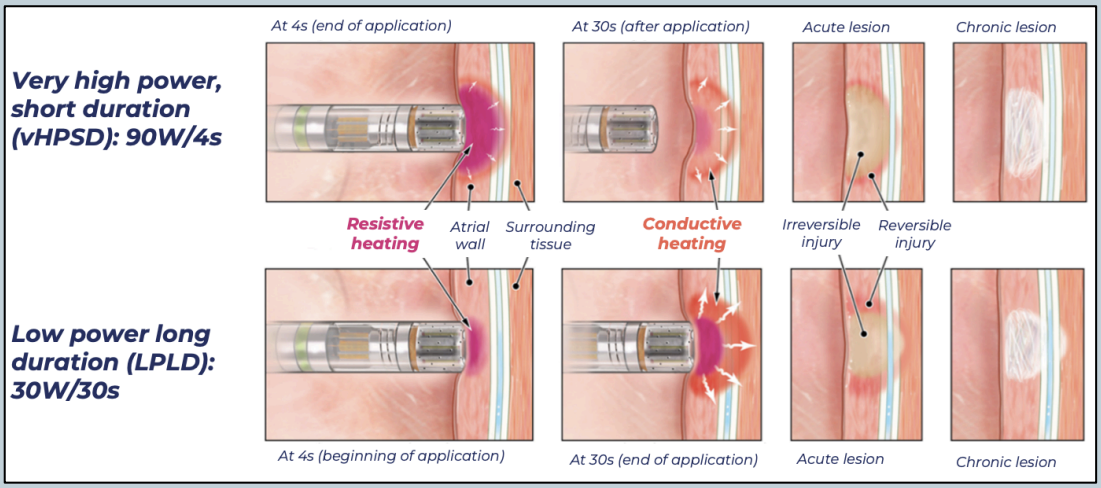

Figure 7. Thermal effects and lesion formation during vHPSD and LPLD ablation. The resistive heating zone is more extensive but conductive heating is less pronounced in vHPSD. The size of the lesion formed is smaller than in LPLD ablation. LPLD = low power long duration; vHPSD = very high power short duration. Reproduced with permission and modified after Barkagan et al. [128]

RF technology itself has evolved significantly over the last decade. In the past, ablation was performed with 25-35W of power at each point for about 20-30 seconds. However, thanks to technical innovations, PVI has been performed worldwide using increasingly higher power over the years. With a higher power output, shorter durations are sufficient to create each lesion. In the case of 50 W (HPSD - high power short-duration) ablation, the RF application at each point lasts only 10-15 seconds. The previous low power setting was subsequently named LPLD (low power long duration) ablation. Recently, HPSD was followed by the development of the latest RF technology, vHPSD (very high power, short

duration) ablation by the QDOT Micro catheter, which delivers 90W of power at each point for only 4 seconds. This is a huge leap from previous lower energy inputs. The main advantage of the 90W ablation is that procede times can be significantly reduced due the extremely fast applications [128-131].

Figure 7. shows the difference between high and low power settings in terms of thermal effects [132]. During ablation, tissues are heated by the radiofrequency current through their resistance, and over time heat is transferred from this resistive heating zone to surrounding areas, creating a conductive heating zone. Compared to low power, resistive heating is much more extensive in vHPSD ablation, but conductive heating is minimal. Accordingly, there is less reversible myocardial injury and more consistent lesion formation [132]. It has also been shown that high-power lesions are shallower, which is ideal for ablation of the thin wall of the left atrium [133]. Also, the steam-pop phenomenon is less common in vHPSD ablation [134].

The QDOT Micro is a CF sensing, RF ablation catheter with 6 thermal sensors, 3 of which are located only 25um from the catheter tip (Figure 8) [135], allowing very accurate local temperature measurement. A 2-second cooling period begins before high-power RF delivery at an irrigation rate of 8 ml/min. To enable safe RF applications with such a high power, an algorithm has been developed to determine the temperature of the catheter tip-tissue interface, allowing real-time temperature feedback for power control. The vHPSD algorithm modulates energy based on the hottest temperature measured by the thermal sensors, with a target temperature of 55°C (Figure 9) [136]. When the target temperature is not reached (Figure 9A), a continuous power output of 90W is applied for 4 seconds continuously. However, when the target temperature is reached (Figure 9B), the power is reduced by the system to prevent tissue overheating. After each RF application, irrigation continues for a further 4 seconds at a rate of 8 ml/min [135]. One of the goals of vHPSD technology is to improve the safety profile of RF ablation by creating a tightly controlled ablation environment with fast temperature feedback, power modulation and continuous irrigation.

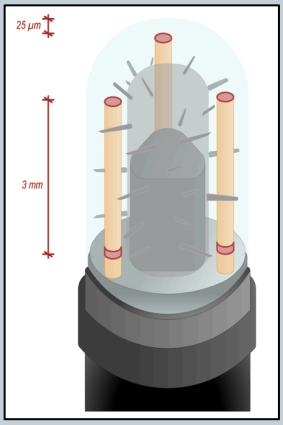

Figure 8. QDOT Micro catheter with 6 thermal sensors, 3 of which are located only 25um from the catheter tip.

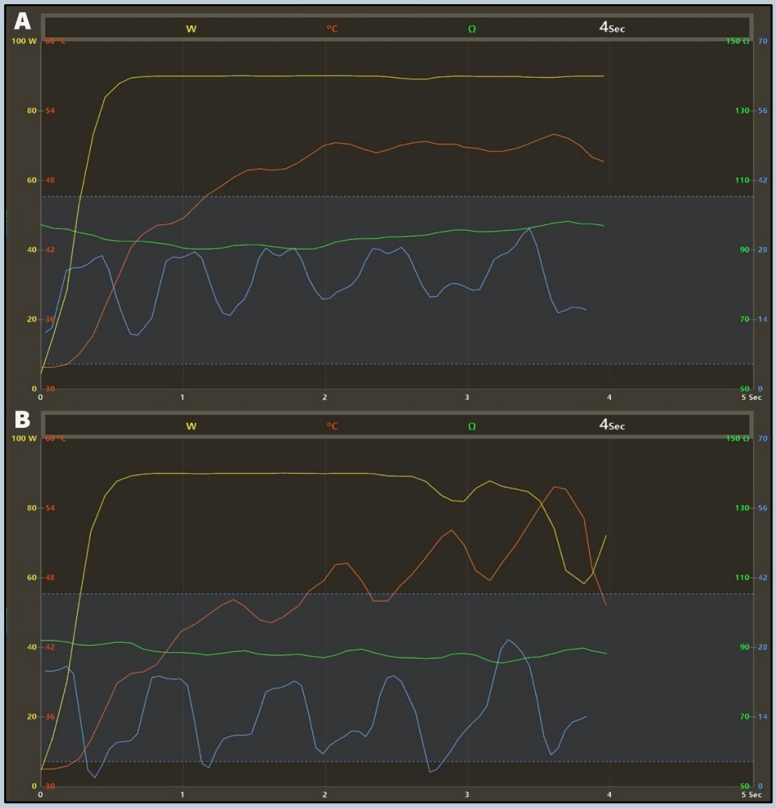

Figure 9. Graph showing the ablation parameters during 4-second RF applications in QMODE+ setting (90W/4sec, temperature-controlled mode). Yellow: power (W); red: temperature (°C); blue: CF (g); green: impedance (Ω). (A) Target temperature of 55 °C is not reached, constant power output of 90 W is applied until 4 seconds have elapsed. (B) Target temperature is reached, power is regulated down to prevent overheating.

1.3. Research rationale

1.3.1. Predictors of PV reconnections

Factors associated with the recurrence of AF after PVI are well known; however, there is a gap in the evidence regarding technical predictors for chronic PV reconnection (PVR) [123]. PVRs represent the primary failure of PVI procedures and are responsible for the majority of AF recurrences and repeated ablation procedures, thus worsening patient outcomes and wasting healthcare resources. Despite the growing use of the CLOSE protocol in PVI, data is scarce on how adherence to this approach impacts the long-term durability of PVI when evaluated through repeated electrophysiological studies. Previous research has shown that achieving FPI is linked to better ablation success rates [128]. Additionally, some studies suggest that the BGI at individual ablation points may influence the efficacy of RF ablation [125-127]. However, their role in the durability of PVI has not yet been explored. Therefore, we investigated key predictors of long-term PVR following PVI procedures to support ongoing efforts to improve the efficacy of AF ablation.

1.3.2. Cerebral safety of vHPSD ablation

The 90W power setting has a number of advantages, but these need to be coupled with efficacy and at least non-inferior safety to be considered a better method than lower power settings. The efficacy and esophageal safety of 90W ablation have been previously demonstrated in several studies [128,130,137,138], however, concerns remained regarding its embolic risk. Two initial studies of vHPSD ablation found an unexpectedly high SCE incidence of 24-26% [138,139], while the SCE rates described for LPLD ablation are much lower (6-16%) [106-114]. The current expert consensus document on AF ablation also implies a higher risk for embolic events with high power settings based on low sample-size studies [140]. A larger-scale investigation on this issue was warranted, and the Electrophysiology Laboratory at the Cardiovascular Center of Semmelweis University as one of the highest volume centers for 90W ablation in the world was ideally positioned to conduct such an investigation. Given that with vHPSD ablation, the left atrial dwell time is shorter, the lesion formed is smaller, and steam-pop is less frequent, we had not expected such a high SCE incidence compared to LPLD ablation [138,139]. We hypothesized that vHPSD PVI with short left atrial time and adequate intraprocedural anticoagulation would be associated with a low incidence of symptomatic and MRI-detected asymptomatic cerebral events.

1.3.3. Ablation parameters of vHPSD ablation

The ideal AI and ILD thresholds are well-established for low-power ablation [121-123]. In contrast, AI is not available for vHPSD ablation, and there is limited evidence regarding the factors that influence both the immediate and long-term success of PVI performed with 90 W. Prior data indicate that vHPSD creates smaller lesions in terms of both width and depth when compared to traditional lower-power settings [133], suggesting a need to reassess ILD targets for the high power approach. While BGI and RF current have been proposed to affect lesion size, as lower impedance may lead to higher current and therefore larger lesions [125-127], their potential influence on the continuity of ablation lines has not yet been explored. Data from a previous randomized remapping study was available to be used for a secondary analysis of ablation parameters of vHPSD ablation and their association with gaps in ablation circles, which had not been studied before.

2. Objectives

2.1. Predictors of PV reconnections

We aimed at identifying predictors of PV reconnections, including adherence to the CLOSE protocol, first-pass isolation, and baseline generator impedance.

2.2. Cerebral safety of vHPSD ablation

Our objective was to evaluate the incidence of procedural complications of vHPSD atrial fibrillation ablation focusing on cerebral safety, and to evaluate predictors of silent cerebral embolisms.

2.3. Ablation parameters of vHPSD ablation

The objective of our secondary analysis was to evaluate the association of ablation parameters of vHPSD ablation with gaps in the ablation circles, and to determine optimal interlesion-distance targets.

3. Methods

3.1. Predictors of PV reconnections

This retrospective, observational study enrolled patients who underwent their first PVI using the CARTO system between January 2018 and November 2023, and also had a repeat procedure within the same timeframe. Patient data were collected from an institutional ablation registry. Individuals were excluded if their initial ablation was performed with the ENSITE or Rhythmia mapping systems, 90W RF ablation, or used cryoablation, as these methods are incompatible with the CLOSE protocol. In addition, patients were excluded if their repeat procedure was required by a mandatory remap study, or lacked data on PVRs. The detailed inclusion and exclusion criteria are illustrated in the study flowchart (Figure 10) [141]. All participants gave written informed consent for the ablation procedures as well as for the use of their data in this analysis. The study protocol received ethical approval from the Regional and Institutional Committee of Science and Research Ethics at Semmelweis University (SE RKEB 268/2023, 18 December 2023).

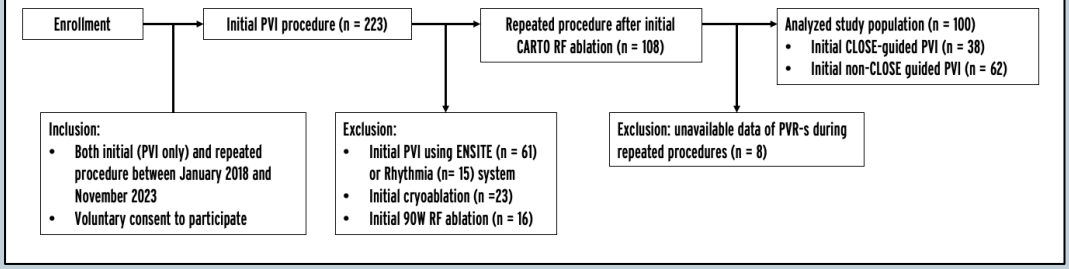

Figure 10. Study flowchart. PVI = pulmonary vein isolation, PVR = pulmonary vein reconnection, RF = radiofrequency.

3.1.1. Study endpoint and procedural parameters

The primary outcome of the study was the presence of pulmonary vein reconnection observed during the repeat ablation procedure. The following procedural variables were collected: BGI of ablation points, achievement of first-pass isolation, PV pair perimeter (as measured in the CARTO system), power settings, total number of RF applications, procedure duration, left atrial dwell time, fluoroscopy duration, dose-area product, time to AF recurrence, and time from initial PVI to the repeat procedure.

3.1.2. Initial PVI procedure

Catheter ablation was performed under conscious sedation with midazolam, propofol, and fentanyl. Femoral vein puncture was followed by fluoroscopy and pressure measurement-guided double transseptal puncture. After left atrial access, an anatomical map of the left atrium was created using an electroanatomical mapping system (CARTO 3, Biosense Webster Inc., Diamond Bar, CA, USA) along with a multipolar mapping catheter (Lasso, Biosense Webster Inc., Diamond Bar, CA, USA). Point-by-point PVI was carried out using a steerable sheath and a CF sensing ablation catheter (either SmartTouch or QDOT Micro, Biosense Webster Inc., Diamond Bar, CA, USA). Power settings and adherence to the CLOSE protocol were determined at the operator's discretion. Energy delivery followed either an LPLD approach with 30–35 W settings or a HPSD strategy at 40–50 W, with consistent power settings maintained throughout each procedure. All operators performed both CLOSE-guided and non-CLOSE PVI procedures. For CLOSE-guided ablations, the objective was to create wide, contiguous circumferential lesions around the ipsilateral pulmonary veins, with ILDs ≤5 mm and AI target of ≥400 on the posterior wall and ≥500 on the anterior wall. In non-CLOSE procedures, there was no strict protocol aside from achieving complete PVI by the end of the procedure. Adherence to the CLOSE protocol was assessed by reviewing CARTO maps, and CLOSE compliance was confirmed when a continuous lesion set with the specified ILD and AI thresholds was achieved. After completing the initial encirclement, the achievement of FPI was evaluated using the multipolar mapping catheter. If isolation was incomplete, additional "touch-up" ablations were performed until full PVI was established. A representative left atrial anatomical map following CLOSE and non-CLOSE PVI is displayed in Figure 11 [141]. No ablation targeting additional arrhythmia substrates was performed.

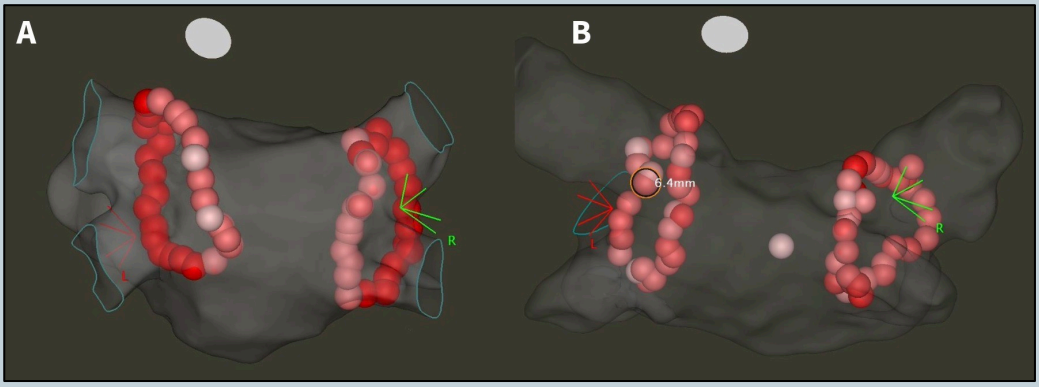

Figure 11. Left atrial map after CLOSE-guided PVI (A) and PVI without adherence to the CLOSE protocol (B). PVI = pulmonary vein isolation [140].

3.1.3. Repeat ablation procedure

After the initial procedure, patients were followed according to standard clinical practice, with 12-lead electrocardiograms and 24-hour Holter monitoring conducted at 3, 6, and 12 months, as well as in response to any arrhythmia-related symptoms. All participants included in this analysis experienced symptomatic AF recurrence and subsequently underwent a repeat ablation procedure. Repeat procedures were performed using either a decapolar Lasso or a PentaRay catheter (Biosense Webster Inc., Diamond Bar, CA, USA) alongside a contact force-sensing ablation catheter. PVR was identified when near-field electrical signals were detected within the pulmonary veins using the multipolar mapping catheter. When PVR was observed, the affected veins were re-isolated. In cases where all pulmonary veins remained isolated at the start of the repeat procedure, ablation was directed at non-PV triggers and, for patients with persistent AF, additional substrate modification was performed.

3.2. Cerebral safety of vHPSD ablation

In this prospective, observational, single-center study, we included 328 patients undergoing their first PVI procedure with the QDOT Micro catheter (Biosense Webster, Inc., Irvine, CA, USA) using the QMODE+ setup (90 W for 4 seconds). A subgroup of participants underwent brain MRI within 24 hours after the procedure to screen for potential SCE. All patients gave written informed consent for the ablation, post-procedure bMRI, data collection, and analysis. The study protocol was approved by the Hungarian National Public Health and Medical Officer Service (approval number 38843-5/2022/EÜIG).

3.2.1. Study endpoints

The primary outcomes of this study were procedure-related cerebral complications: stroke, TIA, and SCE. Secondary outcomes included total procedure duration, left atrial dwell time, FPI and 6-month freedom from AF. In the subgroup undergoing bMRI, additional procedural characteristics were recorded, including the number of RF applications, total RF time, volume of irrigation fluid used, use of ECV, and ACT. Furthermore, in the bMRI subgroup, detailed parameters for each RF application were extracted and analyzed, including delivered power, catheter tip temperature, CF, and BGI. A loss of catheter tissure contact during RF application was defined as any instance where the CF dropped to 0 g during ablation.

3.2.2. Preablation protocol

To rule out thrombus formation in the left atrial appendage (LAA), all patients underwent CTA within 48 hours prior to the procedure. In cases where CTA results were inconclusive for LAA thrombus, transoesophageal echocardiography was performed for further evaluation. All patients were treated with NOACs, with a single dose withheld on the morning of the procedure and anticoagulation therapy resumed 4 hours following the intervention.

3.2.3. Ablation procedures

After the first transseptal puncture, heparin was administered at a dose according to body weight. Further dosing was performed according to ACT measurements every 20 minutes; the target ACT was at least 300 seconds. An anatomical left atrial map was obtained using an electroanatomical mapping system (CARTO 3, Biosense Webster Inc, Diamond Bar, CA) with a multipolar mapping catheter (Lasso or PentaRay, Biosense Webster Inc, Diamond Bar, CA). Point-by-point PVI was performed with a steerable sheath and QDOT Micro catheter (Biosense Webster Inc, Diamond Bar, CA) using an nGEN generator in the QMODE+ setting (90W/4second, temperature-controlled mode) during the entire procedure. The neutral electrode was placed on the patient's back. The target ILD was 5 mm for posterior and <5 mm for anterior applications, as previous studies have suggested the need to reduce ILDs for vHPSD [128]. No further substrate ablation beyond the PVI was performed.

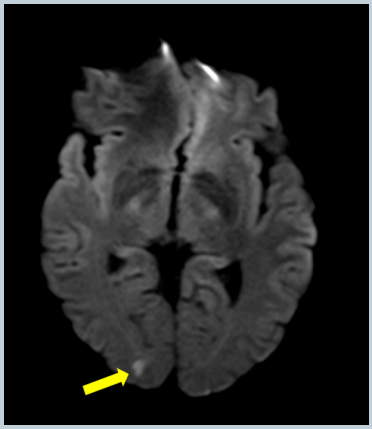

Figure 12. Increased signal intensity (arrow) on the DWI MR sequence indicating an SCE finding. DWI = diffusion-weighted imaging, MR = magnetic resonance imaging, SCE = silent cerebral embolism [132].

3.2.4. Post-ablation bMRI

A subgroup of consecutive patients, without contraindications to MRI and who underwent their procedures between July 2022 and April 2023, received bMRI within 24 hours after PVI. Imaging was conducted on a 1.5 T MR scanner (Magnetom Aera, Siemens) equipped with a 20-channel head coil. The MRI protocol followed the method previously described [15]. Diffusion-weighted imaging was performed using a single-shot spin echo, echo-planar imaging sequence with three

diffusion encoding directions at a b-value of 1000 s/mm² and one acquisition at b = 0, with a repetition time of 9000 ms and an echo time of 88 ms. Full brain coverage was achieved with contiguous axial slices of 5 mm thickness. SCEs were identified by detecting new ischemic lesions demonstrating restricted diffusion on diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) maps (Figure 12.) [136]. The number, size (measured in three perpendicular dimensions), and anatomical location of all detected lesions were recorded using an AGFA PACS workstation (Impax 6.5.2.657, Agfa HealthCare).

3.3. Ablation parameters of vHPSD ablation

Patients in this study underwent 90 W PVI, and three months after the initial procedure left atrial high-density mapping was performed in all participants to evaluate the long-term durability of PVI, as part of the "HPSD Remap" study (URL: ClinicalTrials.gov; Unique identifier: NCT05459831) [142]. All participants gave written informed consent for the ablation and remap procedures, as well as for data retrieval and analysis. Ethical approval was granted by the Hungarian National Public Health and Medical Officer Service (9119-2/2022/EÜIG).

3.3.1. Initial PVI procedure

Using the QDOT Micro catheter (Biosense Webster Inc., Diamond Bar, CA, USA) in QMODE+ mode (90 W for 4 seconds), RF energy was applied in a point-by-point manner around the ipsilateral PVs. The ablation procedure was conducted through a steerable sheath, either Agilis (Abbott, Chicago, IL, USA) or the Vizigo sheath (Biosense Webster Inc., Diamond Bar, CA, USA). To ensure the non-biased evaluation of FPI, operators were blinded to the real-time PV potential assessment, the mapping catheter was positioned in the contralateral PVs during the encirclement process. After completing the circumferential lesion set, the presence of FPI was evaluated using a multipolar mapping catheter. If electrical isolation had not been achieved, additional RF lesions were administered at the same power settings to ensure complete isolation. Following a 20-minute observation period, the PVs were reassessed for signs of acute PVR. If reconnections were identified, additional ablation was performed to restore isolation. All ablation sites corresponding to first-pass conduction gaps and acute PVR were documented. No further lesions were applied beyond PVI.

3.3.2. Repeat electrophysiology study

A protocol-mandated electrophysiological study was performed in all patients three months after the initial ablation, regardless of the presence or absence of symptoms. During pacing from the distal coronary sinus, high-density voltage and activation maps were acquired using the CARTO mapping system in conjunction with a multipolar catheter (either PentaRay or OctaRay). Chronic PVR was assessed based on these electroanatomical maps, which included at least 2000 mapping points uniformly covering the entire left atrium. Reconnection sites were precisely annotated and compared to the original ablation maps to localize the initial lesion sites associated with reconnection (Figure 13.) [142].

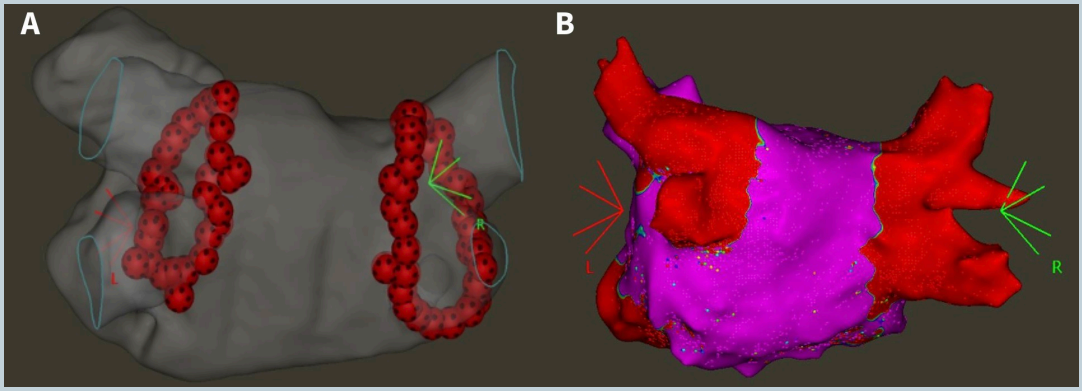

Figure 13. Left atrial map after 90W PVI (A) and high-density voltage map created during the remap procedure (B). PVI = pulmonary vein isolation [141].

3.3.3. Data collection

Data from the CARTO system were used to extract ablation parameters from the initial procedures for further analysis. The collected parameters included: application duration (seconds), average power delivered (P_{mean}, W), peak temperature reached (°C), baseline generator impedance (Z_{gen}, Ω), impedance drop (Ω), minimum contact force (g), mean contact force (g), maximum contact force (g), and the inter-lesion distance (ILD, mm) between adjacent ablation points. From these values, additional parameters were calculated: total radiofrequency energy delivered (E_{total}, J), average RF current applied (I_{mean}, A), and total electrical charge delivered (Q_{total}, C), using the following formulas.

$$E_{total} = P_{mean} \times t_{appl}$$

$$I_{mean} = \sqrt{\frac{P_{mean}}{Z_{gen}}}$$

$$Q_{total} = I_{mean} \times t_{appl}$$

Ablation sites corresponding to gaps in the initial lesion set, as well as acute and chronic PVR locations, were specifically identified, and touch-up lesions at these sites were excluded from analysis. Each lesion was also categorized according to its anatomical position around the PV orifice – anterior vs. posterior and right vs. left. Additionally, all lesions were assessed for intermittent loss of catheter-tissue contact (LOC), defined as any point where the contact force dropped to 0 grams.

3.4. Statistics

Continuous variables are reported as either means with standard deviations or medians with interquartile ranges, depending on the distribution. For comparisons between unpaired groups, the Student's t-test was applied to normally distributed data, while the Mann-Whitney U test was used for non-parametric data. Categorical variables are presented as counts and percentages, with comparisons made using Fisher's exact test. Optimal cut-off values were determined through receiver operating characteristic (ROC) analysis, by the d-min method (shortest distance to 0,1 point on the sensitivity / 1–specificity graph). Predictive performance was reported through sensitivity, specificity, and area under curve (AUC) values. Univariable logistic regression was conducted to identify potential predictors, and covariates with p-values <0.1 were included in multivariable logistic regression models. Effect estimates are expressed as odds ratios (OR) with 95% confidence intervals (CI). A two-tailed alpha level of $p<0.05$ was considered statistically significant. Statistical analysis was performed using GraphPad Prism 10 (GraphPad Software Inc., San Diego, CA, USA).

4. Results

4.1. Predictors of PV reconnections

Baseline characteristics of the 100 patients meeting inclusion and exclusion criteria of this study are shown in Table 3. The mean age was 60 ± 12 years, with women representing 36% of the cohort, and 44% of patients with persistent AF. Of these patients, 38 underwent an initial PVI strictly following the CLOSE protocol, while 62 received non-CLOSE PVI. Thirty procedures were carried out with high-power settings (40–50W), and 70 with low-power settings (30–35W). Baseline characteristics did not differ significantly between the CLOSE and non-CLOSE groups.

Table 3. Baseline characteristics of study population. AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; LAD = left atrial diameter, LVEF = left ventricular ejection fraction; PVI = pulmonary vein isolation, rePVI = repeated pulmonary vein isolation, TIA = transient ischemic attack. Continuous variables are reported as mean ± standard deviation, while categorical variables are reported as frequency and percentage.

		All patients (n=100)	CLOSE (n=38)	no CLOSE (n=62)	P-value
Age, years		60 ± 12	60 ± 12	61 ± 12	0.83
Sex, female (%)		36 (36)	16 (42)	20 (32)	0.39
BMI, kg/m²		28.9 ± 5.0	28.5 ± 5.0	29.1 ± 5.2	0.58
Persistent AF, N (%)		44 (44)	17 (45)	27 (44)	> 0.99
Hypertension, N (%)		70 (70)	28 (74)	42 (68)	0.65
Diabetes, N (%)		18 (18)	6 (16)	12 (19)	0.79
CAD, N (%)		16 (16)	5 (13)	11 (18)	0.59
Prior stroke/TIA, N (%)		8 (8)	2 (5)	6 (10)	0.71
LVEF, %	**initial PVI**	56 ± 9	58 ±6	55 ± 11	0.13
	rePVI	54 ± 8	55 ± 5	53 ± 9	0.68
LAD, mm	**initial PVI**	49 ± 7	49 ± 8	49 ± 6	0.79
	rePVI	51 ± 7	51 ± 7	50 ± 7	0.83

Repeat procedures occurred on average 23 ± 16 months after the initial PVI, during which 200 PV pairs (373 PVs in total) were assessed. PVR was detected in 192 of 373 PVs (51.5%). The distribution of PVRs was: left superior PV – 21.9%, left inferior PV – 19.3%, left common trunk – 3.6%, right superior PV – 29.2%, right inferior PV – 27.6%, and right middle PV – 2.6%. In 17 of 100 patients, all PVs remained isolated at the repeat procedure.

Table 4. Baseline procedural and patient characteristics comparing cases with at least one PVR to cases with all PVs isolated. Categorical variables are presented as counts and percentages, while continuous variables are shown as medians with interquartile ranges. Statistically significant differences ($p < 0.05$) are highlighted in bold. AF = atrial fibrillation; BMI = body mass index; FPI = first-pass isolation; OR = odds ratio; PV = pulmonary vein; PVR = pulmonary vein reconnection; ST = SmartTouch.

	All veins isolated (n=17)	At least 1 PVR (n=83)	P-value
CLOSE protocol, n (%)	15 (88)	23 (28)	**< 0.001**
Catheter, n (%) ST QDOT	12 (71) 5 (29)	70 (86) 11 (14)	0.145
Power setting, W	37.5 (30–50)	30 (30–40)	**0.028**
FPI, n (%)	15 (88.2)	21 (40.4)	**0.001**
Mean PV-pair perimeter, cm	12.2 (11.4–12.9)	12.7 (11.4–13.6)	0.258
Baseline generator impedance, Ω	127.6 (115.8–134.1)	136.6 (131.1–144.8)	**0.003**
Time to first recurrence after initial PVI, months	17.8 (6.2–37.3)	15.5 (5.6–27.8)	0.304
Time to repeated procedure, months	23.8 (6.9–44.5)	18.3 (11.2–32.5)	0.438
Age, years	66 (54–75)	62 (52–70)	0.400
Sex, female (%)	6 (35)	47 (56)	0.120
BMI, kg/m²	27.8 ± 5.0	29.1 ± 5.1	0.333
Persistent AF, n (%)	8 (47)	36 (44)	0.795

Patients and procedures with complete PV isolation were compared to those with at least one PVR (Table 4). Key factors associated with durable PV isolation included adherence to the CLOSE protocol (88% vs. 28%, $p < 0.001$), presence of FPI (88.2% vs. 40.4%, $p = 0.001$), use of higher power (37.5W vs. 30W, $p = 0.028$), and lower BGI (127.6 Ω vs. 136.6 Ω, $p = 0.003$). In the case of CLOSE-guided PVI the PVR rate per PV was significantly lower (26.1% vs. 68.3%, OR = 0.16, 95% CI: 0.10–0.26, $p < 0.001$) and the proportion of patients with all PVs isolated was significantly higher (39.5% vs. 3.5%, OR = 18.26, 95% CI: 2.00–4.47, $p < 0.001$).

Comparisons between CLOSE and non-CLOSE procedures revealed differences in fluoroscopy time (4.7 vs. 5.8 minutes, $p = 0.047$), radiation dose (152.6 vs. 232 uGym², $p = 0.033$), number of RF applications (72 vs. 82, $p = 0.020$), and FPI rate (73.7% vs. 25%, $p < 0.001$). Procedure time, left atrial dwell time, and BGI were not significantly different.

Analysis of 6562 ablation points showed significantly higher mean BGI in procedures with PVR (136.6 Ω vs. 127.6 Ω, p = 0.003). ROC analysis (Fig. 14.)[141] identified a BGI of 130 Ω as the optimal threshold for predicting PVR (AUC = 0.74, 95% CI: 0.61–0.87, p = 0.003), with 77.1% sensitivity, 68.8% specificity, 68.75% positive predictive value,

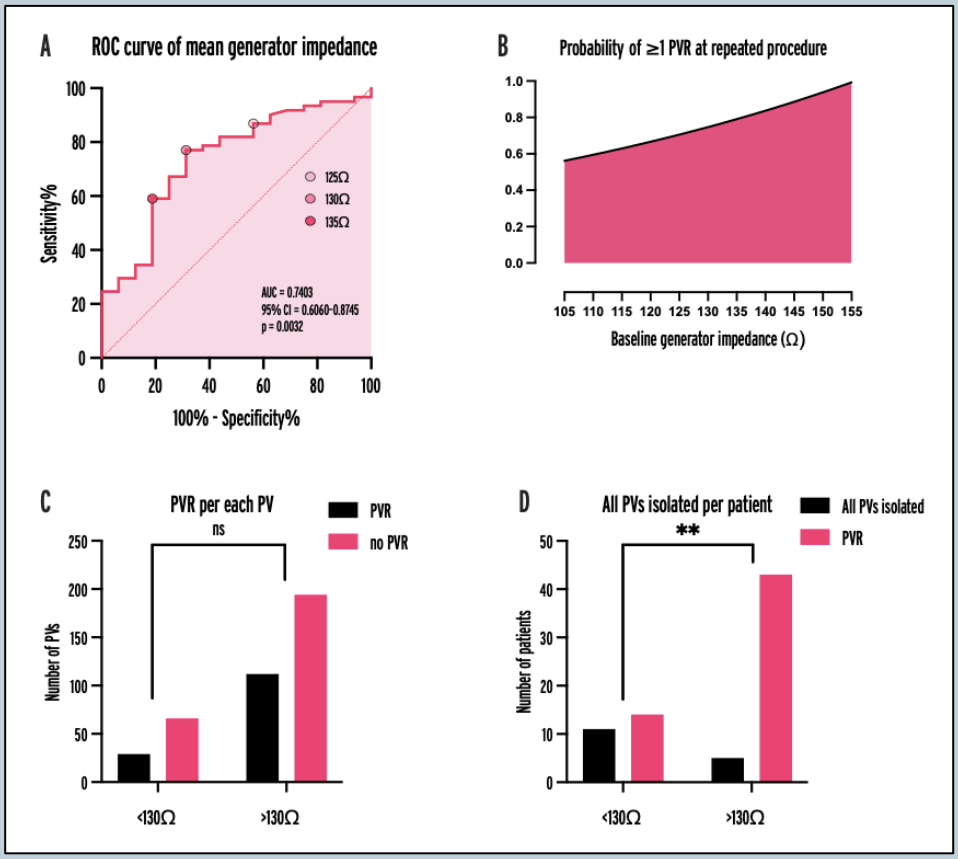

*Figure 14. ROC curve of BGI (A), probability of ≥1 PVR as the logistic regression function of BGI (B), PVR per each PV (C), and all PVs isolated per patient (D) for 130 Ω cut-off. AUC = area under curve; CI = confidence interval; PV = pulmonary vein; PVR = pulmonary vein reconnection; ROC = receiver operating characteristic, **: p < 0.001* [140].

and 75.44% negative predictive value. The odds of PVR were significantly increased when mean BGI was ≥130 Ω (OR = 6.76, 95% CI = 1.98–20.63, p < 0.001).

Bilateral FPI, documented in 70 procedures, was associated with lower PVR rates and higher likelihood of complete PV isolation (OR = 0.32, 95% CI = 0.19–0.53, p < 0.001; and OR = 7.26, 95% CI = 1.92–25.1, p = 0.006, respectively). Bilateral FPI also correlated with adherence to the CLOSE protocol, higher power settings, smaller PV-pair perimeters, fewer RF applications, and lower BGI. Side-specific analysis showed that FPI of either left or right PVs reduced the chance of PVR (OR = 0.15 and 0.14, respectively)

Table 5. Multivariable model for predictors of ≥1 PVR per patient. CI = confidence interval, FPI = first-pass isolation, HPSD = high-power short-duration, OR = odds-ratio, PV = pulmonary vein, PVR = pulmonary vein reconnection.

	OR (95% CI)	P-value
Adherence to CLOSE protocol	0.055 (0.002–0.446)	**0.019**
Catheter (QDOT)	0.234 (0.008–5.260)	0.371
Power (HPSD)	0.448 (0.050–3.885)	0.458
Bilateral FPI	0.116 (0.010–1.354)	0.086
Baseline generator impedance ≥130Ω	16.09 (2.089–220.3)	**0.016**

and increased the likelihood of complete isolation on the respective side (OR = 19.2 and 15.7, respectively).

Variables with $p < 0.1$ in univariate analysis predicting ≥1 PVR included CLOSE adherence, high-power settings, bilateral FPI, BGI ≥130 Ω, and catheter type [141]. Multivariable logistic regression (Table 5.) demonstrated that independent predictors of at least one PVR were CLOSE protocol adherence (OR = 0.055, p = 0.019) and BGI ≥130 Ω (OR = 16.09, p = 0.016), with the model showing strong discriminative ability (AUC = 0.900, positive predictive value = 83.33%, negative predictive value = 87.23%).

4.2. Cerebral safety of vHPSD ablation

A total of 328 consecutive patients were included in the study. Baseline characteristics of the study cohort are presented in Table 6. The mean age of the participants was 62 ± 14 years, with females comprising 36% of the group. Paroxysmal atrial fibrillation was present in 70% of patients. Prior to the procedure, 16 individuals (5%) had a documented history of stroke or TIA. The average CHA_2DS_2-VASc score across the cohort was 3 ± 2.

Across the entire study cohort, the average procedure duration was 69.6 ± 24.1 minutes, while the mean left atrial dwell time was 46.5 ± 21.5 minutes. Intra-procedural cardioversion was required in 68 cases (20%). Within the bMRI subgroup, patients received an average of 79 ± 21 radiofrequency applications, totaling 309 ± 85 seconds of ablation time. The mean irrigation fluid volume was 146 ± 42 mL, and the average ACT was 324 ± 38 seconds. In the total population, acute PVI was achieved in 100% of cases,

while FPI was successful in 82%. At six months, the arrhythmia-free survival rate based on standard monitoring was 84.5%.

Table 6. Baseline characteristics of the study population. BMI = bodymass-index; bMRI = brain magnetic resonance imaging; CAD = coronary artery disease; CHF = chronic heart failure; LA = left atrium; LVEF = left ventricular ejection fraction; AF = atrial fibrillation; SCE = silent cerebral embolism; TIA = transient ischemic attack. Continuous variables presented as mean and standard deviation, binary variables presented as count and percentage.

	All patients (N = 328)	**Patients in the bMRI subgroup (N = 61)**	
		With SCE (N = 5)	Without SCE (N = 56)
Age, years	62 ± 14	60 ± 11	62 ± 11
Sex, female (%)	118 (36)	2 (40)	14 (25)
BMI, kg/m²	28.9 ± 4.4	27.4 ± 4.9	29.4 ± 4.9
CHA_2DS_2-VASc score	2.6 ± 1.7	2.4 ± 1.3	2.3 ± 1.4
Paroxysmal AF, N (%)	231 (70)	5 (100)	38 (68)
LVEF, %	57 ± 8	61 ± 7	56 ± 6
Hypertension, N (%)	222 (68)	2 (40)	33 (59)
Diabetes, N (%)	53 (16)	0 (0)	5 (9)
CAD, N (%)	61 (19)	0 (0)	8 (14)
Prior stroke / TIA, N (%)	16 (5)	0 (0)	3 (5)
CHF, N (%)	16 (5)	0 (0)	3 (5)
LA diameter, mm	48 ± 7	51 ± 3	48 ± 6

No cases of stroke or TIA were observed among the 328 procedures. Vascular access complications occurred in seven instances, including one arteriovenous fistula, one pseudoaneurysm, and five groin hematomas. Two cases of pericardial tamponade were reported, both successfully managed with percutaneous pericardiocentesis. There were no incidents of phrenic nerve injury or clinically significant esophageal complications, and no audible steam pops were recorded during any procedure.

In the subgroup undergoing screening for SCE, brain MRI was performed at a median of 18 hours post-procedure (IQR: 16–22 hours). SCE was identified in 5 out of 61 patients (8.2%). Four patients presented with a single DWI-positive lesion measuring between 2

and 9 mm, while one patient had multiple small lesions (2–4 mm) in the frontal lobe. None of the patients demonstrated any neurological symptoms.

Table 7. Parameters of procedures with and without SCE. ACT = activated clotting time; ECV = electrical cardioversion; FPI = first-pass isolation; RF = radiofrequency; SCE = silent cerebral embolism. Continuous variables presented as mean and standard deviation, binary variables presented as count and percentage.

	Procedures with SCE (N = 5)	Procedures without SCE (N = 56)	P-value
Procedure time, min	55.4 ± 15.2	61.2 ± 15.6	0.43
Left atrial dwell time, min	41.2 ± 15.0	43.6 ± 13.0	0.69
RF-time, sec	322 ± 127	307 ± 81	0.72
RF applications, N	82 ± 31	79 ± 21	0.73
Irrigation volume, mL	150 ± 59	145 ± 41	0.80
FPI, N (%)	5 (100)	45 (80)	> 0.99
ECV, N (%)	2 (40)	6 (11)	0.12
ACT, sec	336 ± 32	323 ± 38	0.41

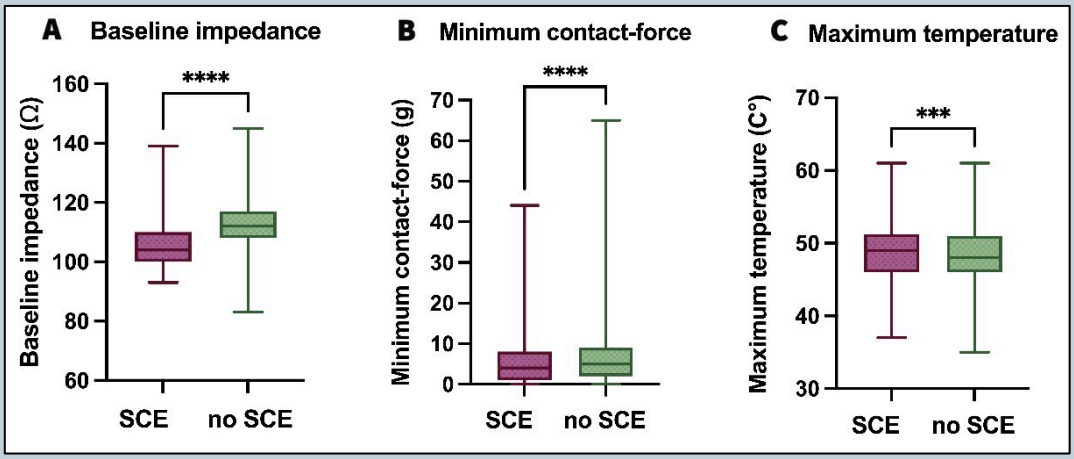

*Figure 15. Baseline generator impedance (A), minimum contact-force (B), and maximum temperature (C) in the case of ablation points with and without SCE. SCE = silent cerebral embolism, *** = p < 0.001, **** = p < 0.0001* [132].

No significant procedural differences were observed between cases with and without SCE (Table 7). In total, 4,773 ablation points were assessed (Table 8). Procedures in which SCE occurred were characterized by significantly lower baseline generator impedance (105.8 vs 112.6 Ω, p < 0.001) and lower minimum contact force (5.9 vs. 7.1 g, p < 0.001; Figure 15) [136]. Additionally, the frequency of catheter–tissue contact loss was notably higher (14.1% vs. 6.1%, p < 0.001). Both maximum temperature (49.2 vs. 48.4°C, p <

0.001) and temperature rise during ablation (15.2 vs. 14.3°C, $p < 0.001$) were significantly elevated in SCE-positive procedures.

Table 8. Parameters of ablation points with and without SCE. CF = contact-force; SCE = silent cerebral embolism. Continuous variables presented as mean and standard deviation, binary variables presented as count and percentage.

	Ablation points with SCE (n = 410)	Ablation points without SCE (n = 4363)	P-value
Mean power, W	81.7 ± 5.0	82.3 ± 3.8	0.186
Minimum temperature, C°	33.9 ± 1.6	34.1 ± 1.5	**0.001**
Maximum temperature, C°	49.2 ± 3.9	48.4 ± 3.9	**0.001**
Temperature rise, C°	15.2 ± 3.9	14.3 ± 4.0	**< 0.001**
Baseline impedance, Ω	105.8 ± 8.3	112.6 ± 7.5	**< 0.001**
Impedance drop, Ω	8.5 ± 3.5	8.6 ± 3.3	0.109
Minimum CF, g	5.9 ± 6.3	7.1 ± 6.7	**< 0.001**
Maximum CF, g	28 ± 15.7	27.8 ± 16.7	0.414
Mean CF, g	15.1 ± 9.0	15.6 ± 9.5	0.235
Applications with loss-of-contact (CF minimum = 0), N (%)	58 (14.1)	273 (6.1)	**< 0.001**

ROC analysis of baseline generator impedance yielded an AUC of 0.753 (95% CI: 0.726–0.781, $p < 0.001$; see Figure 16) [136]. A baseline impedance value of 110 Ω was found to be the optimal cut-off point, offering a sensitivity of 73.9%, specificity of 64.9%, a positive predictive value of 16.5%, and a negative predictive value of 96.4%. The likelihood of SCE was significantly increased in cases of loss of catheter–tissue contact (OR = 2.53, 95% CI = 1.87–3.43, $p < 0.001$) and when the baseline impedance was below 110 Ω (OR = 5.23, 95% CI = 4.16–6.56, $p < 0.001$).

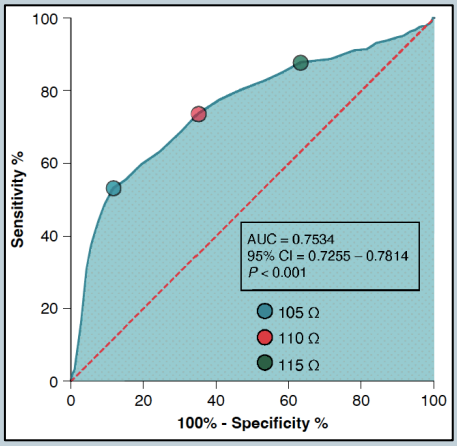

Figure 16. ROC curve of baseline generator impedance for predicting SCE. AUC = area under curve, CI = confidence interval, ROC = receiver operator characteristic, SCE = silent cerebral embolism [132].

Table 9. Number of ablation points with and without SCE in the case of the 110 Ω cutpoint. SCE = silent cerebral embolism.

	Ablation points in procedures with SCE, N	Ablation points in procedures without SCE, N
Baseline impedance < 110 Ω, N	303	1531
Baseline impedance ≥ 110 Ω, N	107	2830

4.3. Ablation parameters of vHPSD ablation

Twenty patients were included in the study, all undergoing 90W PVI followed by a protocol-mandated repeat electrophysiological assessment three months after the index procedure. The average age was 65 ± 8 years, 45% were female, and 43% had persistent AF. The mean procedure time was 75.6 ± 12.9 minutes, with bilateral FPI achieved in 82.5% of cases. No major complications were reported. A total of 1357 ablation points were assessed.

FPI gaps were observed in 4 patients, affecting 7 sites and 19 ablation points. Acute PVR occurred in 1 patient, involving 1 site and 6 points, while chronic PVR was seen in 4 patients, affecting 11 sites and 20 points. The anatomical distribution of these sites around the PV ostia is shown in Figure 17 [143]. Gaps were more frequently located at anterior segments (OR = 2.53, p = 0.008), and a right-sided location showed a non-significant trend towards more gaps (OR = 1.78, p = 0.072). Parameters with significant differences were ILD (3.3 vs 4.0 mm, p < 0.001),

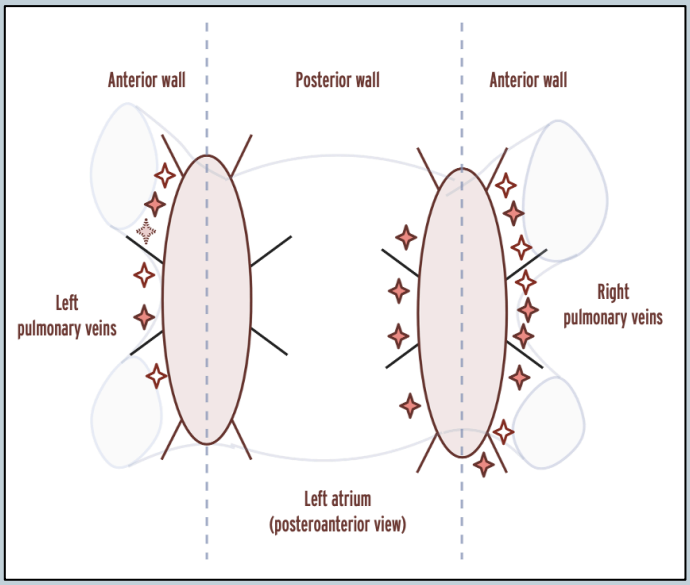

Figure 17. Gap locations around a 16-segment PV ostium model. Empty stars indicate first-pass gaps, dashed stars indicate acute PVR, and bold stars indicate chronic PVR. PV = pulmonary vein, PVR = pulmonary vein reconnection [142].

baseline generator impedance (112 vs 114 Ω, p = 0.018), mean current (858.4 vs 854.7 mA, p = 0.006), total charge (3.43 vs 3.4 C, p = 0.004), and LOC: 2.7% vs 13.3% (p =

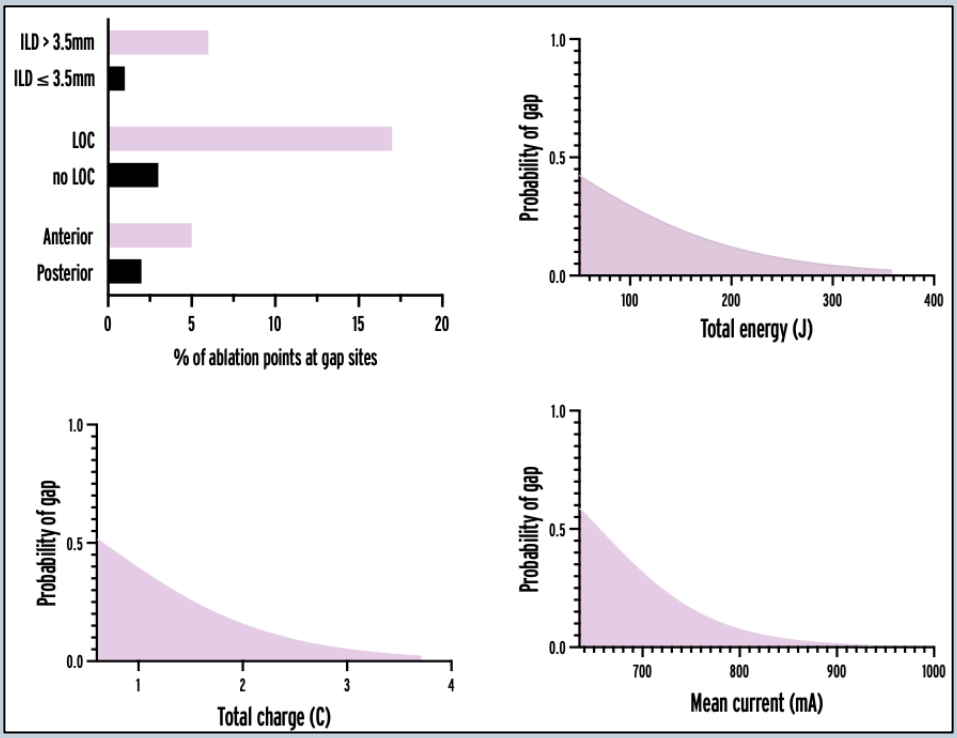

Figure 18. Percentage of ablation points at gap sites according to ILD, occurence of LOC and anterior/posterior location (left upper panel). Probability of gaps in ablation circles as fitted logistic regression functions of total charge (left lower), total energy (right upper), and mean current (right lower). ILD = interlesion-distance, LOC = loss of contact [142].

0.002), see Figure 18 [143].

ROC analysis (Figure 19)[143] was used to identify the optimal ILD cut-off for predicting gaps, yielding a value of 3.5 mm (AUC = 0.61, 95% CI = 0.52–0.69, p = 0.016). ILDs >3.5 mm were associated with a significantly higher likelihood of gaps or reconnections (OR = 6.24; 95% CI = 2.94–13.24, p < 0.001). For anterior and posterior regions separately, optimal cut-offs were 3.5 mm (OR = 6.61, p < 0.001) and 4 mm (OR = 8.71, p < 0.001), respectively.

Variables with p < 0.05 were included in multivariable logistic regression models (Table 10). Due to strong multicollinearity (R^2 > 0.99, VIF > 200) between application time, mean power, generator impedance and the derived variables (total energy, mean current, total charge), six separate models were developed using only one of the correlated variables in each, along with ILD >3.5 mm, LOC, and anterior location. All variables remained independent predictors in all of the models. Out of the separate models, the one

with total charge showed the highest predictive value (AUC = 0.745, $p < 0.001$). Among all predictors, LOC had the strongest association with the presence of gaps.

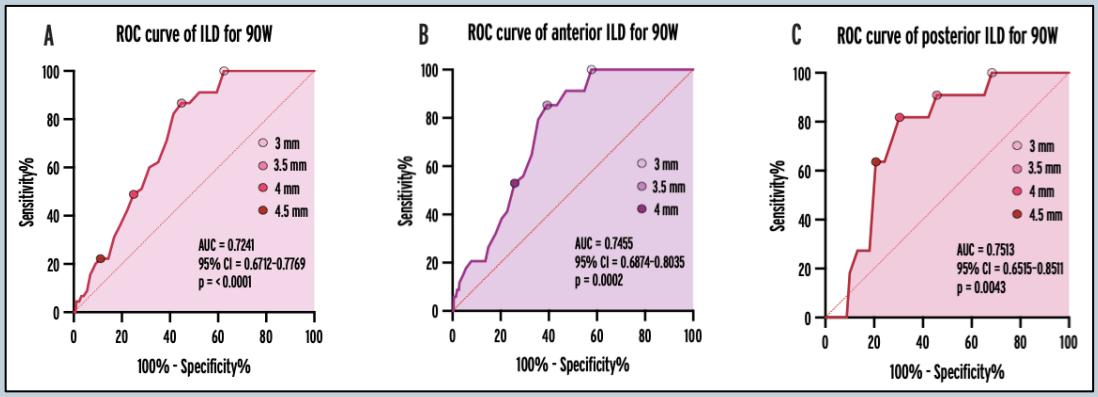

Figure 19. ROC curves of ILD values for prediction of all-around (A), anterior (B), and posterior (C) gaps in the ablation lines. AUC = area under curve; CI = confidence interval; ILD =interlesion distance; ROC = receiver operating characteristic [142].

Table 10. Multivariable models with OR estimates and corresponding 95% CI. AUC = area under curve, BGI = baseline generator impedance, CI = confidence-interval, ILD = interlesion-distance, LOC = loss of contact, OR = odds-ratio.

Multivariable models OR (95% CI)	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
ILD >3.5 mm	2.47 (1.33–4.72)	2.41 (1.30–4.60)	2.45 (1.32–4.69)	2.40 (1.29–4.58)	2.44 (1.31–4.67)	2.52 (1.36–4.79)
Anterior location	3.39 (1.70–7.34)	3.32 (1.67–7.15)	3.37 (1.69–7.29)	3.07 (1.54–6.64)	3.31 (1.65–7.17)	3.18 (1.60–6.88)
LOC	7.95 (2.76–20.13)	8.00 (2.78–20.27)	8.01 (2.78–20.30)	7.45 (2.57–18.90)	7.84 (2.72–19.89)	7.18 (2.48–18.27)
Application time (sec)	0.36 (0.20–0.67)	–	–	–	–	–
Mean power (W)	–	0.91 (0.83–0.98)	–	–	–	–
Total energy (J)	–	–	0.99 (0.98–0.99)	–	–	–
Mean current (A)	–	–	–	0.98 (0.97–0.99)	–	–
Total charge (C)	–	–	–	–	0.29 (0.16–0.58)	–
BGI (Ω)	–	–	–	–	–	1.05 (1.00–1.10)
AUC of models	0.74	0.72	0.74	0.74	0.75	0.72

5. Discussion

5.1. Main message

Our findings indicate that excessively high generator impedance and non-adherence to the CLOSE protocol are strong predictors of PV reconnections. For the first time in a clinical setting, we reported the crucial role of generator impedance during RF ablation. In our 90W PVI cohort –the largest published to date– vHPSD ablation demonstrated favorable mid-term efficacy and a reassuring cerebral safety profile, in contrast to earlier reports. Notably, lower baseline generator impedance and intermittent loss of catheter-to-tissue contact during ablation were associated with SCEs, highlighting potential strategies for reducing the risk of future cerebral complications. Finally, our findings also established the need for smaller interlesion distances with vHPSD PVI compared to lower power settings, which is another novel insight. These findings may help to optimize the efficacy and safety of RF ablation.

5.2. Predictors of PV reconnections

In the study conducted by Phlips et al., ten patients underwent repeat ablation following recurrent atrial tachyarrhythmia [123]. Among them, three had initially received CLOSE-guided PVI, while seven underwent non-CLOSE-guided PVI. In the non-CLOSE group, 23 reconnection sites were identified across 18 PVs, compared to 7 reconnections in 7 PVs in the CLOSE group. However, the small sample size limited the ability to draw firm conclusions about the long-term durability of CLOSE PVI. De Pooter et al. expanded on this with 45 repeat ablations following CLOSE-guided procedures [144]. They observed that 62% of patients had all PVs still isolated, with many showing extensive low-voltage areas in the left atrium, suggesting that AF recurrence may occur through mechanisms unrelated to PV reconnection in this population. Similarly, Pedrote et al. examined 21 patients and found reconnection in 63 of 336 PV segments, which correlated with lower AI values [145].

In our analysis, we compared outcomes in 38 patients with initial CLOSE-guided ablation and 62 with non-CLOSE PVI. After adjusting for potential confounders, patients in the non-CLOSE group had an approximately 18-fold increased likelihood of PV reconnection during repeat procedures. The ability to detect this significant difference is likely due to our larger sample size compared to that of Phlips et al. De Pooter et al. reported a higher rate of durable isolation (62%) following CLOSE ablation than

observed in our study (40%) [144]. This discrepancy may be explained by several factors: (1) A longer interval between procedures in our study (mean 23.5 months vs. 11 months); (2) A higher proportion of patients with persistent AF (60% vs. 0%); (3) Greater comorbidity burden in our cohort.

Importantly, the duration of the initial ablation procedure did not differ significantly between the CLOSE and non-CLOSE groups. However, non-CLOSE procedures were associated with lower rates of FPI and a greater number of RF applications, likely due to the need for additional ablation to close residual gaps. These findings indicate that the CLOSE protocol does not extend procedure time and may, in fact, reduce radiation exposure due to increased reliance on the electroanatomical mapping system, as evidenced by significantly lower fluoroscopy time and dose area product. Collectively, these results provide compelling support for the routine implementation of the CLOSE protocol.

BGI, defined as the impedance of the RF circuit at the start of each application, is not incorporated into the AI calculation used by the CARTO system and is thus excluded from the CLOSE protocol. However, growing evidence suggests that BGI significantly impacts RF lesion quality. Bourier et al. noted that generator impedance significantly affects RF current delivery and varies across patients, with lower values observed in males and those with lower BMI [127]. Because RF lesions are produced by current—not power—lower impedance results in higher current, which in turn raises tissue temperature and increases lesion size. Notably, the relationship between BGI and ablation efficacy in clinical settings has not been studied until now. Our current findings establish BGI as an independent predictor of durable PVI. Specifically, a BGI ≥130 Ω was associated with a 16-fold increase in the likelihood of PV reconnection, even after adjusting for other variables. We hypothesize that, for two ablation lesions with similar AI, the application with lower BGI (and therefore higher current delivery) is likely to produce a more effective lesion. Based on this, we recommend targeting a BGI of <130 Ω to optimize the efficacy of RF PVI.

5.3. Cerebral safety of vHPSD ablation

Numerous studies have explored the incidence of SCE following PVI with low-power (25–35W) RF ablation, reporting SCE rates between 6% and 16% [98,112,113]. While some of these studies included baseline pre-procedural brain MRIs, the frequency of new SCEs

was comparable to those that relied solely on post-procedural DWI, suggesting that post-ablation DWI bMRI alone is sufficient for detecting ablation-related SCEs.

The first study evaluating vHPSD ablation was the QDOT-FAST Trial, which identified SCEs in 12% of patients (6 out of 51) using post-ablation bMRI [146]. All but one lesion had resolved by the one-month follow-up scan. Halbfass et al. later investigated the safety of the vHPSD technique concerning SCEs and silent esophageal injury [138]. Their study reported a mean procedure time of 96 minutes and a FPI rate of only 43%. A subgroup of 21 patients treated with the nGEN RF generator underwent bMRI, revealing catheter-tip charring in 11% and SCEs in 24% (5 out of 21). Due to an increased number of charring events, Biosense Webster issued a safety notice in late 2020 related to the use of QMODE+ with the nGEN generator. A subsequent software update aimed to improve temperature control. The same research group later reassessed the safety of vHPSD ablation with the updated generator [139], but still observed a high SCE rate (26%, 6 out of 23 patients). Both studies had small sample sizes and lacked detailed information on periprocedural anticoagulation strategies and ACT levels which is essential when interpreting their results. Posterior wall ablations were performed with 3-second lesions, and a lenient inter-lesion spacing (<6 mm), which may explain the low FPI rate. A more recent study by Kottmaier et al. reported a 17% incidence of SCE in 23 patients treated with vHPSD [147].

In our current study, we detected SCEs in five patients, though no clinical cerebrovascular events were observed. These findings suggest that vHPSD ablation is generally safe from a neurological perspective and shows a cerebral safety profile similar to LPLD approaches. Notably, the SCE rate in our study was lower than previously reported in vHPSD literature (Fig. 20). Possible reasons include: (1) Longer left atrial dwell times in earlier studies, (2) Unreported ACT

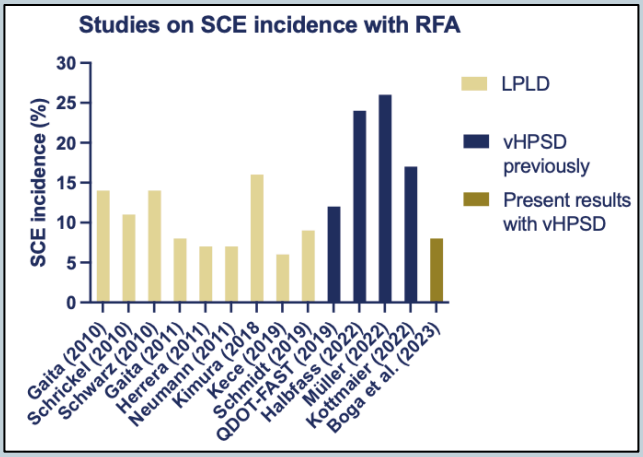

Figure 20. SCE incidence rates with RFA. RFA = radiofrequency ablation; SCE = silent cerebral embolism; vHPSD = very high-power short-duration.

values in prior work, (3) Catheter instability or absence of CF during energy delivery, and (4) Lower baseline generator impedance (Mueller et al. demonstrated that raising baseline impedance from 90 to 110 Ω eliminated catheter-tip coagulum formation) [138,139]. All these studies, similar to ours, used a 1.5 Tesla MRI scanner and shared similar methodologies. Several procedural factors are known to influence the risk of SCE, such as prolonged procedure duration, need for intraprocedural ECV, low ACT levels, and the type of electroanatomical mapping system used [148,149]. Studies have also shown that interrupted anticoagulation can increase SCE incidence [150,151]. However, the exact mechanism behind SCE remains debated – whether it results from solid emboli (e.g., thrombi) or gaseous emboli (e.g., air bubbles or vaporized tissue). Given the variety of potential causes, such as coagulum formation on the catheter or air inflow through the sheath, a single explanation is unlikely [152]. Nevertheless, most risk factors support the thromboembolic hypothesis.

Our findings indicate that low baseline generator impedance and loss of catheter-tissue contact are also associated with higher SCE incidence. We found that aiming for a mean baseline impedance of at least 110 Ω during the procedure appears optimal. This aligns with Mueller et al.'s observation that coagulum formation ceased when baseline impedance was raised to 110 Ω [139]. Therefore, positioning the neutral electrode to achieve a starting impedance of >110 Ω may help reduce SCE risk in patients with initially low impedance. In our previous study, we found that BGI >130 Ω significantly increased the risk of PVR. Based on this, we propose positioning the neutral electrode to achieve a target BGI of 110–130 Ω in patients with initially too low or too high impedance, as a strategy to optimize both the efficacy and safety of PVI.

Catheter-tissue contact is particularly critical in vHPSD ablation, where the entire RF dose is delivered in a very brief 4-second window. Even short lapses in contact can drastically reduce current delivery to the myocardium. Besides lowering ablation efficacy, this could also heighten SCE risk, likely due to excess current being dissipated into the blood pool, leading to coagulum or bubble formation. This may explain the low FPI and high SCE rates reported in earlier vHPSD studies [138,139].

5.4. Ablation parameters of vHPSD ablation

Compared to LPLD ablation, delivering higher RF power over a shorter time in vHPSD ablation enhances resistive heating while minimizing conductive heating. This method

aims to create more consistent lesions. Early animal studies suggested that vHPSD lesions were wider but equally deep [132,153]; however, subsequent findings contradicted this [133]. Nakagawa et al. showed that higher power (90W/4s) resulted in smaller lesion depth and width compared to lower power settings (50W/10s or 30W/30s), with 90W lesions having the smallest volume [133].

As newer studies suggest that higher power produces narrower, shallower lesions, optimal ILD must be redefined for vHPSD PVI. In swine, complete block was achieved with ILDs of 3–4 mm around the right superior PV [153]. Another sheep study found that only 3 mm and 4 mm ILDs produced durable block after 21 days [154]. In our study, the optimal ILD cutoff was 3.5 mm overall—3.5 mm anteriorly and 4 mm posteriorly—indicating that tighter spacing is necessary for durable vHPSD PVI. These low ILD values may be necessary to ensure lesion overlap, especially at the thicker anterior wall of the PVs.

Joule's law ($E = I^2 \times R \times t$) underpins the use of power in RF ablation. However, generator impedance includes all tissues from the catheter tip to the neutral electrode, not just the myocardium. In a simulation, 75% of power was absorbed near the catheter, while 25% was dispersed in other tissues [155]. Fatty tissue and neutral electrode placement affect impedance and therefore lesion formation [127,156]. Current may be a more accurate measure of tissue heating, as it is inversely related to impedance. Charge (current × time) is also proportional to thermal energy and similarly impacted by impedance. In our study, higher baseline impedance predicted gaps, while mean current and total charge were even stronger predictors. These parameters—though not displayed by CARTO—may improve lesion assessment in the absence of AI. Switching to current-based modulation could further improve outcomes [127,136].

CF reflects catheter-tissue contact and stability, affecting current density and heat distribution. If the catheter slides or loses contact, heat spreads inefficiently, compromising lesion quality. Although higher CF improves contact, increasing CF beyond 5g may not enhance stability [135,157]. Our data showed that transient LOC, rather than mean CF, was a stronger predictor of inadequate lesions. With 90W/4s ablation, even brief LOC episodes significantly reduce myocardial current. Notably, sinus rhythm increases LOC risk, likely due to atrial contractions displacing the catheter. Pacing from the coronary sinus could potentially mitigate this, but more research is needed to validate this hypothesis.

The QDOT catheter measures tip temperature accurately, correlating with tissue temperature as sensors are near the tissue interface. Still, actual tissue temperatures may be 15°C higher at the interface and up to 35°C higher at 3 mm depth [133]. Nakagawa et al. reported that a significant portion of heating (thermal latency) occurs after RF stops, especially with very high power. Factors such as irrigation, blood flow, and rhythm influence measured temperatures. In our study, maximum temperature showed only a trend toward gap prediction at 90W, suggesting it may not be a reliable guide for vHPSD efficacy.

Gaps and reconnections were most often seen in anterior PV segments. Given that 90W/4s lesions penetrate to an average depth of 3.6 mm [158], and anterior wall thickness ranges from 0.3–4.5 mm [159], lesions may be insufficient in thicker regions. Our findings support this: 75% of gap sites were locate anteriorly. This could be addressed by reducing ILD in anterior areas and leveraging thermal latency to enhance lesion durability.

5.5. Limitations

These were single-center investigations involving four to six operating physicians, which may limit the generalizability of the findings. Patient selection for bMRI was not randomized; instead, consecutive patients without contraindications and who provided informed consent were enrolled. The sample size in the bMRI subgroup was moderate; however, this remains the largest study investigating cerebral complications associated with vHPSD PVI. A baseline pre-intervention MRI was not performed, as acute lesions could be reliably detected using DWI, minimizing the risk of misclassification with chronic lesions. Additionally, no neurological or cognitive follow-up was conducted. In the PVR study, the choice of power settings and use of the CLOSE protocol were determined by physician preference, though patient characteristics did not differ significantly across groups. While there was no strict protocol requiring uniform catheter types or ablation settings, application of the CLOSE protocol was consistent. For mandatory remap study procedures only 20 patients were enrolled, as invasive remapping in asymptomatic subjects (for scientific purposes) is only justified in the least number of patients necessary to give conclusive results. Matching initial ablation points to later gap sites on voltage mapping may be imprecise, potentially affecting the accuracy of the results.

6. Conclusions

We identified that both non-adherence to the CLOSE protocol and a baseline generator impedance of ≥130Ω are independent predictors of PV reconnections. Our findings confirm that vHPSD radiofrequency ablation offers a favorable cerebral safety profile, characterized by a low incidence of SCEs and high acute procedural success. Baseline generator impedance <110Ω and intermittent loss of catheter-tissue contact during ablation may increase the likelihood of SCEs. In addition, key factors influencing lesion contiguity during vHPSD ablation include ILD, consistent catheter contact, energy delivery, as well as current and charge – all of which are affected by generator impedance. Achieving durable PVI with vHPSD requires smaller ILDs than those typically recommended for lower-power ablation strategies. Finally, given the fixed application time in vHPSD ablation, using reduced ILDs for anterior wall lesions appears necessary in comparison to posterior applications.

7. Summary

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased morbidity, mortality, and reduced quality of life. Pulmonary vein isolation (PVI) is the most effective treatment for AF, with point-by-point radiofrequency (RF) ablation being one of the most widely used techniques. Our research aimed at studying efficacy and safety aspects of modern RF PVI, with special focus on very high-power short-duration (vHPSD) ablation.

Our investigations identified high generator impedance and deviation from the CLOSE protocol as significant predictors of pulmonary vein reconnection. In our 90W PVI cohort –the largest reported to date– vHPSD ablation showed promising mid-term efficacy and a favorable cerebral safety profile, contrasting with previous studies. Importantly, lower baseline generator impedance and transient loss of catheter-to-tissue contact during ablation were linked to the occurrence of silent cerebral events, suggesting possible avenues for minimizing cerebral risks. These studies are the first to highlight the pivotal role of generator impedance in RF ablation in a clinical setting. We propose an optimal generator impedance range from 110Ω to 130Ω in which radiofrequency PVI can be performed safely and effectively. We demonstrated that achieving durable isolation with vHPSD requires smaller interlesion distances (ILDs) than those used in conventional lower-power ablation which is another novel finding. Finally we also showed that given the fixed application time in vHPSD ablation, using reduced ILDs for anterior wall lesions appears necessary in comparison to posterior applications.

Together, these findings may contribute to improving both the safety and efficacy of RF ablation strategies, and thus lead to better outcomes for the large number of patients suffering from AF.

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9. Bibliography of the candidate's publications

9.1. Publications related to the PhD thesis

1. Boga M, Suhai FI, Orbán G, Salló Z, Nagy KV, Szegedi L, Jokkel Z, Csőre J, Osztheimer I, Perge P, et al. Incidence and Predictors of Stroke and Silent Cerebral Embolism Following Very High-Power Short-Duration Atrial Fibrillation Ablation. *EP Europace*. 2023. doi: 10.1093/europace/euad327
   IF: 7.9 (D1)
2. Boga M, Orbán G, Perge P, Salló Z, Tanai E, Ferencz AB, Tóth P, Komlósi F, Osztheimer I, Nagy KV, et al. Adherence to the CLOSE Protocol and Low Baseline Generator Impedance Are Independent Predictors of Durable Pulmonary Vein Isolation. *Journal of Clinical Medicine*. 2024;13:1960.
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3. Boga M, Orbán G, Salló Z, Nagy KV, Osztheimer I, Ferencz AB, Komlósi F, Tóth P, Tanai E, Perge P, et al. Ablation Parameters Predicting Pulmonary Vein Reconnection after Very High-Power Short-Duration Pulmonary Vein Isolation. *J Cardiovasc Dev Dis*. 2024;11. doi: 10.3390/jcdd11080230
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9.2. Publications unrelated to the PhD thesis

1. Boga M, Salló Z, Orbán G, Komlósi F, Padisák A, Tóth P, et al. Impact of response to electrical cardioversion before catheter ablation for persistent atrial fibrillation: a propensity score-matched analysis. *European Heart Journal Open* 2025;5. doi: https://doi.org/10.1093/ehjopen/oeaf084

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5. Orbán G, Dohy Z, Suhai FI, Nagy AI, Salló Z, Boga M, Kiss M, Kunze K, Neji R, Botnar R, et al. Use of a new non-contrast-enhanced BOOST cardiac MR sequence before electrical cardioversion or ablation of atrial fibrillation-a pilot study. *Front Cardiovasc Med*. 2023;10:1177347. doi: 10.3389/fcvm.2023.1177347

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6. Szegedi N, Salló Z, Nagy VK, Osztheimer I, Hizoh I, Lakatos B, Boussoussou M, Orbán G, Boga M, Ferencz AB, et al. Long-Term Durability of High- and Very High-Power Short-Duration PVI by Invasive Remapping: The HPSD Remap Study. *Circ Arrhythm Electrophysiol*. 2024;17:e012402. doi: 10.1161/circep.123.012402

   IF: 9.1 (D1)

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