

A Promising Novel Ablation Technology

Pulsed Field Ablation for the Treatment of Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) has become the most common arrhythmia worldwide and its incidence is increasing. Treatment strategies for symptomatic patients include stroke prevention, management of cardiovascular comorbidities, and direct treatment of AF itself. With regard to interventional AF treatment, a novel technique called pulsed field ablation has emerged. Large registry data in more than 15,000 patients have demonstrated a high efficacy in reducing the burden of AF with a very high safety. This review provides an overview of the technical aspects of pulsed field ablation and the published clinical data.

Keywords: Atrial fibrillation; catheter ablation; efficacy; pulsed field ablation; safety

Introduction

With the increasing prevalence of cardiovascular risk factors, atrial fibrillation (AF) has become the most common arrhythmia worldwide [1]. According to recent calculations, it is expected that the number of affected Europeans will triple by 2050 [2]. Patients suffering from AF experience symptoms like palpitations, dyspnea, dizziness and exercise intolerance [3]. Furthermore, registry analyses show an association between AF and higher mortality [4, 5]. AF treatment includes stroke prevention with oral anticoagulation in those at increased risk for thromboembolic events, control of cardiovascular risk factors (e.g., arterial hypertension, obesity, diabetes mellitus type 2), and treatment of AF itself [3]. Regarding the latter, either a rate control (and hence acceptance of AF), or a rhythm control strategy can be adopted. Recently, an early rhythm control strategy has been shown to improve the prognosis of AF patients regarding death,

stroke and major cardiovascular events [6]. For rhythm control, either antiarrhythmic drugs or a catheter intervention can be selected. The primary goal of a catheter intervention is pulmonary vein isolation (PVI), since seminal studies have identified the triggers which induce AF to be mainly located in the pulmonary veins [7]. Recent randomized trials showed that catheter interventions using either radiofrequency ablation or cryothermal energy are more effective in reducing AF burden and preventing disease progression than antiarrhythmic drugs [8–10]. Even though there were many advances over the past decades in improving efficacy and outcome of PVI, considerable safety concerns remain, including risk of periinterventional stroke, pericardial tamponade, phrenic nerve palsy, pulmonary vein stenosis and atrio-esophageal fistula. The last three complications are typically linked to thermal ablation energy were the ablative heat or cold wave expands through the myocardial

wall potentially damaging the surrounding tissue. Pulsed field ablation (PFA) is a novel nonthermal ablation modality selectively targeting the myocardium. As demonstrated in preclinical as well as clinical studies, PFA significantly reduces the risk for energy-related collateral damage associated with thermal ablation [11, 12].

Pulsed Field Ablation Technology

PFA is a tissue-selective nonthermal cardiac ablation modality [13]. On a cellular level, lesion formation is achieved by applying ultra-rapid (microseconds to nanoseconds) alternating (biphasic) electrical fields, either between two electrical poles of a catheter (bipolar PFA) or between the electrical poles of a catheter and a grounding patch attached to the skin of the patient (unipolar PFA). If the electrical field is strong enough, it leads to irreversible nanopore formation (also referred to as electroporation) in the myocardial cell membrane and subsequent cell death [14]. Of importance is that the myocardial tissue exhibits a higher susceptibility towards electroporation compared to the surrounding tissue like the phrenic nerve or the esophagus. This results in a highly selective ablation of the myocardium by using an optimized PFA waveform [15, 16]. Therefore, PFA has a broad therapeutic window and offers high efficacy (myocardial damage) on one side and excellent safety (little to no collateral damage) on the other side. Indeed, previous preclinical and clinical work confirms the selectivity of PFA towards the myocardium, sparing surrounding nerves, vascular and esophageal tissue [15–17].

Review Article

General Overview of Interventional Catheter Ablation for AF and other PFA Systems

The primary goal of interventional AF ablation is the isolation of the pulmonary veins. This can be achieved by a point-by-point circumferential ablation or by a single-shot ablation technique, where the ablation catheter is placed at the ostium of the pulmonary vein and it is isolated by energy delivery [18]. Over the last decades, radiofrequency energy was the primary type of energy used for the point-by-point technique, while cryoballoon ablation was the preferred method for single-shot ablations [18]. It was demonstrated, that for paroxysmal AF patients, both approaches are equally efficient [19]. In the emerging field of

PFA, different ablation catheters are either already or will soon be approved in clinical use offering both a point-by-point or a single-shot ablation approach (table 1). The Farapulse™ PFA system was the first to receive a CE mark and therefore most available clinical data currently stems from this system.

Workflow of a PFA Procedure Using the FARAPULSE™ System

So far, the largest clinical experience is available for the Farapulse™ PFA system (Boston Scientific Inc., Marlborough, MA, United States). In brief, this system uses a pentaspline catheter with four electrodes on each spline (fig. 1). While all electrodes are used for pulsed field energy application (poles 1–4), the third elec-

trode from the tip is used for electrogram recording and pacing (pole 3). To deliver pulsed field energy, the generator (Farastar™, Boston Scientific Inc.) builds an electrical field of 1,800–2,000 Volts which is then delivered as a bipolar biphasic wave between the electrodes of the catheter [20]. A train of five consecutive bursts of pulsed field energy is applied over a total of 2.5 seconds per application (fig. 2).

After femoral venous access, a single transeptal puncture is performed under fluoroscopy guidance to gain access to the left atrium. Next, a 13Fr deflectable sheath (Faradrive™, Boston Scientific Inc.) is placed in the left atrium and the 12Fr multi-electrode pentaspline PFA catheter (Farawave™, Boston Scientific Inc.) is advanced over the sheath. Alternatively, transeptal access can be directly obtained via the 13Fr deflectable sheath [21]. Over a 0.035” J-guidewire, the PFA catheter is advanced towards the ostium of each pulmonary vein. Using the integrated pulling-wire mechanism of the catheter, the shape of the five splines of the catheter can be changed to a basket-like configuration when partially expanded or to a flower-like configuration when fully retracted (fig. 1 and 3). According to early experience, pulmonary vein ablation is best performed in pairs of energy delivery [20]. A first pair of pulsed field energy application is given in basket configuration with the catheter positioned at the ostium (fig. 3). Next, the device is rotated by 36° to cover the area between the splines of the first application and another pair of pulsed field energy applications is given (fig. 3). Then, the shape of the splines is changed to the flower configuration and the catheter is placed more proximal on the pulmonary vein ostia (fig. 3). The same 2x2 set of pulsed field energy applications as in the basket configuration are delivered. Therefore, as a standard, a total of eight energy application is given to each pulmonary vein [20, 22].

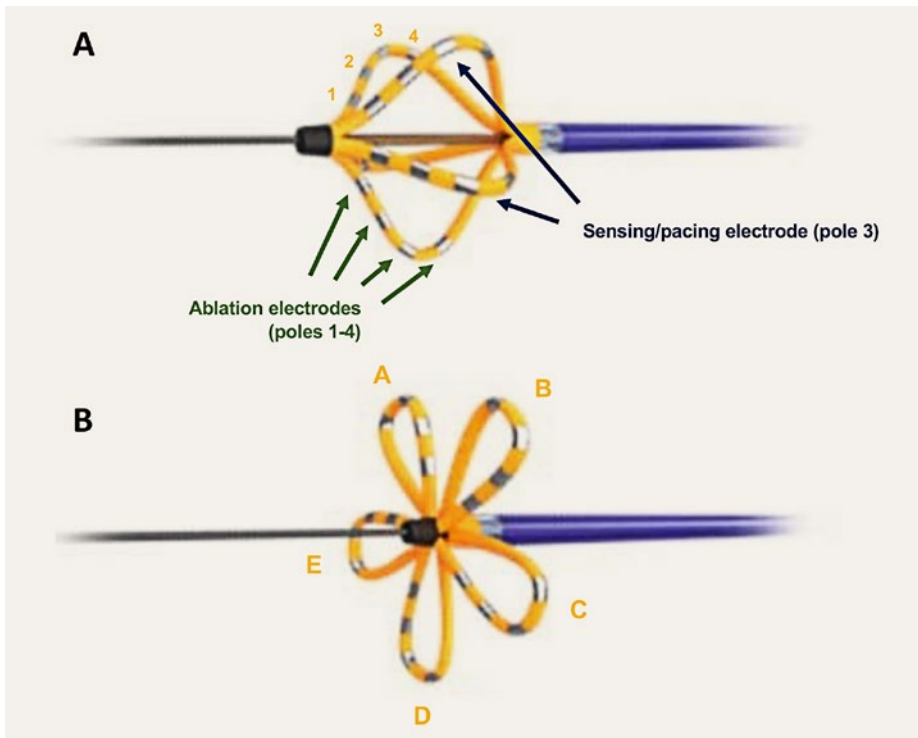


Figure 1: Pentaspline ablation catheter in basket (A) and flower (B) configuration.

Table 1: Overview on Different Pulsed Field Ablation Systems

	Single Shot Approach			Focal Approach		
Company	Boston Scientific/ Farapulse™	Biosense Webster	Medtronic	Medtronic/ Affera™	Galaxy Medical	Biosense Webster
Catheter	Farawave™	Varipulse®	PulseSelect™	Sphere-9™	Centauri Generator	SmartTouch
Catheter design¹						
CE Mark	03/2021	N/A	N/A	03/2023	08/2023	N/A
Patients treated	>15,000	>50	>300	>300	N/A	100

¹ Figures demonstrate the design of the individual catheters but are not shown in comparable scales.

During the intervention, intravenous heparin is given to maintain an activated clotting time (ACT) of more than 350 seconds. Since the application of pulsed field energy is painful even in the bipolar mode, the intervention must be performed either in deep sedation using a combination of midazolam and propofol, or under general anesthesia [22, 23]. However, it is important to mention that patient preparation prior to the intervention as well as patient management during and after the intervention do not differ from traditional PVI ablation approaches such as cryoballoon or radiofrequency ablations. 3D-mapping of the left atrium (fig. 3) can be performed prior to and after the ablation but is not mandatory nor necessary to confirm PVI. Disappearance of the local electrical signal at the pulmonary vein ostia following application (fig. 2) can be used to judge successful energy delivery, while entry and exit block verified by pacing from the PFA catheter at the end of the ablation procedure serves to control for successful PVI [24]. In contrast to radiofrequency ablation, direct visualization of biological effects at the ablated tissue, such as real-time changes in the local electrogram or a drop in the catheter ablation impedance are not available. However, 3D-mapping is especially helpful in more advanced stages of AF (e.g., persistent, or longstanding-persistent AF), where in addition to PVI, the posterior

wall of the left atrium can also be isolated in patients exhibiting extensive electrical scarring on the posterior wall [25].

Procedural Safety of PFA for AF Ablation

As recently confirmed in the CABANA trial, the treatment of AF with catheter ablation is a safe intervention [8]. Complications in the context of catheter ablations can be split into thermal- (related to the energy source chosen for ablation) and non-thermal related complications (resulting from device and sheath handling as well as periinterventional anticoagulation). Independent of catheter design, PFA technology offers a high safety profile since the risk for the feared thermal collateral damage is extremely low [20, 22, 23, 26–28].

Atrio-esophageal Fistula

Atrio-esophageal fistula, a rare but feared thermal complication with a high mortality rate, has not been observed with PFA technology [20, 22, 23]. In patients from the 5S study, during which an esophageal temperature probe was used during the procedure and a post-procedural endoscopy was performed, no relevant rise in intestinal temperature was seen and there was no evidence of thermal-related mucosal injury during endoscopy [22]. Consistently, in the multi-national MANIFEST-PF

survey including more than 1,700 patients without any periinterventional esophageal protection strategy, no esophageal injury was reported during the follow-up period [23]. In contrast, the POTTER-AF study reported an incidence of atrio-esophageal fistula of 0.038% after radiofrequency and 0.0015% after cryoballoon ablation with a mortality of 66% [29].

Pulmonary Vein Stenosis

Scar formation after the ablation procedure can result in narrowing of the pulmonary vein lumen if the ablation lesions are set too distally from the antral pulmonary vein ostium. After radiofrequency ablation, pulmonary vein narrowing has been observed in nearly one third of all cases [30], usually without any clinical relevance, while such narrowing has not been seen using PFA technology [26, 27, 30, 31]. The absence of clinically relevant pulmonary vein stenosis was confirmed by the MANIFEST-PF survey [23].

Persistent Phrenic Nerve Palsy

Phrenic nerve palsy is a rare but relevant adverse event usually occurring after single-shot cryoballoon ablation procedures. In the MANIFEST-PF cohort, there was only one case of persistent palsy of the phrenic nerve after PFA [23], while transient palsy was observed in eight patients (0.46%). The latter most likely

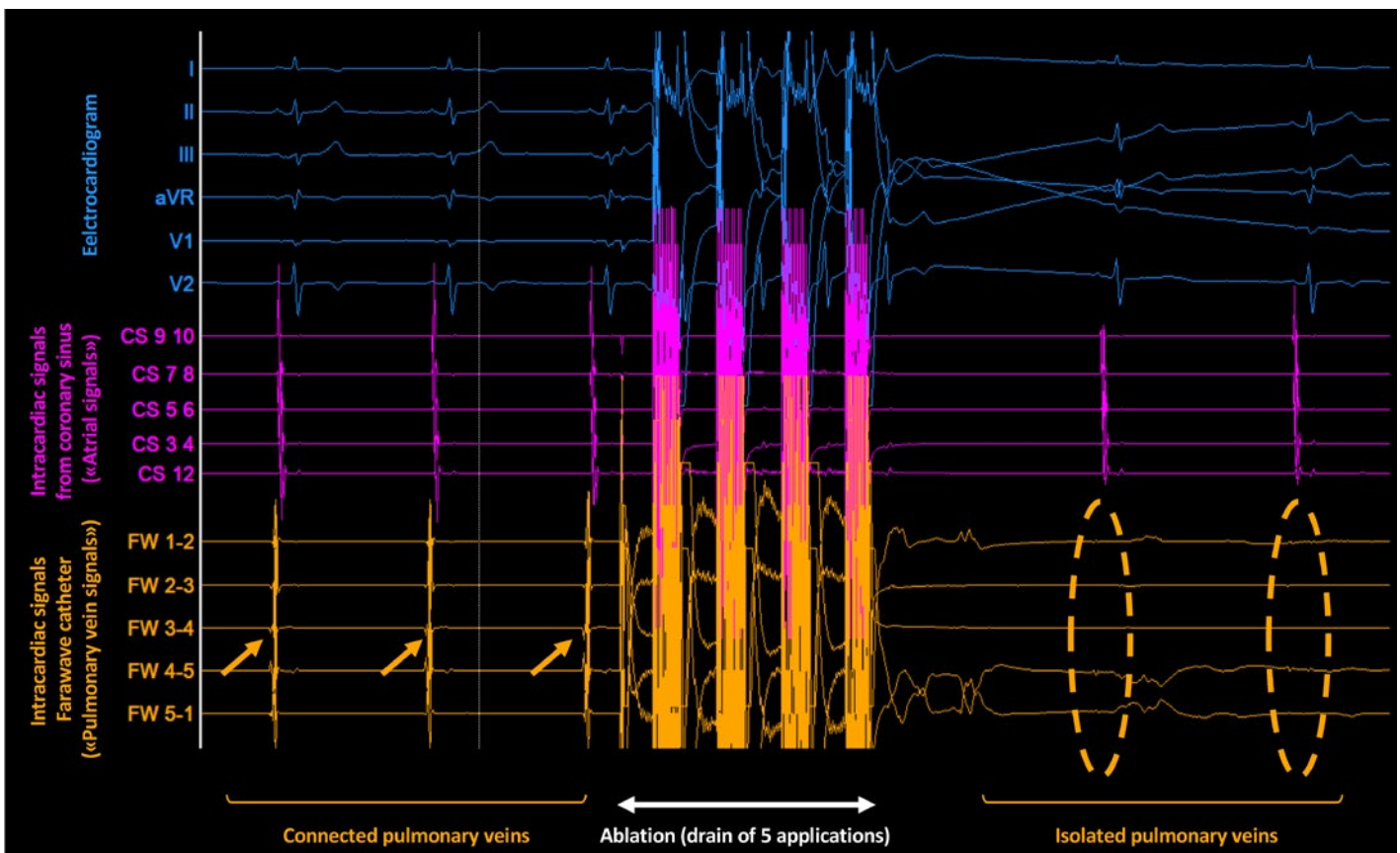


Figure 2: Energy application during pulsed field ablation and acute isolation of the pulmonary veins.

resulted from electrical hyperpolarization of neural cells and regressed within hours after the procedure. In the PULSED AF pivotal trial [27] as well as in the multicenter inspire study [26], no permanent phrenic nerve lesions were observed. The very low risk of permanent nerve palsy is in line with preclinical data confirming preserved nerve fascicles within the ablation area after PFA treatment [32].

Non-thermal Complications

Non-thermal (mechanical) complications following PFA can occur at similar rates as after ablation technologies using thermal energy sources. Pericardial tamponade due to catheter and sheath manipulation occurred in around 1 out of 100 procedures in patients undergoing PFA procedures [20, 22, 23]. Transient ischemic attack or stroke was documented in 0.5% of patients in the MANIFEST-PF survey and in 2 out of 191 patients (1%) in the initial validation phase of the single-center 5S trial (Safe and Simple Single Short Pulmonary Vein Isolation with Pulsed Field Ablation Using Sedation) [22]. These events most likely resulted from air embolism or embolization of small clots emphasizing the need for careful removal of air from the large bore sheath used for the procedure [22].

Silent cerebral lesions were identified in 10 out of 53 patients (19%), which corresponds to the finding in patients undergoing thermal ablation procedures [22]. The most frequent complications in the MANIFEST-PF survey were of vascular origin including groin hematomas (2.44%), of which the majority were managed conservatively [23].

Uncertainties, Limitations and Potential Risks

Selectivity for Myocardial Tissue and Thermal Effects

PFA technology offers PVI with a very low complication rate which is, at least in part, due to the highly specific effect of the applied energy to the myocardial tissue. However, this specificity is not 100% and the risk of collateral damage is not zero. The entire tissue which is exposed to the electrical field during PFA is affected by the applied energy; however, each tissue has a characteristic threshold for irreversible electroporation [18]. According to previous data, this threshold is low for myocardial tissue (thus making the myocardium very susceptible for electroporation), but much higher for red blood cells, vascular smooth muscle cells or endothelium and even higher

for nerve fibers. This difference in susceptibility offers a certain degree of selectivity; still, if the cumulative energy applied by PFA exerts a certain level, the selectivity will decrease and damage to other organs can happen. As an example, in a cohort of patients undergoing either radiofrequency ablation or PFA, lesions at the descending aorta, although without any clinical consequence, have been seen on MRI analysis in nearly half of the patients after both interventions [33]. This knowledge of potential decreasing myocardium-selectivity is of paramount importance, because the observed high safety profile of PFA may potentially mislead operators to perform too many PFA applications.

The effect of PFA results primarily from a non-thermal creation of nanopores into the myocardial cell membrane. However, some degree of heating cannot be avoided and previous animal studies have shown a rise in temperature in proximity of the ablation catheter [34]. While the maximal temperature correlated with the applied energy, the rise in the temperature did not exert an effect beyond the myocardium [34, 35] and therefore is unlikely to cause a relevant clinical effect. However, similar to the specificity of PFA to the myocardium, this also applies to the PFA applications being within the tested energy dosages and do not significantly exceed the recommended number of deliveries. Apart from tissue heating, the blood surrounding the ablation catheter may also be affected by a rise in temperature. Because an increase of blood temperature from 50 to 80 °C can cause the formation of soft thrombi, this can lead to silent as well as clinically relevant strokes. Indeed, in the study by Zang et al, the highest temperature between the catheter and the blood during energy application exceeded 70 °C. Since the energy impulses are of short duration, the clinical relevance is unclear, but to minimize the risk of clot formation it is recommended to keep the ACT above 350 seconds during the intervention.

Coronary Vasospasm

Not rarely, patients with AF suffer from atrial flutter (AFL) as well hence, ablation beyond PVI is necessary to treat this population adequately. This includes ablation at the cavotricuspid isthmus (for typical right-sided AFL), at the left atrial roof (for left-sided roof-dependent AFL) or at the mitral isthmus (for perimitral flutter). Anatomically, the cavotricuspid as well the mitral isthmus are located in the proximity of coronary arteries and ablation at this localization can lead to injury of a coronary artery. For PFA, vasospasms have been described both in animal models as well as in

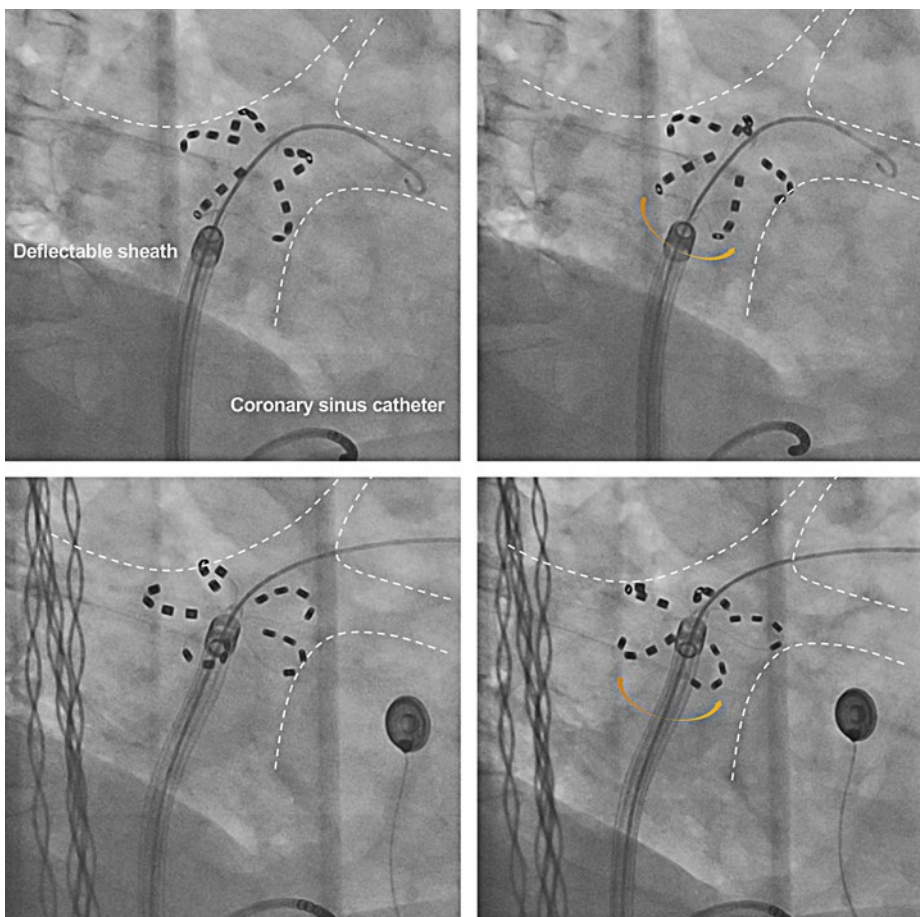


Figure 3: Positioning of the ablation catheter in the left upper pulmonary vein (RAO view).

humans when coronary angiography was performed concomitantly to the PFA energy application [36, 37]. While the majority was sub-clinical without a relevant effect, reports of patients who developed ST-segment elevation and subsequent ventricular fibrillation emphasize the potential risk [37, 38]. It remains unclear whether the design of the pentaspline catheter or PFA itself is responsible for the occurrence of vasospasm, since patients who underwent ablation of the cavotricuspid isthmus using a focal PFA catheter (but with the same energy waveform) showed no signs of vasospasms or ST-segment elevation [25]. However, with the currently available PFA system it is recommended to avoid ablation close to the coronary arteries.

Interaction with Cardiac Implantable Devices

This is indeed a not yet fully resolved issue of PFA ablations, but of growing relevance since the number of patients suffering from AF that also have other devices implanted (e.g., pacemaker, left atrial appendage occluder) is rising. Chen and colleagues published a case series of twenty patients with either a transvenous pacemaker or defibrillator undergoing PFA [39]. One of them also had a left atrial appendage device occluder implanted. In all patients, the ablation procedure (with the goal to avoid direct contact between ablation catheter and the device component) could be performed without any side effects and no long-term de-

lirious effects have been identified on device interrogation. This observation is supported by previous experience with electroporation in oncologic patients with an implantable device where also no negative impacts on the device parameters have been observed [40].

Procedural Efficacy for AF Ablation

Durable isolation of the pulmonary veins is the major determining factor for the efficacy and benefit of catheter ablation in AF. The first three human trials with the Farapulse™ PFA system (IMPULSE, PEFCAT and PEFCAT II) have shown that acute PVI was achieved in 100% with 7.2 ± 2.2 applications per vein [20]. Importantly, during the invasive reassessment performed after a median of 84 days, 96% of the pulmonary veins remained durably isolated in patients treated with the optimized biphasic waveform and there were no signs of lesion regression over time [41]. In the MANIFEST-PF survey enrolling 1,758 patients at 24 centers, acute PVI was achieved in nearly all patients (99.9%) [23]. This is similar to the experience from the single-center 5S trial in which all pulmonary veins were isolated at the end of the procedure (99.5% after the first application of pulsed field energy) [22].

In most cases the ablation procedure was performed under deep sedation using intravenous propofol, midazolam and opioid analgesics. Although, in the MANIFEST registry, more than 80% of all interventions were performed without general anesthesia [23].

The procedure duration (skin-to-skin) in the mentioned trials including both paroxysmal as well as persistent AF patients, declined with greater operator experience from 96.2 ± 30.3 minutes (IMPULSE and PEFCAT) [20] to 65 minutes in the MANIFEST-PF survey [23] and to 39 ± 14 minutes in the 5S study [22].

12-months Outcome

The one-year outcome of the IMPULSE, PEFCAT and PEFCAT II trial, enrolling primarily patients suffering from paroxysmal AF, showed freedom from any atrial arrhythmia longer than 30 seconds in $84 \pm 5.4\%$ for the optimized biphasic bipolar waveform. These results were supported by the recently published data of the MANIFEST-PF trial, which showed freedom from atrial arrhythmias in 78.1% at one-year [42]. A meta-analysis on PVI with PFA confirmed these findings documenting a recurrence of atrial arrhythmia in only 11% of the population after a follow-up of 9 ± 3 months [43]. There is one randomized trial recently presented at the European Society of Cardiology meeting 2023 in Amsterdam and simultaneously published in the New England Journal of Medicine [31], that demonstrates an equal efficacy of PFA versus cryoballoon or radiofrequency ablation in patients with paroxysmal AF with a low rate of major side effects in both groups. There were two tamponades in the PFA group, one of them leading to death due to long resuscitation and multiple organ fail-

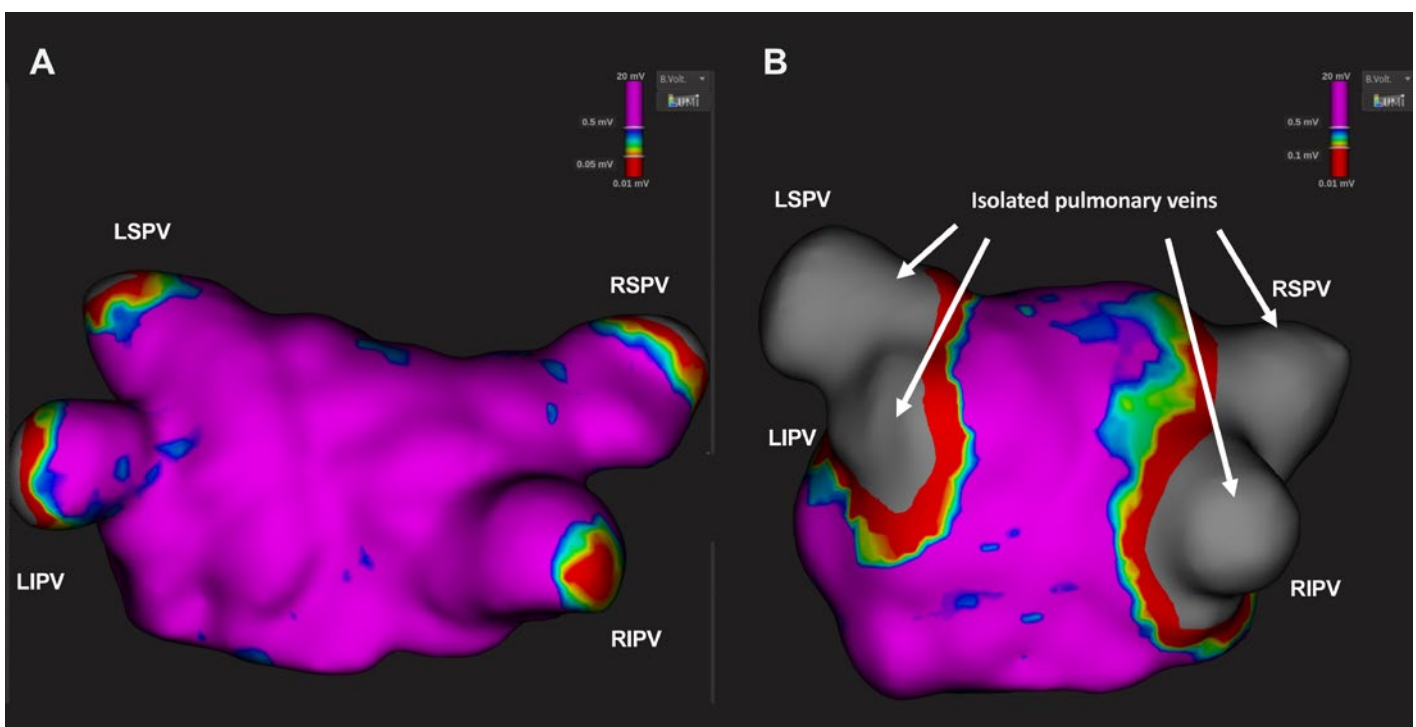


Figure 4: Three-dimensional reconstruction of the left atrium before (A) and after (B) ablation (posterior view).

LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein.

ure, and one stroke in the thermal ablation population. Further trials comparing efficacy and safety of PVI with PFA to PVI with thermal ablation are underway (e.g., SINGLE SHOT CHAMPION Study, NCT05534581).

Conclusion

PFA technology is a novel treatment option for cardiac arrhythmias. So far, the efficacy of PFA for the reduction of AF seems to be at least as good as conventional thermal energy sources, and theoretically with a better thermal collateral damage safety profile. PVI can be accomplished rapidly with similar efficacy and without compromising safety in our patients. In the near future, other ablation devices using electroporation will be available for the treatment of AF and other arrhythmias, like ventricular tachycardias, will be addressed using PFA technology.

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Conflict of Interest Statement

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References

You will find the full list of references online at <https://cvm.swisshealthweb.ch/en/article/doi/cvm.2024.1297020794/>.