REVIEW

Pulsed Field Ablation (PFA) for Pulmonary Vein Isolation in τhe Treatment of Atrial Fibrillation

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Abstract

Pulsed-field ablation (PFA) is a promising new ablation modality for the treatment of atrial fibrillation (AF). Pulmonary vein isolation (PVI) remains the most frequently used treatment strategy of any AF ablation procedure. A major limitation of current catheter ablation procedures is PVI reconnection, reported to be about 20% of patients. Pulsed field ablation is a novel energy source by which high-voltage electric pulses are used to create pores in the cellular membrane (i.e., electroporation), leading to cellular death. The amount of energy required to produce irreversible electroporation is highly tissue dependent reducing the risk of damage to surrounding non-cardiac tissues. The tissue specificity of PFA may result in a wide therapeutic range and improved safety profile during atrial fibrillation ablation. There has been no evidence of incidental phrenic nerve injury, and finally, PFA has been shown not to injure esophageal tissue when directly applied to the esophagus or indirectly through ablation in the left atrium. ***Rhythmos 2022;17(4): 75-78***.

Key words: atrial fibrillation; catheter ablation; radiofrequency ablation; pulmonary vein isolation; pulsed field ablation

Abbreviations: CA = catheter ablation; CMR = cardiac magnetic resonance (imaging); IRE = irreversible electroporation; LA = left atrium; LAPW = left atrial posterior wall; LGE = late gadolinium enhancement; PFA = pulsed field ablation; PVI = pulmonary vein isolation; RF = radiofrequency; RFA = radiofrequency ablation

Conflict of interest: none

Introduction

Catheter ablation (CA) for atrial fibrillation (AF) is a well-recognized treatment option for symptomatic patients with AF for rhythm control.[1] Catheter ablation has been proved to be more effective than antiarrhythmic drugs in reducing hospitalizations and improving symptoms and quality of life.[2] The cornerstone of CA is the electrical isolation of pulmonary veins (PVs) and is typically performed with radiofrequency (RF) or cryotherapy.[3] However, as these thermal approaches do not specifically target the atrial myocardium, anatomical structures surrounding the left atrium, such as esophagus and/or phrenic nerve, are at risk of collateral damage.[4-6] Pulsed-field ablation (PFA) is a non-thermal ablation technology that uses high amplitude pulsed electrical fields to ablate atrial tissues causing irreversible electroporation (IRE).[7] Irreversible electroporation has been used in Oncology targeting to tumor cells death. PFA occurs by creating an electric field with a high voltage ultra – short pulses between electrodes. This increases cell membrane permeability, leading to increased ion transport and overall membrane instability causing cell death. One of the most promising features of PFA is tissue selectivity.[8] The electric field strength threshold required for cell death varies for tissue types and it is among the lowest for cardiac myocytes. Moreover, the degree of PFA effect on tissue is dependent of the special tissue characteristic such as fiber orientation (lesion size is greater when elongated fiber orientated is in parallel to the catheter electrodes)[9,10]

Mechanisms, modulation and protocols of PFA

Electroporation occurs when a strong electric field is applied to a cell and increases its membrane permeability occurring finally an overall membrane instability and cell death. Field exposure parameters and the distance of the tissue from the delivery electrodes determine if the membrane permeability may be reversible or irreversible.[11] A lot of different electric field delivery factors influence this process (i.e., pulse amplitude, pulse width, number of pulses, biphasic or monophasic waveforms, and pulse cycle length). Depending on field exposure parameters and the distance of the tissue from the delivery electrodes, this increased membrane permeability may be reversible or irreversible.[11] Despite the high amount of energy delivered to the tissues, PFA has a weak thermal effect due to the short duration of total application and pulses < 100 μs.[12] Moreover, PFA has been observed to produce more uniform and homogeneous lesions when compared to those created using RF energy independent of a perfect electrode-tissue contact. In patients with paroxysmal AF who underwent PFA vs RFA, magnetic resonance imaging using late gadolinium enhancement (LGE) showed that PFA induced large acute LGE with no signs of microvascular damage or intramural haemorrhage. Most LGE lesions disappeared in the chronic stage, despite durable pulmonary vein isolation and low voltage areas, suggesting a specific reparative process involving less chronic fibrosis. This process may contribute to a preserved tissue compliance and LA reservoir and booster pump functions.[13]

The use of pulsed biphasic, bipolar waveforms is associated not only with confined energy delivery that

surrounds the catheter electrode array with distinct lesion margins, but it is also related with a reduction of undesired muscle contractions and nerve stimulation.[14] For that reason, PFA has been performed under conscious sedation by using biphasic waveforms. In order to achieve successful irreversible electroporation, the following variables must be taken into consideration since they all have a significant impact: wave form, pulse length, electric field intensity, pulse frequency and the number of pulses applied. Typical parameter ranges reported are 500 to 3000 V/cm voltage delivered, 1 to 100 pulses delivered, over a wavelength of microseconds, with a frequency range of 1 to 5 Hz.[15-17] The increase of all these parameters has been associated with lower threshold of irreversible electroporation. In contrast to RF ablation, all commercial PFA systems employ unique and different energy and waveform parameters using different catheters (**Fig**. 1). It must be noticed that the degree of PFA effect on tissue is dependent of the tissue characteristic, fiber orientation, and heterogeneities in the local tissue environment. Although the risk of ventricular fibrillation induction during PFA delivery is very low, ECG gating is important in order to allow R-wave synchronized current delivery and to avoid application of DC current during the vulnerable period of ventricular repolarization. [18]

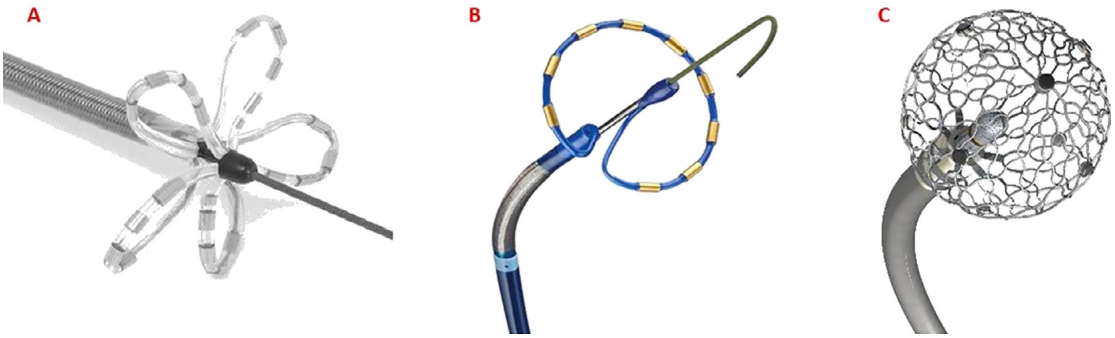

Figure 1. Catheters currently used for PFA. **A**: Farawave catheter (Farapulse, Inc, Menlo Park, CA). **B**: PFA, Pulmonary vein Ablation Catheter GOLD (PVAC GOLD; Medtronic, Inc, Minneapolis, MN). **C**: Lattice-tip PFA and RF ablation, Sphere-9 catheter (Affera, Inc, Watertown, MA). PFA = pulsed-field ablation; PVAC = pulmonary vein ablation catheter; RF = radiofrequency

Efficacy and safety. Data from clinical studies

First initial clinical experience with monophasic PFA in patients with paroxysmal AF was published from Reddy et al[19] using either an endocardial ablation catheter or a linear epicardial catheter designed to wrap around the PVs. This study was performed at two centers and reported data regarding 15 endocardial and 7 epicardial AF ablations. Pulmonary vein isolation was obtained in 100% of patients and surgical box lesions in 86% of patients. The authors used the FARAPULSE™ Pulsed Field Ablation System with the FARAWAVE™ catheter which is an over-the-wire 12F catheter that has a distal portion consisting of 5 splines, each with 4 electrodes per spline. The catheter is advanced in the left atrium through a steerable 13F sheath and can be deployed in a "basket" shape and then deployed in a "flower" configuration (achieving a diameter of up to 31 mm). Acute PVI was achieved in 100% of the PVs (12.4 ±1.0 lesions per patient, 3.26 ±0.5 lesions/PV). The voltage range was 900-2500 V, with a mean energy delivered of 78 J per ablation, and a total ablation time of 26 ±4.3 min.[19]

The IMPULSE, PEFCAT and PEFCAT II are three prospective, non-randomized, single-arm trials that included 121 patients with symptomatic paroxysmal AF scheduled for PVI using the Farapulse system.[20,21] In 121 patients, acute PVI was achieved in 100% of PVs with PFA alone. PV remapping, performed in 110 patients at 93.0±30.1 days, demonstrated durable PVI in 84.8% of PVs (64.5% of patients), and 96.0% of PVs (84.1% of patients) treated with the optimized biphasic energy PFA waveform. Primary adverse events occurred in 2.5% of patients (2 pericardial effusions or tamponade, 1 hematoma). Additionally, there was 1 transient ischemic attack. The 1-year Kaplan-Meier estimates for freedom from any atrial arrhythmia for the entire cohort and for the optimized biphasic energy PFA waveform cohort were 78.5±3.8% and 84.5±5.4%, respectively. Interestingly, although right phrenic nerve capture was common during PFA to the right superior PV, no phrenic nerve palsy was recorded.

Another novel ablation catheter with a lattice-tip design (Sphere-9; Affera, Inc., Watertown, MA, USA) which can deliver RF and PFA was used in a first-in-human trial.[22] This is a 7.5F bidirectional deflectable catheter with an

expandable 9 mm diameter nitinol lattice electrode, containing nine minielectrodes on the spherical surface. Pulmonary vein isolation was performed with a strategy of either PFA posteriorly and RF anteriorly (RF/PF), or PFA throughout (PF/PF). The catheter can deliver RF and PFA, and its generator (HexaGen and HexaPulse, Affera, Inc., Newton, MA, USA) has a dual design in order to permit a switch between two energies. In this 3-center, single-arm, trial 76 patients with symptomatic paroxysmal or persistent AF were enrolled. The ablation energy used was RF/PF in 40 patients and PF/PF in the remaining 36 patients, with PF used on the posterior LA because of the esophagus. In persistent AF patients, additional linear ablation of the posterior mitral isthmus or the LA roof was performed per operator discretion. The primary safety end point rate was 1.3% (one patient with vascular access injury without any pericardial tamponade, phrenic nerve injury, brain lesions, or esophageal injury.

The inspIRE trial is a prospective, non-randomized, multicenter study, planned to enroll up to 550 patients. A decapolar irrigated loop circular ablation catheter has been used with Carto system (Biosense Webster, Irvine, CA, USA) in 35 patients with paroxysmal AF. Acute PVI was achieved in 100% of the patients with zero incidence of primary adverse events.[23]

In a recently published study, Cochet H et al.[24] investigated the extra-atrial damages after AF ablation using both PFA and RF. Cardiac magnetic resonance (CMR) imaging was performed before, acutely (<3 h) and 3 months post-ablation in 41 paroxysmal AF patients undergoing PVI with PFA (N= 18, Farapulse) or thermal methods (N= 23, 16 radiofrequency, 7 cryoballoon). Acutely, RF and cryoablation energies caused 43% of esophageal lesions in the area of direct contact between the atrium and esophagus, while PFA did not cause esophageal lesions. Acute lesions were documented on the descending aorta in 43% of patients after thermal ablation, and in 33% after PFA. At 3 months, all lesions resolved without significant clinical complications.

Left atrial structural and mechanical characteristics were compared after PFA vs RF ablation. The study published by Nakatani Y et al.[25] reported data regarding CMR obtained pre-ablation, within 3 h and 3 months after procedures, in 41 patients with paroxysmal AF undergoing PVI using PFA (18 patients) or thermal ablation (16 radiofrequency ablations and 7 cryoablations). In the acute stage, late gadolinium enhancement (LGE) volume was 60% larger and oedema was 20% smaller after PFA compared to RF. Lesions were more homogeneous after PFA than RF, without signs of microvascular damages or intramural hemorrhage. After 3 months, the majority of acute LGE had disappeared after PFA, whereas most LGE persisted after thermal ablation. These data suggest a low grade of fibrosis in patients ablated using PFA and moreover a preserved tissue compliance and left atrial function.

Pulsed field ablation has been also used in patients with persistent AF. It is known that these patients often require multiple and more extensive ablation procedures, beyond PVI, to maintain sinus rhythm since progressive left atrium structural and electrical remodeling creates a complex substrate. Moreover, persistent AF ablation is associated with higher risk of procedural complications. A recent study reported data safety and efficacy data of PFA for both PVI and left atrial posterior wall (LAPW) ablation in persistent atrial fibrillation. Acute PVI and LAPW ablation were successfully obtained in all patients. Post procedure esophagoscopy and repeat cardiac computed tomography revealed no mucosal lesions or PV narrowing, and invasive remapping demonstrated durable isolation (96% of PVI and 100% of LAPW isolation). [26]

Conclusion

Pulse field ablation is a new technology involved in the field of atrial fibrillation ablation, additionally to RFA and cryoablation. PFA seems to be effective and safe since data from clinical trials have shown an excellent lesion durability and safety in PVI. Moreover, PFA technology eliminates the risk of esophageal injury, a rare but potentially fatal complication for procedures using thermal energy. At this moment, there are no data from large clinical randomized trials to compare PFA with the other technologies in order to show PFA superiority both on efficacy and safety.

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