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REVIEW

Advances in the Application of Pulsed Field Ablation for Arrhythmia Treatment

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Abstract

The increased application of catheter ablation to treat cardiac arrhythmias has contributed to continued exploration of safe and effective tissue ablation tools in the field of electrophysiology. Pulsed field ablation (PFA), a novel recently developed non-thermal energy-based technique, uses trains of microsecond duration high-amplitude pulses to ablate target cells. Several preclinical and clinical studies have demonstrated that PFA is a promising tool for cardiac ablation to treat arrhythmia. In addition to being an effective tissue ablation technique, PFA is safe, because it avoids damage to the surrounding cells/tissues. This review focuses on efficacy and safety outcomes reported in preclinical and clinical studies evaluating the effects of PFA on arrhythmia, and discusses limitations and potential future directions of PFA.

Keywords: Pulsed field ablation; Arrhythmia; Catheter ablation; Atrial fibrillation

Introduction

Catheter ablation is an effective and mainstream therapy for both atrial fibrillation (AF) and ventricular arrhythmias. Recent studies have demonstrated that the effectiveness of catheter ablation in maintaining sinus rhythm, improving quality of life, and decreasing stroke and re-hospitalization is higher than that of anti-arrhythmic drug therapy [1–4]. However, despite recent advances, overall unsatisfactory efficacy and safety have limited the application of catheter ablation, particularly in patients with persistent AF and those with a non-ischemic substrate for ventricular arrhythmias [5, 6]. Moreover, tailoring lesions to enhance effectiveness and safety is challenging during pulmonary vein (PV) isolation (PVI) without increasing the risk of collateral damage to the surrounding structures [7]. Therefore, a need exists to develop effective and safe approaches to improve the therapeutic efficacy of lesion ablation in arrhythmia.

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Pulsed field ablation (PFA) is a promising novel ablation strategy for arrhythmia therapy. This non-thermal ablation modality uses high-intensity electric fields to increase the permeability of the cell membrane through an irreversible electroporation mechanism, which results in cell death and tissue ablation [8, 9]. PFA addresses the limitations of current thermal ablation therapies, and may be an effective and safe therapeutic modality for arrhythmia. Theoretically, PFA can generate contiguous, transmural lesions without tissue heating and can be selective for cells/tissues. PFA has a good safety profile because it does not adversely affect critical surrounding structures [8]. The potential efficacy and safety of PFA in treating AF or ventricular arrhythmias have been supported by several preclinical and clinical studies. Because PFA is a novel technique, this review is aimed at providing a basic understanding of the PFA technique, and examining current and potential future applications of PFA in cardiac arrhythmia treatment.

History of PFA

Between 1900 and 1970, several studies examined the pulsed electrical field-induced irreversible electroporation of the phospholipid bilayer of cellular membranes in vitro and in vivo. In 1982, Neumann et al. [10] first used pulsed electric fields to transfer genes in mice. The first report of direct tissue ablation using a pulsed electrical field without drugs was by Davalos et al. [11] in 2005. Subsequently, direct current delivery via diagnostic catheters was confirmed to cause local ablation of lesions [12]. Pulse amplitude reduction, and damage was associated with the energy applied and electrode surface area. In 2007 Lavee et al. [13] first reported direct PFA of the left atrium on the epicardial surface in pigs, and suggested that this method is a novel and promising ablation technique for AF therapy. In 2011, Wittkampf et al. [14] provided the first demonstration of the feasibility of using PFA for PVI in an animal model, and reported preclinical evidence that PFA as a safe and effective ablation modality for AF. In 2018, Reddy et al. [15] performed the first clinical study on PFA for paroxysmal AF, and confirmed that PFA enhances the effectiveness, safety, and durability of PVI. Subsequently, the same research group extended the clinical application of PFA to persistent AF in 2020 [16]. The results of almost all clinical investigations have indicated the efficacy and safety of PFA application for AF therapy. Figure 1A summarizes key milestones in the development of PFA.

Mechanisms of PFA-Mediated Cell Death

Unlike thermal modalities, PFA does not have contact-dependent effects on tissue because the effects are a result of the generated electric field. In PFA, tissue electroporation is induced by the application of intermittent high-voltage electrical pulses (microseconds or even nanoseconds) to tissue, thus resulting in the loss of biological functions [8, 17]. Electroporation results in rearrangement of phospholipid bilayers in cell membranes induced by the application of an electric field, thereby promoting the formation of hydrophilic pores and increasing the membrane permeability [18, 19]. The effects of electroporation are tiered and range from brief, reversible alterations to irreversible apoptotic death and necrosis (Figure 1B). In PFA, high-voltage electric field strength instantaneously induces irreversible damage in cell membranes, thus resulting in the leakage of potassium ions and enzymes, intracellular calcium ion overload, and ultimately cell necrosis.

Parameters of PFA Delivery

The observed cellular effects depend on the applied electric field, which is determined by various parameters, including pulse duration, amplitude, frequency, and biphasic or monophasic waveforms (Figure 1C). Typical PFA parameters are as follows: voltage, 500–3000 V/cm, number of pulses, 1–100; wavelength, nanoseconds to milliseconds; and frequency, 1–5 Hz [20]. The delivery pulses in the previous studies were predominantly delivered via a monophasic waveform. Currently, biphasic waveforms are widely used in clinics, owing to their favorable safety and effectiveness [21, 22]. In contrast to conventional thermal ablation (cryoablation and radiofrequency ablation), all current commercial PFA systems have unique pulse energy and

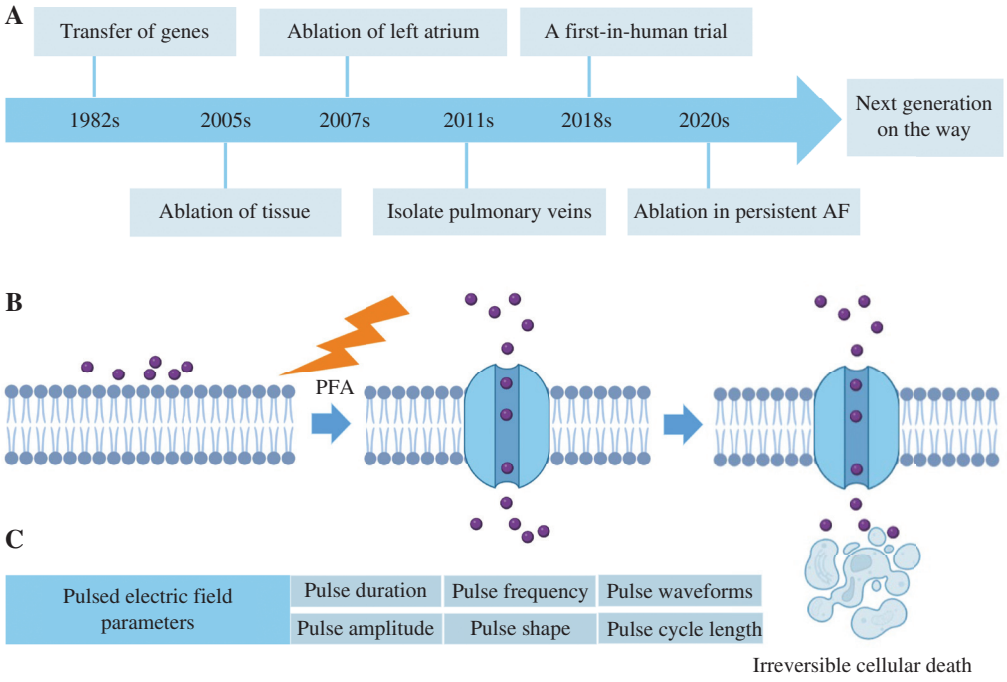

Figure 1 History and Mechanism of Pulsed Field Ablation (PFA).
(A) Milestones in the development of PFA. (B) Molecular simulation of pore formation with PFA. The cellular membrane is impermeable to ions and water, thereby enabling the establishment of a controlled intracellular environment. PFA with high energy levels induces the formation of pores in the cell membrane, thus allowing ions to freely enter the cells. Cell death results from the formation of several permanent and frequently coalescent pores with the application of sufficient energy. (C) PFA parameters influencing the observed effects on tissues.

waveform parameters, and thus no universal PFA ablation system exists. Consequently, the optimal parameters for treating arrhythmias with PFA have not been elucidated, thereby partially limiting the safety and efficacy evaluation of PFA.

Safety of PFA

PFA has a better safety profile than that of thermal ablation, owing to its excellent tissue selectivity; low threshold for myocardial damage; and ability to prevent damage to vascular smooth muscle around the heart, esophagus, nerves, etc. (Figure 2A). The effects of PFA on tissues depend on the voltage, number of pulses, pulse duration, phase (monophasic-biphasic), pulse shape, pulse frequency, and catheter electrode (Figure 2B). The voltage at which tissue damage occurs in different tissues has been reported to be as follows: cardiac myocytes, 400 V/cm; vascular smooth muscle and endothelium, 1750 V/cm; and nerve tissue, 3800 V/cm [15]. Various studies have evaluated the effects of PFA on the ganglion plexus, phrenic nerve, coronary artery, esophageal and aortic injury, and PV stenosis. Table 1 summarizes safety studies on PFA-associated tissue selectivity.

Cardiac Autonomic Nervous System

PFA is frequently reported to elicit a vagal response and phrenic activation. However, whether the vagal responses and phrenic activation are due to nerve damage or to a stress response to electrical stimulation is unclear. Recently, Guo et al. [24] have demonstrated that the PFA system spares nerves during PVI for paroxysmal AF. That study provided the first demonstration that PFA does not affect the cardiac autonomic nervous system or serum biomarker levels of nerve injury, thus suggesting that PFA may selectively spare the ganglionic plexus. However, given that extensive vagal denervation alone without PVI has recently been reported to be as successful as PVI at maintaining sinus rhythm at 1 year postablation, whether the success of AF ablation is due to PVI alone or to changes to neuronal

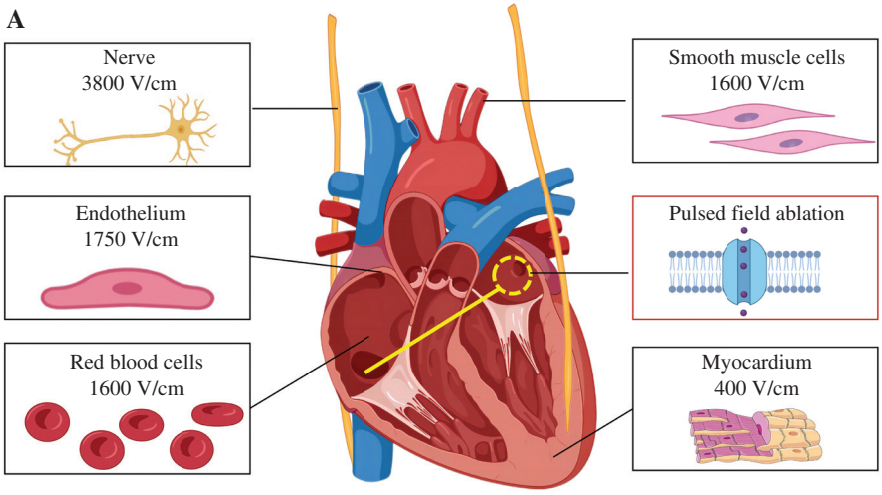

Figure 2 Pulsed Field Ablation (PFA) Thresholds for Various Tissues.
(A) PFA has the potential to specifically target myocardial tissue and does not affect surrounding tissues or cells [23]. (B) PFA parameters influencing the observed effects on tissue.

structures is unclear [41]. Therefore, more studies should be conducted on this issue in the future to provide direct evidence.

Coronary Arteries

The vascular matrix remains largely intact after PFA treatment, which causes no permanent coronary artery damage [35]. However, Neven et al. [42] have reported that coronary artery spasm may be induced after electrical stimulation, although no long-term coronary stenosis occurs. PFA has been used in clinical practice for PVI and left atrial posterior wall ablation to enlarge the lesion and bring the coronary arteries into proximity, thus potentially significantly increasing the probability of coronary artery spasm and catastrophic consequences for patients with coronary artery disease [16]. Recent studies have demonstrated the occurrence of coronary arterial vasospasm during PFA when the ablation catheter is close to the coronary artery, particularly during cavotricuspid isthmus ablation, for which severe vasospasm in the right coronary segment near the PFA catheter has been reported in 100% of patients [30].

Esophagus

Atrial-to-esophageal injury, which leads to atrioesophageal fistula after AF thermal ablation, is an adverse and fatal consequence of the treatment, with a mortality rate of approximately 50% [43]. However, PFA is expected to overcome this complication. Neven et al. [44] have directly applied PFA to the outer wall of the pig esophagus and observed that the mucosal muscle layer remained intact, with no transmural damage/mucosal injury. Additionally, the esophageal architecture remained unaffected after 2 months. Similarly, clinical studies have confirmed that PFA selectively spares the esophagus. No acute esophageal lesions have been detected in cardiac magnetic resonance images of patients treated with PFA [25].

Aorta

After PVI with thermal techniques, aortic late gadolinium enhancement lesions have been reported to be common [45]. Recent studies have indicated that patients treated with PFA exhibit transient late gadolinium enhancement lesions in the descending aorta, although the pathological importance of these

Table 1 Safety Studies Associated with Pulsed Field Ablation Specific Tissue Selectivity.

Author	Subject	Ablation strategy	Catheter design	Waveform style	Pulse amplitude	Follow-up	Outcomes
Clinical studies							
Guo et al. [24]	Paroxysmal AF	PV	circular 7 or 9 electrodes	Biphasic	1800 V/cm	8 months	No nerve injury No new asymptomatic brain emboli No PFA-related complications
Cochet et al. [25]	Paroxysmal AF	PVI	Basket/Flower 20 electrodes	Biphasic	1800–2000 V	3 months	No acute esophageal lesions Transient aortic injuries
Nakatani et al. [26]	Paroxysmal AF	PVI	Basket/Flower 20 electrodes	Biphasic	1800–2000 V	3 months	Large acute late gadolinium enhancement; No microvascular damage or intramural hemorrhage
Kuroki et al. [27]	Paroxysmal AF	PVI	Basket/Flower 20 electrodes	Monophasic Biphasic	900–1000 V 1800–2000 V	3 months	Virtually no PV narrowing/stenosis
Kawamura et al. [28]	Paroxysmal AF	PVI	Flower 20 electrodes	Biphasic	1800–2000 V	75 days	Created chronic PV antral isolation areas
Füting et al. [29]	Paroxysmal AF	PVI	Basket/Flower 20 electrodes	Biphasic	1900 V	90 days	No phrenic nerve or esophageal damage Cardiac tamponade in one patient
Reddy et al. [30]	Paroxysmal AF	PVI	Basket/Flower 20 electrodes	Biphasic	Not specified	Acute	PVI and LAPW: no evidence of coronary arterial spasm
	Persistent AF	LAPW, CTI					CTI: subtotal vasospasm of the right coronary arterial
Preclinical studies							
Jiang et al. [31]	Porcine Canine	Endocardium SVC	circular 7 electrodes	Biphasic	1000–1500 V	3 weeks	Without phrenic palsy, sinus node injury, and SVC stenosis
Howard et al. [32]	Porcine	Endocardium Phrenic nerve	Circular 9 electrodes	Biphasic	700–1500 V	4 months	No phrenic nerves and diaphragms injury No evidence of inflammation
Koruth et al. [33]	Porcine	Endocardium PV and SVC	Basket 20 electrodes	Monophasic and biphasic	800–2000 V	2 months	Spared of nerves and venous tissue
Koruth et al. [34]	Porcine	Endocardium PV and SVC	Lattice-tip 9 mini electrodes	Biphasic	Not specified	4 weeks	Without epicardial fat, nerve, or vessel involvement
Du Pré et al. [35]	Porcine	Epicardial left ventricle	Circular 10 electrodes and linear electrode	Not specified	50–360 J	3 weeks	Coronary arteries remain free of damage amid huge transmural myocardial lesions

Table 1 (continued)

Author	Subject	Ablation strategy	Catheter design	Waveform style	Pulse amplitude	Follow-up	Outcomes
Bi et al. [36]	Porcine	Endocardium PV	Basket 8 electrodes	Biphasic	1000 V	30 days	No damage to other tissues
Yavin et al. [37]	Porcine	Endocardium right atrial	Circular 10 electrodes	Biphasic	1800 V	30 days	No effect on the esophagus or the phrenic nerve
Deodhar et al. [38]	Swine	Epicardial left ventricle	NanoKnife needles	Biphasic	1667–1700 V	Acute	Unsynchronized electroporation can cause fatal ventricular arrhythmias
Witt et al. [39]	Canine	Endocardium PV	Balloon	Biphasic	1000–2000 V	44 days	No PV stenosis
Livia et al. [40]	Canine	Purkinje tissue	Single electrode	Monophasic	750–2500 V	Acute	Purkinje tissue can be ablated with PFA without myocardial damage

AF, atrial fibrillation; PVI, pulmonary vein isolation; LAPW, left atrial posterior wall; CTI, cavotricuspid isthmus.

lesions is unclear [25]. This finding suggests that, similarly to the myocardium, the aorta may have a low field threshold.

Pulmonary Veins

PV stenosis is a common complication of thermal ablation techniques, such as radiofrequency ablation. A preclinical study comparing the effects of PFA and radiofrequency ablation directly within the PVs has demonstrated that PVs subjected to radiofrequency ablation exhibit progressive stenosis, on the basis of serial computed tomography scans. In contrast, veins subjected to PFA do not exhibit substantial stenosis [46]. Similarly, a clinical study has confirmed that, in contrast to radiofrequency ablation, PFA eliminates the incidence and severity of PV narrowing/stenosis after PVI [27].

Pre-Clinical Studies

The preclinical studies on PFA are summarized in Table 2. Although these studies used different PFA catheters, pulse amplitudes, and electrode configurations, the data support the efficacy and safety of this novel ablation technique to treat atrial and ventricular arrhythmias.

Atrial Myocardium

Preclinical studies have preliminarily demonstrated the safety and efficacy of PFA in treating atrial arrhythmias. Lavee et al. [13] first used PFA to ablate the left and/or right atrial appendages in pigs by applying direct current pulses of 1500–2000 V (each lasting 100 μs) at 5 pulses per second. Real-time measurements revealed that no temperature change occurred during ablation, and 100% transmural ablation was achieved at all sites. Next, the feasibility and safety of the PFA monophasic waveform for PVI were explored. The PFA monophasic waveform effectively isolated the PVs, which did not exhibit stenosis at the 3-week follow-up. Moreover, histological examination revealed lesions with a depth as great as 3.5 mm [14].

One study has evaluated a novel biphasic asymmetric PFA model and validated its focal persistence and safety for PVI in Bama miniature pigs [36]. Biphasic asymmetric PFA has been found to

Table 2 Preclinical Studies of the Efficacy of Pulsed Field Ablation.

Author	Subject	Target application	Catheter design	Waveform style	Pulse amplitude	Follow-up	Outcomes
Atrial myocardium							
Zhu et al. [31]	Porcine Canine	Endocardium SVC	circular 7 electrodes	Biphasic	1000–1500 V	3 weeks	Effective isolation of SVC Complete transmural lesions
Lavee et al. [13]	Porcine	Epicardial atrial appendages	Homemade clamp	Not specified	1500–2000 V	Acute	Complete transmural destruction and no local heating effects
Wittkampf et al. [14]	Porcine	Endocardium PV	Circular 10 electrodes	Not specified	200 J	3 weeks	PV electrogram amplitude decreased
Bi et al. [36]	Porcine	Endocardium PV	Basket 8 electrodes	Biphasic	1000 V	30 days	Complete transmural lesions
Stewart et al. [47]	Porcine	Endocardium PV	Circular 9 electrodes	Biphasic	500 V	2 weeks	Consistent transmural and homogeneous replacement fibrosis devoid of lingering myocyte "sequesters"
Van Driel et al. [48]	Porcine	Endocardium PV	Circular 10 electrodes	Monophasic	200 J	3 months	PV ostial diameter decreased 11% ± 10% directly after ablation, but had increased 19% ± 11% after 3 months
Koruth et al. [33]	Porcine	Endocardium PV and SVC	Basket 20 electrodes	Monophasic and biphasic	800–2000 V	2 months	Effective isolation of PVs and SVC
Grimaldi et al. [49]	Swine	Endocardium PV and SVC	Circular 10 electrodes	Biphasic	Not specified	30 days	Durable lesions were observed at the target areas, with inflammation occurring at 7 days
Yavin et al. [37]	Swine	Endocardium right atrial	Circular 10 electrodes	Biphasic	1800 V	30 days	Transmural and contiguous atrial lesions
Yavin et al. [50]	Swine	Endocardium right atrial	Lattice-tip 9 mini-electrodes	Biphasic	400 V	35 days	Produced durable atrial lesions, lower vulnerability to the esophageal or phrenic nerve
Ventricular myocardium							
Al-Khadra et al. [51]	Rabbit	Epicardial ventricle	Not specified	Monophasic	50–500 V	Acute	Electroporation and conduction block thresholds in papillary muscles were 281+/−64 V and 380 +/−79 V, respectively
Neven et al. [52]	Porcine	Epicardium left ventricle	Linear electrode	Monophasic	30, 100, 300 J	3 months	Positive correlation between pulse energy and myocardial lesion size

Table 2 (continued)

Author	Subject	Target application	Catheter design	Waveform style	Pulse amplitude	Follow-up	Outcomes
Neven et al. [42]	Porcine	Epicardium left ventricle	Circular 8 electrodes	Monophasic	50, 100, 200 J	3 months	Average lesion depths of the 50-, 100-, and 200-J lesions were 5.0 ± 2.1, 7.0 ± 2.0, and 11.9 ± 1.5 mm, respectively
Koruth et al. [53]	Swine	Endocardium left and right ventricles	Basket 12 electrodes	Biphasic	2200 V	35.5 days	Ventricular substrate ablation, the lesion dimensions were 6.5 ± 1.7 mm deep
Zhao et al. [54]	Rabbit	Epicardial left ventricle	Circular 2 electrodes	Biphasic	800 V	1–4weeks	Myocardial cells showed apoptosis and necrosis with clear ablation borders
Im et al. [55]	Swine	Endocardium left ventricular	Linear focal and basket electrodes	Biphasic	Focal: 2000 V Basket: 800 V	Acute	PFA lesions were feasible in infarcted myocardium

PV, pulmonary vein; SVC, superior vena cava.

effectively decrease muscle contraction and the ablation threshold. In that study, electroanatomic mapping revealed that the ablation site exhibited a continuous low-potential zone. The atria were not captured 1 month after pacing. Histological analysis revealed that 100% of lesions were transmural and that good safety (with an absence of thromboembolism, intracardiac injury, or acute or chronic collateral tissue damage) was maintained at weeks 1 and 4.

Technical developments and well-designed preclinical studies have provided a scientific basis for human endocardial PFA studies. Koruth et al. [33] have compared the safety and feasibility of durable PVs and superior vena cava isolation between radiofrequency ablation and bipolar PFA with monophasic and biphasic waveforms. The durability of the biphasic waveform (18/18 (100%)) was better than that of the monophasic waveform (10/18 (55.6%)) and radiofrequency (3/6 (50%)). Additionally, in contrast to radiofrequency, PFA did not induce nerve injury or PV stenosis. Similarly, Stewart et al. [47] have reported that, compared with radiofrequency ablation lesions, PFA lesions do not exhibit a thermal signature, lack lingering "sequestered" cardiomyocyte and epicardial fat inflammation, and exhibit diminished vascular remodeling.

Recent studies have further confirmed these preclinical data. Yavin et al. [37, 50] have observed that PFA generated an acute block in 100% of the line, whereas focal ablation with PFA (biphasic, 1800 V), compared with standard radiofrequency ablation, generated sustainable atrial lesions with less vulnerability to esophageal or phrenic nerve injury. Grimaldi et al. [49] have further validated the short-term and long-term safety and efficacy of PFA for PVI and superior vena cava isolation, and observed 100% lesion persistence in both subchronic (1 week) and chronic (1 month) cohorts, including continued resolution of electrical activity in the left atrial apex and right posterior atrial wall. Inflammatory responses occurred mainly in week 1. No collateral structural changes were associated with PFA treatment.

Ventricular Myocardium

Limited data are available on the use of PFA for ventricular ablation. Early PFA has been used for ventricular ablation, mainly to study its effects on coronary arteries. du Pré et al. [35] have used PFA

to ablate the base of the left ventricle in the porcine epicardium, and have reported that, even in large left ventricular lesions, coronary arteries did not exhibit substantial stenosis within 3 weeks of ablation, although the epicardial disposition was close to the ablation electrode. Koruth et al. [53] have further evaluated the safety and feasibility of PFA for ventricular ablation in a proof-of-concept study. PFA was applied to the left and right ventricles of healthy pigs, thus resulting in significant electrogram attenuation without ventricular arrhythmias. Measurements of 28 ablation sites revealed that the lesions exhibited adequate width and depth, with a maximum depth and width of 9.4 mm and 28.6 mm, respectively. Additionally, arterial vessels and nerves within the lesions were unaffected, thus confirming the known myocardial specificity of PFA. In agreement with the safety profile reported in preclinical studies, Zhao et al. [54] have applied the PFA system to ablate the left ventricle in New Zealand rabbits, and have demonstrated the occurrence of apoptosis and subsequent necrosis of cardiomyocytes after ablation. However, the ablated blood vessels and nerves were not affected.

Previous studies have focused on the effects of PFA on healthy ventricular tissues. However, limited studies have focused on the characteristics of lesions in the presence of myocardial scarring. Im et al. [55] have recently used two types of catheters (linear focal and basket) to assess the lesion profiles of bipolar, biphasic PFA in healthy and infarcted left ventricular myocardium from pigs. The three main highlights of this study are as follows: the lesion depth with PFA was higher than that with radiofrequency ablation in an ischemic scar; PFA rapidly, safely, and effectively ablated the left ventricular infarcted myocardium and the lesion size did not significantly differ between the left ventricular infarcted myocardium and healthy myocardium; and basket catheters generated deeper and more extensive lesions than focal catheters. This study provides new evidence supporting the use of PFA in the treatment of ventricular tachycardia associated with myocardial infarction in humans. PFA may be more useful for the treatment of ventricular arrhythmias, particularly ischemia-associated arrhythmias, than for the treatment of atrial arrhythmias. However, further preclinical supporting evidence is needed to validate this hypothesis.

Clinical Studies

Reddy et al. performed the initial clinical study on PFA, in 22 patients with paroxysmal AF treatment at two centers with a bipolar PFA waveform for endocardial and epicardial ablation [15]. Catheter PVI was achieved in 57 PVs of 15 patients, with a procedure time of 67 ± 10.5 min. Surgical box lesions were achieved in six patients (86%), on the basis of two lesions per patient. However, follow-up data on safety and efficacy were lacking. On the basis of that study, two further clinical trials (IMPULSE and PEFCAT were conducted by Reddy et al. [56] The studies included 81 patients with paroxysmal AF who received either monophasic (n = 15) or biphasic iterations (n = 66). Acute PVI was achieved in all patients. The durability improved from 18% to 100% over 3 months in all patients with PVI with continuous waveform refinement.

The same research group has also reported the 1-year follow-up data of PFA for paroxysmal AF. In addition to the two clinical trials described above, 40 patients from another clinical trial (PEFCAT II) were included, thereby increasing the total number of patients to 121 [57]. In that study, PFA alone achieved acute PVI in all patients. PV remapping for 110 patients at month 3 revealed durable PVI in 64.5% of patients, as well as in 84.1% of patients who received the optimized biphasic energy PFA waveform. In the overall cohort and the optimized biphasic energy PFA waveform cohort, the 1-year Kaplan-Meier estimates for atrial arrhythmia-free events were 79% and 85%, respectively. All PVs were successfully and safely ablated in one study in 30 patients with paroxysmal AF undergoing biphasic waveform PFA with a 20-pole basket or flower catheter [29]. No PFA-associated adverse complications, or phrenic nerve or esophageal injury, were observed within 1 month, and 29 of 30 patients exhibited sinus rhythm at the 3-month follow-up.

Favorable results have been obtained with PFA for the treatment of paroxysmal AF. Hence, several research groups are examining the therapeutic effects of PFA on persistent AF. Verma et al. [58] have performed a multicenter clinical study to evaluate the feasibility and safety of PFA in patients with paroxysmal and persistent AF. This pilot study achieved successful acute PVI in all patients. Gunawardene et al. [59] have applied ultrahigh-density mapping to

verify the durability of PFA lesions in patients with paroxysmal and persistent AF. Of the 20 patients included in the study, 11 underwent only PVI, whereas nine underwent additional ablation. The first use of ultrahigh-density mapping of PFA generated large antral circumferential lesions for PVI with minimal tissue voltage depression. Although 100% acute PVI was achieved, ultrahigh-density mapping after PVI revealed early PV reconnection in 6.25% of PVs. Reddy et al. [16] have also evaluated the safety and lesion durability of PFA for both PVI and left atrial posterior wall (LAPW) ablation in 25 patients with persistent AF. Acute PVI, LAPW ablation, and bidirectional cavotricuspid isthmus block were achieved in all 25 patients. Invasive remapping revealed durable isolation in 96% and 100% of PVs and LAPWs at month 3, respectively.

In addition, Reddy et al. [60] have used a lattice-tip focal ablation catheter, which delivers both radiofrequency ablation and PFA and allows for free switching between energies, to treat paroxysmal and persistent AF. In that study, 76 patients with AF underwent PFA posteriorly and radiofrequency ablation anteriorly (RF/RF; n = 40 patients) or PFA throughout (PF/PF; n = 36 patients). Post-procedure esophagogastroduodenoscopy revealed mild mucosal heat damage in 5.6% and 0% of the patients who underwent RF/PF and PF/PF, respectively. The use of PFA to treat atrial arrhythmias has been confirmed in several clinical studies. The safety and efficacy of PFA are not inferior to those of radiofrequency ablation and cryoablation. However, PFA has not been applied to the ventricle. Clinical validation must be performed in the future to confirm the therapeutic effects of PFA on ventricular arrhythmias. A summary of salient findings of clinical studies is provided in Table 3.

Limitations and Future Perspectives

The Need to Evaluate the Risk of Microbubble Formation and Asymptomatic Cerebral Embolism

The safety of PFA can be attributed to its tissue selectivity. However, intracardiac echocardiography during PFA treatment has revealed microbubble generation and rupture [56], which are potentially associated with cerebral embolism risk. Reddy et al. [60] have performed post-PFA brain magnetic resonance imaging and reported diffusion-weighted imaging+/fluid attenuated inversion recovery– and diffusion-weighted imaging+/fluid attenuated inversion recovery+ asymptomatic lesions in 9.8% and 5.9% of 51 patients, respectively. Recent studies have similarly confirmed that the incidence of magnetic resonance imaging+ asymptomatic thromboembolic brain events or lesions in patients with PFA is as low as 3%, although no neurological deficits were detected [61]. Limited studies have examined microbubble production during PFA and the risk of asymptomatic cerebral embolism. Preliminary studies have suggested the potential risk of asymptomatic cerebral embolism with PFA application and the need for continued systematic studies in this area.

The Need to Further Explore the Tissue Specificity of PFA

Limited studies have evaluated the PFA thresholds of different tissue or cell types. The PFA thresholds of different tissues reported by Reddy et al. [15] are currently used. However, these thresholds are influenced by several factors. Previous studies have focused on the electric field strength, although other factors, such as pulse width, number of pulses, and frequency, are also important. Most early studies on PFA used monophasic pulses, whereas the current PFA system uses predominantly bidirectional pulses. Hence, the generalization of previous results must be reconsidered. The PFA thresholds are critical for the safety and precision of ablation. Therefore, further studies are needed to explore the PFA thresholds of different tissues or cells.

The Need to Set Up a Unified or Interoperable PFA System

The biological effects of radiofrequency ablation and cryoablation are reproducible. Additionally, the experiences of different centers using different thermal ablation systems are comparable, thus indicating the universality of these techniques. In contrast, the results obtained from a given PFA system are not comparable to those obtained from other PFA systems. Several types of PFA systems have been

Table 3 Clinical Studies of the Efficacy of Pulsed Field Ablation.

Author	Study design	Sample	Catheter design	Waveform style	Pulse amplitude	Ablation strategy	Follow-up	Outcomes
Reddy et al. [15]	Prospective open-label nonrandomized	22 paroxysmal	Basket 20 electrodes and linear 30 electrodes	Biphasic	900–2400 V	PVI	Acute	Endocardium: 100% acute PVI Epicardium: 86% acute PVI
Reddy et al. [56]	Prospective nonrandomized feasibility trials	81 paroxysmal	Basket/Flower 20 electrodes	Monophasic Biphasic	900–1000 V 1800–2000V	PVI	3 months	100% acute PVI 18%–100% PVI at 3 months
Reddy et al. [57]	Prospective multi-center nonrandomized	121 paroxysmal	Basket/Flower 20 electrodes	Biphasic	900–2000 V	PVI	1 year	100% acute PVI 78.5% and 84.5% arrhythmia freedom for the entire cohort and the optimized energy cohort at 1 year
Füting et al. [29]	Prospective nonrandomized	30 paroxysmal	Basket/Flower 20 electrodes	Biphasic	1900 V	PVI	3 months	100% acute PVI 97% in sinus rhythm at 3 months
Guo et al. [24]	Prospective single-arm nonrandomized	18 paroxysmal	circular 7 or 9 electrodes	Biphasic	1800 V/cm	PVI	8 months	100% acute PVI
Verma et al. [58]	Prospective interventional single-arm multicenter	35 paroxysmal, 3 persistent	Circular 9 electrodes	Biphasic	500–1500 V	PVI	1 month	100% acute PVI No serious adverse events
Gunawardene et al. [59]	Prospective single-center observational	7 paroxysmal, 13 persistent	Basket/Flower 20 electrodes	Biphasic	1800–2000 V	PVI LAPW MI	Acute	100% acute PVI Early PV reconnection in 6.25% of PVs using UHDx mapping.
Reddy et al. [16]	Single-arm multicenter feasibility study	25 persistent AF	Basket/Flower 20 electrodes	Biphasic	1600–2000 V	PVI LAPW CTI	3 months	100% acute PVI and LAPWs ablation 96% durable PVI and 100% LAPW isolation upon remapping at 3 months

Table 3 (continued)

Author	Study design	Sample	Catheter design	Waveform style	Pulse amplitude	Ablation strategy	Follow-up	Outcomes
Reddy et al. [60]	Prospective Multicenter single-arm	55 paroxysmal 21 persistent	Lattice-tip 9 mini-electrodes	Biphasic	24–32 A	PVI MI CTI	Acute	All lesion sets were acutely successful Mucosal heat damage in 5.6% of RF/PF and 0% of PF/PF patients.

PVI, pulmonary vein isolation; LAPW, left atrial posterior wall; CTI, cavotricuspid isthmus; MI, mitral isthmus; UHDx, ultrahigh-density; RF/RF, radiofrequency ablation anteriorly; PF/PF, PFA throughout.

developed in China and other countries. However, the PFA systems lack uniform standards, because different manufacturers use different designs for the modulation of parameters as well as different designs of ablation catheters. Hence, the results obtained from PFA are not universal. To address this limitation, the optimal combination of parameters in terms of efficacy and procedures must be established to enable the generalization and universal interpretation of the findings from different systems. This aspect is important, because the PFA system exhibits tissue selectivity, which is expected to enable personalized and precise ablation.

The Need to Explore the Effectiveness and Safety of the Combination of PFA and Thermal Ablation for Arrhythmias

Verma et al. [62] have combined PFA and ultra-low temperature cryoablation (PFCA) as a new energy source and demonstrated that, in contrast to PFA, PFCA does not induce muscle contraction or microvesicle formation but instead induces myocardial necrosis in a swine model. The optimized PFCA regimen generates markedly deep and large lesions in thick cavotricuspid isthmus tissues. The combination of PFA and radiofrequency ablation has also been explored. Reddy et al. [60] have integrated high-resolution mapping into a single catheter capable of switching freely between high-power radiofrequency and PFA for PVI, and have demonstrated its short-term safety and efficacy. Limited studies have focused on the combination of PFA and thermal ablation. Multicenter randomized trials must be performed in the future to validate the safety and efficacy of the combination of PFA and thermal ablation relative to PFA or thermal ablation strategies.

Other

Several remaining issues must be addressed to support the promotion of PFA strategies. The first is the need for general anesthesia and intubation before the interventional procedure. In addition, the need for optimal sedation protocols for PFA must be further explored to decrease pain and muscle contractions in patients, and to avoid patient intubation. Finally, devices and catheters used for PFA must

consider several variables, such as the amount of contact, number of electrodes, and catheter position at the PV ostia.

Conclusion

PFA is a promising novel treatment for cardiac arrhythmias. PFA provides the unique advantage of preventing damage to the surrounding tissue during PVI, owing to its non-thermal characteristics and tissue selectivity. Almost all preclinical and clinical studies examining the potential of PFA in treating arrhythmia have reported favorable outcomes in terms of both effectiveness and safety. Further studies are needed to elucidate the long-term safety, efficacy, and optimal procedure parameter combinations of PFA.

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None

Conflicts of Interest

The authors confirm that there are no conflicts of interest.

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