Pulsed Field Ablation for Pulmonary Vein Isolation in Atrial Fibrillation

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ABSTRACT

BACKGROUND Catheter ablation of atrial fibrillation using thermal energies such as radiofrequency or cryothermy is associated with indiscriminate tissue destruction. During pulsed field ablation (PFA), subsecond electric fields create microscopic pores in cell membranes—a process called electroporation. Among cell types, cardiomyocytes have among the lowest thresholds to these fields, potentially permitting preferential myocardial ablation.

OBJECTIVES The purpose of these 2 trials was to determine whether PFA allows durable pulmonary vein (PV) isolation without damage to collateral structures.

METHODS Two trials were conducted to assess the safety and effectiveness of catheter-based PFA in paroxysmal atrial fibrillation. Ablation was performed using proprietary bipolar PFA waveforms: either monophasic with general anesthesia and paralytics to minimize muscle contraction, or biphasic with sedation because there was minimal muscular stimulation. No esophageal protection strategy was used. Invasive electrophysiological mapping was repeated after 3 months to assess the durability of PV isolation.

RESULTS In 81 patients, all PVs were acutely isolated by monophasic (n = 15) or biphasic (n = 66) PFA with ≤3 min elapsed delivery/patient, skin-to-skin procedure time of 92.2 ± 27.4 min, and fluoroscopy time of 13.1 ± 7.6 min. With successive waveform refinement, durability at 3 months improved from 18% to 100% of patients with all PVs isolated. Beyond 1 procedure-related pericardial tamponade, there were no additional primary adverse events over the 120-day median follow-up, including: stroke, phrenic nerve injury, PV stenosis, and esophageal injury. The 12-month Kaplan-Meier estimate of freedom from arrhythmia was 87.4 ± 5.6%.

CONCLUSIONS In first-in-human trials, PFA preferentially affected myocardial tissue, allowing facile ultra-rapid PV isolation with excellent durability and chronic safety. (IMPULSE: A Safety and Feasibility Study of the IOWA Approach Endocardial Ablation System to Treat Atrial Fibrillation; NCT03700385; and PEFCAT: A Safety and Feasibility Study of the FARAPULSE Endocardial Ablation System to Treat Paroxysmal Atrial Fibrillation; NCT03714178) (J Am Coll Cardiol 2019;74:315–26) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A trial fibrillation (AF) is the most commonly ablated arrhythmia. Although largely safe and effective in the hands of expert operators, the procedure is still associated with severe complications, including pulmonary vein (PV) stenosis, stroke, phrenic nerve palsy, and the most feared complication, atrioesophageal fistula, which when it occurs, has a mortality exceeding 50% (1,2). Common

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to all thermal energies, including radiofrequency energy, cryothermy, laser, ultrasound, and microwave (even x-ray or proton beam therapy), is their propensity to ablate all tissues indiscriminately. There is a zero-sum relationship between safety and efficacy—greater efficacy is achieved with more ablation but at the expense of safety, and vice versa.

In contrast, pulsed field ablation (PFA) is a nonthermal ablative modality in which ultrarapid (<1 s) electrical fields are applied to target tissue. This destabilizes cell membranes by forming irreversible nanoscale pores and leakage of cell contents, culminating in cell death (3-6). Importantly, various tissues have specific characteristic threshold field strengths that induce necrosis (7-9). Indeed, PFA is used to treat solid tumors that are unresectable because of close proximity to major blood vessels or nerves, as these structures are relatively resistant to pulsed electric fields. Similarly, PFA seems uniquely suited for cardiac ablation, because cardiomyocytes have among the lowest threshold values of any tissue (7). This myocardial sensitivity could potentially limit collateral damage of nontarget tissue such as the esophagus and phrenic nerve.

Beyond safety, it is well-appreciated that the primary mechanism for AF recurrence after conventional ablation procedures is electrical PV reconnection over time—because of incomplete lesion transmurality and/or contiguity. The frequency of all PVs durably isolated per patient has been reported to range from ~20% to 80%. But unlike other energies, multiple parameters can be fine-tuned with PFA, resulting in different lesion profiles and efficacy. We previously reported that catheter-based PFA using a monophasic waveform could acutely isolate PVs; however, this first-generation waveform was used in only 15 patients, and there was no safety or efficacy follow-up data available (10). Herein, in 2 first-in-human clinical trials of paroxysmal AF, we studied the extended outcomes of the monophasic waveform-treated patients, as well as in a substantially larger cohort treated with next-generation biphasic PFA waveforms. We assessed both the long-term safety of PFA and the durability of electrical PV isolation using protocol-mandated invasive remapping procedures.

METHODS

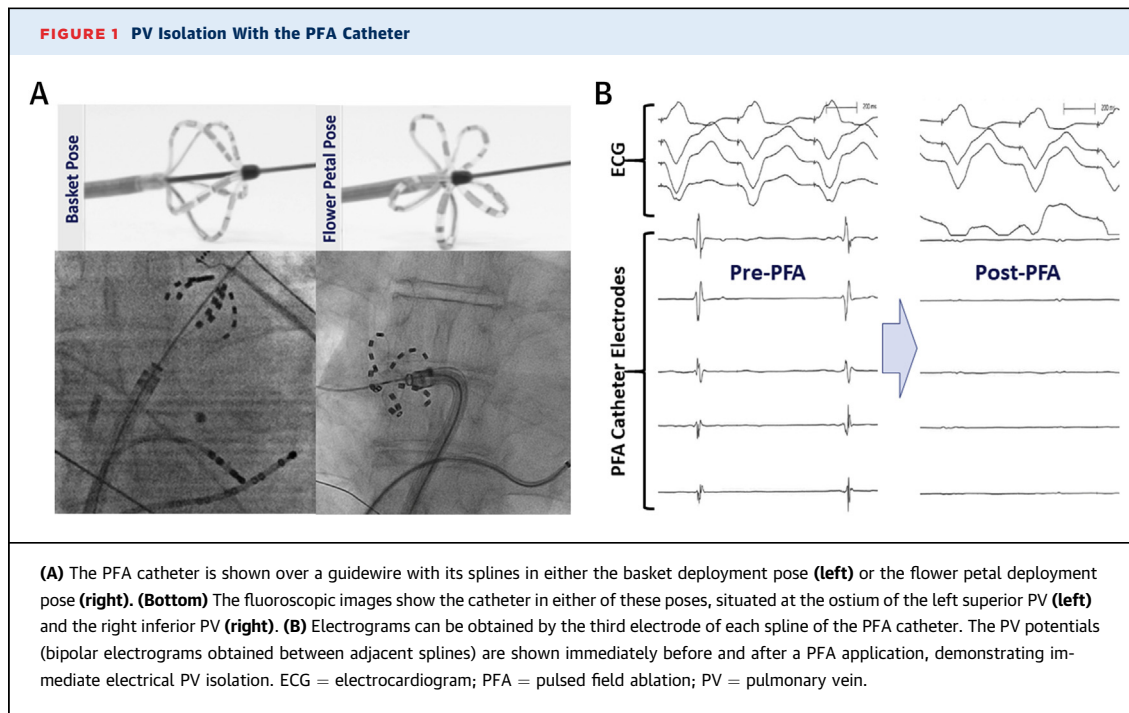**TRIAL DESIGN.** The IMPULSE (A Safety and Feasibility Study of the IOWA Approach Endocardial Ablation System to Treat Atrial Fibrillation) (NCT03700385) and PEFCAT (A Safety and Feasibility Study of the FARAPULSE Endocardial Ablation System to Treat Paroxysmal Atrial Fibrillation) (NCT03714178) studies were first-in-human, 2-center, nonrandomized feasibility trials of PFA conducted at Homolka Hospital, Prague, and the Centre Hospitalier Universitaire de Bordeaux, France. An independent clinical events committee adjudicated endpoint events. Farapulse of Menlo Park, California (formerly Iowa Approach), the manufacturer of the PFA system, funded the trials. The study was conducted by Farapulse with partial monitoring by a clinical research organization: MedPass International. The trials were approved by each center's local ethics committees, and corresponding national regulatory agencies.

After IMPULSE was initiated, process differences in the French and Czech regulatory bodies prompted the sponsor to initiate the PEFCAT trial. Because the trials enrolled nearly-identical patients with nearly-identical follow-up and endpoints, these datasets are combined and presented as 1 coherent clinical experience. The trial protocols are available online; relevant minor differences are detailed in Online Table 1.

STUDY POPULATION. The trials enrolled patients with symptomatic paroxysmal AF resistant to class I to IV antiarrhythmic medications, with left ventricular ejection fraction >40% and with left atrial (LA) anteroposterior dimension <5.0 cm (IMPULSE) or <5.5 cm (PEFCAT). There were no exclusions for PV anatomy. Detailed inclusion and exclusion criteria are in Online Table 2.

PFA SYSTEM. The PFA system has 3 components: a custom generator that delivers a high-voltage pulsed field waveform over multiple channels (while the unit is programmable with various waveform and bipolar electrode pairing options, for convenience of waveform iteration, the waveform is fixed in a given clinical version), a PFA catheter, and a 13-F steerable sheath (Farapulse).

The 12-F over-the-wire PFA ablation catheter (Farawave, Farapulse) has 5 splines that each contain 4 electrodes, and it can be deployed in either a flower petal or basket configuration (Figure 1). When fully deployed into a flower pose, the diameter of the distal portion is 31 mm. The catheter is advanced over a guidewire such that the splines achieve circumferential contact/proximity with the PV antra. The ablative energy is delivered from all electrodes; the third electrode on each spline can also record electrograms. The catheter was rotated between applications to ensure circumferential PV ostial and antral

FIGURE 1 PV Isolation With the PFA Catheter

(A) The PFA catheter is shown over a guidewire with its splines in either the basket deployment pose **(left)** or the flower petal deployment pose **(right). (Bottom)** The fluoroscopic images show the catheter in either of these poses, situated at the ostium of the left superior PV **(left)** and the right inferior PV **(right). (B)** Electrograms can be obtained by the third electrode of each spline of the PFA catheter. The PV potentials (bipolar electrograms obtained between adjacent splines) are shown immediately before and after a PFA application, demonstrating immediate electrical PV isolation. ECG = electrocardiogram; PFA = pulsed field ablation; PV = pulmonary vein.

coverage. During ablation, a standard electrophysiology catheter paced the ventricles to synchronize the pulses to just after QRS onset.

The IMPULSE and PEFCAT feasibility protocols were designed to optimize PFA by allowing flexibility in the delivered dose and waveform. The therapeutic waveform is structured as a hierarchical set of microsecond-scale pulses in bipolar fashion across electrodes, with ablation delivery synchronized to pacing over a small number of heartbeats (4 to 10 heartbeats). The ablation protocol underwent consecutive evolutionary modifications: from monophasic to biphasic pulses, and then optimizing the biphasic waveform morphology and pulse sequence composition (Online Table 3).

PROCEDURAL WORKFLOW. After written informed consent, patients underwent pre-procedural computed tomography (CT) scanning of PV anatomy. The monophasic PFA cases were performed under general anesthesia with succinylcholine neuromuscular paralysis (0.5 to 1 mg/kg) to suppress skeletal muscle stimulation. Except for the first biphasic PFA case, which was also performed with general anesthesia (no paralytics), the remaining biphasic cases were performed with sedation alone (fentanyl, benzodiazepines, propofol).

Procedures were performed with uninterrupted oral anticoagulation and intravenous heparin, administered pre-transseptal puncture. The LA appendage was assessed for thrombus by either pre-procedure CT or intracardiac echocardiography (ICE) (Acunav, Siemens, Munich, Germany). After femoral venous access, followed by a single transseptal puncture with an 8.5-F sheath, the 13-F PFA sheath was exchanged into the LA; in a subset of patients (n = 10), transseptal puncture was performed directly with the 13-F sheath. In selected patients, a baseline voltage amplitude map was created using multielectrode catheters and standard electroanatomic mapping systems.

Pre- and post-procedure phrenic nerve function was evaluated in all patients by observing diaphragmatic motion during either patient inspiration or direct phrenic pacing. In recognition of PFA's nonthermal mechanism of ablation, neither luminal esophageal temperature monitoring nor lateral esophageal displacement were employed. ICE imaging and fluoroscopy were used to optimize PFA catheter positioning at the PV ostia. For the monophasic and biphasic waveforms, the generator outputs ranged between 900 to 1,000 V and 1,800 to 2,000 V per application, respectively. After ablation, a circular mapping catheter (Lasso, Biosense Webster, Irvine, California) assessed electrical PV activity, followed by post-ablation voltage mapping. At investigator discretion, adenosine boluses (12 to 18 mg each) were administered to identify dormant PV conduction.

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TABLE 1 Baseline Patient Characteristics

	IMPULSE (n = 40)	PEFCAT (n = 41)	Total Cohort (N = 81)
Age, yrs	58.5 ± 9.0	57.6 ± 12.1	58.0 ± 10.7
Male	28 (70.0)	32 (78.0)	60 (74.0)
LA diameter, mm	41.0 ± 4.3	41.4 ± 5.6	41.2 ± 5.0
LVEF, %	63.2 ± 5	63.3 ± 3.7	63.3 ± 4.3
Hypertension	20 (50)	30 (73.2)	50 (61.7)
Diabetes	3 (7.5)	5 (12.2)	8 (9.9)
Stroke or TIA	0 (0.0)	3 (7.3)	3 (3.7)
CAD (MI/CABG)	1 (2.5)	0 (0.0)	1 (1.2)
Anticoagulation			
Warfarin	15	17	32
NOAC	21	14	35
Aspirin	0	2	2
None	4	8	12
Antiarrhythmics			
Class I	21	25	46
Class II	28	27	45
Class III	1	0	1
None	8	4	12

Values are mean ± SD, n (%), or n.

AF = atrial fibrillation; CABG = coronary artery bypass grafting; CAD = coronary artery disease; IMPULSE = A Safety and Feasibility Study of the IOWA Approach Endocardial Ablation System to Treat Atrial Fibrillation; LA = left atrium; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NOAC = novel oral anticoagulants; PEFCAT = A Safety and Feasibility Study of the FARAPULSE Endocardial Ablation System to Treat Paroxysmal Atrial Fibrillation; TIA = transient ischemic attack.

FOLLOW-UP. Patients were planned for repeat invasive electrophysiological mapping at 75 days (PEFCAT) or 90 days (IMPULSE) after the index ablation procedure. During this repeat procedure, the LA-PVs were assessed for PV reconnection using a multielectrode catheter. If electrically reconnected, a standard irrigated radiofrequency ablation catheter (Thermocool, Biosense Webster) was used to ablate the point of PV reconnection. A voltage amplitude map was again created.

Clinical follow-up visits were scheduled at 7 days; 30 days; and 3, 6, and 12 months after the index procedure. To assess for recurrence, patients received: 1) a trans-telephonic monitor at the time of the remapping study to send transmissions weekly and with symptoms; and 2) 24-h Holter monitors at 6 and 12 months. Patients were scheduled for repeat CT or cardiac magnetic resonance imaging (CMR) scanning of the PV anatomy at 3 months.

ENDPOINTS. The endpoints for IMPULSE and PEFCAT are similar (Online Table 1). The primary safety endpoint was a composite of major safety events including cardiac tamponade, stroke or transient ischemic attack (TIA), diaphragmatic paralysis, PV stenosis, heart block, atrioesophageal fistula,

myocardial infarction, and death. In IMPULSE and PEFCAT, the endpoint included events that occurred within 7 and 30 days post-procedure, respectively. The primary feasibility/effectiveness endpoint in both trials was the proportion of subjects with all PVs electrically isolated with PFA alone.

There were also several secondary safety endpoints in both studies related to serious adverse events. The secondary feasibility/effectiveness endpoints were: 1) proportion of patients with all PVs durably isolated at remapping (both trials); and 2) proportion of patients remaining free of atrial arrhythmias (including atrial fibrillation, flutter, or tachycardia) from the end of the 3-month blanking period to 1 year; this latter endpoint was specified as a secondary endpoint in PEFCAT, and as an additional endpoint in IMPULSE.

STATISTICAL ANALYSES. IMPULSE and PEFCAT were feasibility studies with no formal hypothesis testing and, therefore, no required sample size. Subjects were followed on an intent-to-treat basis. The device performance was assessed based on a per-protocol analysis of the primary safety and feasibility endpoints and secondary efficacy endpoints. Study results are presented using descriptive statistics. For continuous variables, the results include number, mean, SD, and 95% bilateral confidence intervals (CIs), where pertinent. Presented data for categorical variables include the number and percent of subjects.

RESULTS

PATIENTS. A total of 81 consecutive patients with symptomatic paroxysmal AF were enrolled in the 2 studies between January 2018 and March 2019. The baseline demographics of the combined cohort are shown in Table 1. The cohort was relatively young (age 58.0 ± 10.7 years), and male predominant (74%). Left ventricular function was largely preserved (63.3 ± 4.3%), and the LA dimension was 41.2 ± 5.0 mm. A class I or III antiarrhythmic medication was previously ineffective in just over one-half (58%) of the cohort. PV remapping procedures occurred at a median of 84 days (first and third quartiles: 69 to 95 days) and the total duration of follow-up was median 120 days (first and third quartiles: 77 to 302 days).

PROCEDURAL CHARACTERISTICS. Of the 81 patients who underwent PFA, monophasic waveforms were used in 15 patients and biphasic in 66 patients. All patients undergoing monophasic PFA required general anesthesia and neuromuscular paralysis; accordingly, skeletal muscle and diaphragmatic

TABLE 2 Procedural Characteristics of the Total Cohort (n = 81)	
Procedure time, min	92.2 ± 27.4
Mapping time	18.2 ± 10.3
Catheter dwell time	33.7 ± 16.6
Fluoroscopy time, min*	13.1 ± 7.6
Acute isolation success	315 of 315 PVs (100%)

Values are mean ± SD, unless otherwise indicated. *Data available for 77 of 81 patients.

activation were not observed. Most biphasic PFA procedures (65 of 66) were performed with conscious sedation; this resulted in only mild degrees of muscle activation that was tolerated well without procedural interruption or catheter dislocation during pulse delivery. Patients did occasionally experience transient intraprocedural cough with the PFA applications.

The mean fluoroscopy time was 13.1 ± 7.6 min (Table 2). The mean total skin-to-skin procedure time was 92.2 ± 27.4 min (including 18.2 ± 10.3 min for voltage mapping). The mean PFA catheter dwell time, defined as the time transpiring from introduction of the ablation catheter to removal from the body, was 33.7 ± 16.6 min (Online Table 4). The time required to administer the ablative PFA pulses for complete PV isolation amounted to no more than 3 min/patient, consistent with the subsecond nature of the pulses. Post-ablation voltage maps revealed a PV antral level of electrical isolation (Figure 2).

There were no PFA catheter-related complications associated with deployment failure, catheter entrapment within the PVs or valvular apparatus, or evidence of charring or thrombus upon catheter removal. PFA applications were typically accompanied by immediate ultrasonic microbubbles observed on ICE, presumably electrolysis related to these pulses; this rapidly resolved and was not associated with any appreciable physiological effects. No applications resulted in waveform discontinuities suggestive of arcing. There were no instances of atrial or ventricular tachyarrhythmias, or significant repolarization abnormalities on the 12-lead electrocardiogram. All patients had unremarkable recovery without evidence of significant thoracic or upper extremity

FIGURE 2   Electroanatomic Voltage Mapping to Assess PV Isolation Level
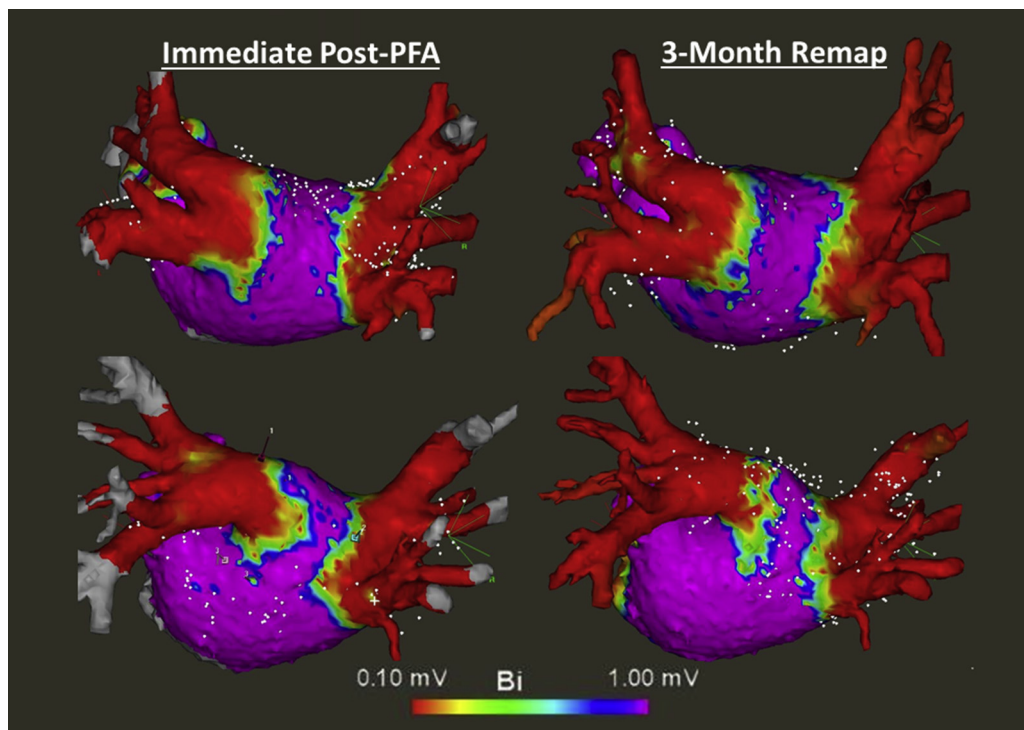
Voltage mapping was performed both at the end of the index PFA procedure **(left)** and at the time of the 3-month remapping procedure **(right)**. The color scale of the bipolar voltage values is shown at the **bottom**: values above 1 mV are considered normal atrial tissue and depicted in **purple**. Abbreviations as in **Figure 1**.

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TABLE 3 Primary Endpoints			
	IMPULSE (n = 40)	PEFCAT (n = 41)	Total Cohort (N = 81)
Primary feasibility			
Acute PV isolation	40 (100.0)	41 (100.0)	81 (100.0)
Primary safety			
Total	1 (2.5)	0 (0.0)	1 (1.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)
Diaphragmatic paralysis	0 (0.0)	0 (0.0)	0 (0.0)
Stroke or TIA	0 (0.0)	0 (0.0)	0 (0.0)
Other thromboembolism	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac perforation or tamponade	1 (2.5)	0 (0.0)	1 (1.2)
Vascular complications	0 (0.0)	0 (0.0)	0 (0.0)
Prolonged or repeat hospitalization	0 (0.0)	0 (0.0)	0 (0.0)
Heart block	0 (0.0)	0 (0.0)	0 (0.0)
PV stenosis >70%	0 (0.0)	0 (0.0)	0 (0.0)
Atrioesophageal fistula	0 (0.0)	0 (0.0)	0 (0.0)
Pericarditis requiring intervention	0 (0.0)	0 (0.0)	0 (0.0)
Pneumothorax	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary edema	0 (0.0)	0 (0.0)	0 (0.0)

Values are n (%).
PV = pulmonary vein; TIA = transient ischemic attack.

muscular discomfort or neurological motor or sensory symptoms post-procedure.

PRIMARY ENDPOINTS. The primary feasibility endpoint of acute PV isolation was met in 100% of patients. Of the 315 PVs targeted in 81 patients, 100% of PVs were isolated using 6.4 ± 2.3 applications per PV. There were no PV reconnections during either the 20-min waiting period or, when performed (n = 36 patients), upon provocative adenosine testing.

The primary safety endpoint occurred in 1 patient (1.2%) who experienced a major procedure-related acute adverse event of pericardial tamponade. This was not related to the ablation itself, but rather to vigorous manipulation of the PFA catheter at the right inferior PV. The pericardial fluid was successfully drained by percutaneous pericardiocentesis. There were no additional primary adverse events during follow-up (Table 3, Online Table 5). Importantly, there were no clinical instances of pulmonary vein stenosis, stroke or TIA, or atrioesophageal fistula. There were also no instances of phrenic nerve injury despite frequent phrenic capture during PFA pulses to the right superior PV.

SECONDARY ENDPOINTS. Of 62 patients scheduled for remapping, 52 (84%) actually presented for this invasive PV reassessment at a median of 84 days following the index procedure. With successive refinements to the waveforms, the proportion of patients (and PVs) with durable electrical isolation progressively improved from 18% of patients (45% of PVs) with the initial waveform (monophasic) to 100% of patients (100% of PVs) with the most optimized waveform (biphasic-3) (Figure 3). The remapping procedures were performed without complications. Repeat electroanatomic voltage mapping again revealed the level of electrical isolation to be at the PV antra, consistent with that observed in the index procedure (Figure 2).

Based upon a median clinical follow-up of 120 days, the 6- and 12-month Kaplan-Meier estimates of freedom from recurrent atrial fibrillation, atrial flutter, or atrial tachycardia were $90.9 \pm 4.6\%$ (95% CI: 82.0% to 99.9%) and $87.4 \pm 5.6\%$ (95% CI: 76.5% to 98.4%) (Figure 4). During follow-up, there were no further primary adverse events.

OTHER SAFETY ASSESSMENTS. In addition to the absence of clinically-evident esophageal injury, esophageal endoscopy was performed in 29 PFA patients, at a mean of 3.4 days post-ablation (Table 4). In all patients, there was no evidence of esophageal luminal irregularities or lesions. In these patients, pre-procedural CT scans demonstrated that, as expected, at least 1 PV was adjacent to the course of the esophagus in each patient. Additionally, 8 patients underwent post-procedure contrast-enhanced CMR (Figure 5). This showed no esophagus enhancement despite clear enhancement of the immediately adjacent LA myocardium and PVs: intense circumferential enhancement was observed for all but 1 of the 28 veins assessed by delayed enhancement imaging. Similarly, T_2 imaging also identified no evidence of esophageal damage.

No patient presented with clinical evidence of thromboembolism—stroke, TIA, or system embolism. Furthermore, brain magnetic resonance imaging was performed in 13 patients (Table 4). They were negative for lesions using both diffusion-weighted imaging and fluid attenuated inversion recovery imaging, thus revealing no evidence of silent cerebral ischemic events.

At the end of the index procedure, in all patients, the integrity of the phrenic nerve was verified by phrenic capture during pacing from the superior vena cava or by observing diaphragm movement during spontaneous respiration (Table 4). Furthermore, fluoroscopy was performed in those patients presenting for the remapping procedures (n = 52), revealing no diaphragmatic impairment in any patient.

Beyond the absence of clinical PV stenosis, the PV caliber was studied using 2 approaches. During invasive remapping, there was no evidence of PV stenosis upon catheter-based electroanatomic mapping

FIGURE 3   Durability of PV Isolation With Successive Waveforms
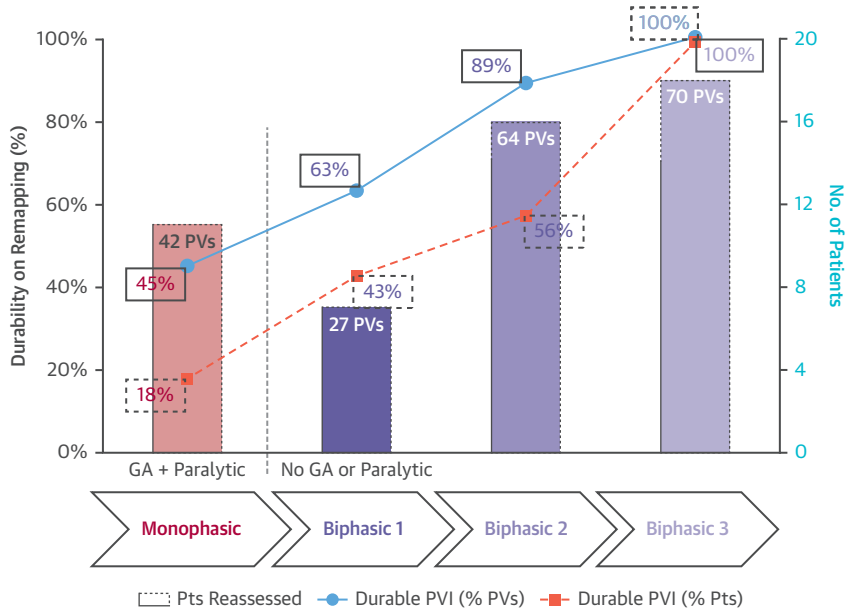
The bar graph demonstrates the durable pulmonary vein (PV) isolation rates during invasive electrophysiological remapping procedures. For each of the successive waveform protocols for which remapping data was obtained, shown are: 1) the number of patients (Pts) who presented for the remapping procedures **(bars)**; 2) the percentage of PVs that remained durably electrically isolated **(solid line)**; and 3) the percentage of patients with all PVs durably electrically isolated **(dashed line)**.

FIGURE 4   Kaplan-Meier Analysis of Freedom From Atrial Arrhythmias
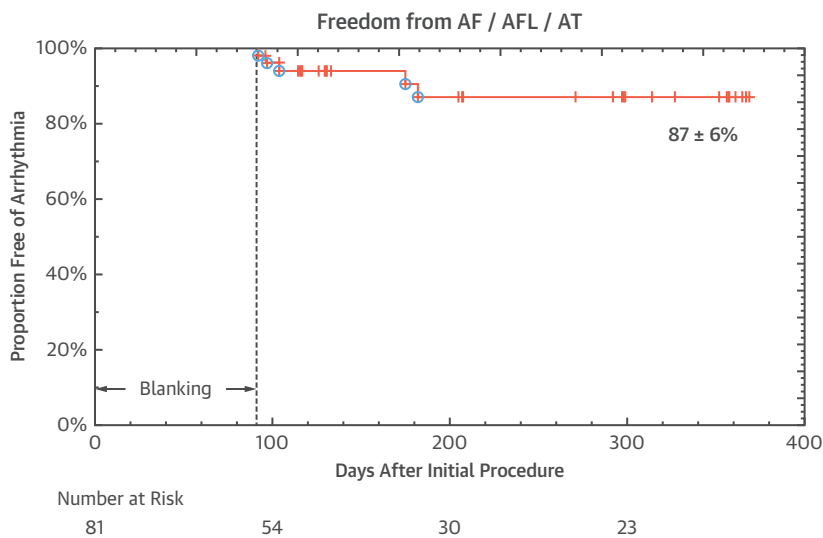
Not including the 3-month blanking period, shown is the freedom for atrial arrhythmias, including any atrial fibrillation (AF), atrial flutter (AFL), or atrial tachycardia (AT) episode exceeding 30 s.

TABLE 4   Additional Safety Assessments

	Patients With Assessment	Findings
Esophageal findings		
Esophagogastroduodenoscopy	29	No esophageal lesions
Chest CMR	8	No esophageal enhancement
Brain MRI	13	Negative for DWI/FLAIR
Phrenic nerve		
Phrenic nerve assessment*	81	No paresis/palsy
Chest x-ray at 3 months	37	No paresis/palsy
Pulmonary vein stenosis		
EAM at 3 months	52	No PV stenosis/narrowing
CT scanning at 3 months	29	No PV stenosis/narrowing

Values are n. *Either by observation of diaphragmatic motion with patient inspiration, or by diaphragmatic capture with phrenic nerve pacing from within the superior vena cava.

CMR = cardiac magnetic resonance; CT = computed tomography; DWI = diffusion weighted imaging; EAM = electroanatomic mapping; FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; PV = pulmonary vein.

(Table 4). In addition, a quantitative assessment of the PV caliber was performed in 29 patients who underwent 3-month CT scans, compared with the baseline CT scans (Online Figure 1). A total of 95 individual PVs was assessed with follow-up CT scans at a mean of 118 ± 55 days post-ablation: not only was there no evidence of PV stenosis, there was also no evidence of significant PV narrowing in any PV (Table 5).

DISCUSSION

In a combined analysis of 2 first-in-human studies, we evaluated the feasibility, safety, and efficacy of pulsed field ablation to electrically isolate pulmonary veins in patients with paroxysmal atrial fibrillation. The rate of primary safety events was low (1.2%), and due to a case of pericardial tamponade. There were no subsequent primary adverse events during follow-up. Importantly, the tissue-selective nature of PFA was confirmed with no evidence of esophageal or phrenic nerve damage, and no evidence of PV stenosis or narrowing (Central Illustration). In 81 patients, 100% of PVs were acutely isolated with ≤3 min of PFA time per patient. During invasive remapping procedures, the rates of durable PV isolation improved with successive waveform modifications such that the most optimized PFA group demonstrated 100% durability.

Pulsed field ablation is an adaptation of direct current (DC) ablation, which was first used to treat cardiac arrhythmias in the 1980s (11). High-energy DC shocks (pulse duration of a few milliseconds) were applied between a catheter electrode positioned adjacent to the target myocardium and an external patch. This crude method of ablation often resulted in expanding gas bubbles at the catheter tip, arcing,

explosion, and subsequent pressure waves, which culminated in barotrauma to adjacent structures and complications such as cardiac perforation (12). This ablative methodology was replaced by radio-frequency energy, given its more efficient and precise energy delivery.

However, PFA is a more controlled form of energy delivery that uses multiple, brief DC pulses that comprise the waveform (pulse duration in the scale of microseconds or nanoseconds) delivered over a few seconds across multiple electrodes without the use of an external patch. Adjacent myocardial cell membranes are destabilized, resulting in nanoscale pores and increased cell membrane permeability and leakage of cell contents. This phenomenon, also referred to as irreversible electroporation, subsequently results in either immediate necrosis or delayed apoptotic cell death (3-6).

Somewhat unique to PFA: 1) the electric field strength thresholds required for myocardial cell death are among the lowest of any tissue type (Online Figure 2); and 2) because the mechanism of cell death is nonthermal, the propensity for collateral damage appears to be lower than with thermal energy sources (7-9). Preclinical experiments have shown that there is no significant PV stenosis, phrenic nerve injury, or esophageal injury with PFA delivered even directly atop those structures (13-15). This tissue-selective property of PFA was confirmed in the present study. Despite using no esophageal protection strategy, there was no evidence of esophageal necrosis by either CMR (delayed enhancement or T_2 imaging) or endoscopy. Similarly, the proximity of the phrenic nerve to the right superior PV was evidenced by diaphragmatic capture during PFA applications, but there was no evidence of phrenic paresis, let alone palsy. Finally, the absence of thermal coagulative necrosis translated to no PV stenosis or even PV narrowing, and no evidence of thrombus leading to stroke. The overall number of patients with negative brain magnetic resonance imaging was not large, but it *was* sufficient to verify that microbubble formation during PFA is not physiologically relevant (similar to the eruption of spontaneous echocardiographic contrast observed upon cryoballoon thawing).

The rates of atrioesophageal fistula, phrenic nerve injury, stroke/TIA, and PV stenosis requiring intervention following radiofrequency or cryoballoon ablation are not particularly frequent: 0.04% to 0.15%, 2.7%, 0.94%, and 0.29% respectively; however, they are associated with significant morbidity and mortality (1,16-18). But, unlike thermal energy sources, which have a predictable dose-safety relationship, PFA fundamentally alters this calculus because

FIGURE 5 Tissue Specificity of PFA by CMR
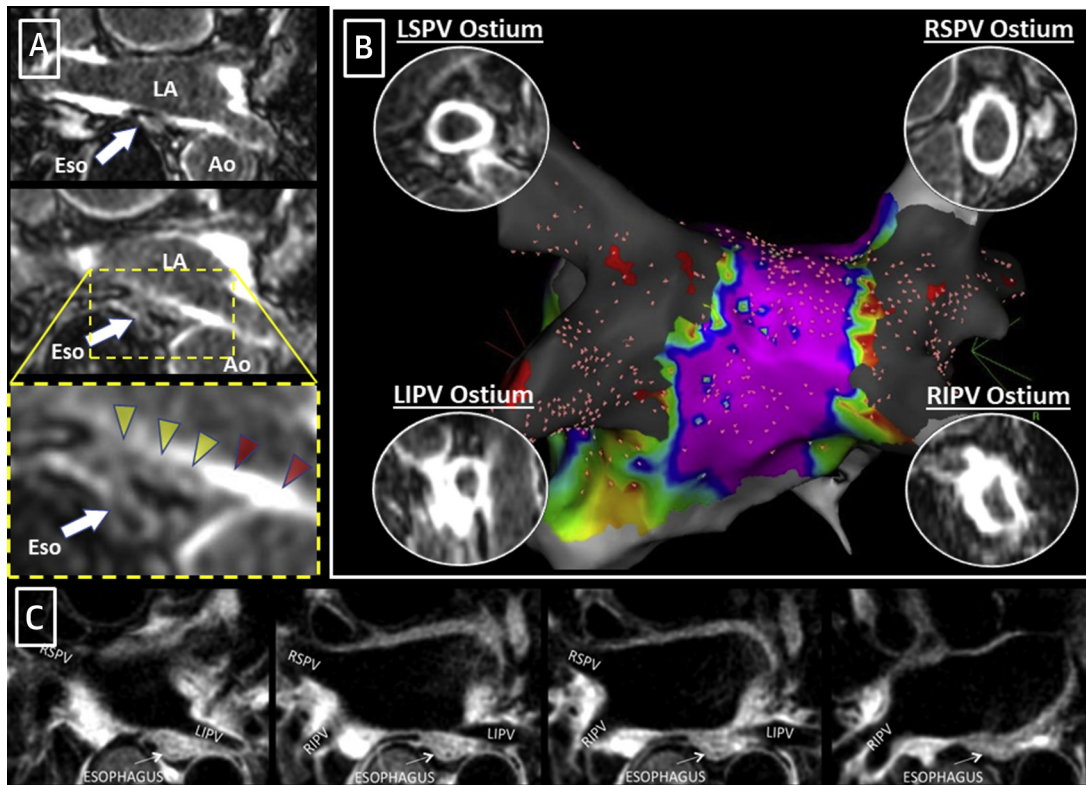
(A) Delayed gadolinium-enhanced cardiac magnetic resonance imaging (CMR) was performed immediately after the PFA procedure. On 2 different slices of the left atrium **(top and middle)**, transmural enhancement of the ablated atrial tissue is observed, but there was a complete lack of enhancement of the immediately-adjacent esophagus. The **bottom** image shows a zoomed version of the esophagus with the enhanced atrial tissue **(red arrowheads)** and the nonenhanced esophageal tissue **(yellow arrowheads)**. **(B)** The corresponding post-PFA electro-anatomic voltage amplitude map is shown, color-coded such that **purple** (>1.0 mV) represents normal tissue, and **gray** represents scar (<0.1 mV). In addition, on oblique cuts of the delayed-enhanced CMR, circumferential, uninterrupted, and transmural enhancement of all 4 PVs is observed (Online Video 1). **(C)** These 4 panels represent typical findings on T_2-weighted CMR acutely after PFA. Intense edema is seen on all PVs, with no sign of injury to the adjacent esophagus. Ao = aorta; Eso = esophagus; LA = left atrium; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; other abbreviations as in **Figure 1**.

**TABLE 5** Dimensional Analysis of the PV Diameters

	n*	Pre-PFA (mm)	Pre-PFA (mm)	p Value
LSPV	20	20.4 ± 2.4	20.7 ± 2.1	0.424
LIPV	23	16.6 ± 1.9	17.0 ± 2.0	0.206
LCPV	3	28.5 ± 2.1	27.5 ± 0.5	0.368
RSPV	22	20.0 ± 2.7	20.0 ± 2.1	0.960
RIPV	27	18.6 ± 2.7	17.9 ± 2.6	0.108

Values are n or mean ± SD. *PVs that underwent additional radiofrequency ablation (RFA) of PV reconnection gaps during the remapping procedure were excluded.

LCPV = left common pulmonary vein; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; PFA = pulsed field ablation; PV = pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

safety is maintained through a wide range of doses. Of course, these favorable safety data must be corroborated by larger PFA trials with similarly detailed follow-up.

PFA's qualitative safety edge also has meaningful implications for the *durability* of electrical PV isolation—arguably the most meaningful endpoint in AF ablation procedures—given that the primary mechanism of recurrence following ablation is electrical PV reconnection. Because multiple PFA lesions could be placed per vein without paying a safety penalty, as the PFA waveform was optimized to the final refinement, the durability of isolation in this subset of 18 patients improved to per vein and per patient rates of

CENTRAL ILLUSTRATION Pulmonary Vein Isolation for Atrial Fibrillation by Pulsed Field Ablation
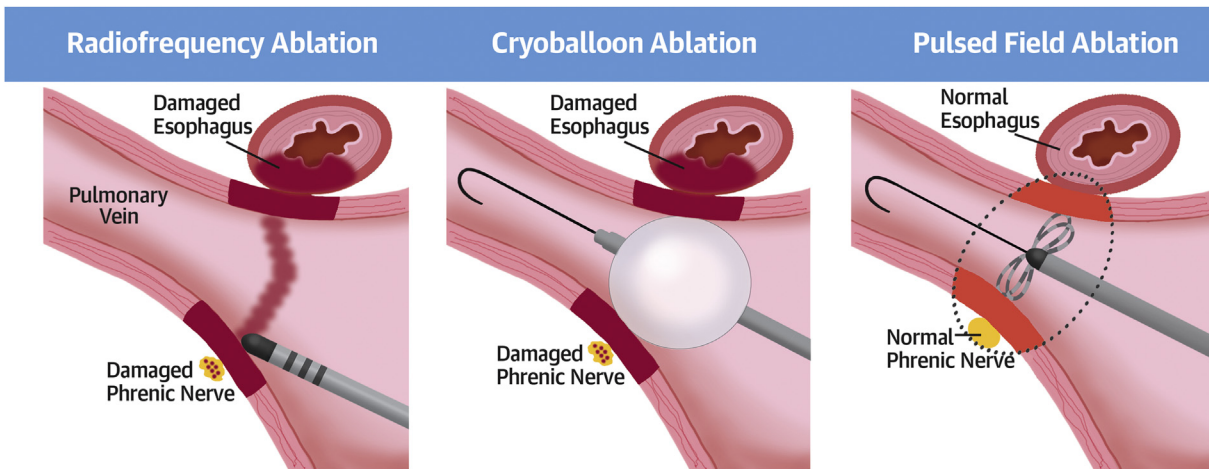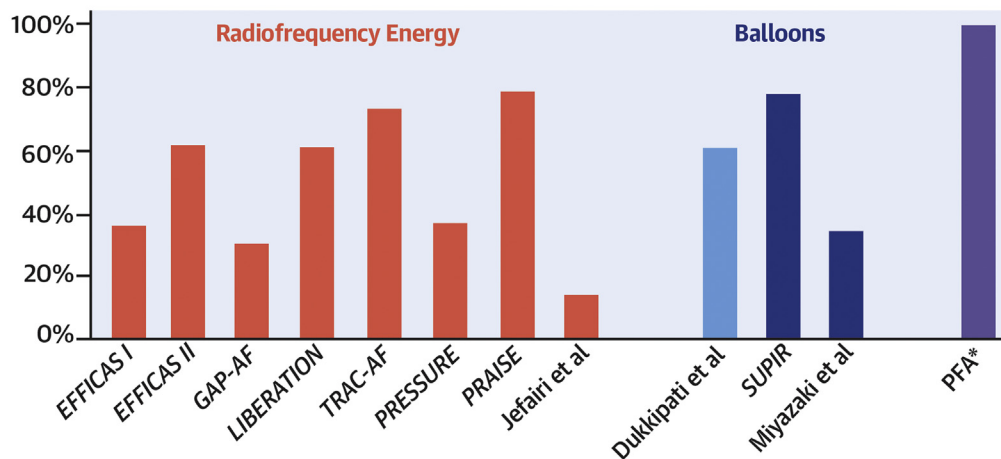
Reddy, V.Y. et al. J Am Coll Cardiol. 2019;74(3):315-26.

(Top) Thermal ablation using radiofrequency or cryoballoon catheters damages all tissue types indiscriminately, potentially damaging adjacent structures such as the phrenic nerve and esophagus. Conversely, pulsed field ablation (PFA) was shown to preferentially affect myocardial tissue, thus sparing these adjacent structures. **(Bottom)** The durability of pulmonary vein (PV) isolation can be determined by invasive remapping at ~3 months post-ablation. In prior studies using radiofrequency **(red bars)**, laser balloon **(light blue bar)** or cryoballoon **(dark blue bars)** catheters, all PVs remained durably isolated in <80% of patients. Conversely, using the optimized Biphasic 3 waveform, 100% of PFA patients had all PVs durably isolated **(purple bar)** (see also Online Table 6). EFFICAS = Efficacy Study on Atrial Fibrillation Percutaneous Catheter Ablation With Contact Force Support; GAP-AF = Gap-Atrial Fibrillation; LIBERATION = Outcome of Atrial Fibrillation Ablation After Permanent Pulmonary Vein Antrum Isolation With or Without Proven Left Atrial Posterior Wall Isolation; PRAISE = Pulmonary Vein Reconnection Following Ablation Index-guided Ablation: A Success Evaluation; PRESSURE = Pulmonary Vein Re-isolation as a Routine Strategy: A Success Rate Evaluation; SUPIR = SUstained PV Isolation With aRctic Front Advance; TRAC-AF = TempeRAture-Controlled and Contact Sensing RF Ablation Clinical Trial for Atrial Fibrillation.

100%. For comparison, no thermal ablation technology has been able to demonstrate such a low rate of PV reconnection; indeed, the published rates of durable isolation on a per-vein and per-patient basis have ranged from 51% to 93% and 21% to 79%, respectively (Online Table 6). It should also be noted that protocols that mandate invasive remapping procedures regardless of arrhythmia recurrence are notoriously difficult to conduct. Despite this complexity of study design, the number of patients we enrolled exceeded what most previous remapping studies were able to enroll (Online Table 6).

Consistent with our previous experience with monophasic PFA pulses in paroxysmal AF patients (n = 15) (10), we demonstrated that biphasic PFA resulted in rapid PV isolation (Online Figure 3), typically requiring only 1 application per PV and a total of ≤3 min of energy application per patient. The mean total procedure time of 92.2 min compares favorably with the recent FIRE and ICE study, in which the mean procedure times were 124 and 141 min for cryoballoon and radiofrequency ablation, respectively (16). Furthermore, in first-in-human trials, there are often study-related aspects of the procedure not related to clinical care that make it difficult to compare across studies. A better cross-trial comparator is LA ablation catheter dwell time—defined as the time transpiring from catheter entry to exit from the body. We observed a mean PFA catheter dwell time of 34 min, which also compares favorably to the FIRE and ICE dwell times of 92 and 109 min for cryoballoon and radiofrequency ablation, respectively (16).

STUDY LIMITATIONS. This study sample size was limited, and not all patients underwent the mandated remapping procedure. The observational design precluded direct comparison of PFA with thermal ablation, thereby limiting our ability to draw definitive conclusions about relative safety and efficacy. A multicenter study of PFA compared with thermal ablation should be conducted in the future. Due to differences in regional regulatory approval policies, 2 similar but separate studies were conducted and subsequently combined for this analysis. The median follow-up duration was only 120 days; however, it is arguable that the durable PV isolation data is a better predictor of long-term success than even 1-year clinical outcome data. Also, the changes to the pulse waveform over the course of the trials were not pre-specified.

The PFA catheter was only designed for PV isolation, and not for other lesion sets—cavotricuspid/mitral isthmus lines and posterior wall ablation. Radiofrequency ablation of AF can be performed with little to no fluoroscopy use, but fluoroscopy-free PFA is currently not possible—this would require integration with an electroanatomic mapping system (19). Various implementations of PFA are possible, and the outcomes observed in our study may or may not be applicable to future implementations of PFA using different catheter technologies and waveform compositions. Importantly, if the magnitude of the pulse amplitude is high enough, the tissue selective properties of PFA would likely be lost and indiscriminate tissue necrosis could ensue. Finally, there may be as yet unrecognized challenges or complications associated with PFA that may only manifest after thousands of procedures are performed; however, this seems unlikely as PFA has been used in oncology for over a decade.

CONCLUSIONS

We demonstrate that in patients with paroxysmal atrial fibrillation, PFA rapidly and efficiently isolates PVs with a degree of tissue selectivity and a safety profile heretofore not described for cardiac ablation. Furthermore, invasive electrophysiological studies demonstrated that PFA can achieve a high degree of durable PV isolation.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: PFA is a novel modality that can be performed without general anesthesia, reduces the risk of damaging adjacent structures, and results in durable pulmonary vein isolation.

TRANSLATIONAL OUTLOOK: Larger, multicenter trials are needed to compare safety, early success, and long-term durability of pulsed field PV isolation versus standard thermal ablation in patients with atrial fibrillation.

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KEY WORDS atrial fibrillation, catheter ablation, electroporation, esophageal damage, pulmonary vein isolation, pulsed field ablation

APPENDIX For a supplemental video as well as supplemental tables and figures, please see the online version of this paper.