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FOCUS ON NOVEL OBSERVATIONS IN AF ABLATION

Ablation of Atrial Fibrillation With Pulsed Electric Fields

An Ultra-Rapid, Tissue-Selective Modality for Cardiac Ablation

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ABSTRACT

OBJECTIVES The authors report the first acute clinical experience of atrial fibrillation ablation with PEF—both epicardial box lesions during cardiac surgery, and catheter-based PV isolation.

BACKGROUND Standard energy sources rely on time-dependent conductive heating/cooling and ablate all tissue types indiscriminately. Pulsed electric field (PEF) energy ablates nonthermally by creating nanoscale pores in cell membranes. Potential advantages for atrial fibrillation ablation include: 1) cardiomyocytes have among the lowest sensitivity of any tissue to PEF—allowing tissue selectivity, thereby minimizing ablation of nontarget collateral tissue; 2) PEF is delivered rapidly over a few seconds; and 3) the absence of coagulative necrosis obviates the risk of pulmonary vein (PV) stenosis.

METHODS PEF ablation was performed using a custom over-the-wire endocardial catheter for percutaneous transseptal PV isolation, and a linear catheter for encircling the PVs and posterior left atrium during concomitant cardiac surgery. Endocardial voltage maps were created pre- and post-ablation. Continuous and categorical data are summarized and presented as mean ± SD and frequencies.

RESULTS At 2 centers, 22 patients underwent ablation under general anesthesia: 15 endocardial and 7 epicardial. Catheter PV isolation was successful in all 57 PVs in 15 patients (100%) using 3.26 ± 0.5 lesions/PV: procedure time 67 ± 10.5 min, catheter time (PEF catheter entry to exit) 19 ± 2.5 min, total PEF energy delivery time <60 s/patient, and fluoroscopy time 12 ± 4.0 min. Surgical box lesions were successful in 6 of 7 patients (86%) using 2 lesions/patient. The catheter time for epicardial ablation was 50.7 ± 19.5 min. There were no complications.

CONCLUSIONS These data usher in a new era of tissue-specific, ultrarapid ablation of atrial fibrillation.
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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ICE = intracardiac echocardiography

LA = left atrium

PEF = pulsed electric field

PV = pulmonary vein

Catheter ablation of atrial fibrillation (AF) is frequently performed using either radiofrequency or cryothermal energy. Although uncommon, there continue to be reports of severe complications such as pulmonary vein (PV) stenosis, phrenic nerve palsy, and atrioesophageal fistula, with the latter often culminating in death (1). Common to these thermal energy sources is their reliance on time-dependent conductive heating/cooling, and the fact that these modalities ablate all tissue types indiscriminately. In contrast, pulsed electric field (PEF) energy ablates nonthermally by creating microscopic pores in cell membranes (2–4). Also referred to as irreversible electroporation, PEF ablation has been used to treat solid tumors, and more recently is being investigated for cardiac ablation (5–9). Unlike conventional energy sources, such as radiofrequency, cryotherapy, and laser, PEF energy is applied ultrarapidly (in seconds), and when applied to tissue at a dose above a specific threshold, will destabilize biological cell membranes by forming irreversible nanoscale pores and leakage of cell contents, ultimately culminating in cell death (2–4).

SEE PAGE 996

Most unique to PEF is its tissue selectivity: tissues have specific characteristic threshold field strengths that induce necrosis (10–12). Thus, PEF may be uniquely suited for AF ablation because: 1) cardiomyocytes have among the lowest threshold values (400 V/cm) of any tissue—potentially limiting collateral damage of periatrial nontarget tissue, such as the esophagus and phrenic nerve; 2) the absence of coagulative necrosis obviates the risk of PV stenosis; and 3) the speed of PEF has advantages for both lab workflow and safety of left-sided procedures (10–17). Herein, we report the first clinical experience of AF ablation with PEF—both epicardial box lesions during cardiac surgery and catheter-based PV isolation.

METHODS

We report the first evaluation of novel endocardial and epicardial ablation systems that employs PEF ablation of the PV or the PVs plus posterior left atrium (LA), respectively. This report focuses on the acute procedural performance and safety of this novel ablative approach. The study was approved by the human ethics committees at Homolka Hospital, Prague, Czech Republic, and the Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France, as well as the corresponding regulatory agencies. Written informed consent was obtained from all patients.

CLINICAL STUDIES. The endocardial ablation protocol was a prospective, open-label, nonrandomized study of patients with symptomatic paroxysmal AF planned for AF ablation. Patients age 18 to 70 years were entered into the study if they had paroxysmal AF refractory to or intolerant of at least 1 antiarrhythmic drug. Other key inclusion criteria included a requirement for the anteroposterior LA diameter to be <5.5 cm and left ventricular ejection fraction $\geq 40\%$.

The epicardial ablation protocol was a prospective, open-label, nonrandomized, safety and feasibility study of patients undergoing cardiac surgery with paroxysmal AF. It included patients age 18 to 70 years with a diagnosis of paroxysmal AF, who were scheduled to undergo elective on-pump cardiac surgery—either mitral or aortic valve repair or replacement, or coronary artery bypass grafting.

Exclusion criteria common to both studies included: previous AF ablation or any LA intervention, such as LA appendage occlusion; presence of prosthetic heart valves; severe gastroesophageal reflux disease; bleeding or clotting disorders; active infections; stroke/transient ischemic attack within 6 months; and class NYHA functional class IIIb or greater. Additionally, the absence of major surgery, unstable angina, myocardial infarction, coronary intervention, cardiac device implants, or LA thrombus within the preceding 3 months was required. Additional exclusion criteria for the surgical cohort included: prior cardiac surgery, prior pericardial interventional procedures, known pericardial abnormalities, or history of pericarditis within 3 months. Consecutive patients underwent epicardial ablation at both centers between December 2017 and March 2018; endocardial ablation was performed at Homolka Hospital, Prague, between January 2018 and March 2018.

PEF SYSTEM. Endocardial ablation. The PEF system for endocardial applications is comprised of 3 components: a custom-built generator for producing high-voltage PEF waveforms, an endocardial ablation

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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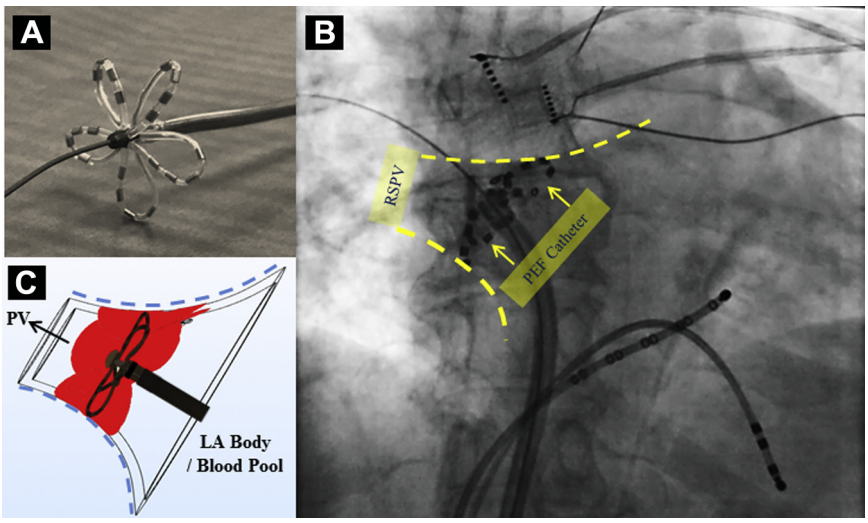
FIGURE 1 Catheter-Based Endocardial PEF Ablation



(A) The fully-deployed endocardial PEF catheter is shown over a guidewire with its splines as it exits the transseptal sheath. **(B)** The in vivo fluoroscopic view depicts the fully deployed ablation catheter positioned at the right-superior PV ostium. The PV is outlined by contrast injection performed through the sheath. Pacing catheters in coronary sinus and right ventricular (RV) apex are also present. **(C)** The ablation zone of a PEF application is modeled: in this cross-sectional, long-axis view of the LA-PV junction, the **shaded red area** represents the circumferential ablation zone. LA = left atrium; PEF = pulsed electric field; PV = pulmonary vein; RSPV = right-superior pulmonary vein.

catheter designed for delivering energy at a PV antrum, and a 13-F steerable sheath to navigate and position the PEF ablation catheter in the LA (Iowa Approach Inc., Menlo Park, California). The PEF generator can be programmed to deliver a variety of waveforms over multiple channels, with various bipolar electrode pairing options.

The 12-F over-the-wire PEF ablation catheter has a deployable distal portion and 5 splines, with each spline containing 4 separate electrodes (Figure 1). The basket-like distal portion of the multispline ablation catheter can be deployed from a small-diameter closed-basket form to a larger-diameter open-basket form. Electrodes along the splines are used to deliver the ablative PEF energy. When fully deployed into a flower-shaped configuration, the distal portion has a diameter of 30 mm.

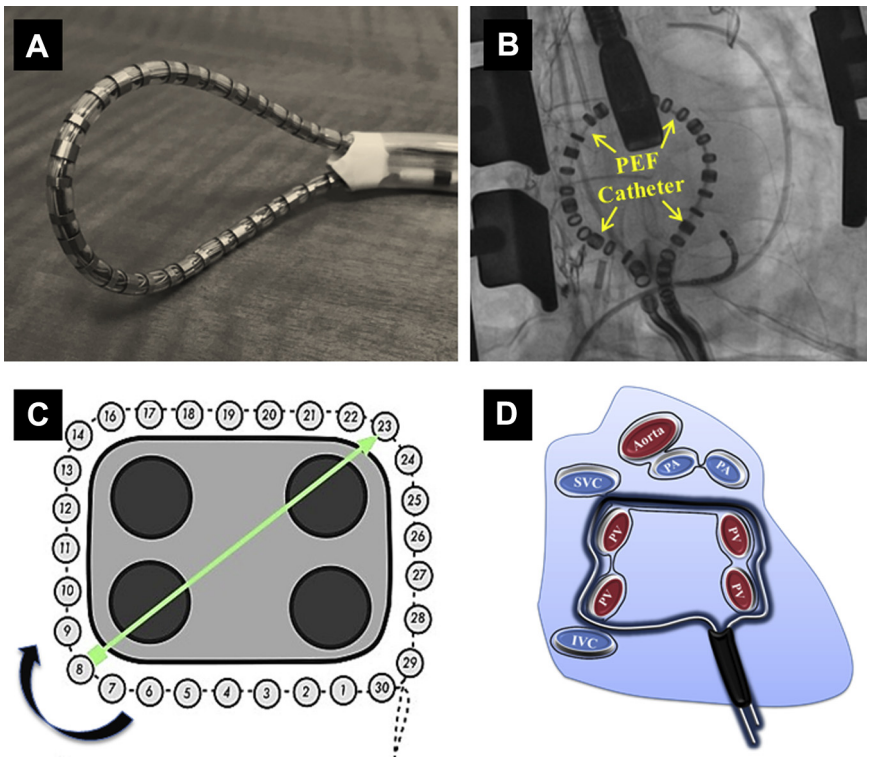
The catheter is maneuvered to each PV over the guidewire and advanced after full deployment such that splines achieve circumferential proximity with the PV antral walls. The catheter was rotated between applications to optimize coverage and proximity (patients were not excluded based on PV anatomy). This first-generation catheter was not capable of displaying electrical data from the electrodes. A compatible cardiac pacing stimulator allows for delivery of the pulses synchronized to simultaneous atrial and ventricular pacing via standard catheters.

Epicardial ablation. The PEF system for epicardial applications used the same generator for producing high-voltage PEF waveforms, a linear epicardial PEF ablation catheter designed for delivering PEF energy in a box lesion format around all 4 PVs, and a cinch tool for adjusting and tightening the positioning of the epicardial ablation catheter around the four PVs (Iowa Approach Inc.). This is a flexible linear epicardial catheter and incorporates a guidewire lumen (Figure 2). Electrodes for PEF ablation energy delivery are distributed in the midportion of the catheter—the portion that wraps around the PVs and posterior LA.

The cinch tool is a double-barreled straw-like device designed for positioning the epicardial ablation catheter firmly around the posterior LA. It has a long straight portion and a distal, gently curved short portion designed to generally conform to the curvature of the epicardium. It was placed with the ends of the epicardial PEF ablation catheter inserted into the barrels of the cinch tool. The ends of the catheter are tightened by the cinch tool in a necktie fashion until the catheter is firmly wrapped around the posterior LA (Figure 2).

Therapy delivery. The generator outputs a pulsed voltage waveform to the ablation catheter electrodes for PEF energy delivery. The waveform is structured as a hierarchical set of millisecond pulses in bipolar fashion across electrodes, delivered as a train over a

FIGURE 2 Surgical Epicardial PEF Ablation



(A) The epicardial PEF catheter with multiple electrodes is shown exiting the cinching tool. **(B)** The fluoroscopic image demonstrates proper positioning of the ablation catheter electrodes en bloc around the 4 PVs and posterior LA. A pulmonary artery catheter and coronary sinus catheter are in place. **(C)** The PEF application between a single pair of electrodes **(green arrow)** during sequential activation around the entire loop to complete a full ablation sequence. **(D)** The pericardial reflections and sinuses as seen with the heart removed. The ablation catheter is positioned encircling the posterior LA and the 4 PVs. Abbreviations as in Figure 1.

few seconds; no external patch is employed. The voltage is the only controllable parameter; other waveform parameters are pre-determined. The voltage applied to the electrodes determines the generated electric field around the electrodes (Figure 1). The voltage delivered for endocardial and epicardial ablation ranged from 900 to 2,500 V.

PROCEDURAL WORKFLOW. Endocardial ablation. Procedures were performed under general anesthesia. Femoral venous access was obtained, and after single transseptal puncture, the PEF ablation catheter was placed within the LA using the 13-F deflectable sheath. Standard anticoagulation parameters were followed with uninterrupted oral anticoagulation periprocedurally and intraprocedural intravenous heparin. Patients underwent pre-procedural computed tomography scanning to characterize PV anatomy. Baseline voltage maps were created using a multispline catheter (Pentaray, Biosense Webster, Irvine, California) with an electroanatomical mapping system (CARTO, Biosense Webster). Pre- and post-procedural phrenic nerve pacing was performed in all patients. Luminal esophageal temperature monitoring was not performed in view of its nonthermal ablative mechanism. Intracardiac echocardiography (ICE) imaging and contrast injections with fluoroscopy helped optimize PEF catheter positioning at the PV ostia. All patients received succinylcholine neuromuscular paralysis (0.5 to 1 mg/kg) immediately prior to PEF applications to suppress skeletal muscle stimulation. Additionally, simultaneous atrial/ventricular pacing was performed using coronary sinus and right ventricular catheters, so that the PEF pulses could be synchronized to the refractory periods of both the atria and ventricles. Each PV received at least 3 PEF applications (900 to 1,000 V), with the splines rotated between applications to ensure circumferential PV coverage. Additional paralytic agents were administered as needed between applications. After ablation, electrical PV isolation was

TABLE 1 Baseline Characteristics

	Endocardial Cohort (n = 15)	Epicardial Cohort (n = 7)
Age, yrs	63.8.0 ± 4.6	69.0 ± 6.4
Male	7/15 (46.6)	5/7 (71.4)
CHA_2DS_2-VASc	1.7 ± 0.8	2.9 ± 1.3
LVEF, %	65 ± 2.8	58.8 ± 4.5
LA diameter, mm	40 ± 2.8	46 ± 6.5
Hypertension	9/15 (60)	7/7 (100)
Stroke/TIA	0/15 (0)	1/7 (14)
MI/PCI/CABG	0/15 (0)	0/7 (00
Anticoagulation		
Warfarin	8/15 (53.3)	3/7 (42.8)
NOAC	7/15 (46.7)	4/7 (57.1)
Antiarrhythmic		
Class I	9/15 (60)	0/7 (0)
Class II	4/15 (26.7)	4/7 (57.1)
Class III	2/15 (13.3)	5/7 (71.4)

Values are mean ± SD or n/N (%).

CABG = coronary artery bypass graft; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 (2 points), Diabetes, Stroke (2 points), Vascular disease, Age 65–75, Sex; LA = left atrium; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NOAC = novel oral anticoagulants; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

assessed with the multispline catheter, followed by creation of an immediate post-ablation voltage map.

Epicardial ablation. All study procedures were performed under general anesthesia. Voltage maps were created using a basket catheter and compatible electroanatomical mapping system (Orion and Rhythmia, Boston Scientific, St. Paul, Minnesota). Post-ablation voltage mapping was performed in all patients; pre-ablation mapping was performed in a subset to minimize procedural duration. Pre- and post-procedural phrenic nerve pacing was performed in all patients. Prior to the concomitant surgery, the cardiac surgeon exposed the necessary areas of the pericardium and positioned the ablation catheter to encircle both the PVs and posterior LA. Catheter placement and tissue proximity was optimized and the position of the electrodes was confirmed by fluoroscopic imaging (Figure 2). Simultaneous atrial/ventricular pacing was performed via epicardial pacing wires for synchronization of the PEF pulses to atrial and ventricular refractoriness. All patients received 2 consecutive PEF applications (2,100 V to 2,400 V).

Continuous and categorical data are summarized and presented as mean ± SD and frequencies.

RESULTS

A total of 15 patients with paroxysmal AF underwent endocardial PEF ablation of their PVs, and 7 AF patients (6 paroxysmal, 1 persistent) underwent surgical epicardial PEF ablation of their LA posterior wall and PVs. The baseline demographic and clinical data are shown in Table 1. The catheter-based endocardial and surgical epicardial procedures were performed by 2 and 6 operators, respectively.

In the endocardial cohort, baseline PV potentials were documented in all 57 PVs in 15 patients (3 patients had left common PVs). Voltage maps were created and pre-procedural phrenic nerve capture was confirmed in all patients. The PEF ablation catheter was successfully maneuvered to the PV ostia in all patients. In the epicardial cohort, baseline voltage maps were created in 3 of 7 patients. Baseline phrenic nerve capture was confirmed in all patients. As confirmed by fluoroscopy, the epicardial PEF ablation catheter was then successfully positioned by the surgeons in all patients.

ENDOCARDIAL PEF DELIVERY. PEF ablation electrically isolated all 57 PVs in 15 patients (100%) using a mean of 3.26 ± 0.5 lesions/PV, or 12.4 ± 1.0 lesions/patient. After PEF delivery, post-ablation voltage maps were created in all patients. The level of isolation was appreciated to be at least ostial (Figure 3). The procedure was completed in a mean of 67 ± 10.5 min (range 52 to 84 min). The total catheter time, defined as time transpiring from PEF catheter entry into the LA to time of removal, was 26 ± 4.3 min (range 19 to 33 min), and the total ablation time (defined as time transpiring from delivering the first to last ablation) was 19 ± 2.5 min (range 16 to 23 min). Because of the millisecond nature of the PEF pulses, the actual time of PEF energy delivery of all lesions was <60 s/patient. The combined time for baseline and post-ablation LA-PV voltage mapping was 42.6 ± 9.4 min (range 28 to 56 min). The total fluoroscopy time per patient was 12.3 ± 4.0 min (Table 2). PEF was delivered successfully in all 186 applications, and all PVs were isolated with the initial isolation strategy of ~3 ablations/PV. The mean energy delivered during endocardial PV ablation approximated 78 J per ablation delivery. As seen with standard thermal ablation, vagal responses were seen in 5 of 15 patients (33%) during PEF energy delivery—all during ablation of the left superior PV.

EPICARDIAL PEF DELIVERY. The patients in this arm were undergoing surgery for either the mitral (n = 3) or aortic (n = 3) valves or coronary artery bypass grafting (n = 1). PEF ablation system was able to successfully deliver ablation lesions in 6 of 7 (85.7%) patients; the system failed to deliver appropriately in 1 patient due to technical problems. Two consecutive applications were delivered in the remaining 6 patients. Post-ablation voltage maps were created in all patients, and electrical isolation was confirmed in all

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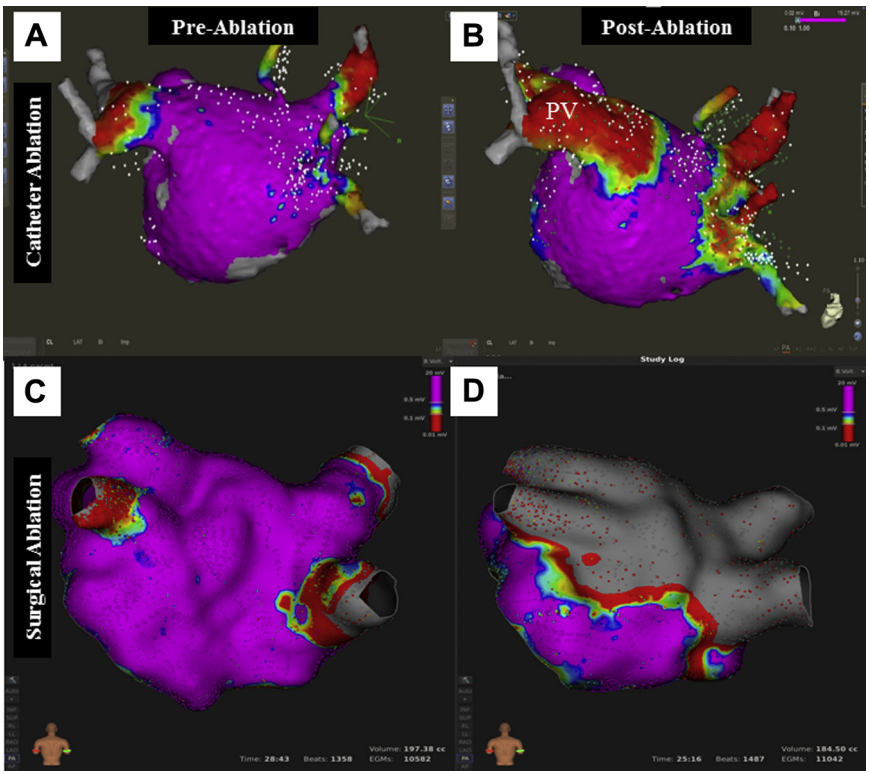
AUGUST 2018:987–95

FIGURE 3 Baseline and Post-Ablation Electroanatomical Voltage Mapping



Posterior LA views from representative endocardial **(A and B)** and epicardial **(C and D)** PEF ablation cases. **A and C** were baseline maps, while **B and D** were post-ablation maps. **Purple** represents normal bipolar voltage amplitude, while **red and gray** represent diminished amplitudes—indicating the absence of electrical potentials. At baseline, the electrical activity was noted at the PV ostia; the low voltage observed distally in the PVs is normal. After endocardial ablation **(B)**, the voltage amplitudes are diminished in the PVs—electrical isolation was confirmed using a multielectrode catheter (not shown); the residual color seen in some of the PVs (such as the right inferior PV here) simply represent far-field potentials. After epicardial ablation **(D)**, the electrical activity along the entire posterior LA and PVs are replaced with low voltage **(red and gray)**. Abbreviations as in Figure 1.

6 patients in whom the lesions were delivered. As demonstrated by post-ablation voltage mapping, both the PVs and posterior LA were electrically isolated (Figure 3). The total catheter time, defined as time transpiring from epicardial PEF catheter insertion to removal, was 50.7 ± 19.5 min (range 30 to 75 min), and the total ablation time, defined as time transpiring from first to last PEF application, was 25.0 ± 17.5 min (range 5 to 48 min) (Table 2).

TABLE 2 Procedural Characteristics of Endocardial and Epicardial Cohorts

	Endocardial Cohort (n = 15)	Epicardial Cohort (n = 7)
Procedure time	67.0 ± 10.5	N/A
Mapping time	41.4 ± 9.3	N/A
Catheter time	26.0 ± 4.3	50.7 ± 19.5
Ablation time	19.0 ± 2.5	25.0 ± 17.5
Fluoroscopy time	12.3 ± 4.0	6.6 ± 3.8
Isolation success	15/15 (100)	6/7 (86)

Values are mean ± SD or n/N (%). All time is expressed in minutes.

PEF was delivered successfully in 12 of 14 applications, and the posterior wall and PVs were isolated in 6 of 7 patients—that is, in all patients that received successful delivery of PEF pulses. The mean energy delivered during epicardial ablation to isolate the posterior LA-PVs approximated 1,146 J per ablation delivery.

SAFETY. All PEF applications were accompanied by minimal thoracic and diaphragmatic stimulation; there were no instances of catheter dislocation during PEF delivery. There were no PEF catheter-related complications such as deployment failure, cardiac perforation, or catheter entrapment within the PVs or valvular apparatus. There was no evidence of charring or thrombus formation upon catheter removal

from the LA. Applications were often accompanied by ultrasound contrast formation that was visualized on ICE immediately after the application; these rapidly resolved. None of the applications resulted in waveform discontinuities suggestive of arcing. There was no evidence of acute PV narrowing as confirmed by post-ablation ICE imaging and voltage mapping. ICE imaging at the end of the procedure did not demonstrate pericardial effusion in any patient. The right phrenic nerve was intact in all 15 endocardial and 7 epicardial ablation patients at procedural end. Esophagogastroduodenoscopies were performed in only 2 of the patients, but these did not reveal any abnormalities.

There were no instances of atrial or ventricular tachyarrhythmias, as well as no evidence of significant repolarization abnormalities on the 12-lead electrocardiogram. All patients were successfully extubated and had unremarkable recovery with no evidence of significant thoracic or upper-extremity muscular discomfort or any focal neurological motor or sensory symptoms upon awakening. The 1-month follow-up visits were completed in 14 of 15 catheters and 5 of 7 surgical ablation patients; these patients reported no adverse events.

DISCUSSION

We demonstrate the first-ever clinical use of PEF ablation for the treatment of AF. PEF-based ablation was acutely safe and feasible using both percutaneously-delivered endocardial and surgically-placed epicardial catheters. Unlike thermally-based energy technologies, PEF ablation was distinguished by its ability to achieve ultrarapid PV isolation or posterior box (posterior LA plus PVs) isolation with total ablation times of <60 s.

PEF ABLATION. Mechanism and tissue selectivity. Electrical pulse applications exceeding a certain threshold create irreversible pores within cell membranes, leading to cell death (2–4). PEF ablation has a unique mechanistic signature in that it spares the extracellular matrix. In comparison, other heat-based energy sources rely on coagulative necrosis, which extends as far as lethal temperatures reach (18). Cryothermy largely spares the extracellular matrix from direct ablation; however, it causes destruction of all cellular tissue elements indiscriminately, and by virtue of its effect on vascular structures, can cause downstream generalized tissue necrosis (19). In contrast, PEF ablation preserves the integrity of the tissue matrix within its ablation zone (10–17).

Furthermore, PEF ablation is characterized by tissue-specific thresholds, thereby facilitating preferential ablation of certain tissues (e.g., myocardium) with relative sparing of collateral organs (10). (The electric field thresholds that generate irreversible electroporation through PEF ablation for a variety of tissue types are shown in Online Table 1.) Myocardial tissue has a lower threshold for PEF ablation than many other tissue types, thereby providing the mechanistic basis for the relative selectivity to myocyte necrosis during cardiac ablation, while yet sparing collateral structures such as the esophagus or the phrenic nerve (10–17).

Indeed, there is a significant body of preclinical work on the safety of cardiac electroporation in the context of the esophagus, phrenic nerve, coronary arteries, and pulmonary vein stenosis (13–17). In these studies, a high level of safety was demonstrated despite purposeful direct ablation deliveries to the relevant structures. Furthermore, using the epicardial system described in the present report, direct PEF applications to the esophagus were studied, demonstrating good safety outcome (20). Similarly, preclinical PEF ablation studies with the endocardial system discussed in the present report were also recently performed. Although these preclinical studies indicate an excellent safety profile to cardiac ablation with PEF, there is considerable variability in pulse delivery methods, and it is possible that collateral damage may yet occur with certain doses and pulse configurations.

Taken together, PEF energy has certain specific theoretical advantages for cardiac ablation including: 1) a nonthermal ablative mechanism that eliminates high temperature phenomena like catheter tip char and steam pops; 2) the absence of PV stenosis, because the PEF does not rely on coagulative necrosis; and 3) the ability to minimize damage to non-myocardial collateral tissue, such as the coronary vessels, phrenic nerve, and esophagus (10–17).

In addition to these safety advantages, there are potential technical and practical advantages to PEF ablation: 1) the lack of dependency on contact force and need for achieving lethal tissue temperatures; 2) the ability to create large homogenous lesions; and 3) the speed of PEF applications. From a practical perspective, the millisecond nature of the PEF pulses potentiates ultrarapid lesions and short procedure times favorable to laboratory workflow. However, the PEF approach studied here also has some disadvantages, such as the need for general anesthesia and neuromuscular paralysis to avoid skeletal muscle stimulation. This is particularly relevant for endocardial PEF, as some conventional approaches to PV isolation are performed under conscious sedation. Future work with PEF ablation using other novel

waveforms might obviate this requirement. Although the exact degree of tissue proximity requisite for successful PEF energy delivery remains to be defined accurately, ablation is probably most successful with electrode-tissue contact. The need for proximity introduces a potential limitation that has historically been a limiting factor with other ablation energy sources.

Efficacy of LA ablation. Wittkampf et al. (7) were the first to demonstrate the preclinical feasibility of employing electroporation to electrically isolate PVs. In a chronic swine series, they administered up to 4 200-J shocks per PV, delivered between a circular multielectrode catheter and a return patch (7). At 3 weeks, they demonstrated reduced PV electrogram amplitude and increased pacing thresholds, with histological lesions as deep as 3.5 mm. Similarly, in preclinical swine experiments, we have demonstrated the feasibility and safety of PV and LA ablation, as well as durability of PV isolation, using both the endocardial PEF catheter and a previous-generation epicardial PEF catheter (21-23).

From an acute efficacy and a safety standpoint, our first-in-human report of endocardial PEF-based PV isolation and epicardial PEF-based posterior box isolation compares favorably to other conventional catheter or surgical techniques. In fact, the first-pass PV isolation rate was 100% in the endocardial cohort and 87.5% in the epicardial cohort in this report—with the 1 case of acute surgical failure being related to a technical issue with the stimulator used to synchronize the PEF pulses. Catheter manipulation was straightforward, as evidenced by the overall short catheter times in both cohorts. There were no unexpected observations during PEF applications, such as catheter dislocation with pulses, malignant arrhythmias, significant electrocardiographic repolarization changes, or ventricular dysfunction.

The total ablation time of <60 s (ultrarapid) is markedly shorter than other contemporary endocardial technologies. These short ablation times, combined with the relative ease of PEF catheter manipulation, account for the short mean catheter dwell time of 19 min, with a relatively tight spread to the range (16 to 23 min). Furthermore, the total fluoroscopy time per patient was low at ~12 mins, which compares favorably to conventional ablation approaches.

In the epicardial cohort, despite the unfamiliarity of the surgeons with this novel catheter, a high degree of success was achieved with a total catheter time of ~50 mins and total ablation time of ~25 mins. PEF energy was delivered successfully in 12 of 14 applications, and the posterior wall and PVs were isolated in 6 of 7 patients—that is, in all patients who received successful delivery of energy.

Regarding energy dosage, conceptually, PEF ablation depends on the electric field generated in tissue by the ablation device. The electric field is typically expressed in as volts/centimeter. Because the electric field generated in tissue depends on the voltage applied to the device electrodes, the applied voltage, expressed in volts, is the most relevant dosing parameter that characterizes PEF ablation. For example, the endocardial clinical applications reported here were performed at voltages of 900 to 1,000 V—a dose above the electric field threshold for cardiac myocytes (400 V/cm).

In previously reported preclinical experiments with endocardial PEF ablation, a defibrillator was used to generate the PEF lesions; the typical energy values were on the order of 200 J/delivery per PV (7). In our study, using the custom PEF generator, the mean energy delivered was 78 J/PV lesion. In contrast, during conventional radiofrequency ablation, a single typical focal RF application delivered at 30 W for 30 s deposits 900 J/lesion, and the total number of RF applications per PV often exceeds 20 lesions/PV. These data indicate that PEF ablation can generate effective lesions efficiently at a fraction of the energy employed by other ablation modalities. Although energy is not the only metric for describing ablation, the low level of energy employed herein to generate successful lesions is noteworthy because it indicates that tissue heating is minimal; this adds a further element of safety beyond the tissue selectivity discussed earlier. Indeed, the absence of observed intraprocedural complications and preserved phrenic nerve function signal that this modality has a favorable periprocedural safety profile. However, despite the theoretical and preclinical basis for PEF's safety profile, in the absence of cardiac imaging for PV assessment and detailed endoscopic examination, its long-term safety remains to be demonstrated. Ultimately, the theoretical safety of PEF-based ablation must be confirmed in larger clinical trials with detailed safety assessments.

STUDY LIMITATIONS. This is a dual-center report of acute procedural outcomes only, and no comment can be made on the chronic efficacy of PEF ablation. Although the acquisition of post-ablation voltage maps indicated that immediate electrical PV reconnection did not occur, as can be observed with other ablation energy sources, provocative testing with adenosine or isoproterenol was not performed. Ultimately, the durability of PEF ablation must be examined with protocol-driven invasive second procedures to assess PV electrical activity during follow-up. Similarly, although there were no acute safety issues observed in

these patient cohorts, as noted in the previous text, longer-term safety studies are needed that specifically assess for PV stenosis with computed tomography/magnetic resonance imaging, esophageal damage, and cerebral microemboli assessed by magnetic resonance imaging. Finally, it must be noted that there may be as yet unrecognized challenges or complications associated with PEF ablation. Ultimately, this first-in-human report is best viewed as the proof-of-concept that this novel energy technology is feasible and acutely safe, but considerably more clinical work must be performed to ensure its safety and efficacy.

CONCLUSIONS

Ultrarapid PEF-based PV and LA ablation is both feasible and safe and is associated with excellent acute efficacy. Although several aspects of the procedure, such as the durability, level of pulmonary vein isolation, and effect on clinical recurrence of atrial fibrillation, remain to be confirmed, PEF ablation is a paradigm-shifting energy source that has the potential to transform the field of AF ablation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Conventional ablation technologies, such as radiofrequency and cryoablation, rely on time-dependent conductive heating/cooling, and ablate tissues indiscriminately. PEF energy ablates nonthermally by creating nanoscale pores in cell membranes. Potential advantages for AF ablation include cardiomyocyte tissue selectivity to reduce collateral tissue damage and rapid ablation times.

TRANSLATIONAL OUTLOOK: Large-scale randomized studies are needed to compare the outcomes of ablation procedures performed with PEF ablation catheters versus conventional catheters.

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

APPENDIX For a supplemental table and references, please see the online version of this paper.