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ORIGINAL RESEARCH

CATHETER ABLATION OF ATRIAL FIBRILLATION

A Focal Ablation Catheter Toggling Between Radiofrequency and Pulsed Field Energy to Treat Atrial Fibrillation

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ABSTRACT

BACKGROUND Because of its safety, "single-shot" pulsed field ablation (PFA) catheters have been developed for pulmonary vein isolation (PVI). However, most atrial fibrillation (AF) ablation procedures are performed with focal catheters to permit flexibility of lesion sets beyond PVI.

OBJECTIVES This study sought to determine the safety and efficacy of a focal ablation catheter able to toggle between radiofrequency ablation (RFA) or PFA to treat paroxysmal or persistent AF.

METHODS In a first-in-human study, a focal 9-mm lattice tip catheter was used for PFA posteriorly and either irrigated RFA (RF/PF) or PFA (PF/PF) anteriorly. Protocol-driven remapping was at ~3 months postablation. The remapping data prompted PFA waveform evolution: PULSE1 (n = 76), PULSE2 (n = 47), and the optimized PULSE3 (n = 55).

RESULTS The study included 178 patients (paroxysmal/persistent AF = 70/108). Linear lesions, either PFA or RFA, included 78 mitral, 121 cavotricuspid isthmus, and 130 left atrial roof lines. All lesion sets (100%) were acutely successful. Invasive remapping of 122 patients revealed improvement of PVI durability with waveform evolution: PULSE1: 51%; PULSE2: 87%; and PULSE3: 97%. After 348 ± 652 days of follow-up, the 1-year Kaplan-Meier estimates for freedom from atrial arrhythmias were 78.3% ± 5.0% and 77.9% ± 4.1% for paroxysmal and persistent AF, respectively, and 84.8% ± 4.9% for the subset of persistent AF patients receiving the PULSE3 waveform. There was 1 primary adverse event—inflammatory pericardial effusion not requiring intervention.

CONCLUSIONS AF ablation with a focal RF/PF catheter allows efficient procedures, chronic lesion durability, and good freedom from atrial arrhythmias—for both paroxysmal and persistent AF. (Safety and Performance Assessment of the Sphere-9 Catheter and the Affera Mapping and RF/PF Ablation System to Treat Atrial Fibrillation; NCT04141007 and NCT04194307) (J Am Coll Cardiol EP 2023;9:1786-1801) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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Since its introduction in the late 1990s, catheter ablation for atrial fibrillation (AF) has been performed using thermal energy, including radiofrequency ablation (RFA), cryoablation, or laser ablation. These energy technologies are limited by their indiscriminate ablative properties—as the temperature wave propagates, all cellular elements of affected tissue are ablated, raising the possibility of inadvertent collateral injury to nontarget structures, such as the esophagus and phrenic nerve.[1,2] On the other hand, more recent preclinical studies have demonstrated that myocardial tissue is preferentially (though not exclusively) ablated when exposed to pulsed electrical fields.[3-8] Indeed, using a pentaspline pulsed field ablation (PFA) catheter, clinical studies revealed that pulmonary veins (PVs) can be electrically isolated with high durability without some of the major nonspecific injuries characteristic of thermal ablation, including no esophageal damage, pulmonary vein stenosis, or permanent phrenic nerve palsy.[9-13]

However, PFA catheters in clinical trials are: 1) largely "single-shot" devices designed for PV isolation (PVI) alone, with limited ability to deliver extra-PV lesion sets;[12,14,15] and 2) limited to delivering PF energy alone—a potential limitation in certain conditions such as ablation adjacent to conduction tissue. Recently, a 7.5-F catheter with a compressible 9-mm lattice tip and large ablative "footprint" was developed to facilitate overlap of contiguous lesions.[16,17] Importantly, this catheter can easily toggle between RFA and PFA. In an initial 76-patient report of acute procedural outcomes, this RF/PF lattice tip catheter could isolate PVs and create linear atrial lesions.[18] Herein, we now report the results of the multicenter, single-arm, first-in-human clinical trial of this lattice tip catheter to treat a large (178-patient) cohort of patients with paroxysmal or persistent AF. Importantly, we assessed both lesion durability with invasive remapping studies and 1-year clinical outcomes of freedom from atrial arrhythmias.

METHODS

STUDY DESIGN. This study was conducted according to the Declaration of Helsinki after approval by the corresponding ethics committees and regulatory agencies and after informed consent from all subjects.

This was a first-in-human, prospective, multicenter, single-arm, clinical study of the lattice tip catheter RF/PF ablation system conducted in 2 countries at 3 centers—2 in the Czech Republic and 1 in Lithuania. The trials were funded by the manufacturer of the lattice tip catheter system, Affera Inc. The sponsor initiated 2 nearly identical trials (NCT04141007 and NCT04194307); given that identical patient populations were enrolled, with identical follow-up and endpoints, these datasets are combined in this paper.

PATIENT POPULATION. Patients with symptomatic paroxysmal or persistent AF were eligible for enrollment if they met the following criteria: age of ≥18 years, AF resistant to class I to IV antiarrhythmic medications, planned for a first-ever AF ablation procedure, with left atrial (LA) anteroposterior dimension of ≤5.5 cm, and with a left ventricular ejection fraction of >40%. There were no exclusions for PV anatomy or history of AF/atrial flutter. The Supplemental Appendix contains the full details of the inclusion and exclusion criteria.

LATTICE TIP ABLATION SYSTEM. System description. The system has been previously described.[16-18] Briefly, the 8-F bidirectional deflectable catheter (Sphere-9, Affera Inc) has a compressible 9-mm-diameter nitinol lattice tip electrode, with 9 nodes (0.7-mm diameter each) on its spherical surface, each containing a minielectrode and thermocouple. There is a central noncontact indifferent electrode within the lattice and 2 ring electrodes on the distal shaft. The system also includes RF and PF generators (HexaGen and HexaPulse, respectively, Affera Inc), a peristaltic saline infusion pump (HexaFlow, Affera Inc), and an electroanatomic mapping system (including the HexaMap catheter interface unit and Prism-1 mapping software, Affera Inc) (Supplemental Figure 1). This dual-generator design (RF or PF) permits toggling between RFA and PFA by simply stepping on a foot pedal.

Saline-irrigated RFA. Temperature-controlled RF energy is delivered from the entire conductive lattice tip, with saline homogeneously sprayed from a central irrigation nozzle during mapping (4 mL/min) or during RFA (30 mL/min), respectively. RF applications were typically 5 to 7 seconds in duration, with a target surface temperature of 73 °C to 75 °C, the current limit varying between 80% and 90%, and a goal center-to-center distance of 6 to 8 mm between adjacent lesions.

Pulsed field ablation. A proprietary biphasic monopolar PF waveform is delivered from the entire lattice tip. In contrast to the modulating role of temperature feedback during RFA, the thermocouples do not modulate energy during PFA. The PFA

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CEC = Clinical Events Committee
CS = coronary sinus
CTI = cavotricuspid isthmus
DWI = diffusion-weighted imaging
EGD = esophagogastroduodenoscopy
FLAIR = fluid-attenuated inversion recovery
LA = left atrium
MRI = magnetic resonance imaging
PF = pulsed field
PFA = pulsed field ablation
PV = pulmonary vein
PVI = pulmonary vein isolation
RF = radiofrequency
RFA = radiofrequency ablation

waveforms consist of a train of microsecond-scale pulses delivered over 3 to 5.5 seconds, driven with up to ±2 kV. These pulses are delivered without cardiac synchronization, with saline irrigation at 4 mL/min during mapping, or 4 to 30 mL/min during PFA and a goal center-to-center distance of 5 to 6 mm between adjacent lesions. The PFA waveforms evolved over time: PULSE1 (3- to 5.5-s lesions; saline at 4-30 mL/min), PULSE2 (4-s lesions; saline at 15 mL/min), and PULSE3 (4-s lesions; saline at 15 mL/min).

Electroanatomic mapping. The electroanatomic mapping system uses magnetic localization with sensors situated within the lattice tip, and after respiratory gating, mapping is performed. Catheter-tissue contact is continuously assessed based on the impedance values of the minielectrode. Voltage and activation maps are created simultaneously with anatomy acquisition. Bipolar electrograms are configured between each minielectrode and the center electrode.

PROCEDURAL WORKFLOW. As previously described,[18] procedures were performed under general anesthesia, typically endotracheal intubation but also laryngeal mask, per physician preference, and muscle relaxants. Esophageal temperature monitoring using a multithermocouple temperature probe was often used in cases in which RFA was used, particularly in early procedures. A decapolar catheter was placed in the coronary sinus (CS) (various types including the 8-F Arc-10 CS catheter, Affera), an intracardiac echocardiography catheter (8-F or 10-F AcuNav, Siemens) guided transseptal puncture, and the lattice catheter was maneuvered through a fixed-curve or steerable sheath (SL or Agilis NxT, Abbott). Either a single (n = 173) or dual (n = 5) transseptal puncture approach was used. Intravenous heparin was administered before transseptal puncture, with a goal activation clotting time of 300 to 350 seconds.

Ipsilateral PVs were circumferentially isolated together. PFA was universally used for posterior LA applications of the PV isolating lesion set, but the anterior LA applications were performed using either RFA (RF/PF strategy) or PFA (PF/PF strategy). The strategy used was per operator preference.

After bidirectional block of the PVs (confirmed by pacing from the lattice tip), the potentials for latent PV reconnection and exit block were reassessed after either a 20-minute wait or intravenous adenosine challenge. For PV reconnection, additional ablation was applied to breakthrough sites. According to operator preference or as needed to treat an organized atrial tachycardia, other linear lesions included cavotricuspid isthmus (CTI) ablation, ablation of the posterior or anterior mitral isthmus, and/or LA roof/posterior ablation—the latter 2 primarily in patients with persistent AF. Linear lesions were placed using either RF or PF energy, but the latter was used in locations of esophageal proximity.

For posterior mitral isthmus ablation, adjunctive ablation (beyond the LA endocardial posterior mitral line) could include ablation within the CS. This latter CS ablation was almost exclusively performed with the lattice catheter—sometimes using a "CS-first" strategy in which a CS-specific PFA dose was first delivered with the lattice catheter advanced to as far a distal CS position as possible, followed by LA endocardial ablation to create a mitral line adjacent to this CS lesion (see the example in Figure 6 of Reddy et al[18]).

FOLLOW-UP. Immediate postablation. Within 1 to 5 days of the procedure, patients were planned to undergo esophagogastroduodenoscopy (EGD). The RF/PF ablation strategy should avoid esophageal damage because PF energy is used along the posterior LA, but we previously observed that during anterior RFA at the ridge between the LA appendage and the left inferior PV, inadvertent posterior LA (plus esophageal) heating can simultaneously occur because of the size/width of the lattice tip (Supplemental Figure 2).[18] Subsequent to this learning, in latter RF/PF cases, PF energy was used at this inferior ridge location. Accordingly, for this analysis, the patient cohort was divided into 3 groups: the PF/PF group and the RF/PF group dichotomized by our awareness of this inadvertent posterior heating phenomenon—pre (RF/PF_{PRE}) vs post (RF/PF_{POST}).

Screening brain magnetic resonance imaging (MRI) was performed between 1 and 3 days of the procedure—imaging was not related to symptomatology. The latter included both diffusion-weighted imaging (DWI) and T_2-weighted fluid-attenuated inversion recovery (FLAIR)—per convention, DWI-positive/FLAIR-negative lesions were termed silent cerebral ischemic events, and DWI-positive/FLAIR-positive lesions were termed silent cerebral lesions.[19] These images were interpreted by an independent neuroradiologist.

Invasive remapping. Per protocol, patients were planned for an invasive redo mapping procedure at 75 ± 15 days after the index ablation procedure (though not all patients presented for the second procedure). This procedure was typically performed using a conventional commercially available mapping system

(typically CARTO, Biosense-Webster Inc). Any electrical gaps in the PVI or linear lesion sets were mapped and targeted for additional ablation with conventional irrigated RFA catheters.

Late follow-up. Either intracardiac echocardiography (n = 92), cardiac computed tomography (n = 62) scanning, or both (n = 15) were performed at ~3 months or beyond to assess PV anatomy. Patients were then followed for up to 12 months, including 48-hour Holter monitoring at 6 and 12 months after the index ablation procedure. Transtelephonic monitoring was performed weekly through 8 weeks after the 90-day blanking period and monthly thereafter, as well as when symptoms occurred.

STUDY OUTCOMES. The primary efficacy endpoint was acute electrical isolation of all PVs using the lattice catheter. Secondary efficacy endpoints included: 1) acute efficacy—the rate of acute block across all linear applications; 2) durability—during remapping procedures, PVI durability on both a per-vein and per-patient basis as well as linear lesion durability; and 3) long-term efficacy—freedom from atrial arrhythmia recurrence (outside of a 90-day blanking period). Transpired ablation time reflects the time elapsing from the start of the first application to the end of the last application for any particular lesion set.

The primary safety endpoint was the composite occurrence of study device-related major adverse events within 7 days, including death, myocardial infarction, PV stenosis (through study exit), persistent diaphragmatic paralysis, atrioesophageal fistula (through study exit), stroke/transient ischemic attack/thromboembolism, cardiac tamponade or perforation, pneumothorax, major vascular complications, pulmonary edema, hospitalization (initial and prolonged), or heart block. A secondary safety outcome was the proportion of subjects experiencing device- or procedure-related serious adverse events out to 12 months of follow-up. All complications were adjudicated by the Data Safety Monitoring Board/Clinical Events Committee (CEC).

STATISTICAL ANALYSIS. Being a feasibility study for a new technology, descriptive statistics were used to characterize study outcomes and safety parameters; there was no formal hypothesis testing or power calculation. The Kaplan-Meier estimator was used to calculate event-free survival outcomes. Continuous variables are reported as mean ± SD (or median and range as appropriate), and categorical variables are reported as number and percentage.

DATA AVAILABILITY STATEMENT. Data will be provided upon reasonable request.

TABLE 1 Baseline Patient Characteristics

	Full AF Cohort (n = 178)	RF/PF Cohort (n = 79)	PF/PF Cohort (n = 99)
Age, y	59.7 ± 9.4	58.9 ± 9.8	60.4±9.0
Male	128 (72)	56 (71)	72 (73)
Body mass index, kg/m^2	30.0 ± 4.2	30.0 ± 4.1	30.0 ± 4.3
Medical history			
Type of AF			
Paroxysmal AF	70 (39)	34 (43)	36 (36)
Persistent AF	108 (61)	45 (57)	63 (64)
Hypertension	124 (70)	61 (77)	63 (64)
Diabetes	23 (13)	9 (11)	14 (14)
LVEF, %	58.8 ± 5.8	58.6 ± 6.0	59.0 ± 5.6
LA dimension, mm	43.3 ± 5.1	43.0 ± 4.6	43.6 ± 5.5
Medications			
Warfarin	43 (24)	15 (19)	28 (28)
NOAC	125 (70)	61 (77)	64 (65)
Antiarrhythmic drugs			
Class I-IV	177 (99)	78 (99)	99 (100)
Class I or III	135 (76)	57 (72)	78 (79)

Values are mean ± SD or n (%).
AF = atrial fibrillation; LA = left atrium; LVEF = left ventricular ejection fraction; NOAC = nonwarfarin oral anticoagulant; PF = pulsed field; RF = radiofrequency.

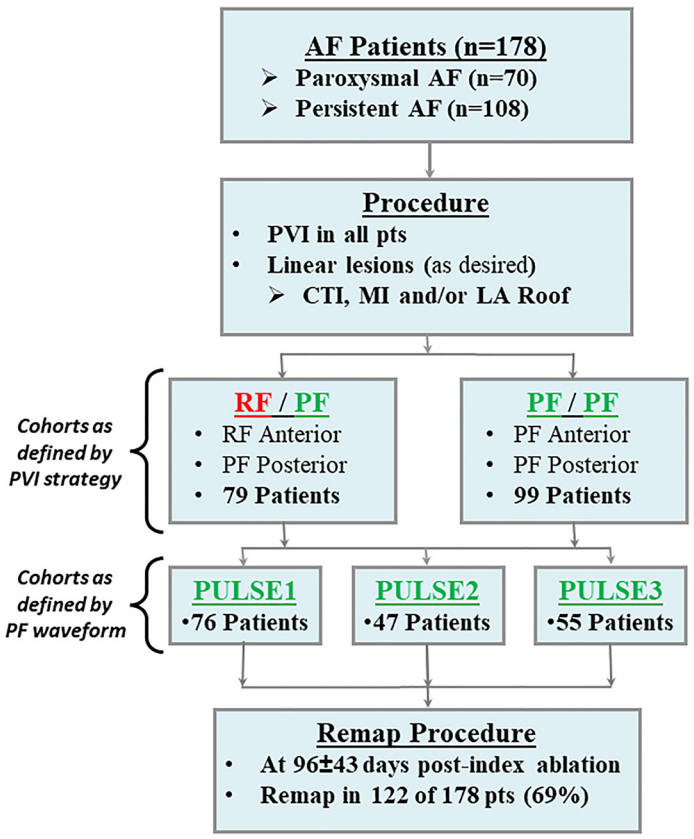
RESULTS

BASELINE PATIENT CHARACTERISTICS. At 3 centers, 14 operators performed the catheter ablation procedures for 178 patients—70 with paroxysmal and 108 with persistent AF. (Enrollment by center is shown in Supplemental Table 1). As shown in **Table 1**, the population was typical for an AF ablation cohort: age of 59.7 ± 9.4 years and 70% with hypertension, albeit with fewer female patients (28%). The left ventricular ejection fraction was preserved (58.8% ± 5.8%), and the LA size was 43.3 ± 5.1 mm—with larger LA in the persistent vs paroxysmal cohort: 44.5 ± 5.2 mm vs 41.5 ± 4.3 mm, respectively (Supplemental Table 2). Most patients (70%) were receiving an oral anticoagulant, and >99% and 76% had received either a class I to IV or class I/III antiarrhythmic medication, respectively.

As shown in **Figure 1**, there were 2 patient cohorts based on the PV encirclement strategy, with 79 and 99 patients in the RF/PF or PF/PF group, respectively. These 2 cohorts were relatively well matched in clinical characteristics, including a similar distribution of paroxysmal vs persistent AF patients (**Table 1**).

ACUTE PROCEDURAL CHARACTERISTICS. General. Most procedures were performed using a deflectable sheath (n = 167), with the remaining using a fixed-curve sheath (n = 11). The total procedural fluoroscopy time was 4.4 ± 3.1 minutes (range: 0-14.1 min). The volume of saline irrigation was 534 ± 186 mL. The total procedure time was 99 ± 34 minutes.

FIGURE 1 The CONSORT Diagram



Shown are the patient populations, defined based on either the energy strategy during PVI or the PF waveform used. AF = atrial fibrillation; CTI = cavotricuspid isthmus; LA = left atrium; MI = mitral isthmus; PF = pulsed field; PVI = pulmonary vein isolation; RF = radiofrequency.

Pulmonary vein isolation. The ablation energy used for PVI was RF/PF in 79 (44.4%) patients and PF/PF in the remaining 99 (55.6%) patients (Figures 1 and 2). For PFA, the waveform used was PULSE1, PULSE2, and PULSE3 in 76 (43%), 47 (26%), and 55 (31%) patients, respectively. Electrical PVI was achieved in all 356 of 356 ipsilateral PV pairs (719 of 719 PVs [100%]) using the lattice catheter alone (Tables 2 and 3), translating to a primary efficacy outcome for PVI of 100%. First-pass PVI occurred in 95% of PV pairs, increasing from 89% for PULSE1 to 99% for both PULSE2 and PULSE3. PVI was reconfirmed following either a 20-minute wait (n = 109) and/or adenosine challenge (n = 84): acute PV reconnections required additional ablation in 36 of 356 (10%) PV pairs, again improving with successive PFA waveforms from 18% with PULSE1 to 5.3% with PULSE3 and, finally, 2.7% with PULSE3 (Figure 3). These acute PV reconnections were predominantly (82%) at the areas of PF ablation. The total transpired ablation time was 21.3 ± 5.8 minutes, similar for both the RF/PF and PF/PF groups and for the various PFA waveforms (Figure 3).

Additional lesion overview. The performance outcome for linear lesions (defined as acutely achieving conduction block) was 100% (367 of 367 lines) (Table 3). Using the lattice tip catheter alone, conduction block was achieved in 99.7% (366 of 367 lines)—early in the experience (patient no. 6 of 178), mitral isthmus ablation required ablation in the CS, which was performed using a standard irrigated RF catheter. Also, all spontaneously occurring atrial flutters (24 typical CTI-dependent flutters and 25 atypical flutters) were mapped and successfully targeted for ablation (example in Supplemental Figure 3).

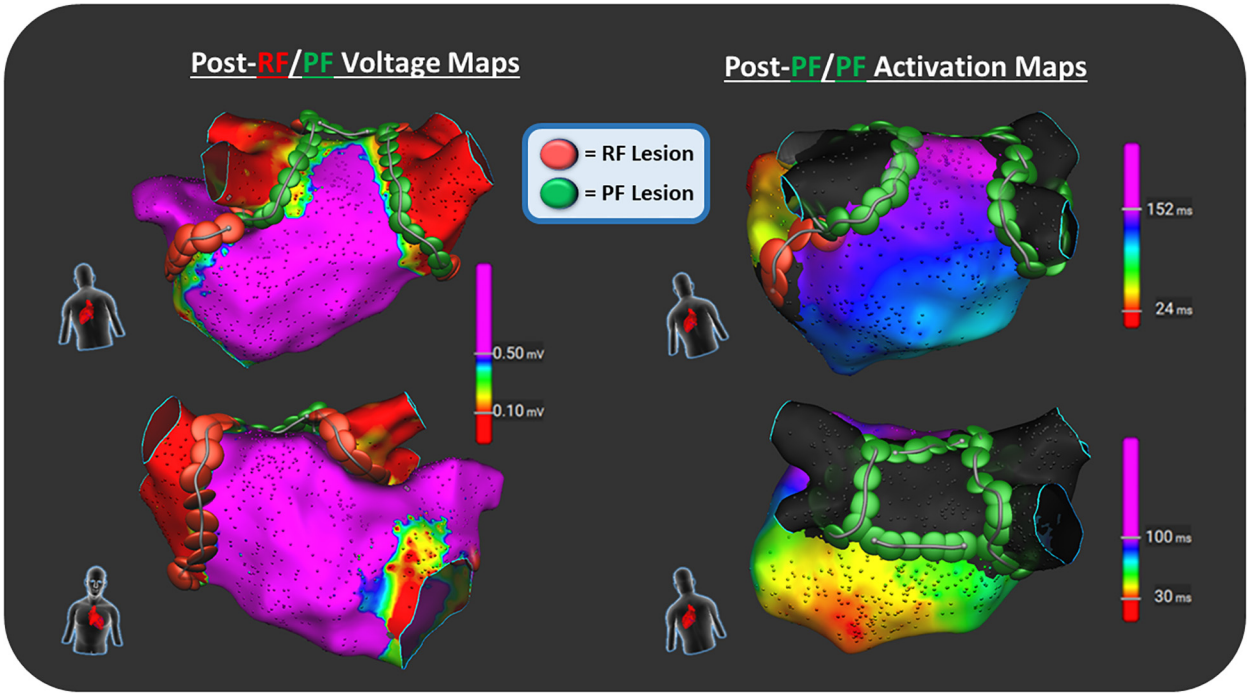
Left atrial roof line. Using the lattice tip catheter, bidirectional block across the LA roof was successfully achieved in all 130 of 130 (100%) patients in whom it was attempted—10 using RF energy, 116 with PF energy, and 4 using both RF and PF energy (Tables 2 and 3), with a transpired ablation time of 1.9 ± 1.7 minutes (Figure 3A). In addition, in 38 of 38 (100%) patients, an inferior line was also successfully placed on the posterior LA between the PVs using PF energy (typically as part of a posterior box lesion).

Mitral isthmus line. Bidirectional conduction block across the posterior mitral isthmus was achieved in all 78 of 78 (100%) patients with attempts (Tables 2 and 3), with a transpired ablation time of 3.9 ± 2.2 minutes (Figure 3A). The energies employed included various combinations of RF or PF (Table 3), including CS ablation in 25 patients with the lattice catheter. (Although in 1 early case, a standard irrigated RFA catheter [Flexability, Abbott Inc] was used.) Alcohol infusion into the vein of Marshall was not required in any patient.

Cavotricuspid isthmus line. As shown in Tables 2 and 3, bidirectional CTI block was achieved with the lattice catheter in all attempted patients (n = 121 [100%]), using RF and/or PF energy. The transpired ablation time was 2.0 ± 1.4 minutes.

LESION DURABILITY. At 96 ± 43 days after the index procedure, 122 patients (69%) presented for the protocol-mandated invasive remapping procedure. The overall PV durability rate on a per-vein basis was 75%, translating to 58% of patients with all veins durability isolated. However, importantly, durability improved with successive PF waveforms, from only 51% with PULSE1 to 97% with PULSE3—translating to a per-patient durability rate of 90% with PULSE3 (Figure 4). For patients receiving this optimized

FIGURE 2 **Ablation Strategies Based on PVI: RF/PF vs PF/PF**



The 2 types of PVI strategies are shown. Note that in both, PF energy is used for ablation along the posterior LA, but anterior ablation varies between the 2 strategies. Abbreviations as in Figure 1.

PULSE3 waveform, the PV durability rates were similar for the RF/PF and PF/PF cohorts, at 97% and 96%, respectively ($P = 0.74$).

For the linear atrial lesions, the overall durability for the LA roof, mitral isthmus, and CTI lines were 82%, 68%, and 87%, respectively. Again, linear lesion durability improved with waveform evolution from PULSE1 to PULSE3 (Figure 5A). Because various combinations of RF and PF were used for the linear lesions (Table 3), the relative contribution of PF waveform evolution to linear lesion durability is difficult to tease out, except for the LA roof line. The roof line was largely created using PF energy (RFA was used in only a few of the initial patients in the series); and indeed, durability improved from 63% for PULSE1 to 100% with the PULSE3 waveform (Figure 5B).

LONG-TERM EFFICACY. After 348 ± 52 days of follow-up, compliance with monitoring was good: overall transtelephonic monitoring compliance was 96.8%, and Holter monitoring compliance was 97.2%. The 1-year Kaplan-Meier estimate for freedom from atrial arrhythmias for the full cohort is 78.1% ± 3.2%; the outcomes for the paroxysmal and persistent AF subgroups are similar at 78.3% ± 5.0% and 77.9% ± 4.1%, respectively (P = NS) (Figure 6). When partitioned by the PVI cohorts, the outcomes were similar: the 1-year Kaplan-Meier estimates for freedom from atrial arrhythmias for the RF/PF and PF/PF subgroups are 79.1% ± 4.6% and 77.3% ± 4.3%, respectively (P = NS) (Figure 6). For the optimized PULSE3 cohort alone, at a mean of 324 days, the 1-year Kaplan-Meier estimate for freedom from atrial arrhythmias for the persistent AF group was 84.8% ± 4.9%. (There was only 1 paroxysmal AF patient treated with the PULSE3 waveform.) At the

TABLE 2 **Ablation Lesion Sets: Frequency and Technical Success**

	Patients With Lesion Set	Paroxysmal AF	Persistent AF	Acute Success
Pulmonary vein isolation	178 (100)	70 (100)	108 (100)	100
Linear atrial lesions				
Mitral isthmus line	78 (44)	7 (10)	71 (66)	100
Left atrial roof line	130 (73)	30 (43)	100 (93)	100
Posterior inferior line	38 (21)	2 (3)	36 (33)	100
Cavotricuspid isthmus line	121 (68)	39 (56)	82 (76)	100

Values are n (%) or %.

TABLE 3 Lesion Set Details

	Full AF Cohort (n = 178)	RF/PF Cohort (n = 79)	PF/PF Cohort (n = 99)
Pulmonary vein isolation			
Successful PVI lesion sets	178/178 (100)	79/79 (100)	99/99 (100)
Success with lattice tip only	178/178 (100)	79/79 (100)	99/99 (100)
Number of RF applications	8.5 ± 10.1	19.0 ± 5.2	N/A
Total RF time, min[a]	0.7 ± 0.8	1.6 ± 0.4	N/A
Number of PF applications	48.2 ± 19.7	32.6 ± 12.0	60.6 ± 15.4
Total PF time, min[a]	3.1 ± 1.3	2.1 ± 0.8	3.9 ± 1.1
Transpired ablation time, min[b]	21.3 ± 5.8	20.8 ± 5.7	21.8 ± 5.8 min
Mitral isthmus line			
Successful linear lesion	78/78 (100)	38/38 (100)	40/40 (100)
Success with lattice tip only	77 (99)	37/38 (97)	40/40 (100)
Patients with CS lesions	24/78 (31)	2/38 (5)	22/40 (55)
Number of RF applications in the CS[c]	0	0	0
Number of PF Applications in the CS[c]	1.5 ± 4.4	0.3 ± 1.3	2.7 ± 5.7
Number of RF applications	7.6 ± 7.1	11.9 ± 6.0	3.5 ± 5.3
Total RF time, min	0.7 ± 0.8	1.2 ± 0.7	0.3 ± 0.5
Number of PF applications	6.4 ± 8.3	1.4 ± 3.0	11.2 ± 8.9
Total PF time, min	0.4 ± 0.5	0.1 ± 0.2	0.7 ± 0.6
Transpired ablation time, min	3.9 ± 2.2	4.2 ± 2.4	3.6 ± 1.9
Roof line			
Successful linear lesion	130 (100)	57 (100)	73 (100)
Success with lattice tip only	130 (100)	57 (100)	73 (100)
Number of RF applications	0.5 ± 1.6	0.9 ± 2.0	0.2 ± 1.1
Total RF time, min	0.0 ± 0.1	0.1 ± 0.2	0.0 ± 0.1
Number of PF applications	6.8 ± 4.1	5.5 ± 3.4	7.9 ± 4.3
Total PF time, min	0.4 ± 0.3	0.4 ± 0.2	0.5 ± 0.3
Transpired ablation time, min	1.9 ± 1.7	1.9 ± 2.1	1.9 ± 1.3
Posterior inferior line			
Successful linear lesion	38 (100)	7 (100)	31 (100)
Success with lattice tip only	38 (100)	7 (100)	31 (100)
Number of RF applications	0	0	0
Total RF time, min	0	0	0
Number of PF applications	11.3 ± 4.0	10.4 ± 3.0	11.5 ± 4.2
Total PF time, min	0.7 ± 0.3	0.7 ± 0.2	0.8 ± 0.3
Transpired ablation time	2.8 ± 1.5	2.9 ± 1.1	2.7 ± 1.6
Cavotricuspid isthmus line			
Successful linear lesion	121 (100)	58 (100)	63 (100)
Success with lattice tip only	121 (100)	58 (100)	63 (100)
Number of RF applications	5.4 ± 3.1	6.4 ± 2.4	4.5 ± 3.4
Total RF time, min	0.4 ± 0.3	0.5 ± 0.2	0.4 ± 0.3
Number of PF applications	1.4 ± 3.4	0.2 ± 0.7	2.6 ± 4.4
Total PF time, min	0.1 ± 0.2	0.01 ± 0.04	0.2 ± 0.3
Transpired ablation time, min	2.0 ± 1.4	2.0 ± 1.4	2.0 ± 1.4

Values are n/N (%), mean ± SD, or n (%). [a]Defined as total time that energy (RF or PF) was being delivered for the particular lesion set. [b]Defined as time transpiring from the first to last lesion of the particular lesion set. [c]Includes only CS lesions made by the lattice tip catheter.

CS = coronary sinus; PVI = pulmonary vein isolation; other abbreviations as in Table 1.

last follow-up, 19% of patients were still receiving a class I/III antiarrhythmic drug.

SAFETY. Serious adverse events. Primary adverse events, defined as investigational device-related major adverse events as adjudicated by the CEC, occurred in 1 patient–hospitalization in an RF/PF patient 20 days after the ablation procedure because of an inflammatory pericardial effusion managed with anti-inflammatory medications. There were no instances of atrioesophageal fistula or gastric dysmotility, stroke or transient ischemic attack, pericardial tamponade, phrenic nerve paralysis, PV stenosis, or other late safety events (Table 4). This translated to a protocol-defined primary safety endpoint rate of 0.6% (1 of 178 patients).

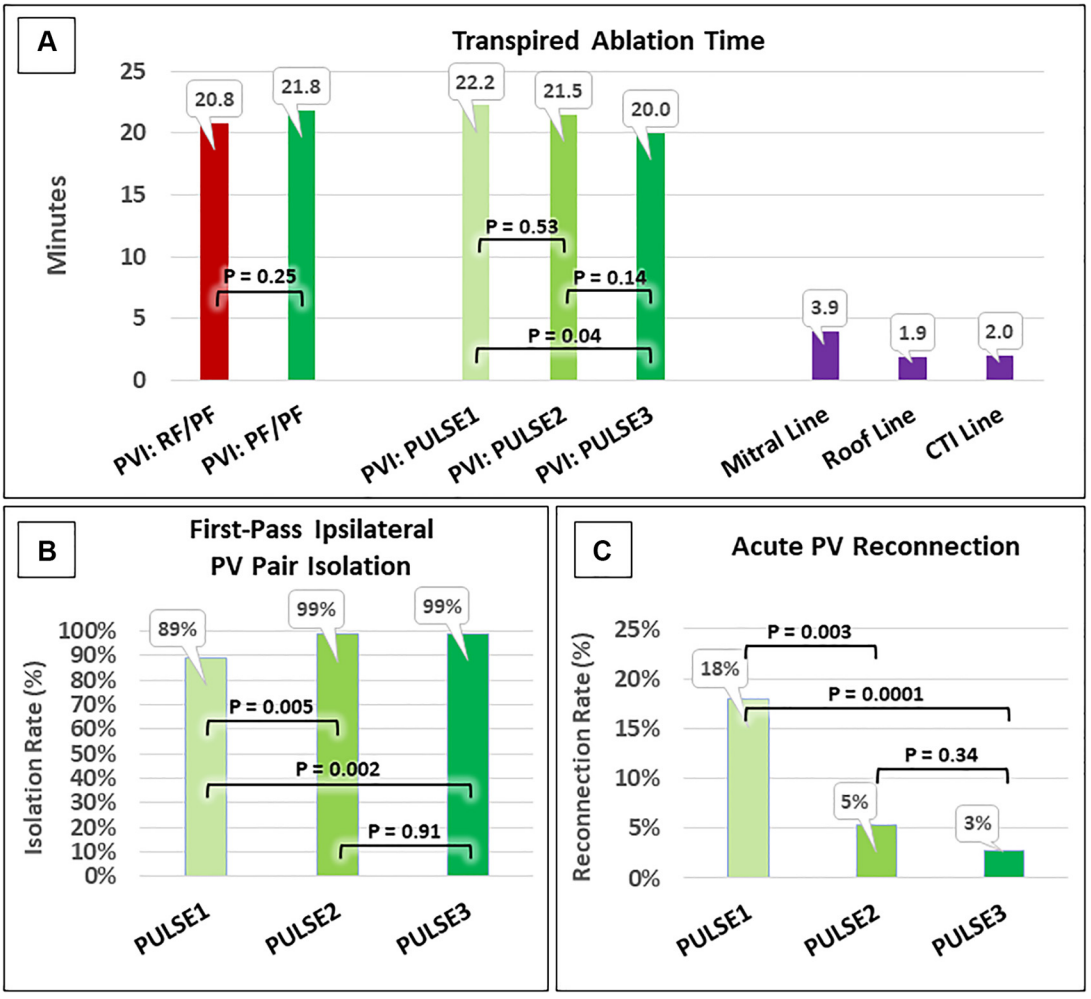
Four early-onset serious adverse events were related to the procedure but not to the study device. One patient each experienced groin hematoma that required surgical intervention, groin puncture bleeding treated with compression, pericardial effusion requiring drainage (as adjudicated by the CEC, this was related to a difficult transeptal puncture requiring RF energy application to the transeptal needle), and transient (<10 min) ST-segment elevation following atropine administration in a patient with prior myocardial infarctions and unknown residual right coronary arterial stenosis later requiring angioplasty/stenting. A serious adverse event was also reported for a patient who fell 13 days after the procedure and sustained a head contusion; neurologic examination and imaging did not identify any relationship to the procedure.

Esophagogastroduodenoscopy. During PF ablation along the posterior LA wall, when esophageal temperature probes were used, the expected low-level esophageal heating (typically ~2-3 °C) occurred. Postprocedure EGD was performed in 124 patients at 1.8 ± 1.1 days. There were 3 instances (8.3%) of asymptomatic minor mucosal thermal injury in the RF/PF_{PRE} cohort (n = 36) related to inadvertent posterior heating during LA appendage ridge ablation, as previously described.[18] However, there were no instances of esophageal thermal injury in either: 1) all RF/PF_{POST} cases, in which specific attention was paid to avoid inadvertent posterior heating; or 2) all PF/PF cases, in which no RF energy was used during PVI (Table 5).

Asymptomatic brain MRI screening. Postprocedure brain MRIs were performed in 89 of 178 (50%) patients at 1.2 ± 0.6 days, revealing silent cerebral events (DWI-positive/FLAIR-negative) and silent cerebral lesions (DWI-positive/FLAIR-positive) in 7 (7.9%) and 6 (6.7%) patients, respectively. All of these lesions were asymptomatic.

PV stenosis. Acute postablation remapping and intracardiac echocardiography catheter imaging revealed no evidence of PV stenosis in all 122 patients who underwent invasive remapping. Furthermore, cardiac computed tomography scans were performed

FIGURE 3 Procedural Parameters



(A) The transpired ablation times, defined as the time transpiring from the beginning of the first lesion to the end of the last lesion, are shown for the various lesion sets. Also shown for the 3 PFA waveforms are the rates of **(B)** first-pass PVI and **(C)** acute PV reconnection. Comparisons in **A** were made with unpaired 2-tailed t tests, whereas in **B** and **C**, comparisons were made with 2 proportion *z*-score tests, 2-sided. Abbreviations as in Figure 1.

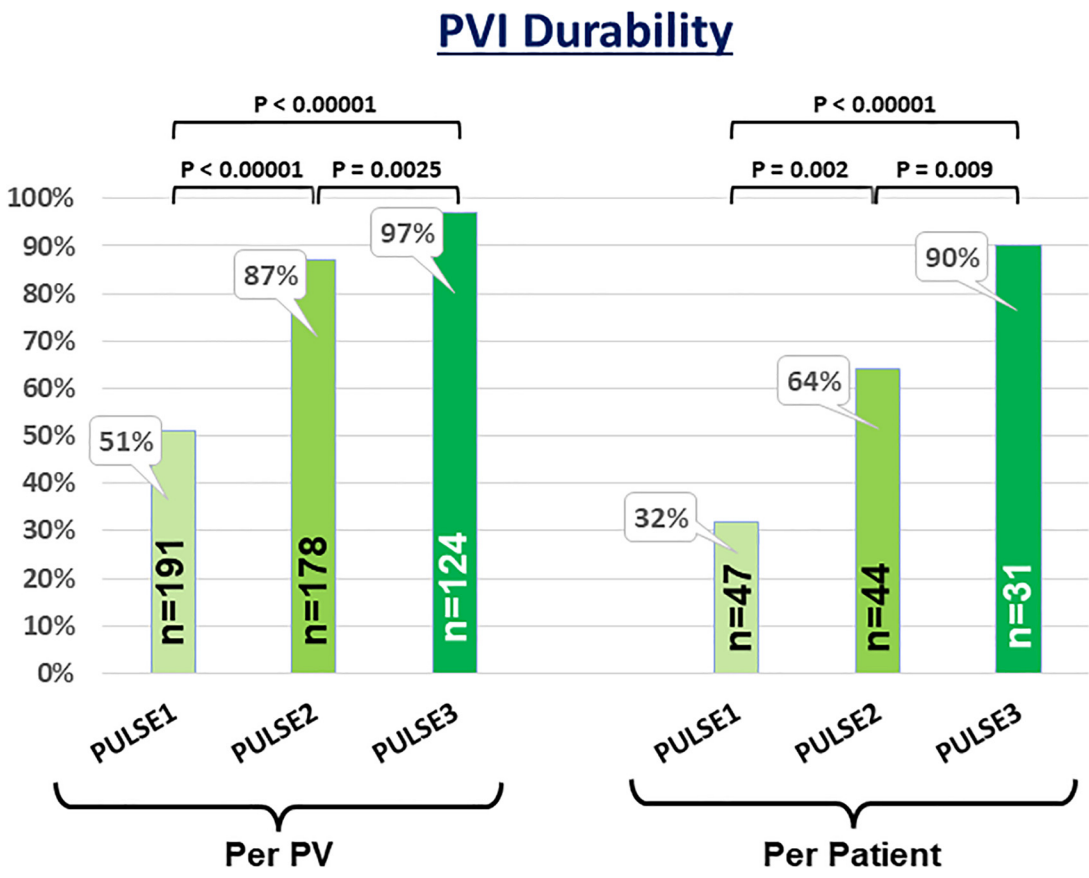
at 129 ± 93 days in 77 of 178 patients (43.3%)—all revealing no evidence of PV stenosis.

DISCUSSION

In this first-in-human clinical trial, the focal lattice tip ablation catheter was able to: 1) efficiently isolate PVs using a strategy of either PFA posteriorly and RFA anteriorly (RF/PF) or PFA throughout—both anteriorly and posteriorly (PF/PF); 2) efficiently create linear atrial ablation lesions—mitral, LA roof, and CTI lines—each typically in under 5 minutes; 3) demonstrate long-term durability of the PVI and roof line lesion sets using the optimized PF waveforms upon invasive chronic remapping studies—a point underscored by the very large number of patients (n = 122) who presented for the invasive remapping; 4) result in favorable 1-year freedom from arrhythmia recurrence, with an overall success rate for the persistent AF cohort to be as good as that for the paroxysmal AF cohort; and 5) achieve these outcomes with a low safety event rate (Central Illustration).

"SINGLE-SHOT" VS FOCAL CATHETER TECHNOLOGIES. Most PFA catheters in clinical trials are "single-shot" devices designed for PVI alone, with limited ability to deliver extra-PV lesion sets such as linear lesions.[9-15]

FIGURE 4 Durability of PVI on Invasive Remapping



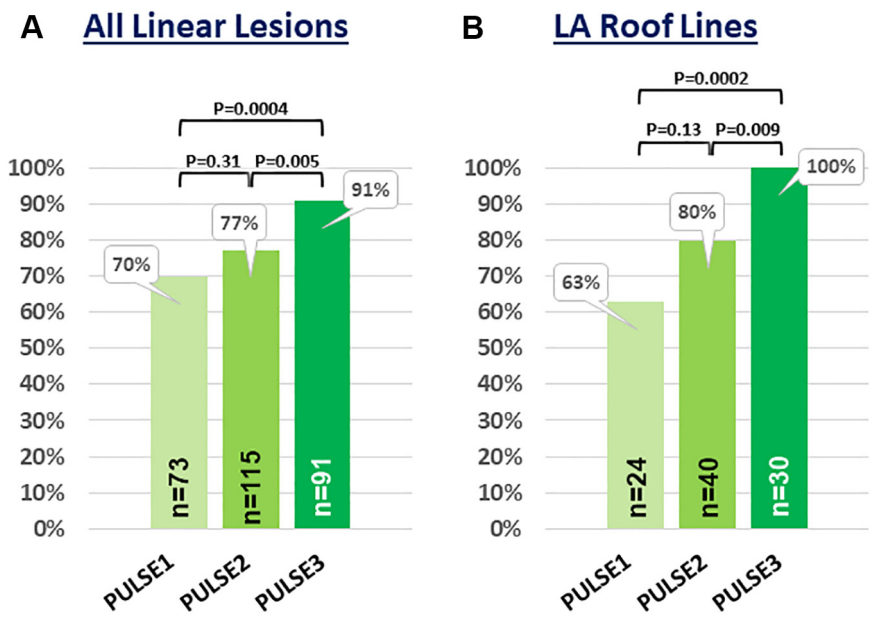
During invasive remapping at 96 ± 43 days, PVI durability, assessed on either **(left)** a per-vein or **(right)** per-patient basis, improved with successive PF waveform evolution. Comparisons were made with 2 proportion *z*-score tests, 2-sided. Abbreviations as in Figure 1.

This stands in stark contrast to the dominant role of "point-by-point" focal ablation catheters in clinical practice around the world—primarily because of the flexibility in lesion design that they afford. Indeed, *focal* catheter ablation technologies, invariably using RF energy, have advanced rapidly over the past several decades. The initial nonirrigated RF catheters created ablation lesions of limited depth (and, hence, efficacy) and were associated with a significant incidence of thrombus/char, leading to embolic stroke. However, RF catheters rapidly evolved to including saline irrigation; tissue contact/force sensing; surface thermocouples; and now, with the lattice tip, a large ablative "thermal" footprint to potentiate rapid point-by-point ablation with a proclivity for good lesion overlap.[20-26]

This lattice tip catheter has a traditional "standard"-sized (8-F) catheter shaft for facile maneuverability and a compressible spheroid 9-mm-diameter lattice electrode that delivers lesions that are contact sensing facilitated, saline irrigated, and temperature guided. The catheter was initially developed and studied as an RFA-only catheter and, indeed, proved capable of rapidly and durably isolating PVs and creating linear lesions with a high degree of clinical success.[25,26] However, given the persistent concern for esophageal complications with RF energy, the advent of PFA prompted an expansion of the lattice catheter system to also permit focal delivery of pulsed electrical field energy—thereby allowing facile toggling between RFA and PFA.[18]

EFFECTIVENESS OF THE LATTICE TIP CATHETER TECHNOLOGY. The most immediate measure of efficacy is the ability of the ablation catheter to achieve bidirectional block across the delivered lesion sets. To this point, block was noted in 100% of all lesion sets, both PVI and the various right and left atrial linear lesions. Furthermore, this was achieved in an

FIGURE 5 **Durability of Linear Lesions on Invasive Remapping**



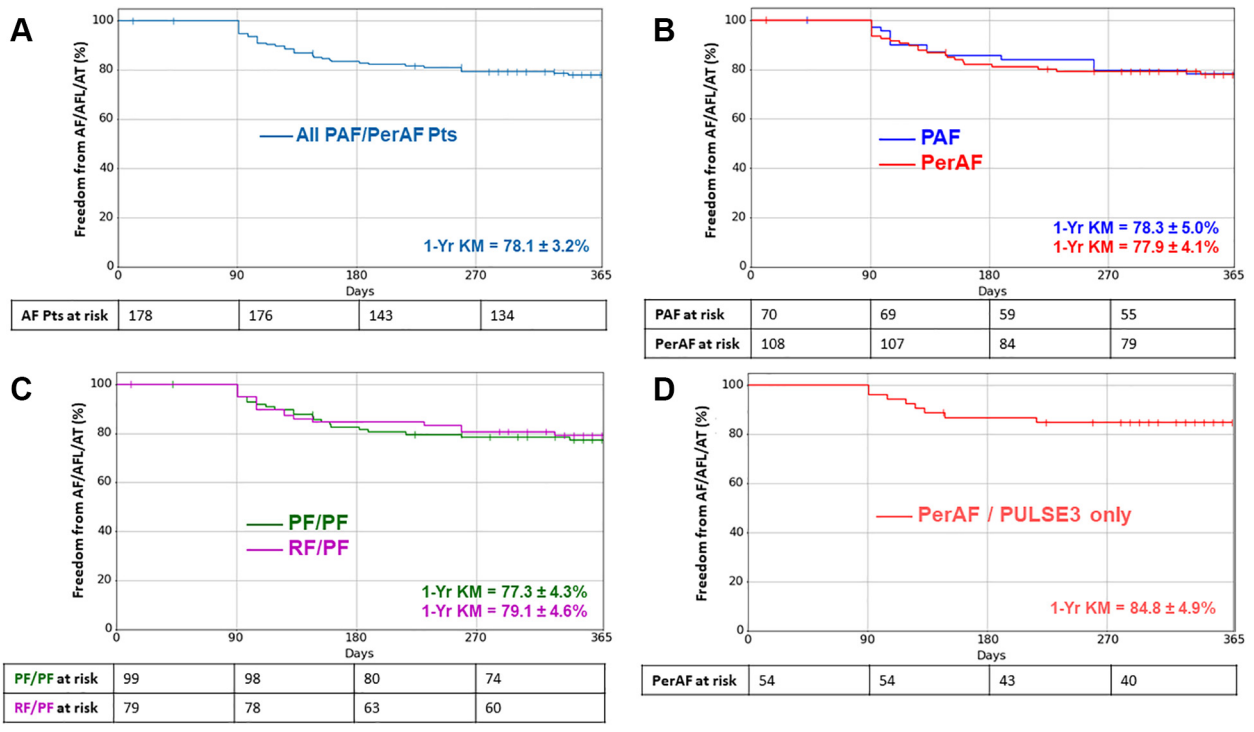
During invasive remapping at 96 ± 43 days, the durability of both **(A)** the aggregate linear lesion group and **(B)** the LA roof line alone improved with successive evolution of the PF waveform. Comparisons were made with 2 proportion *z*-score tests, 2-sided. Abbreviations as in Figure 1.

efficient manner, best exemplified by the low transpired ablation times—just over 20 minutes for PVI, 4 to 5 minutes for mitral lines, and ~2 minutes for the CTI and LA roof lines (Figure 3). Indeed, these times were similar for both the RF/PF and PF/PF cohorts, as well as similar to the previously published highly efficient times observed with lattice tip-based *RFA* (Supplemental Table 3, Supplemental Figure 4).[25,26] Also, for both the PULSE2 and PULSE3 waveforms, the first-pass PVI rates were >99%, and the acute PV reconnection rates were ≤5% (Figure 3).

However, the most important measure of technical success was the high rates of durable PVI observed upon invasive remapping. As observed with other PF technologies, durability was not particularly good with the initial waveform, but it did improve with waveform evolution.[10,11] Indeed, with the PULSE3 waveform, durability was 97% on a per-vein basis and 90% on a per-patient basis, whether using an RF/PF or PF/PF strategy. These data compare quite favorably with other PVI durability outcomes, including the PVI durability outcomes with the pentaspline PFA catheter (Supplemental Figure 5).[11] Similarly, linear lesion durability with the lattice catheter was also high. While various combinations of RF and PF were used for the linear lesions, it is instructive to look at the LA roof line—the only linear lesion for which PFA was almost exclusively used. With the PULSE3 waveform, 100% of these roof lines remained durably blocked. It is likely that these exceptional durability outcomes are related to 2 unique aspects to the lattice tip: 1) catheter stability related to both the compressibility of the lattice mesh and irregular topography that minimize sliding on tissue; and 2) a wide ablative footprint that optimizes lesion overlap of adjacent lesions.[16,17,25,26]

CLINICAL EFFECTIVENESS. These favorable durability results were reflected in the clinical effectiveness outcomes—though 19% of the cohort were receiving a class I/III antiarrhythmic drug at last follow-up. Interestingly, the Kaplan-Meier estimate of 1-year freedom from recurrent atrial arrhythmias, 78.1% ± 3.2%, did not differ between the paroxysmal and persistent subgroups (78.3% ± 6.0% and 77.9% ± 4.1%, respectively). There are several possibilities for this similarity. First, the 2 populations did receive different lesion sets—beyond PVI, the persistent cohort more often received LA linear lesions (Table 2). Perhaps, therefore, a combination of good PVI plus linear lesion durability might indeed translate to excellent freedom from recurrent atrial arrhythmias in a persistent AF population. Second, the more effective PULSE3 waveform was predominantly used in the persistent AF patients, while the paroxysmal

FIGURE 6 Kaplan-Meier Estimates of 1-Year Freedom From Atrial Arrhythmia Recurrence



Shown are **(A)** recurrence of any atrial arrhythmia in the full patient cohort, **(B)** a comparison of the paroxysmal vs persistent AF subgroups, **(C)** a comparison of the PF/PF and RF/PF subgroups, and **(D)** the persistent AF subgroup in whom the PULSE3 PFA waveform was used. The 1-year estimates for freedom from atrial arrhythmias are shown in the bottom right corner of each graph. KM = Kaplan-Meier; other abbreviations as in Figure 1.

AF patients were largely ablated using the earlier PULSE1 and PULSE2 waveforms. Indeed, it was striking that when including only the PULSE3 cohort of persistent AF patients, the 1-year freedom from atrial arrhythmias was even higher (84.8% ± 4.9%) (Figure 6D).

To put the paroxysmal AF outcomes in context, the only other PFA catheter for which there is clinical outcome data is the pentaspline PFA catheter. In the IMPULSE (A Safety and Feasibility Study of the IOWA Approach Endocardial Ablation System to Treat Atrial Fibrillation)/PEFCAT (A Safety and Feasibility Study of the FARAPULSE Endocardial Ablation System to Treat Paroxysmal Atrial Fibrillation)/PEFCAT2 (Expanded Safety and Feasibility Study of the FARAPULSE Endocardial Ablation System to treat Paroxysmal Atrial Fibrillation) trials of 121 paroxysmal AF patients receiving PVI alone, the Kaplan-Meier estimate of 1-year freedom from atrial arrhythmias was 78.5% ± 3.8%—an outcome comparable to the 78.3% ± 6.0% outcome with the lattice tip.[10,11]

To contextualize the persistent AF outcomes, in Prospective Review of the Safety and Effectiveness of the THERMOCOOL SMARTTOUCH SF Catheter Evaluated for Treating Symptomatic PersistenT AF, the recent large multicenter U.S. Food and Drug Administration trial of an irrigated force-sensing RFA catheter, the 15-month freedom from atrial arrhythmias was 61.7%.[27] The current lattice tip results certainly compare favorably to these data—both for the persistent AF cohort and the PULSE3 subset of the persistent AF cohort. Similarly, in Pulsed Fields for Persistent Atrial Fibrillation, the only published persistent AF trial with PFA, the 1-year success of PVI plus LA posterior wall ablation was 92% ± 5.4%, but this was only a 25-patient/2-center feasibility study.[12,28] The most informative data will likely come from the ongoing randomized multicenter U.S. Food and Drug Administration clinical trial of ~480 persistent AF patients undergoing ablation with either the lattice tip RF/PF catheter or a conventional irrigated force-sensing RFA catheter (Treatment of

Persistent Atrial Fibrillation With Sphere-9 Catheter and Affera Mapping and Ablation System [SPHERE Per-AF]; NCT05120193).

Finally, clinical efficacy of the overall cohort did not change whether using an RF/PF or PF/PF strategy for PVI. This is consistent with the hypothesis that what is crucial for clinical success is durable lesion sets, regardless of the means by which they are generated. On the other hand, if focused only on the persistent AF population, the 1-year clinical success rate for the RF/PF cohort (86.2% ± 5.2%) was substantially better than the PF/PF cohort (72.3% ± 5.8%) (Supplemental Figure 6). Indeed, in the first-in-human study of 65 AF patients (62% paroxysmal/38% persistent) undergoing RF-only ablation with the lattice tip catheter, there was 96% PVI lesion durability by remapping coupled with a Kaplan-Meier 1-year estimate of freedom from atrial arrhythmias at 94.4% ± 3.2%.[26] This improvement in clinical efficacy when RF energy is combined with PF is intriguing. However, these are nonrandomized comparisons between cohorts and are subject to multiple potential confounders—including potential variability in patient characteristics, differential lesion deployment between groups, and so on. Alternatively, it is possible that these differences are "real" and may be related to other effects, such as differential sensitivity of periatrial ganglionated plexi to RF vs PF energy. Future well-controlled randomized trials are necessary to explore these intriguing, but by no means definitive, comparative outcomes between PF-only, RF/PF, and RF-only ablation strategies.

SAFETY. There were no clinical manifestations of PF-related esophageal injury, including no atrioesophageal fistula or gastric motility disorders. Of the 124 patients who underwent postprocedure EGD, there were 3 patients with instances of thermal injury (minor erythema). However, all of these patients were in the RF/PF_{PRE} cohort; no patient in the RF/PF_{POST} or PF/PF cohorts sustained any EGD evidence of thermal injury. These data are particularly compelling given the large number of patients who underwent post-PFA endoscopy without lesions, despite the near-universal placement of PFA lesions directly atop the esophagus. Furthermore, esophageal sparing is entirely consistent with preclinical porcine studies demonstrating clear histologic sparing of the esophagus during lattice tip PFA.[16,17] This esophageal sparing is also consistent with prior PFA clinical studies with the pentaspline catheter, including: 1) clinical studies reporting endoscopy outcomes without thermal damage; and 2) the 1,758-patient Multi-national survey on the methods, efficacy, and safety on the post-approval clinical use of pulsed field ablation survey with no instances of esophageal complications.[9-13,29-31] Postprocedure MRI to image the esophagus could provide further information not revealed by EGD alone.[10,11,32]

There were no thromboembolic complications, including no strokes, transient ischemic attacks, or

TABLE 4 Major Adverse Events

	CEC Definition of Primary Adverse Events[a]	Alternate Definition of Adverse Events[b]
Death	0	0
Myocardial infarction	0	0
Pulmonary vein stenosis	0	0
Persistent diaphragmatic paralysis	0	0
Atrioesophageal fistula	0	0
Transient ischemic attack	0	0
Stroke/cerebrovascular accident	0	0
Thromboembolism	0	0
Cardiac tamponade/perforation	0	1 (0.6)[c]
Pneumothorax	0	0
Major vascular access complications	0	1 (0.6)[d]
Pulmonary edema	0	0
Hospitalization	1 (0.6)[e]	0
Heart block	0	0

Values are n or n (%). [a]Data Safety Monitoring Board-adjudicated device-related adverse events occurring within 7 days of the procedure except pulmonary vein stenosis and atrioesophageal fistula, which are evaluated through study exit. [b]This represents a conventional definition of adverse events that is more focused on procedure-related complications, regardless of the relationship to the investigational device technology. [c]Related to a difficult transeptal puncture procedure requiring radiofrequency energy being applied to the transeptal needle (as adjudicated by the CEC). [d]Groin hematoma requiring surgical intervention. [e]Hospitalization for an inflammatory pericardial effusion not requiring catheter/surgical intervention but instead treatment with anti-inflammatory medications.

CEC = Clinical Events Committee.

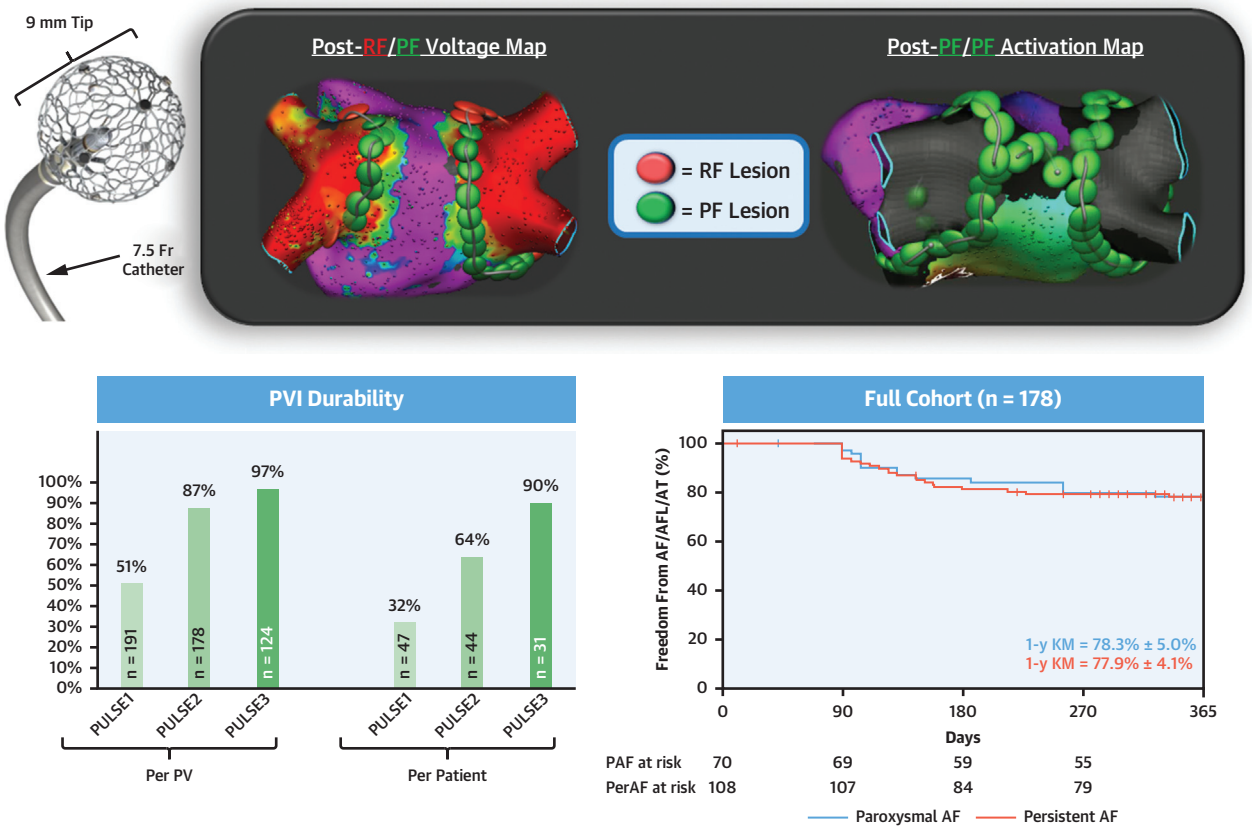
TABLE 5 Summary of Prospective Safety Assessments

	Full Cohort (n = 178)	RF/PF_{PRE} (n = 36)	RF/PF_{POST} (n = 43)	PF/PF (n = 99)
Esophageal observations				
Any esophageal abnormality		3 (8.3)	0 (0)	0 (0)
Minor erythema		3 (8.3)	0 (0)	0 (0)
Moderate erosion		0 (0)	0 (0)	0 (0)
Ulceration		0 (0)	0 (0)	0 (0)
Phrenic nerve injury				
Fluoroscopy at the end of the procedure	0 (0)			
Fluoroscopy at ~3-month redo procedure	0/122 (0)			
Brain MRI findings				
SCE (DWI-positive/FLAIR-negative)	7 (7.9)			
SCL (DWI-positive/FLAIR-positive)	6 (6.7)			
Pulmonary vein stenosis				
EAM at ~3-month redo procedure	0/107 (0)			
CT scanning at ~3 months	0/77 (0)			

Values are n (%) or n/N (%).

CT = computed tomography; DWI = diffusion weighted imaging; EAM = electroanatomic mapping; FLAIR = fluid-attenuated inversion recovery; SCE = silent cerebral event; SCL = silent cerebral lesion; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Atrial Fibrillation Ablation With a Combination RF/PF Focal Ablation Catheter**



Reddy VY, et al. J Am Coll Cardiol EP. 2023;9(8):1786-1801.

AFL = atrial flutter; Pf = pulsed field; PV = pulmonary vein; PVI = pulmonary vein isolation; REF = radiofrequency.

systemic embolisms. To search for silent cerebral events, routine postprocedure brain MRI was performed in 89 patients—revealing DWI-positive/FLAIR-negative lesions in 7.9% and DWI-positive/FLAIR-positive lesions in 6.7%. This asymptomatic cerebral event rate compares favorably to prior studies of either PFA or thermal ablation. Regarding the former, at the 3 sites that performed routine post-PFA brain MRI (n = 114), there was a reported 17.5% rate of silent cerebral events.[13] And for the latter, silent brain MRI lesions were observed in ~12% of 168 patients and 26.1% of 321 patients, respectively, in the ELIMINATE-AF (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Catheter Ablation) and AXAFA-AFNET5 (Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy) trials of anticoagulation strategies after thermal (RF or cryo) ablation.[33,34] Importantly, although cognitive testing was not performed in the present study, in AXAFA-AFNET5, careful cognitive assessments revealed that the MRI lesions are not associated with cognitive decline at 3 months postablation.[34]

Other potential complications, such as PV stenosis and phrenic nerve paralysis, were not observed, despite specific assessment for these complications. There were no lattice catheter-related pericardial tamponades, though there was 1 late inflammatory pericardial effusion in 1 patient and a second patient who sustained a pericardial effusion unrelated to the catheter. This is likely related to both the atraumatic compressible lattice tip and the fact that the lattice catheter with its 8-F shaft is fundamentally quite

similar to conventional catheters with which most electrophysiologists are quite familiar.

Indeed, the most frequent complication observed with this lattice catheter was related to vascular access. This is quite consistent with the MANIFEST-PF survey, where the most common complications were of vascular origin (3.5%).[13] Consistent with both the lattice catheter and the MANIFEST-PF survey, the majority of these vascular complications were of minor severity.

Finally, it is worth noting recent data regarding coronary spasm after PFA. There is a published case report of ST-segment elevation after PFA with the pentaspline catheter prompting immediate angiography that revealed coronary spasm.[35] In addition, recently, PF applications delivered near a coronary artery have been shown to induce subclinical arterial spasm in a manner responsive to parenteral nitroglycerin.[36,37] However, in the present report, there were no documented instances of clinical spasm despite the fact that the lattice tip catheter was used for PFA at the mitral and CTI lines (both being adjacent to coronary arteries). There was 1 patient with transient ST-segment elevation, but this appeared to be related to demand ischemia secondary to a sudden elevation in heart rate following atropine administration in a patient with an unrecognized high-grade atherosclerotic coronary arterial lesion. Indeed, coronary angiography had been immediately performed in this patient but did not reveal vascular spasm. Future studies are needed to determine the propensity for coronary spasm after lattice tip PFA (or RFA).

STUDY LIMITATIONS. Despite the large number of patients included in this study, there were few centers in this first-in-human study. However, this is mitigated by the relatively large number of operators (n = 14). Also, the SPHERE Per-AF trial (NCT05120193) should eventually provide additional insight into the safety and efficacy of the lattice catheter. Second, the energy strategy used for PVI was clear and well documented, but for linear lesions, various combinations of PFA and RFA were used. Accordingly, it is difficult to discern the effectiveness of PFA alone to achieve durable conduction block across any particular linear lesion. Finally, the optimized PULSE3 waveform was largely focused on a persistent AF population, as few paroxysmal AF patients were treated with this waveform. Therefore, it remains possible that the efficacy of the PULSE3 waveform in paroxysmal AF patients may be higher than that observed in the paroxysmal population herein.

CONCLUSIONS

This first-in-human multicenter study demonstrates that the focal lattice tip ablation catheter can toggle between high-power RFA or PFA to treat patients with either paroxysmal or persistent AF in an efficient, safe, and clinically efficacious manner, using a variety of ablation lesion sets—including curvilinear isolation of pulmonary veins and linear right/left atrial linear lesions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with paroxysmal or persistent AF, a lattice catheter can toggle between delivering RF and PF energy to electrically isolate pulmonary veins and create linear atrial lesions along the mitral isthmus, left atrial roof, and cavotricuspid isthmus. These lesion sets are largely electrically durable upon invasive remapping evaluation and ultimately result in favorable 1-year freedom from clinical arrhythmia recurrence.

TRANSLATIONAL OUTLOOK: Future trials are needed to determine the relative safety and efficacy of this RF/PF lattice catheter technology as compared to conventional thermal ablation.

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KEY WORDS atrial fibrillation, catheter ablation, cavotricuspid isthmus, lattice tip, lesion durability, mitral isthmus, pulmonary vein isolation, pulsed field ablation, roof line, temperature controlled

APPENDIX For a list of the participating centers and staff as well as supplemental figures, tables, and references, please see the online version of this paper.