Pulsed Field Ablation of Paroxysmal Atrial Fibrillation

1-Year Outcomes of IMPULSE, PEFCAT, and PEFCAT II

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ABSTRACT

OBJECTIVES This study sought to determine whether durable pulmonary vein isolation (PVI) using pulsed field ablation (PFA) translates to freedom from atrial fibrillation recurrence without an increase in adverse events.

BACKGROUND PFA is a nonthermal ablative modality that, in preclinical studies, is able to preferentially ablate myocardial tissue with minimal effect on surrounding tissues. Herein, we present 1-year clinical outcomes of PFA.

METHODS In 3 multicenter studies (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], and PEFCAT II [Expanded Safety and Feasibility Study of the FARAPULSE Endocardial Multi Ablation System to Treat Paroxysmal Atrial Fibrillation]), paroxysmal atrial fibrillation patients underwent PVI using a basket or flower PFA catheter. Invasive remapping was performed at ~2 to 3 months, and reconnected PVs were reisolated with PFA or radiofrequency ablation. After a 90-day blanking period, arrhythmia recurrence was assessed over 1-year follow-up.

RESULTS In 121 patients, acute PVI was achieved in 100% of PVs with PFA alone. PV remapping, performed in 110 patients at 93.0±30.1 days, demonstrated durable PVI in 84.8% of PVs (64.5% of patients), and 96.0% of PVs (84.1% of patients) treated with the optimized biphasic energy PFA waveform. Primary adverse events occurred in 2.5% of patients (2 pericardial effusions or tamponade, 1 hematoma); in addition, there was 1 transient ischemic attack. The 1-year Kaplan-Meier estimates for freedom from any atrial arrhythmia for the entire cohort and for the optimized biphasic energy PFA waveform cohort were 78.5±3.8% and 84.5±5.4%, respectively.

CONCLUSIONS PVI with a “single-shot” PFA catheter results in excellent PVI durability and acceptable safety with a low 1-year rate of atrial arrhythmia recurrence. These data mitigate concern that the nonthermal ablative mechanism of PFA might mask undiscovered compromises to clinical success. (IMPULSE: A Safety and Feasibility Study of the IOWA Approach Endocardial Ablation System to Treat Atrial Fibrillation, NCT03700385; A Safety and Feasibility Study of the FARAPULSE Endocardial Ablation System to Treat Paroxysmal Atrial Fibrillation, NCT03714178; PEFCAT II Expanded Safety and Feasibility Study of the FARAPULSE Endocardial Multi Ablation System to Treat Paroxysmal Atrial Fibrillation [PEFCAT II], NCT04170608) (J Am Coll Cardiol EP 2021;7:614–27) © 2021 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/).
Pulse field ablation (PFA) is a novel nonthermal ablation modality unlike every other ablation energy source in that it can preferentially ablate myocardial tissue. During PFA, ultrarapid (micro- to nanosecond) electrical pulses are applied to destabilize cell membranes by forming irreversible nanoscale pores, culminating in cell death, a phenomenon called electroporation (1–4). However, the propensity for dielectric cell membrane breakdown varies between tissues: the threshold field strength for tissue necrosis appears to be lower for some tissues such as the myocardium than for other tissues such as blood vessels or nerve fibers (5–7). Preclinical studies with the same PFA system used in this study have confirmed this property of tissue selectivity (8,9). This differential tissue sensitivity to pulsed electrical fields has prompted its application to catheter ablation for atrial fibrillation (AF) with the goal of improving safety by decreasing collateral damage.

Preclinical experiments have confirmed the relative tissue selectivity of PFA (8–13). Most recently, in paroxysmal AF, we demonstrated that electrical pulmonary vein isolation (PVI) could be achieved without any of the major adverse effects of thermal ablation—stroke, PV stenosis, phrenic nerve injury, or esophageal damage—despite not using any esophageal protection strategy such as temperature monitoring or esophageal displacement (14). Furthermore, protocol-mandated invasive remapping procedures at ~2 to 3 months post-ablation demonstrated that the durability of electrical isolation improved with successive evolution of the PFA waveform such that the final optimized waveform achieved 100% durability—a success rate heretofore not achieved (15–22).

Although promising, it is unknown whether this translates to freedom from AF recurrence (unlike PVI with thermal ablation). Indeed, the major residual question about PFA for AF ablation relates to whether this novel nonthermal ablation mechanism masks undiscovered compromises to clinical success. Herein, we pooled data from 3 nearly identical trials (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], and PEFCAT II [Expanded Safety and Feasibility Study of the FARAPULSE Endocardial Multi Ablation System to Treat Paroxysmal Atrial Fibrillation]) in which PFA was employed to perform PVI in 121 paroxysmal AF patients. In addition to comprehensive procedural data, safety, and durability outcomes, we present the 1-year freedom from atrial arrhythmias.

**METHODS**

**TRIAL DESIGN.** The total cohort consisted of subjects enrolled in 3 studies: the IMPULSE (NCT03700385), PEFCAT (NCT03714178), or PEFCAT II (NCT04170621) studies. Trial registration for IMPULSE occurred midway through the trial; the PEFCAT and PEFCAT II studies were registered prior to any patient enrollment (details in the Supplemental Appendix). The 3 trials represent the first-in-human use of PFA for the treatment of paroxysmal AF. The IMPULSE and PEFCAT studies investigated the use of an over-the-wire, single shot-type multielectrode PFA catheter to achieve PVI. The PEFCAT II study utilized the same catheter for the treatment of the PVs, while also investigating the first-in-human treatment of cavitricuspid isthmus (CTI)-dependent flutter with a novel, deflectable focal PFA catheter.

The IMPULSE and PEFCAT studies are prospective, single-arm safety and feasibility trials performed at 2 sites (Homolka Hospital, Prague, Czech Republic, and Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France). The PEFCAT II study is a prospective, single-arm feasibility trial performed at 2 sites (Homolka Hospital, Prague, Czech Republic, and CHU Split, Split, Croatia). Trials were approved by each center’s local ethics committee and corresponding national regulatory agency. Farapulse (Menlo Park, California, formerly Iowa Approach) funded and acted as the sponsor for the studies. MedPass International SAS (Paris, France) was the clinical research organization that provided data monitoring for the studies, while Medical Data Transfer (Brno, Czech Republic) acted as the independent core lab for event and Holter monitoring.

**PATIENT SELECTION.** The IMPULSE, PEFCAT, and PEFCAT II studies all enrolled patients with paroxysmal AF resistant to at least 1 Class I to IV antiarrhythmic drug. Detailed inclusion and exclusion criteria are in the Supplemental Appendix (Supplemental Table 1).

**ABLATION SYSTEM.** The PFA system has been previously described in detail (14). The system consists of 4 components: a custom PFA generator (Farastar, Farapulse, Menlo Park, California) that delivers high-voltage, high-frequency pulses over multiple channels; an over-the-wire 12-F multielectrode PFA catheter (Farawave, Farapulse); a 12-F steerable focal PFA...
catheter (Faraflex, Farapulse); and a 13-F steerable sheath (Faradrive, Farapulse).

The PFA generator’s ablation waveform was limited in each patient to programmed pulse parameters and was not modifiable by the investigator. Modifiable generator outputs ranged from 900 to 1,000 V in the monophasic cohort, and 1,800 to 2,000 V in the biphasic cohort. Four different waveforms were employed, and the number of pulses varied from 4 to 10 for each application. Initial procedures had applications synchronized with dual-chamber pacing, while later procedures were performed with asynchronous PFA delivery.

For PVI, the “single-shot” multielectrode PFA catheter was used. This catheter consists of 5 splines, with 4 electrodes per spline and 1 electrode available for intracardiac electrogram recording or 3-dimensional electroanatomic visualization. When used in conjunction with the PFA generator, an electric field is created that ablates tissue using irreversible electroporation. The catheter shape is changed through the manipulation of a slider mechanism on the handle of the catheter. The diameter of the catheter is measured in the fully deployed “flower” configuration and is available in 2 sizes (31 or 35 mm). Energy is delivered through all of the electrodes in a proprietary sequence (Figure 1).
CTI ablation with PFA in the PEFCAT II study was performed with the focal PFA catheter. This catheter consists of 4 splines, with 4 electrodes per spline, and can be deployed into a small basket-like shape (Figure 2). When used in conjunction with the generator, the electrodes can deliver PFA to the desired tissue, as well as allowing for intracardiac electrogram analysis and 3-dimensional electroanatomic mapping visualization when therapy is not being delivered.

The number of applications, output of the generator, and shape of the splines (flower or basket) were adjusted based on results from the remapping procedures, at the discretion of the investigator. These first-in-human studies were designed to allow for flexibility in the delivered dose and waveform as remapping data was obtained to optimize output and applications for chronic durability. Therapeutic dosing evolved from a monophasic to biphasic waveform and optimizations were made to the number of applications per vein, spline shape, and the number of rotations between ablations.

PROCEDURE. All patients were consented for their respective protocol prior to undergoing study-specific pre-procedure testing, which included computed tomography (CT) to assess left atrial size and PV anatomy. The initial IMPULSE study cases employed a monophasic waveform and were performed with general anesthesia and paralytics to account for the skeletal muscle capture inherent with that type of waveform. All but the first of the biphasic procedures were performed with conscious sedation and propofol bolus synchronized to sets of PFA applications. The procedures were performed with uninterrupted oral anticoagulation, and left atrial thrombus was excluded either through pre-procedure CT or intracardiac echocardiography (ICE) (AcuNav, Siemens, Munich, Germany) at the time of the procedure. Pre- and post-ablation diaphragm motion was evaluated to observe for changes in phrenic nerve function.
TABLE 1  Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total Cohort (N = 121)</th>
<th>Optimized Waveform Cohort (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>57.4 ± 10.3</td>
<td>56.9 ± 10.4</td>
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<tr>
<td>Male</td>
<td>89 (73.6)</td>
<td>32 (65.3)</td>
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<tr>
<td>LA diameter, mm</td>
<td>40.5 ± 4.5</td>
<td>40.0 ± 5.0</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62.5 ± 5.7</td>
<td>61.2 ± 7.2</td>
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<tr>
<td>Sleep apnea</td>
<td>4 (3.3)</td>
<td>2 (4.1)</td>
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<tr>
<td>Hypertension</td>
<td>68 (56.2)</td>
<td>29 (59.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (9.1)</td>
<td>3 (6.1)</td>
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<tr>
<td>Dyslipidemia</td>
<td>41 (33.9)</td>
<td>17 (34.7)</td>
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<tr>
<td>Stroke or TIA</td>
<td>6 (5.0)</td>
<td>3 (6.1)</td>
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<tr>
<td>CAD (MI/CABG)</td>
<td>4 (3.3)</td>
<td>2 (4.1)</td>
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<tr>
<td>Antiarrhythmics</td>
<td>118 (97.5)</td>
<td>49 (100.0)</td>
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<tr>
<td>Class I</td>
<td>83 (68.6)</td>
<td>38 (77.6)</td>
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<tr>
<td>Class III</td>
<td>23 (19.0)</td>
<td>8 (16.3)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>44 (36.4)</td>
<td>18 (36.7)</td>
</tr>
</tbody>
</table>

Values are mean ± SEM or n (%).

CABG = coronary artery bypass grafting; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; LA = left atrium; LVEF = left ventricular ejection fraction; MI = myocardial infarction; TIA = transient ischemic attack.

TABLE 2  Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total Cohort (N = 121)</th>
<th>Optimized Waveform (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVI success</td>
<td>475/475 (100)</td>
<td>57/57 (100)</td>
</tr>
<tr>
<td>Number of lesions/PVs</td>
<td>57/57 (100)</td>
<td>223/223 (100)</td>
</tr>
<tr>
<td>LCPV</td>
<td>7.2 ± 2.2</td>
<td>3.3 ± 0.5</td>
</tr>
<tr>
<td>LSPV</td>
<td>12.9 ± 6.1</td>
<td>6.3 ± 0.6</td>
</tr>
<tr>
<td>LIPV</td>
<td>7.3 ± 2.4</td>
<td>3.0 ± 0.0</td>
</tr>
<tr>
<td>RSPV</td>
<td>6.9 ± 2.2</td>
<td>3.0 ± 0.0</td>
</tr>
<tr>
<td>RIPV</td>
<td>7.2 ± 2.4</td>
<td>3.4 ± 1.1</td>
</tr>
<tr>
<td>Procedure time, min</td>
<td>96.2 ± 30.3</td>
<td>84.1 ± 13.1</td>
</tr>
<tr>
<td>Mapping time, min</td>
<td>19.3 ± 12.0</td>
<td>23.6 ± 10.0</td>
</tr>
<tr>
<td>Catheter dwell time, min</td>
<td>34.4 ± 15.8</td>
<td>27.3 ± 4.1</td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>13.7 ± 7.8</td>
<td>12.2 ± 4.0</td>
</tr>
<tr>
<td>CTI block success</td>
<td>4/4 (100)</td>
<td>4/4 (100)</td>
</tr>
<tr>
<td>Catheter dwell time, min</td>
<td>8.5 ± 7.7</td>
<td>8.5 ± 7.7</td>
</tr>
</tbody>
</table>

Values are n/N (%) or mean ± SEM. *Defined as the time transpired between insertion to removal of the focal PF ablation catheter.

CTI = cavitricuspid isthmus; LCPV = left common pulmonary vein; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; PF = pulsed field; PV = pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

A single transseptal puncture was performed with an 8.5-F sheath and exchanged for the 13-F PFA sheath in the left atrium, or transseptal puncture was performed directly with the PFA sheath. Intravenous heparin was administered as boluses and continuous infusions to obtain an activated clotting time ≥300 s prior to ablation and throughout the procedure. A 0.035-inch, 180-cm extra-stiff, straight guidewire was used to cannulate each vein over which the multi-electrode PFA catheter was deployed into the desired shape and advanced into position at the antrum of each vein. The antral level of catheter positioning was monitored with ICE imaging and fluoroscopy. Patients with left common PV anatomy received therapy at the level of the common antrum with 2 sets of therapy delivered, 1 with the guidewire in a superior branch and 1 with the guidewire in an inferior branch.

Acute isolation of the treated vein was determined by the mapping electrodes on each spline of the PFA catheter. Once all veins had been treated, a 3-dimensional electroanatomic voltage map was performed directly with the PFA catheter. Intravenous heparin was administered as boluses and continuous infusions to obtain an activated clotting time ≥300 s prior to ablation and throughout the procedure. A 0.035-inch, 180-cm extra-stiff, straight guidewire was used to cannulate each vein over which the multi-electrode PFA catheter was deployed into the desired shape and advanced into position at the antrum of each vein. The antral level of catheter positioning was monitored with ICE imaging and fluoroscopy. Patients with left common PV anatomy received therapy at the level of the common antrum with 2 sets of therapy delivered, 1 with the guidewire in a superior branch and 1 with the guidewire in an inferior branch.

During the procedure, Esophageal temperature monitoring was not utilized due to the nonthermal nature of PFA. Post-procedure esophagogastroduodenoscopy (EGD) and cranial magnetic resonance imaging (MRI) was performed at the investigators’ discretion.

FOLLOW-UP. Subjects returned for follow-up visits at 30 days, 75 days (PEFCAT and PEFCAT II studies) or 90 days (IMPULSE study), 6 months, and 12 months. Patients were assessed for safety events, arrhythmia recurrence, and antiarrhythmic drug use at each visit. A repeat CT/MRI was performed at either the 75-day (PEFCAT and PEFCAT II studies) or 90-day (IMPULSE study) visit to assess for PV stenosis. At investigator discretion, subjects were eligible to undergo a remapping procedure at the 75- or 90-day
follow-up visit to assess the durability of PVI. PV reconnections found during remapping procedures performed within the 90-day blanking window were reisolated with either PFA or a commercially available irrigated radiofrequency ablation catheter at the investigator’s discretion.

Patients were assessed for recurrence of AF, atrial tachycardia (AT), or AFL after the 90-day blanking window from the time of the index procedure by weekly transtelephonic electrocardiogram transmissions as well as 24-h Holter monitoring at 6 and 12 months. Antiarrhythmic drugs were allowed during the blanking period but recommended to be discontinued after day 90 unless clinically indicated.

ENDPOINTS. Primary safety endpoints for the study included the incidence of early and late onset serious adverse events, which were device or procedure related as determined by the independent Clinical Events Committee. Events included death, myocardial infarction, persistent diaphragmatic paralysis, stroke or transient ischemic attack (TIA), peripheral or organ thromboembolism, pericarditis, cardiac tamponade or perforation, vascular access complications, hospitalization, or heart block within 7 days (IMPULSE study) or 30 days (PEFCAT and PEFCAT II studies). PV stenosis (>70% diameter reduction from baseline) and atrioesophageal fistula were included in the primary endpoint at any time during follow-up.

The primary feasibility endpoint for the studies was the proportion of subjects that achieve acute PV isolation. Secondary feasibility endpoints included the proportion of patients that had durable PVI at the remap procedure, and the proportion of subjects that achieved therapeutic success, defined as freedom from AF, AFL, or AT after the 90-day blanking period. Patients that had additional ablation after the
90-day blanking period were considered therapeutic failures.

**Statistical Analysis.** As the IMPULSE, PEFCAT, and PEFCAT II studies were feasibility studies without any formal hypothesis testing, sample size calculations were not performed. A per-protocol analysis was used for assessment of the primary safety, primary efficacy, and secondary efficacy endpoints. Continuous variables are summarized as mean ± SD or as median (interquartile range [IQR]). Categorical variables are presented as proportions. Arrhythmia-free survival estimates were calculated using the Kaplan-Meier method. Analysis of variance was used to compare procedural characteristics based on the type of energy waveform employed (monophasic, non-optimized biphasic, and optimized biphasic) with Tukey tests for pairwise comparisons. The proportion of pulmonary veins that remained isolated at repeat procedures was compared based on the use of ICE imaging during the index procedure through chi-square tests. All tests of significance were 2-sided, with p ≤ 0.05 considered statistically significant.

**Results**

**Patient Characteristics and Follow-Up Duration.** At 3 enrolling centers, 5 operators performed PVI procedures using PFA on a total of 121 patients (mean age 57.4 ± 10.3 years, 73.6% male). Baseline demographics are shown in Table 1 for the entire cohort, as well as stratified by study in Supplemental Table 2 (Supplemental Appendix). The median duration of AF in these patients was 13.8 months (IQR: 8.0 to 46.2 months), and 79.3% failed at least 1 Class I or III antiarrhythmic drug. Antiarrhythmic regimens as a percentage of total subjects included a nonwarfarin oral anticoagulant in 66.1%, warfarin in 31.4%, or aspirin in 4.1%. Most patients (n = 97 of 121) reached the 1-year milestone: the median follow-up duration was 360 days (IQR: 352 to 365 days).

**PFA Cohorts and Observations.** Monophasic or biphasic PFA waveforms were used in the first 15 and subsequent 106 patients, respectively. All monophasic and the first biphasic PFA were performed under general anesthesia; the remaining 105 biphasic procedures utilized conscious sedation. Biphasic deliveries were well tolerated; energy delivery was not interrupted by the mild degree of muscle activation and occasional transient cough. Study subjects are grouped according to treatment: 15 patients ablated with monophasic PFA, 57 patients with the early biphasic PFA waveforms or other delivery protocols (PFA-E0), and 49 patients with the optimized biphasic PFA waveform and delivery protocol (PFA-OW).

Positioning of the PFA catheters in all of their deployment states—the single-shot catheter at PV ostia and the focal catheter on the CTI—was achieved without difficulty, including no evidence of catheter entrapment by the PVs or the valvular apparatus (Figures 1 and 2). Consistent with the microsecond nature of the pulsed field applications, the cumulative time over which the ablation lesions were delivered did not exceed 3 min/patient. During PFA applications, there was no evidence of: 1) waveform discontinuities suggestive of “arching”; 2) ventricular tachyarrhythmias; or 3) significant repolarization abnormalities on 12-lead electrocardiography. Echogenic bubble formation was observed by ICE without any appreciable physiologic effects (including negative brain MRI in a subset of patients, see subsequent sections).

**Procedural Characteristics.** As shown in Table 2, the mean total procedure time for the full cohort was 96.2 min—inclusive of the time required (19 min) to perform protocol-mandated electroanatomical voltage mapping. The left atrial catheter dwell time, defined as the time transpiring between introduction to removal of the flower or basket PFA catheter from the left atrium, and fluoroscopy times
for the full cohort were 34.4 ± 15.8 min and 13.7 ± 7.8 min, respectively. In an analysis of variance models, the mean number of total applications differed based on the waveform used (12.5 ± 1.1 for monophasic waveform, 26.9 ± 6.5 for early biphasic, and 34.3 ± 3.5 for optimized biphasic; p < 0.05 for all pairwise comparisons). Procedure time, mapping time, PVI dwell time, fluoroscopy time, and mapping time did not differ among the groups (Table 2). For the 4 patients in whom CTI ablation was performed (all enrolled in the PEFCAT II study), the right atrial catheter dwell time for the focal PFA catheter was 19.5 min.

Post-procedure electroanatomical voltage mapping revealed that the level of electrical PV isolation was antral in nature (Figure 3). Anomalous PV anatomy was not excluded and when encountered was treated successfully in all cases using the study catheter. For left common PVs, 2 sets of individual PV applications were applied with a superior and inferior venous branch wired to facilitate a circumferential lesion at the common PV antrum.

**PRIMARY OUTCOMES.** The primary efficacy endpoint of complete electrical PV isolation was achieved in 100% of patients. All 475 targeted PVs were electrically isolated, receiving a mean of 7.2 ± 2.2 ablation lesions per PV and 28.1 ± 8.5 lesions per patient. These repetitive lesions were aimed at achieving durable isolation: all PVs acutely isolated within the first 1 or 2 applications. There were no instances of PV reconnection observed during the waiting period or with provocative adenosine testing. Bidirectional CTI block was achieved using the focal catheter with a mean of 18.0 ± 8.5 pulsed field applications per patient.

The primary safety endpoint occurred in 2.5% of patients. Pericardial effusion occurred in 2 patients. One effusion was attributed to aggressive manipulation of either the study or mapping catheter and led to tamponade requiring pericardiocentesis. The patient recovered safely. In a second patient, a small effusion was discovered hours after the remapping procedure in which the study catheter had been used to reablate a PV reconnection. This effusion did not cause tamponade but was drained (350 cm³) prior to an otherwise uneventful discharge. One vascular hematoma occurred, prolonging the index hospitalization. No other primary adverse events occurred during follow-up (Table 3). Importantly, there were no cases of atrioesophageal

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**FIGURE 4 - Durability of PV Isolation With Pulsed Field Ablation**

The durability of pulmonary vein isolation (PVI) improved with modification of energy delivery waveforms from a monophasic waveform to nonoptimized biphasic waveform, and increased further with the final optimized biphasic waveform.
fistula, stroke, PV stenosis >70%, or phrenic nerve injury.

SECONDARY OUTCOMES. Durability. A total of 110 of 121 (90.9%) patients underwent PV remapping at a mean of 93.0 ± 30.1 days following the index procedure. In the entire cohort, durable PVI was observed in 364 of 429 (84.8%) PVs and 71 of 110 (64.5%) patients. As previously reported, the monophasic energy delivery in 11 remapped patients resulted in durable PV isolation of only 45.2% (n = 19 of 42) of PVs and 18.1% (n = 2 of 11) of patients (14). For the patients that received the nonoptimized PFA-EO therapy, durable PV isolation was observed in 83.6% (n = 179 of 214) of PVs and 58.2% (n = 32 of 55) of patients (Figure 4). Finally, for patients that received PFA-OW, durable PV isolation was observed in 96.0% (n = 166 of 173) of PVs and 84.1% (n = 37 of 44) of patients. Most patients without durability had single PV reconnections, and these reconnections were concentrated in the superior PVs (Supplemental Tables 3 and 4).

For the PFA-OW cohort, durability was also analyzed as a function of whether ICE imaging was employed during the index procedure (ICE was not employed at 1 center): PVI durability was present in 98.2% (n = 110 of 112) and 91.8% (n = 56 of 61) of PVs when ICE had or had not been employed, respectively (p = 0.022). Finally, for patients receiving CTI ablation with focal PFA, remapping revealed durable CTI block in 2 of 3 patients.

Arrhythmia recurrence. At 1 year, the Kaplan-Meier estimate for freedom from AF was 81.1 ± 3.8% and for freedom from AF, AFL, or AT was 78.5 ± 3.8% (Figure 5 and Supplemental Table 5). The single procedure (i.e., no ablation during the remapping procedure or otherwise) Kaplan-Meier estimates for freedom from AF and AF, AFL, or AT were 79.4 ± 4.9% and 79.3 ± 4.6%, respectively (Figure 6). In the final 49 patients treated with the optimized PFA waveform (PFA-OW), the Kaplan-Meier estimates for freedom from AF and AF, AFL, or AT were 84.6 ± 6.0% and 84.5 ± 5.4%, respectively. The data resolution on which recurrence was measured was high, owing to compliance with scheduled event monitor and Holter recordings: 86.1% and 98.2% on a per-week and per-Holter basis, respectively. At 12 months, Class I or III antiarrhythmic drug use was 18.0% and 13.0% in the full PFA and PFA-OW cohorts, respectively. In the PFA-OW cohort, there were 7 patients with recurrence of AF, AFL, or AT—all had durable PVI at remapping and were on antiarrhythmic drugs, suggesting a non-PV trigger as the mechanism of recurrence.

ADDITIONAL SAFETY ASSESSMENTS. After the index PFA procedure, EGD was performed in 38 patients for assessment of esophageal injury at a mean of 4.9 ± 1.9 days post-procedure (Table 4). There were no esophageal lesions observed. Additionally, cardiac magnetic resonance imaging with late gadolinium enhancement was performed.
in 18 patients to visualize acute lesion formation. This revealed homogeneous atrial enhancement at sites of ablation around the PVs but without any adjacent esophageal enhancement. Brain MRI was performed on 18 patients at a median of 5 (IQR: 1.0 to 18.5) days post-procedure. One subject with a history of TIA, who experienced a TIA post-ablation, exhibited diffusion-weighted positivity indicative of an acute lesion. This patient reported very brief dysphasia 1 day post-procedure. A second patient receiving a screening MRI also presented diffusion-weighted positivity. The remaining 16 subjects undergoing brain MRIs, including the 5 prospectively scanned patients receiving the PFA-OW dose, exhibited no diffusion-weighted positivity. Finally, to assess for PV stenosis, 74 patients underwent repeat CT or MRI at a mean of 99.7 ± 38.9 days following the procedure: there were no instances of PV stenosis (defined as >70% decrease in size).

**DISCUSSION**

In paroxysmal AF patients, PVI with the flower or basket PFA catheter was safe, efficient, durable, and resulted in a high rate of freedom from recurrent atrial arrhythmias (Central Illustration).

**LESION DURABILITY.** In this study, invasive remapping in a large number of patients (n = 110) at ~2 to

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**FIGURE 6** Freedom From Atrial Arrhythmias Following a Single Procedure and for Patients Treated With Optimized Waveforms

- **A** Freedom from AF: Single Procedure
  - 365-day K-M Estimate 79.4 ± 4.9%
  - No. at Risk: 76, 66, 60, 54
  - Time to Failure (Days)

- **B** Freedom from AF, AFL, or AT: Single Procedure
  - 365-day K-M Estimate 79.3 ± 4.6%
  - No. at Risk: 76, 66, 59, 53
  - Time to Failure (Days)

- **C** Freedom from AF: PFA-OW Cohort
  - 365-day K-M Estimate 84.6 ± 6.0%
  - No. at Risk: 46, 43, 41, 37
  - Time to Failure (Days)

- **D** Freedom from AF, AFL, or AT: PFA-OW Cohort
  - 365-day K-M Estimate 84.5 ± 5.4%
  - No. at Risk: 46, 43, 40, 36
  - Time to Failure (Days)

The K-M survival curves for (A) freedom from AF and (B) freedom from AF, AFL, or AT for patients that underwent only a single procedure. The K-M survival curves for (C) freedom from AF and (D) freedom from AF, AFL, or AT for patients treated with the optimized pulsed field ablation waveform (PFA-OW). Abbreviations as in Figure 5.
3 months revealed that 84.8% of PVs (64.5% of patients) in the entire PFA cohort had durable PVI, with minimal differences between groups (Supplemental Table 6). Although these durability rates are comparable to the more favorable data reported with thermal ablation, these PFA results incorporated all patients over the course of PFA waveform or delivery evolution—including monophasic PFA, PFA-EO, and PFA-OW (15–22). But for the most advanced delivery, PFA-OW, the PVI durability rate of 96.0% for PVs (84.1% of patients) is substantially higher than reported previously (15–22).

On the other hand, this is lower than the 100% we previously reported with this waveform, but this not surprising, as “one-shot” ablation technologies are not technique independent (14). When ICE was used to facilitate catheter positioning, the rate of durable PVI improved to 98.2% of PVs, compared with 91.8% when ICE was not used. Accordingly, durability seems highest when combining the optimized waveform and ICE imaging. However, it should be acknowledged that this was not a randomized evaluation, and is confounded by preferential operator use. It is notable that this is one of the largest PV remapping studies to date. The marked discordance between acute and durable isolation observed in the monophasic and PFA-EO cohorts may represent a more severe decoupling than is typically observed with thermal ablation. This highlights the need to perform prospective invasive reassessments to delineate the true ablation efficacy of PVI with individual PFA systems.

CLINICAL SUCCESS. Prior to this study, it was an open question as to whether durable PVI with PFA would yield the same results as thermal ablation. After all, could its myocardial preferential ablation properties, which are so beneficial on the safety side, hinder efficacy? However, PFA durability did indeed translate to clinical success. The Kaplan-Meier estimates for freedom from AF or freedom from any atrial arrhythmia were 81.1% and 78.5%, respectively. Because some of these patients underwent reisolation of reconnected PVs at the time of remapping studies, we also analyzed patients with durable isolation after
a single ablation procedure: freedom from AF or from any atrial arrhythmia were 79.4% and 79.3%, respectively. And finally, when using the optimized PFA-OW waveform, freedom from AF or from any atrial arrhythmia were 84.6% and 84.5%, respectively. There were 7 PFA-OW patients with clinical recurrences despite documented durable PVI in 6 of 7 patients—likely owing to non-PV triggers (reported in up to 27% of AF patients, and as high as 69% if left ventricular dysfunction is present) (23–25). Interestingly, vagal responses were commonly observed during PFA, and were reproducible with subsequent energy applications. It is unclear whether the observed clinical efficacy may, in part, be due to necrosis of periatrial ganglionated plexi, as the sensitivity of the structures to pulsed electric fields is, to the best of our knowledge, unknown (26,27).

These favorable clinical outcomes were achieved with short procedure times. In >100 patients and with 5 operators, the mean procedure times were only 96.2 ± 30.3 min, inclusive of ~20 min of voltage mapping time after PVI (required by protocol). These are faster than procedure times with other technologies (28,29). With increased operator experience and elimination of voltage mapping, procedure times should improve further.

**SAFETY OF PFA.** PFA was safe, with a primary adverse event rate of 2.5%, consisting of only 3 primary safety events: 1 cardiac tamponade, 1 pericardial effusion, and 1 vascular hematoma. One TIA was also observed. There were no further major safety events during follow-up, including no atrioesophageal fistulas, phrenic nerve palsy, PV stenosis, or stroke. A unique feature of PFA is its ability to “selectively” ablate myocardial tissue while sparing neighboring structures such as the esophagus and phrenic nerve. This is because the energy thresholds required for PFA to induce myocardial cell necrosis appears to be among the lowest values of any tissue type, with tissue selectivity observed in the preclinical setting using the same system described in this report (5,8,9).

In a subset of patients, MRI with late gadolinium enhancement demonstrated uniform peri-PV ablation, with complete sparing of the neighboring esophagus. Additionally, EGD was performed in 38 additional patients, and did not reveal any esophageal lesions. It is important to note that none of the patients had received esophageal protection or deviation devices during the procedures. These findings are consistent with preclinical studies demonstrating no chronic changes to esophageal architecture either grossly or microscopically when PFA was applied directly apposed against all porcine esophageal tissue (9,12). In comparison, asymptomatic esophageal injury has been observed in ~19% of patients with radiofrequency ablation and cryoballoon ablation and atrioesophageal fistulas in 0.02% to 0.11% (1,29–33).

PFA is characterized by diaphragmatic capture during right superior PV ablation because of the close proximity of the right phrenic nerve. However, there was no phrenic nerve paresis or palsy. There was also no evidence of PV narrowing or stenosis with PFA. These findings are consistent with those seen in preclinical PFA experiments, and our recent comparison of patients undergoing PVI with PFA vs radiofrequency ablation (10,11,34). Finally, there were no strokes; only a single TIA occurred. This may be explained by both the nonthermal nature of PFA, and the aforementioned, relatively low-energy thresholds needed to ablate myocardial tissue. It should be noted that left atrial instrumentation carries risks (i.e., air introduction) and in this regard, PFA is no different. For reference, recall that the rates of phrenic nerve palsy, PV stenosis requiring intervention, and stroke or TIA with radiofrequency ablation are 0.4%, 0.29%, and 0.94%, respectively (32,35). With more than 100 patients treated in this study, these safety findings should largely allay most safety concerns regarding PFA. Of course, only much larger studies (n = >1,000) would reveal rarer unanticipated safety issues.

**STUDY LIMITATIONS.** This study is a pooled analysis of 3 separate, nonrandomized, prospective studies without a comparator group. Therefore, comparisons
with other technologies should be interpreted with caution. Multicenter randomized studies are necessary to directly compare the relative efficacy and safety of PFA to thermal technologies such as radiofrequency ablation, cryoballoon and laser balloon—ideally with implantable monitors to assess AF burden, though this benchmark is still being established. These trials should incorporate screening brain MRI substudies with a control group. Also, the findings of this study are unique to the PFA catheters and waveforms or dosing regimen investigated herein and cannot be extrapolated to other PFA technologies or waveforms. Finally, PFA was performed in paroxysmal AF patients only, and the results in persistent AF patients may differ. To this end, we recently completed a separate feasibility study evaluating PFA in 25 persistent AF patients with an ablation strategy including both PVI and posterior left atrial wall isolation.

CONCLUSIONS

In paroxysmal AF patients, PVI with a “one-shot” PFA catheter results in excellent lesion durability and safety. At 1 year, this translated to low rates of AF and other atrial arrhythmia recurrence. Improvements in PFA dosing and optimization of the biphasic waveforms employed in the study resulted in 96.0% of PVs remaining durably isolated. These data help allay concern that the novel nonthermal ablative mechanism of this energy modality masks undiscovered compromises to clinical success. Multicenter, randomized studies comparing PFA with other ablation energy sources are necessary to confirm the favorable findings observed in this study.

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COMPETENCY IN MEDICAL KNOWLEDGE: PFA is a nontermal ablation modality that: 1) allows for preferential myocardial ablation without damage to pericardiac structures such as the esophagus or phrenic nerve; 2) results in durable PVI when using an optimized biphasic waveform; and 3) provides excellent 1-year freedom from AF, AFL, and AT.

TRANSLATIONAL OUTLOOK: In this nonrandomized analysis, the major safety and efficacy issues relevant to PFA have been addressed. This provides the preliminary clinical experience to initiate a larger multicenter randomized trial comparing PFA with standard thermal ablation.


