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Brief Title: Pulsed Field Ablation for AF

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Tweet: Pulsed field ablation (#PFA) treats AF in a tissue-selective manner (avoids damage to esophagus & phrenic nerve) but maintains durable PV isolation.

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Abstract

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

Objectives: To determine whether PFA allows durable pulmonary vein (PV) isolation without damage to collateral structures.

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

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

Conclusions: In first-in-human trials, pulsed field ablation preferentially affected myocardial tissue, allowing facile ultra-rapid PV isolation with excellent durability and chronic safety.

Condensed Abstract

During pulmonary vein isolation (PVI), standard thermal ablation such as radiofrequency or cryothermy is associated with indiscriminate tissue destruction. Alternatively, pulsed field ablation (PFA) is a non-thermal ablation modality wherein sub-second electric fields create microscopic pores in cell membranes – a process termed electroporation. Pre-clinical studies indicated that myocardial cells are particularly susceptible to PFA. In paroxysmal atrial fibrillation patients, we demonstrate that: i) PFA can preferentially ablate myocardial tissue without affecting adjacent structures such as the esophagus or phrenic nerve, and ii) using an optimized biphasic waveform, PFA achieved durable PVI – heretofore not described for any other energy source.

Key Words: Atrial fibrillation, Catheter ablation, Pulmonary vein isolation, Pulsed field ablation, Electroporation, Esophageal damage

Abbreviations

AF = atrial fibrillation
CT = computed tomography
ICE = intracardiac echocardiography
MRI = magnetic resonance imaging
PFA = pulsed field ablation
PV = pulmonary vein

Introduction

Atrial fibrillation (AF) is the most commonly ablated arrhythmia. While largely safe and effective in the hands of expert operators, the procedure is still associated with severe complications including pulmonary vein (PV) stenosis, stroke, phrenic nerve palsy and the most feared complication, atrio-esophageal fistula, which when it occurs, has a mortality exceeding 50%.[1-2] Common to all thermal energies including radiofrequency energy, cryothermy, laser, ultrasound and microwave (even x-ray or proton beam therapy) is their propensity to ablate all tissues indiscriminately. There is a zero-sum relationship between safety and efficacy – greater efficacy is achieved with more ablation but at the expense of safety, and *vice versa*.

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

Beyond safety, it is well-appreciated that the primary mechanism for AF recurrence after conventional ablation procedures is electrical PV reconnection over time—because of incomplete lesion transmurality and/or contiguity. The frequency of all PVs durably isolated per patient has been reported to range from ~20-80%. But unlike other energies, multiple parameters can be fine-tuned with PFA, resulting in different lesion profiles and efficacy. We previously

reported that catheter-based PFA using a monophasic waveform could acutely isolate PVs; however, this first-generation waveform was used in only 15 patients, and there was no safety or efficacy follow-up data available.[10] Herein, in two first-in-human clinical trials of paroxysmal AF, we studied the extended outcomes of the monophasic waveform-treated patients, as well as a substantially larger cohort treated with next-generation biphasic PFA waveforms. We assessed both the long-term safety of PFA, and the durability of electrical PV isolation using protocol-mandated invasive remapping procedures.

Methods

Trial Design

The *IMPULSE* (NCT03700385) and *PEFCAT* (NCT03714178) studies were first-in-human, two-center, non-randomized, feasibility trials of PFA conducted at Homolka Hospital, Prague, and the Centre Hospitalier Universitaire de Bordeaux, France. An independent clinical events committee adjudicated endpoint events. Farapulse of Menlo Park, California, (formerly Iowa Approach), the manufacturer of the PFA system, funded the trials. The study was conducted by Farapulse with partial monitoring by a clinical research organization: MedPass International, Paris, France. The authors had full access to the primary data, take full responsibility for its accuracy and integrity, performed the analyses and interpretation, made the decision to publish, wrote the initial draft, and had final authority over the manuscript content. The trials were approved by each center's local ethics committees, and corresponding national regulatory agencies.

After *IMPULSE* was initiated, process differences in the French and Czech regulatory bodies prompted the sponsor to initiate the *PEFCAT* trial. Because the trials enrolled nearly-identical patients with nearly-identical follow-up and endpoints, these datasets are combined and

presented as one coherent clinical experience. The trial protocols are available online; relevant minor differences are detailed in the **Online Appendix.**

Study Population

The trials enrolled patients with symptomatic paroxysmal AF resistant to Class I–IV antiarrhythmic medications, with left ventricular ejection fraction > 40%, with left atrial antero-posterior dimension < 5.0 (*IMPULSE*) or < 5.5 cm (*PEFCAT*). There were no exclusions for PV anatomy. Detailed inclusion and exclusion criteria are in the **Online Appendix.**

Pulse Field Ablation System

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

The 12-French over-the-wire PFA ablation catheter (Farawave, Farapulse, Menlo Park, California) has 5 splines with each spline containing 4 electrodes, and it can be deployed in either a flower petal or basket configuration (**Figure 1**). When fully deployed into a flower pose, the diameter of the distal portion is 31 mm. The catheter is advanced over a guidewire such that the splines achieve circumferential contact/proximity with the PV antra/PV. The ablative energy is delivered from all electrodes; the third electrode on each spline can also record electrograms. The catheter was rotated between applications to assure circumferential PV ostial and antral coverage. During ablation, a standard electrophysiology catheter paced the ventricles to synchronize the pulses to just after QRS onset.

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

Procedural Workflow

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

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

Pre- and post-procedure phrenic nerve function was evaluated in all patients – by observing diaphragmatic motion during either patient inspiration or direct phrenic pacing. In recognition of PFA's non-thermal mechanism of ablation, neither luminal esophageal temperature monitoring nor lateral esophageal displacement were employed. ICE imaging and fluoroscopy were used to optimize PFA catheter positioning at the PV ostia. For the monophasic and biphasic waveforms, the generator outputs ranged from 900-1000V to 1800-2000V per application, respectively. After ablation, a circular mapping catheter (Lasso, Biosense Webster, Irvine, California) assessed electrical PV activity, followed by post-ablation voltage mapping. At investigator discretion, adenosine boluses (12-18 mg each) were administered to identify dormant PV conduction.

Follow-Up

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

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

Endpoints

The endpoints for *IMPULSE* and *PEFCAT* are similar (**Online Appendix**). The primary safety endpoint was a composite of major safety events including cardiac tamponade, stroke or transient ischemic attack (TIA), diaphragmatic paralysis, PV stenosis, heart block, atrio-esophageal fistula, myocardial infarction and death. In *IMPULSE* and *PEFCAT,* the endpoint included events that occurred within 7- and 30-days post-procedure, respectively. The primary feasibility/effectiveness endpoint in both trials was the proportion of subjects with all PVs electrically isolated with PFA alone.

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

Statistical Analyses

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

Results

Patients

A total of 81 consecutive patients with symptomatic paroxysmal AF were enrolled in the two studies between January 2018 and March 2019. The baseline demographics of the combined cohort are shown in ***Table 1***. The cohort was relatively young (58.0±10.7 years), and male predominant (74%). Left ventricular function was largely preserved (63.3±4.3%), and the LA dimension was 41.2±5.0 mm. A Class I or Class III antiarrhythmic medication was previously ineffective in just over half (58%) the cohort. PV remapping procedures occurred at a median of 84 days (1st and 3rd quartiles: 69 – 95 days) and the total duration of follow-up was median 120 days (1st and 3rd quartiles: 77 – 302 days).

Procedural Characteristics

Of the 81 patients that underwent PFA, monophasic waveforms were used in 15 patients and biphasic in 66 patients. All patients undergoing monophasic PFA required general anesthesia and neuromuscular paralysis; accordingly, skeletal muscle and diaphragmatic activation were not observed. Most biphasic PFA procedures (65 of 66) were performed with conscious sedation; this resulted in only mild degrees of muscle activation that was tolerated well without procedural interruption or catheter dislocation during pulse delivery. Patients did occasionally experience transient intraprocedural cough with the PFA applications.

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

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

Primary Endpoints

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

The primary safety endpoint occurred in one patient (1.2%) who experienced a major procedure-related acute adverse event of pericardial tamponade. This was not related to the ablation itself, but rather to vigorous manipulation of the PFA catheter at the right inferior PV. The pericardial fluid was successfully drained by percutaneous pericardiocentesis. There were no additional primary adverse events during follow-up (***Table 2***). Importantly, there were no clinical instances of pulmonary vein stenosis, stroke or TIA, or atrio-esophageal fistula. There were also no instances of phrenic nerve injury despite frequent phrenic capture during PFA pulses to the right superior PV.

Secondary Endpoints

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

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

Other Safety Assessments

In addition to the absence of clinically-evident esophageal injury, esophageal endoscopy was performed in 29 PFA patients, at a mean of 3.4 days post-ablation (***Table 4***). In all patients, there was no evidence of esophageal luminal irregularities or lesions. In these patients, pre-procedural CT scans demonstrated that, as expected, at least one PV was adjacent to the course of the esophagus in each patient. Additionally, 8 patients underwent post-procedure contrast-enhanced MRI (***Figure 5***). This showed no esophagus enhancement despite clear enhancement of the immediately adjacent LA myocardium and PVs: intense circumferential enhancement was observed for all but 1 of the 28 veins assessed by delayed enhancement imaging. Similarly, T2 imaging also identified no evidence of esophageal damage.

No patient presented with clinical evidence of thromboembolism – stroke, TIA or system embolism. Furthermore, brain MRIs were performed in 13 patients (***Table 4***). They were negative for lesions using both diffusion-weighted imaging and FLAIR imaging, thus revealing no evidence of silent cerebral ischemic events.

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

Beyond the absence of clinical PV stenosis, the PV caliber was studied using two approaches. During invasive remapping, there was no evidence of PV stenosis upon catheter-based electroanatomical mapping (***Table 4***). In addition, a quantitative assessment of the PV caliber was performed in 29 patients who underwent 3-month CT scans, as compared to the baseline CT scans. A total of 95 individual PVs was assessed with follow-up CT scans at a mean of 118±55 days post-ablation: not only was there no evidence of PV stenosis, there was also no evidence of significant PV narrowing in any PV (***Table 5***).

Discussion

In a combined analysis of two first-in-human studies, we evaluated the feasibility, safety and efficacy of pulsed field ablation to electrically isolate pulmonary veins in patients with paroxysmal atrial fibrillation. The rate of procedure-related complications was low (1.2%), and due to a case of pericardial tamponade. There were no subsequent primary adverse events during follow-up. Importantly, the tissue-selective nature of PFA was confirmed with no evidence of esophageal or phrenic nerve damage, and no evidence of PV stenosis or narrowing (**Central**

Illustration). In 81 patients, 100% of PVs were acutely isolated with ≤3 minutes of PFA time per patient. During invasive remapping procedures, the rates of durable PV isolation improved with successive waveform modifications such that the most optimized PFA group demonstrated 100% durability.

Pulsed field ablation is an adaptation of direct current (DC) ablation which was first used to treat cardiac arrhythmias in the 1980s.[11] High energy DC shocks (pulse duration of a few milliseconds) were applied between a catheter electrode positioned adjacent to the target myocardium and an external patch. This crude method of ablation often resulted expanding gas bubbles at the catheter tip, arcing, explosion, and subsequent pressure waves culminating in barotrauma to adjacent structures, and complications such as cardiac perforation [12]. This ablative methodology was replaced by radiofrequency energy, given its more efficient and precise energy delivery.

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

Somewhat unique to PFA, i) the electric field strength thresholds required for myocardial cell death are among the lowest of any tissue type, and ii) since the mechanism of cell death is non-thermal, the propensity for collateral damage appears to be lower than with thermal energy sources.[7-9] Pre-clinical experiments have shown that there is no significant PV stenosis,

phrenic nerve injury or esophageal injury with PFA delivered even directly atop those structures.[13-15] This tissue-selective property of PFA was confirmed in the present study. Despite using no esophageal protection strategy, there was no evidence of esophageal necrosis by either MRI (delayed enhancement or T2 imaging) or endoscopy. Similarly, the proximity of the phrenic nerve to the right superior PV was evidenced by diaphragmatic capture during PFA applications, but there was no evidence of phrenic paresis, let alone palsy. Finally, the absence of thermal coagulative necrosis translated to no PV stenosis or even PV narrowing, and no evidence of thrombus leading to stroke. The overall number of patients with negative brain MRIs was not large, but it *was* sufficient to verify that microbubble formation during PFA is not physiologically relevant (similar to the eruption of spontaneous echocardiographic contrast observed upon cryoballoon thawing).

The rates of atrio-esophageal fistula, phrenic nerve injury, stroke / TIA and PV stenosis requiring intervention following radiofrequency or cryoballoon ablation are not particularly frequent: 0.04 – 0.15%, 2.7%, 0.94% and 0.29% respectively; however, they are associated with significant morbidity and mortality.[1,16-18] But unlike thermal energy sources which have a predictable dose-safety relationship, PFA fundamentally alters this calculus since safety is maintained through a wide range of doses. Of course, these favorable safety data must be corroborated by larger PFA trials with similarly detailed follow-up.

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

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

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

Study Limitations

This study sample size was limited, and not all patients underwent the mandated remapping procedure. The observational design precluded direct comparison of PFA with thermal ablation, thereby limiting our ability to draw definitive conclusions about relative safety and efficacy. A multicenter study of PFA compared to thermal ablation should be conducted in

the future. Due to differences in regional regulatory approval policies, two similar but separate studies were conducted and subsequently combined for this analysis. The median follow-up duration was only 120 days; however, it is arguable that the durable PV isolation data is a better predictor of long-term success than even 1-year clinical outcome data. Also, the changes to the pulse waveform over the course of the trials were not pre-specified.

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

Conclusions

In summary, we demonstrate that in patients with paroxysmal atrial fibrillation, pulsed field ablation rapidly and efficiently isolates pulmonary veins with a degree of tissue selectivity and a safety profile heretofore not described for cardiac ablation. Furthermore, invasive electrophysiologic studies demonstrated that PFA can achieve a high degree of durable PV isolation.

Clinical Perspectives

Competency in Patient Care and Procedural Skills: Pulsed field ablation is a novel ablation modality that: i) can be performed without general anesthesia and paralytics, ii) demonstrates preferential myocardial ablation without damage to adjacent structures such as the esophagus or phrenic nerve, and iii) exhibits durable PV isolation when using an optimized biphasic waveform.

Translational Outlook: Although this is only a two-center study of a relatively modest number of patients, the major safety and efficacy issues relevant to pulsed field ablation have been addressed. It would be appropriate to now commence a larger multicenter study of pulsed field ablation – preferably in comparison to standard thermal ablation.

References

1) Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14(10):e275-e444.
2) Singh SM, d'Avila A, Singh SK, et al. Clinical outcomes after repair of left atrial esophageal fistulas occurring after atrial fibrillation ablation procedures. Heart Rhythm 2013;10:1591–1597.
3) Davalos RV, Mir IL, Rubinsky B. Tissue ablation with irreversible electroporation. Ann Biomed Eng 2005;33:223-231.
4) Rubinsky B, Onik G, Mikus P. Irreversible electroporation: a new ablation modality – clinical implications. Technol Cancer Res Treat 2007;6:37–48.
5) Edd JF, Horowitz L, Davalos RV, Mir LM, Rubinsky B. In vivo results of a new focal tissue ablation technique: irreversible electroporation. IEEE Trans Biomed Eng 2006;53(7):1409–1415.
6) Kotnik T, Kramar P, Pucihar G, Miklavcic D, Tarek M. Cell membrane electroporation—Part 1: the phenomenon. IEEE Electrical Insulation 2012;28:14-23.
7) Kaminska I, Kotulska M, Stecka A, et al. Electroporation-induced changes in normal immature rat myoblasts (H9C2). Gen. Physiol. Biophys 2012;31:19-25.
8) Li W, Fan Q, Ji Z, Qiu X, Li Z. The effects of irreversible electroporation on nerves. PLoS One 2011;6:e18331.
9) Maor E, Ivorra A, Rubinsky B. Non thermal irreversible electroporation: novel technology for vascular smooth muscle cells ablation. PLoS One 2009;4:e4757.

10) Reddy VY, Koruth J, Jais P, et al. Ablation of Atrial Fibrillation With Pulsed Electric Fields: An Ultra-Rapid, Tissue-Selective Modality for Cardiac Ablation. J Am Coll Cardiol EP 2018;4(8):987-995.

11) Gallagher JJ, Svenson RH, Kasell JH, et al. Catheter technique for closed-chest ablation of the atrioventricular conduction system. N Engl J Med 1982;306:194–200.

12) Bardy GH, Coltorti F, Stewart RB, Greene HL, and Ivey TD. Catheter-mediated electrical ablation: the relation between current and pulse width on voltage breakdown and shock-wave generation. Circ Res 1988;63:409-414.

13) van Driel VJ, Neven KG, van Wessl H, et al. Pulmonary vein stenosis after catheter ablation: Electroporation versus radiofrequency. Circ Arrhythm Electrophysiol 2014 Aug;7(4):734-8.

14) van Driel VJ, Neven K, van Wessel H, Vink A, Doevendans PA, Wittkampf FH. Low vulnerability of the right phrenic nerve to electroporation ablation. Heart Rhythm 2015;12:1838-1844.

15) Neven K, van Es R, van Driel V, et al. Acute and long-term effects of full-power electroporation ablation directly on the porcine esophagus. Circ Arrhythm Electrophysiol 2017 May;10(5). pii: e004672. doi: 10.1161/CIRCEP.116.004672.

16) Kuck KH, Brugada J, Fürnkranz A, et al; FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Eng J Med 2016;374:2235-2245.

17) Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol 2010;3:32-38.

18) Ghia KK, Chugh A, Good E, et al. A nationwide survey on the prevalence of atrioesophageal fistula after left atrial radiofrequency catheter ablation. J Interv Card Electrophysiol 2009;24:33-36.

19) Reddy VY, Morales G, Ahmed H, et al. Catheter ablation of atrial fibrillation without the use of fluoroscopy. Heart Rhythm 2010;7:1644–1653.

Figure Legends

Central Illustration: Pulmonary Vein Isolation for Atrial Fibrillation by Pulsed Field Ablation. **A)** PFA spares esophageal and nerve tissue, while radiofrequency and cryoballoon ablation ablates tissues indiscriminately. **B)** The PV electrograms are eliminated by the train of PFA pulses delivered over five heartbeats (*). **C)** The antral level of PV isolation is evident by voltage mapping, obtained 3 months post-ablation. **D)** By delayed enhancement MRI, the ablated atrial tissue is shown enhanced white with contrast uptake, but the adjacent esophageal tissue (dotted outline) has no evidence of enhancement / necrosis. Eso = esophagus; LA = left atrium; PFA = pulsed field ablation; PV = pulmonary vein.

Figure 1: **Pulmonary Vein Isolation with the Pulsed Field Ablation Catheter.** **A**) The PFA catheter in shown over a guidewire with its splines in either the basket deployment pose (left) or the flower petal deployment pose (right). On bottom, the fluoroscopic images show the catheter in either of these poses, situated at the ostium of the left superior PV (left) and the right inferior PV (right). **B)** Electrograms can be obtained by the third electrode of each spline of the PFA catheter. The PV potentials (bipolar electrograms obtained between adjacent splines) are shown immediately before and after a PFA application – demonstrating immediate electrical PV isolation.

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

Figure 3: Durability of Pulmonary Vein Isolation with Successive Waveforms. The bar graph demonstrates the durable PV isolation rates during invasive electrophysiologic remapping procedures. For each of the successive waveform protocols for which remapping data was obtained, shown are i) the number of patients that presented for the remapping procedures (bars), the percentage of PVs that remained durably electrically isolated (solid line), and the percentage of patients with all PVs durably electrically isolated (dashed line).

Figure 4: Kaplan-Meier Analysis of Freedom from Atrial Arrhythmias. Not including the 3-month blanking period, shown is the freedom for atrial arrhythmias – including any atrial fibrillation, atrial flutter or atrial tachycardia episode exceeding 30 seconds.

Figure 5: Tissue Specificity of Pulsed Field Ablation by Magnetic Resonance Imaging. A) Delayed gadolinium-enhanced MRI was performed immediately after the PFA procedure. On two different slices of the left atrium (top and middle), transmural enhancement of the ablated atrial tissue is observed, but there was a complete lack of enhancement of the immediately-adjacent esophagus. The bottom image shows a zoomed version of the esophagus with the enhanced atrial tissue (red arrowheads), and the non-enhanced esophageal tissue (yellow arrowheads). **B**) The corresponding post-PFA electroanatomic voltage amplitude map is shown, color-coded such as that purple (> 1.0 mV) represents normal tissue, and gray represents scar (< 0.1 mV). In addition, on oblique cuts of the delayed-enhanced MRI, circumferential, uninterrupted and transmural enhancement of all four PVs is observed. **C**) These four panels represent typical findings on T2-weighted MRI acutely after PFA. Intense edema is seen on all PVs, with no sign of injury to the adjacent esophagus. LA = left atrium, Ao = aorta, Eso = esophagus, LSPV = left superior PV, LIPV = left inferior PV, RSPV = right superior PV, RIPV = right inferior PV.

Online Movie: Three-Dimensional Reconstruction of Delayed-Enhancement on MR Imaging. The video displays a maximum intensity projection of a non-thresholded gadolinium delayed enhancement dataset acquired acutely after PFA. The yellow represents delayed enhanced tissue.

Table 1. Baseline Patient Characteristics

Characteristics	*IMPULSE* N=40	*PEFCAT* N=41	Total Cohort N=81
Age, years	58.5 ±9.0	57.6 ±12.1	58 ±10.7
Male, n (%)	28, (70%)	32, (78%)	60 (74%)
LA diameter, mm	41.0±4.3	41.4±5.6	41.2±5.0
LVEF, %	63.2±5%	63.3± 3.7%	63.3±4.3%
Hypertension, n (%)	20 (50%)	30 (73.2%)	50 (61.7%)
Diabetes, n (%)	3 (7.5%)	5 (12.2%)	8 (9.9%)
Stroke or TIA, n (%)	0 (0%)	3 (7.3%)	3 (3.7%)
CAD (MI / CABG), n (%)	1 (2.5%)	0 (0%)	1 (1.2%)
Anticoagulation			
Warfarin	15	17	32
NOAC	21	14	35
Aspirin	0	2	2
None	4	8	12
Antiarrhythmics			
Class I	21	25	46
Class II	28	27	45
Class III	1	0	1
None	8	4	12

* Plus-minus values are mean ± SD. AF = atrial fibrillation, CABG = coronary artery bypass grafting, CAD = coronary artery disease, LA = left atrium, LVEF = left ventricular ejection

fraction, MI = myocardial infarction, NOAC = novel oral anticoagulants, TIA= transient ischemic attack.

Table 2. Primary Endpoints

	IMPULSE N=40	*PEFCAT* N=41	Total Cohort N=81
Primary Feasibility			
Acute PV isolation, n (%)	40 (100%)	41 (100%)	81 (100%)
Primary Safety			
Total, n (%)	1 (2.5%)	0 (%)	1 (1.2%)
Death, n (%)	0 (0%)	0 (0%)	0 (0%)
Myocardial infarction, n (%)	0 (0%)	0 (0%)	0 (0%)
Diaphragmatic paralysis, n (%)	0 (0%)	0 (0%)	0 (0%)
Stroke or TIA, n (%)	0 (0%)	0 (0%)	0 (0%)
Other thromboembolism, n (%)	0 (0%)	0 (0%)	0 (0%)
Cardiac perforation or tamponade, n (%)	1 (2.5%)	0 (%)	1 (1.2%)
Vascular complications, n (%)	0 (0%)	0 (0%)	0 (0%)
Prolonged or repeat hospitalization, n (%)	0 (0%)	0 (0%)	0 (0%)
Heart Block, n (%)	0 (0%)	0 (0%)	0 (0%)
PV stenosis >70%, n (%)	0 (0%)	0 (0%)	0 (0%)
Atrio-esophageal fistula, n (%)	0 (0%)	0 (0%)	0 (0%)
Pericarditis requiring intervention, n (%)	0 (0%)	0 (0%)	0 (0%)
Pneumothorax, n (%)	0 (0%)	0 (0%)	0 (0%)
Pulmonary edema, n (%)	0 (0%)	0 (0%)	0 (0%)

Table 3: Procedural Characteristics

	Total Cohort (n=81)
Procedure time *	92.2 ± 27.4
Mapping time	18.2 ±10.3
Catheter dwell time	33.7 ± 16.6
Fluoroscopy time †	13.1 ± 7.6
Acute isolation success	315 of 315 PVs (100%)

* All time are expressed in minutes; † Data available on 77 of 81 pts

Table 4: Additional Safety Assessments

	No. of Patients with Assessment (n)	Findings
Esophageal findings		
Esophagogastroduodenoscopy	29	No esophageal lesions
Chest MRI	8	No esophageal enhancement
Brain MRI	13	Negative for DWI / FLAIR
Phrenic nerve		
Phrenic nerve assessment *	81	No paresis / palsy
Chest X-Ray at 3 months	37	No paresis / palsy
Pulmonary vein stenosis		
EAM at 3 months	52	No PV stenosis / narrowing
CT scanning at 3 months	29	No PV stenosis / narrowing

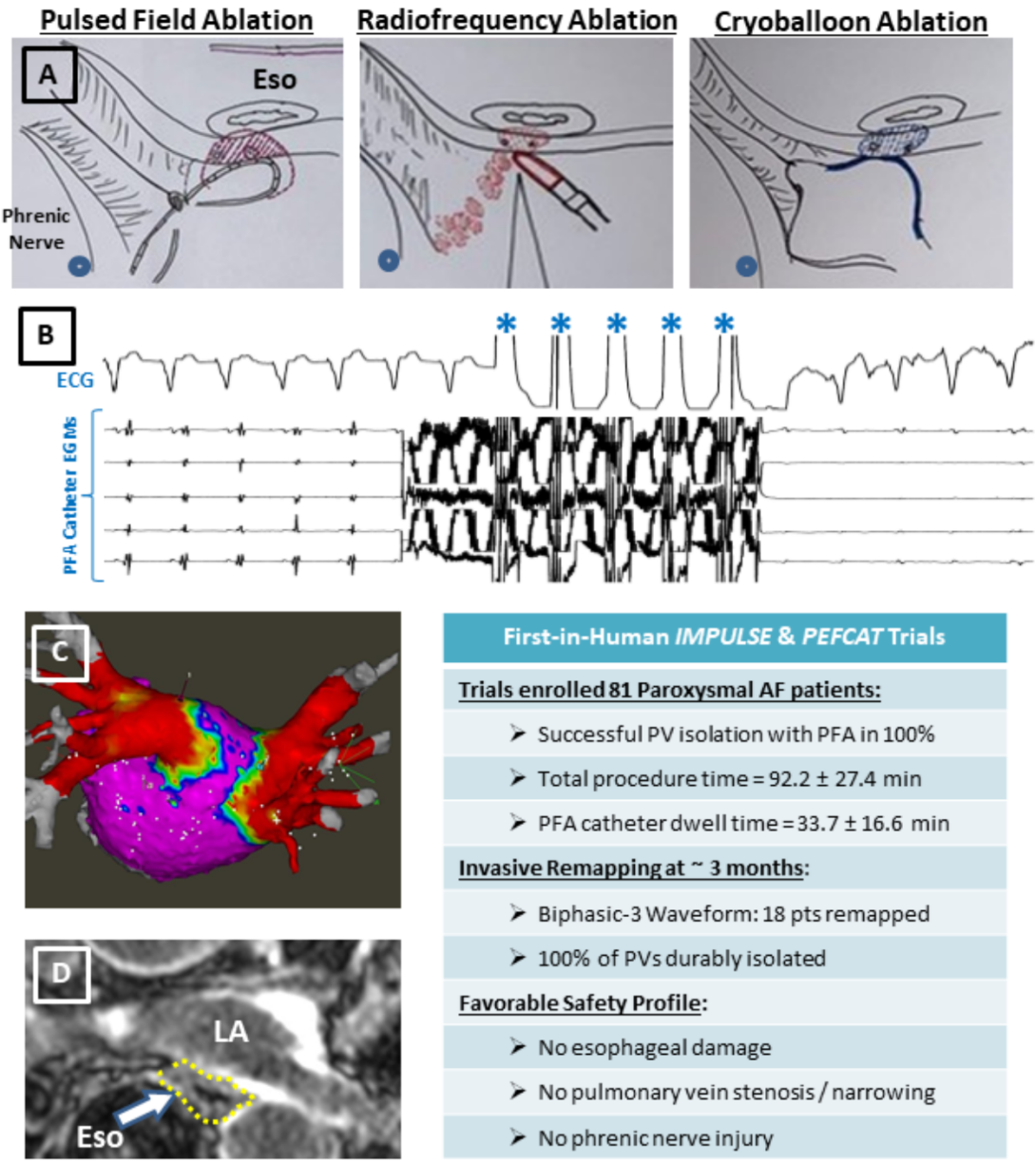
MRI = magnetic resonance imaging, DWI = diffusion weighted imaging, FLAIR = fluid attenuated inversion recovery, EAM = electroanatomical mapping, PV = pulmonary vein, CT = computed tomography

***** By either observation of diaphragmatic motion with patient inspiration, or by diaphragmatic capture with phrenic nerve pacing from within the superior vena cava.

Table 5: Dimensional Analysis of the Pulmonary Vein Diameters

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

* PVs that underwent additional RF ablation of PV reconnection gaps during the remapping procedure were excluded.



First-in-Human *IMPULSE* & *PEFCAT* Trials

Trials enrolled 81 Paroxysmal AF patients:

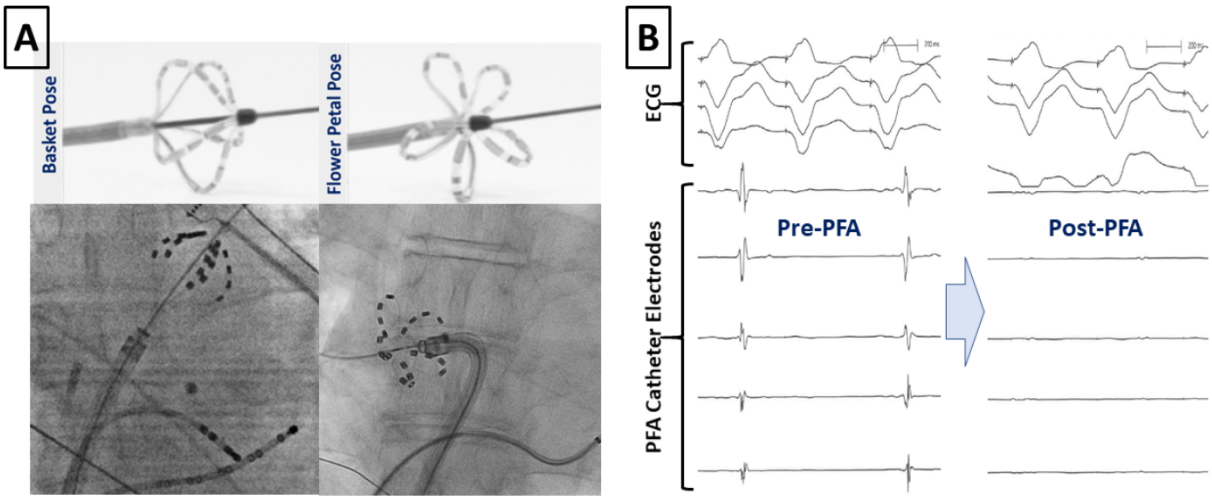
- Successful PV isolation with PFA in 100%
- Total procedure time = 92.2 ± 27.4 min
- PFA catheter dwell time = 33.7 ± 16.6 min

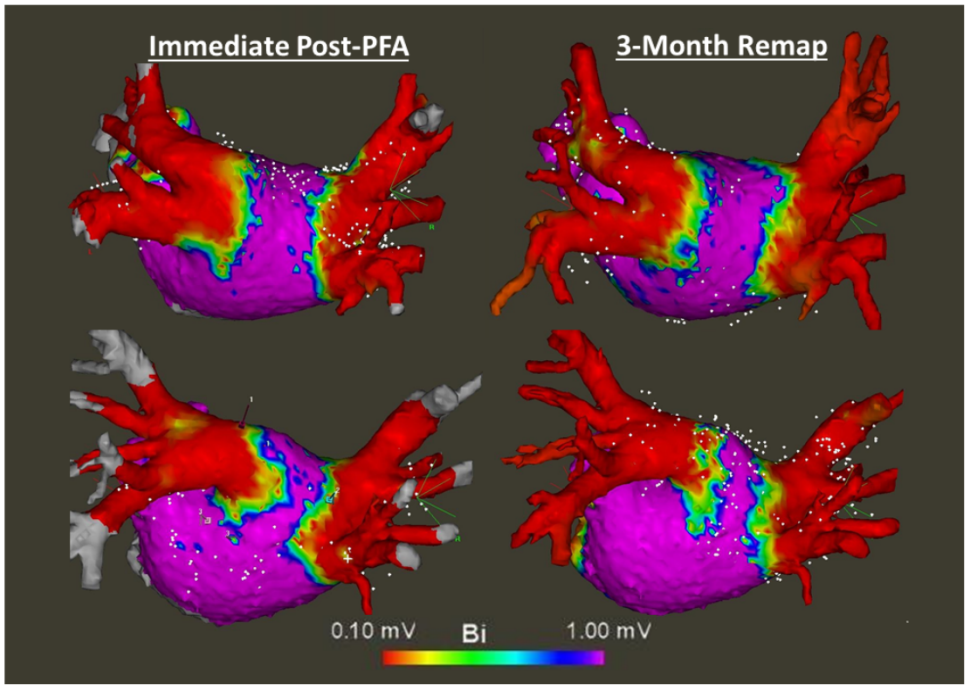
Invasive Remapping at ~ 3 months:

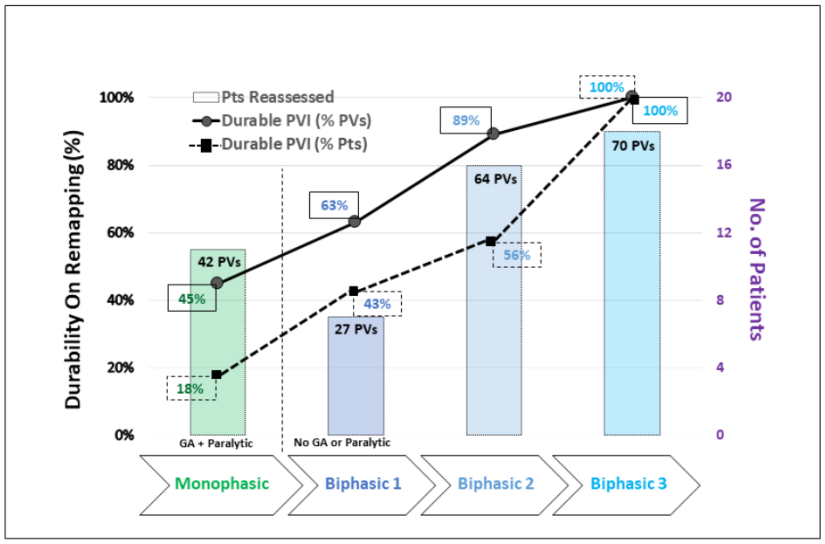
- Biphasic-3 Waveform: 18 pts remapped
- 100% of PVs durably isolated

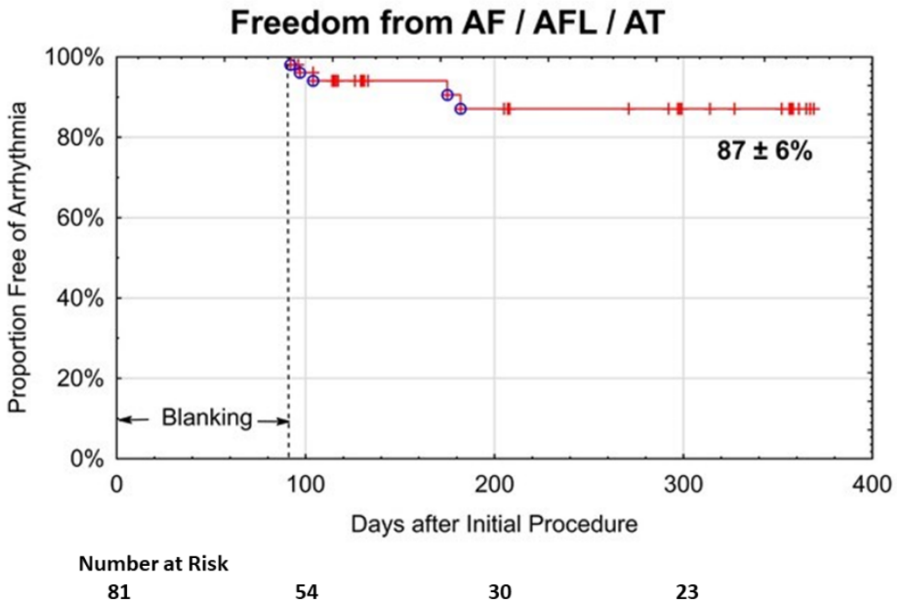
Favorable Safety Profile:

- No esophageal damage
- No pulmonary vein stenosis / narrowing
- No phrenic nerve injury

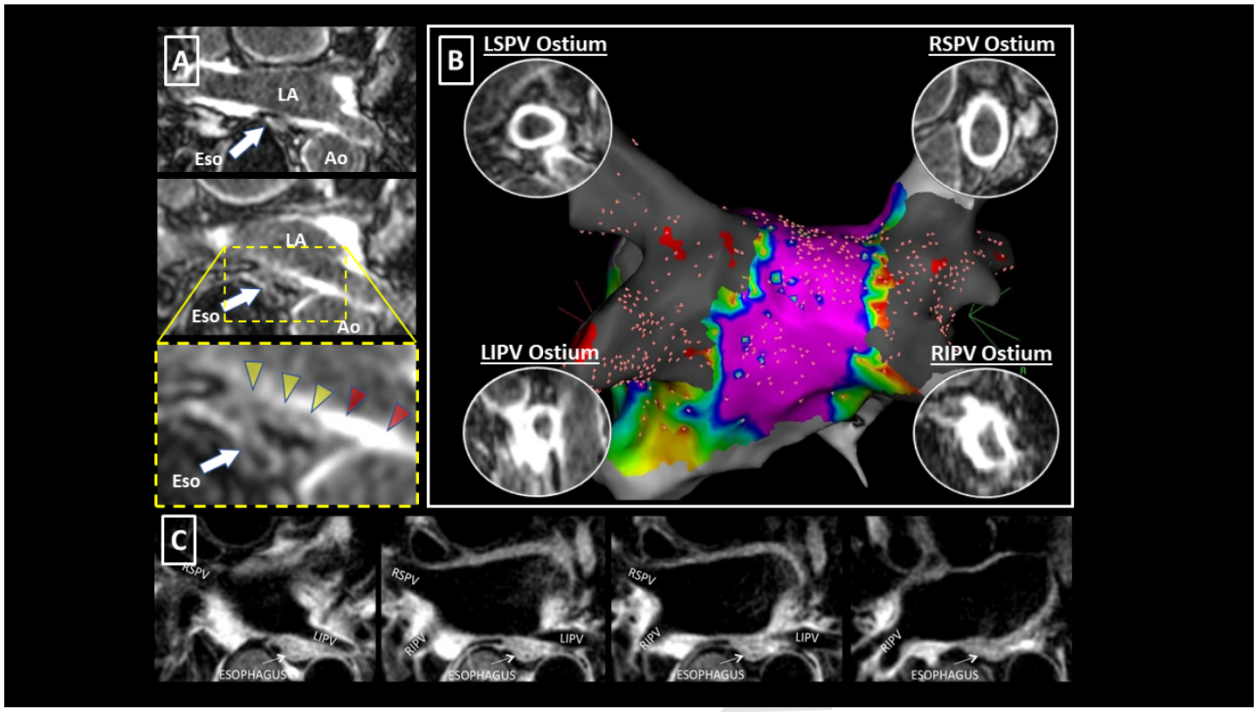


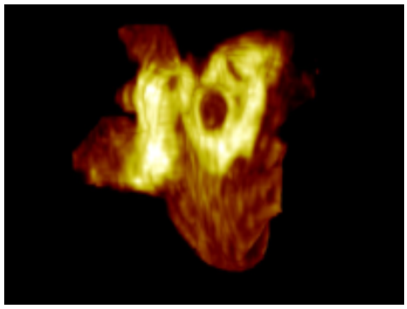






Number at Risk			
81	54	30	23





Pulsed Field Ablation for Pulmonary Vein Isolation: Lesion Durability and Chronic Safety

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Additional Conflicts of Interest

Vivek Reddy's disclosures with other medical companies not related to this manuscript include: Abbott (Consultant), Acutus Medical (Consultant, Equity), Affera (Consultant, Equity), Apama Medical (Consultant, Equity), Aquaheart (Consultant, Equity), Autonomix (Consultant, Equity), Axon (Consultant), Backbeat (Consultant, Equity), BioSig (Consultant, Equity), Biotronik (Consultant), Cardiofocus (Consultant), Cardionomic (Consultant), CardioNXT / AFTx (Consultant), Circa Scientific (Consultant, Equity), Corvia Medical (Consultant, Equity), East End Medical (Consultant, Equity), EBR (Consultant), EPD (Consultant, Equity), Epix Therapeutics (Consultant, Equity), EpiEP (Consultant, Equity), Eximo (Consultant, Equity), Impulse Dynamics (Consultant), Javelin (Consultant, Equity), Keystone Heart (Consultant, Equity), LuxCath (Consultant, Equity), Manual Surgical Sciences (Equity), Medlumics (Consultant, Equity), Medtronic (Consultant), Middlepeak (Consultant, Equity), Newpace (Equity), Nuvera (Consultant, Equity), Philips (Consultant), Stimda (Consultant), Surecor (Equity), Thermedical (Consultant), Valcare (Consultant, Equity), Vizara (Equity) and VytronUS (Consultant, Equity).

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Supplemental Table S1: Primary and Secondary Endpoints for *IMPULSE* and *PEFCAT*

IMPULSE	*PEFCAT*
Primary Safety Endpoints	**Primary Safety Endpoints**
Early onset (within 7 days of procedure) Death Myocardial infarction (MI) Diaphragmatic paralysis Stroke/ Transient Ischemic Attack (TIA)/ Thromboembolism Pericarditis requiring intervention (major) Cardiac Tamponade/Perforation Vascular Access Complications Pulmonary vein (PV) stenosis within 7 days Atrio-esophageal fistula within 7 days Pneumothorax Pulmonary edema Hospitalization (initial or prolonged)* Heart block	**Early onset (within 30 days of procedure)** Death Myocardial infarction (MI) Persistent diaphragmatic paralysis Stroke or transient ischemic attack (TIA) Peripheral or organ thromboembolism Pericarditis Cardiac tamponade / perforation Vascular access complications Hospitalization (initial or prolonged)* Heart block **Late onset** Pulmonary vein stenosis (> 70% diameter reduction from baseline) Atrio-esophageal fistula
Secondary Safety Endpoints	**Secondary Safety Endpoints**
The proportion of subjects reporting one or more SAEs for each follow-up interval. The intervals will include the period from PEF ablation procedure through: 1 month follow-up 1 month follow-up visit through the 3 month follow-up 3 month follow-up visit through the 6 month follow-up 6 month follow-up visit through the 12 month follow-up	Proportion of subjects reporting one or more device- or procedure-related SAEs, as assessed at 30 days, 75 days, 6 months and 12 months of follow-up. Proportion of subjects with stroke/TIA through 12 months. Proportion of subjects with major bleeding related to anticoagulation treatment through 12 months. Proportion of subjects requiring cardioversion through 12 months. Proportion of subjects requiring an arrhythmia-related hospitalization through 12 months.
Primary Feasibility Endpoints	**Primary Feasibility Endpoints**
Proportion of subjects that achieved pulmonary vein isolation (PVI) using PFA	Proportion of subjects that achieved pulmonary vein isolation (PVI) using PFA as assessed by entrance and/or exit block performed ≥ 20 minutes after the last PVI lesion is made
Secondary Feasibility Endpoints	**Secondary Feasibility Endpoints**

Proportion of subjects that achieve electrical isolation of the pulmonary veins assessed during an electroanatomical mapping procedure performed 3-months following the index procedure.	Proportion of subjects that achieve persistent electrical isolation of all initially ablated pulmonary veins assessed during an electroanatomical mapping procedure performed 75 days following the index procedure Proportion of subjects that achieve therapeutic success, defined as freedom from a) AF, AFL or AT from blanking period through assessment, or ablation for AF/AFL/AT using the study device, b)at any time: ablation for AF/AFL/AT with a non- study device Therapeutic success will be assessed from the end of the blanking period at months 6 and 12 and will be subdivided by on / off antiarrhythmic drugs post blanking period.
Additional Observations	**Additional Endpoints**
Proportion of subjects that achieve freedom from AF, AFL and AT following the blanking interval through 12 months.	Proportion of all ablated pulmonary veins that are isolated at the index procedure using the study device. Proportion of all ablated pulmonary veins acutely isolated using the study device that remains isolated at the 75-day remapping procedure.

MI- Myocardial Infarction, TIA- Transient ischemic attack, PV- pulmonary vein, SAE serious adverse events, PVI- pulmonary vein isolation, PFA- pulse field ablation, AF- atrial fibrillation, AFL- atrial flutter, AT- atrial tachycardia

* Excludes hospitalization (initial & prolonged) solely due to arrhythmia (AF/AFL/AT) recurrence or due to non-urgent cardioversion (pharmacological or electrical). Hospitalization excludes visits to hospital associated outpatient facilities such as clinics or emergency wards.

Supplemental Table S2: Inclusion and Exclusion Criteria for *IMPULSE* and *PEFCAT*

IMPULSE	*PEFCAT*
Inclusion criteria (Required to meet all of the criteria)	**Inclusion criteria (Required to meet all of the criteria)**
Patients with PAF who have had at least two (2) episodes of PAF documented within one (1) year prior to enrollment Documentation may include ECG, TTM, HM, or telemetry strip Patients should have failed at least one antiarrhythmic drug (AAD; class I- IV) as shown by recurrent symptomatic AF, or intolerance to the AAD or AV nodal blocking agents	Patients with symptomatic PAF who have at least 30 seconds of AF recorded within one year prior to enrollment and with at least ≥ 2 episodes within 6 months of enrollment Documentation may include ECG, TTM, HM, implanted devices or telemetry strip Patients should have failed at least one antiarrhythmic drug (AAD; class I – IV) as shown by recurrent symptomatic AF, or intolerance to the AAD or AV nodal blocking agents
Patients who are ≥ 18 and ≤ 70 years of age on the day of enrollment	Patients who are ≥ 18 and ≤ 75 years of age on the day of enrollment
Is willing and capable of providing informed consent to undergo study procedures Is willing to participate in all examinations and follow-up visits and tests associated with this clinical study All patients are to be members of or covered under a French national health insurance plan Received a standard cardiac work up and is an appropriate candidate for an investigational procedure as determined by study investigators.	Is willing and capable of providing informed consent to undergo study procedures Is willing to participate in all examinations and follow-up visits and tests associated with this clinical study Lives locally
Exclusion criteria	**Exclusion criteria**
Use of amiodarone within 3 months prior to enrollment	Use of amiodarone within 3 months prior to enrollment
AF secondary to electrolyte imbalance, thyroid disease or reversible or non-cardiac causes	AF secondary to electrolyte imbalance, thyroid disease, alcohol abuse or other reversible / non-cardiac causes
AF episodes lasting > 7 days.	AF that is persistent (by diagnosis or duration > 7 days) or if requiring ≥ 3 cardioversions in the preceding 12 months

Cardiac anatomical exclusions by imaging within 3 months prior to enrollment: Left atrial anteroposterior diameter ≥ 5.5 cm as documented by transthoracic echocardiography (TTE) or computed tomography (CT) Left ventricular ejection fraction ≤ 40% as documented by TTE	Cardiac anatomical exclusions by imaging within 3 months prior to enrollment: Left atrial anteroposterior diameter ≥ 5.0 cm as documented by transthoracic echocardiography (TTE) or computed tomography (CT) Left ventricular ejection fraction ≤ 40% as documented by TTE
Uncontrolled brady-arrhythmias, ventricular arrhythmias Previous ablation for AF. Prosthetic heart valve NYHA class IIIb or IV CHF and/or any heart failure Hospitalization within 3 months prior to enrollment. Patient has a left atrial appendage device Prior history of pericarditis or pericarditis within 3 months based on the TTE examination. Prior history of instrumentation of the left atrium (previous ablation, ASD closure) Prior history of rheumatic fever History of untreated and serious hypotension, bradycardia or chronotropic incompetence	Clinically significant arrhythmias other than AF Previous endocardial/epicardial ablation or surgery for AF Prosthetic heart valve NYHA Class III or IV CHF Left atrial appendage device or occlusion History of pericarditis Atrial or ventricular septal defect closure Atrial myxoma History of rheumatic fever Significant or symptomatic hypotension, bradycardia or chronotropic incompetence Hemodynamically significant valvular disease
History of abnormal bleeding and/or clotting disorder	History of abnormal bleeding and/or clotting disorder
Contraindication to anticoagulation (i.e., heparin, dabigatran, Vitamin K Antagonists such as warfarin).	Contraindication to, or unwillingness to use, systemic Anticoagulation
Pregnant and/or nursing women.	Women of childbearing potential who are pregnant, lactating or not using birth control
Patients with any other significant uncontrolled or unstable medical condition (such as, hyperthyroidism). Solid organ or hematologic transplant, or currently being evaluated for an organ transplant	Serious or untreated medical conditions that would prevent participation in the study, interfere with assessment or therapy, or confound data or its interpretation, including but not limited to Solid organ or hematologic transplant, or currently being evaluated for an organ transplant

History of pulmonary hypertension with Pulmonary systolic artery pressure >50 mm Hg, severe chronic obstructive pulmonary disease or restrictive lung disease	Severe lung disease, pulmonary hypertension, or any lung disease involving abnormal blood gases or significant dyspnea
Estimate glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2 or has ever received dialysis.	Chronic renal insufficiency of < 60 mL/min/1.73 m2, any history of renal dialysis, or history of renal transplant
History of severe chronic gastrointestinal problems involving the esophagus, stomach and/or untreated acid reflux	Clinically significant gastrointestinal problems involving the esophagus, stomach and/or untreated acid reflux
Active malignancy or history of treated cancer within 24 months of enrollment	Active malignancy or history of treated cancer within 24 months of enrollment
Clinically significant infection or sepsis	Clinically significant infection
Life expectancy less than one year	Life expectancy less than one year
Clinically significant psychological condition that in the physician's opinion would prohibit the subject's ability to meet the protocol requirements	Clinically significant psychological condition that in the investigator's opinion would prohibit the subject's ability to meet the protocol requirements
Enrolled in another cardiac clinical study that would interfere with this study	Current or anticipated enrollment in any other clinical study
Body mass index > 35	Body Mass Index > 35
Vulnerable subjects for instance, persons under tutelage and guardianship.	Distorted cardiac anatomy due to congenital heart disease Contraindications to CT or MRI Sensitivity to contrast media not controlled by Premedication
Any of the following within 3 months of enrollment: Major surgery, Myocardial infarction, Unstable angina, Percutaneous coronary intervention, Sudden cardiac death event, left atrial thrombus that has not resolved, implant of pacemaker, ICD or CRT History of stroke or TIA within prior 6 months	Any of the following within 3 months of enrollment: Myocardial infarction, Unstable angina, Percutaneous coronary intervention, Heart surgery (coronary artery bypass grafting/atriotomy), heart failure hospitalization, stroke or TIA, significant bleeding, pericarditis /effusion, left atrial thrombus, implant of pacemaker, ICD or CRT

PAF- paroxysmal atrial fibrillation, AF- atrial fibrillation, ECG- electrocardiogram, TTM- transtelephonic monitoring,, HM- Holter monitoring ,AAD- antiarrhythmic drugs, NYHA- New York Heart Association, CHF- congestive heart failure , TTE- transthoracic echocardiography, TIA, ASD- atrial septal defect, CT- computer tomography, MRI- magnetic resonance imaging, ICD – implantable cardiac defibrillator, CRT- cardiac resynchronization therapy, TIA- transient ischemic attack

Supplemental Table S3: Details of the Various Waveform Cohorts

	Monophasic	Biphasic-1	Biphasic-2	Biphasic-3	Biphasic-3x
Waveform polarity	Monophasic	Biphasic	Biphasic	Biphasic	Biphasic
Waveform composition *	Protocol A	Protocol B	Protocol C	Protocol D	Protocol D
No. of heartbeats over which pulses are delivered	4	10	8	5	5
Voltage amplitude	900 V	1800 V	1800 V	2000 V	1800 V – 2000 V
Catheter pose	Flower	Flower	Flower and Basket	Flower and Basket	Flower and/or Basket

***** Waveform composition refers to the proprietary details of the actual pulse sequence.

Supplemental Table S4: Procedural Characteristics by Waveform Cohorts

	Monophasic (n=15)	Biphasic-1 (n=8)	Biphasic-2 (n=17)	Biphasic-3 (n=20)	Biphasic-3x (n=21)
Procedure time*	82.3±10.9	91.1±18.1	123.3±36.2	84.1±16.6	82.8±21.4
Mapping time	23.6±10.1	20.5±7.9	24.9±14.9	12.1±2.7	13.9±5.7
Catheter dwell time	26.9±4.4	29.5±11.3	60.8±18.0	30.1±7.9	24.5±6.5
Fluoroscopy time	12.0±4.0	13.6±4.6	24.2±8.0	9.5±2.7	8.2± 3.1
Acute isolation success	100% (57/57PVs)	100% (31/31PVs)	100% (68/68PVs)	100% (78/78PVs)	100% (81/81PVs)

* All times are in minutes

Supplemental Table S5: Adverse Events

Event	Patient Cohort (n=81) n (%)
Ablation Catheter Insertion	**4 (4.9%)**
Hematoma	1 (1.2%)
AV Fistula *	2 (2.5%)
DVT	0 (0%)
Air embolism †	1 (1.2%)
Catheter Manipulation within the Heart	**1 (1.2%)**
Cardiac tamponade §	1 (1.2%)
TIA	0 (0%)
Myocardial infarction	0 (0%)
Complete heart block	0 (0%)
Valvular damage	0 (0%)
Ablation-related events	**1 (1.2%)**
Phrenic Nerve Injury	0 0%)
PV Stenosis > 75%	0 (0%)
AE Fistula	0 (0%)
Pericarditis-related pain	1 (1.2%)

* One patient required vascular surgical repair, and the other didn't require intervention.

† Air inadvertently entered the circulation from the transseptal sheath, prior to introducing the PFA catheter. This resulted in transient ST elevation and ventricular fibrillation requiring defibrillation. The ST segment changes resolved spontaneously, a coronary angiogram revealed no obstruction or slow flow, and intracardiac ultrasound revealed normal ventricular wall motion and ejection fraction. The patient was normal on neurological assessment, so the procedure was continued without further incident.

§ This patient is the same as the primary adverse event described for the Primary Safety Endpoint.

Supplemental Table S6: Durability of PV Isolation from Previous Studies

	No. of Pts	No. of Pts w/ Remaps	Pt. Cohort	Ablation Tool	Durability of PVI	
					% of PVs Isolated	% of Pts (with all PVs Isolated)
Dukkipati et al [1]	56	52	Paroxysmal AF	Visually guided laser balloon	86%	62%
EFFICAS I [2]	46	40	Paroxysmal AF	Force (blinded) Irrigated RF	51%	35%
EFFICAS II [3]	26	24	Paroxysmal AF	Force sensing Irrigated RF	85%	63%
SUPIR [4]	21	19	Paroxysmal AF	2nd Generation cryoballoon	91%	79%
GAP-AF [5]	117	93	Paroxysmal AF	Irrigated RF	n/a	30%
LIBERATION [6]	52	52	Persistent AF	Irrigated RF	n/a	62%
Miyazaki et al [7]	32	32	Paroxysmal AF	2nd Generation cryoballoon	73%	34%
TRAC-AF [8]	35	23	Paroxysmal AF	Temp-Controlled Irrigated RF	85%	74%
PRESSURE [9]	40	40	Paroxysmal AF	Force sensing Irrigated RF	74%	38%
PRAISE [10]	40	40	Paroxysmal AF	Force sensing Irrigated RF	93%	78%
Jefairi et al [11]	51	51	Paroxysmal AF	Irrigated RF ***or*** Multielectrode Irrigated RF *	51%	12%

[1] Dukkipati SR, Neuzil P, Kautzner J, et al. *Heart Rhythm* 2012;9(6):919-25; [2] Neuzil P, Reddy VY, Kautzner J, et al. *Circ Arrhythm Electrophysiol*. 2013;6:327-333; [3] Kautzner J, Neuzil P, Lambert H, et al. *Europace* 2015;17:1229–1235; [4] Reddy VY, Sediva L, Petru J, et al. *J Cardiovasc Electrophysiol* 2015;26:493-500; [5] Kuck KH, Hoffmann BA, Ernst S, et al. *Circ Arrhythm Electrophysiol* 2016;9:e003337; [6] Bai R, DiBiase L, Mohanty P, et al, *Heart Rhythm* 2016;13:132–140; [7] Miyazaki S, Taniguchi H, Hachiya H, et al, *Circ Arrhythm Electrophysiol* 2016;9:e003879; [8] Iwasawa J, Koruth JS, Petru J, et al, *J Am Coll Cardiol* 2017;70:542–53; [9] Das M, Wynn GJ, Saeed Y, et al, *J Am Coll Cardiol EP* 2017;3(6):602-611; [10] Hussein A, Das M, Riva S, et al, *Circ Arrhythm Electrophysiol* 2018;11(9):e006576; [11] Jefairi NA, Camaioni C, Sridi S, et al, *J Cardiovasc Electrophysiol* 2019 Mar 7. doi: 10.1111/jce.13908.

* The Multielectrode Irrigated RF catheter refers to the nMARQ catheter (Biosense Webster Inc)

Abbreviations: Pts = patients, PV = pulmonary vein, PVI = pulmonary vein isolation, AF = atrial fibrillation, RF = radiofrequency

<u>Supplemental Figure S1</u>: Pulmonary Vein Diameters Pre- and Post- PFA

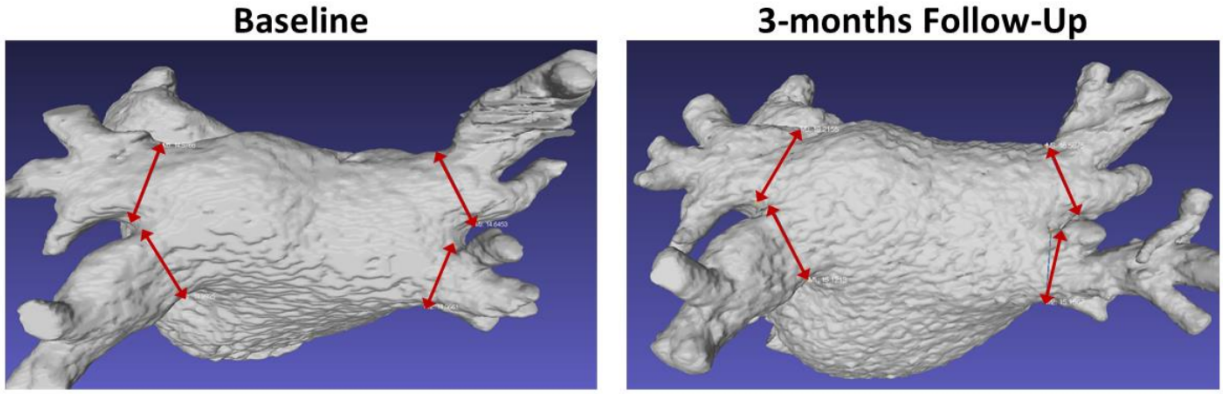

Figure S1: Pulmonary Vein Diameters Pre- and Post- PFA. For patients that underwent both baseline and 3-month CT scanning, the CT scan Dicom datasets were segmented and then imported into a software that allowed manipulation and detailed analysis of the 3D image (Meshlab). After matching the baseline and 3-month images side-by-side, the ostial PV diameters were measured.

Supplemental Figure S2: Thresholds of Various Cell Types to PFA

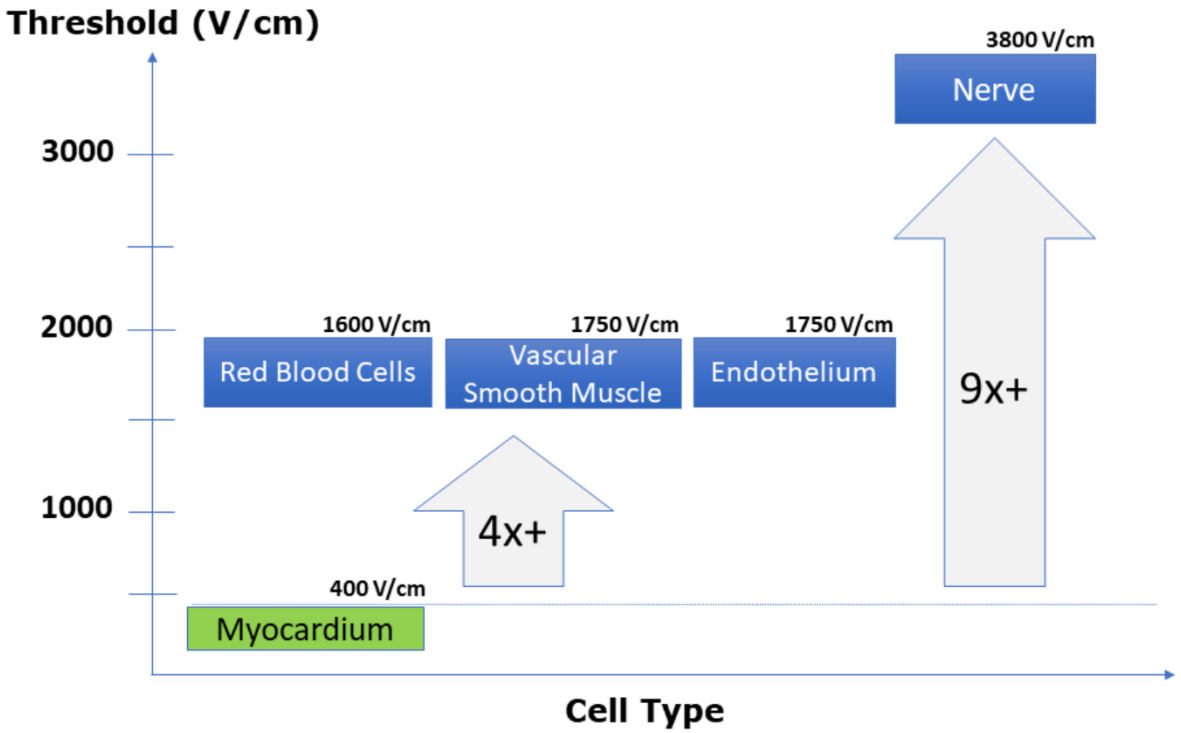

Figure S2: Thresholds of Various Cell Types to PFA. The relative sensitivity of myocardial cells to PFA is shown relative to various other cell types. The data is based on the electrical field threshold values obtained from the literature: Kaminska I, et al, *Gen. Physiol. Biophys.*, 31 (2012) 19 – 25. Bao N, et al, *Interg. Biol. (Camb).*, 2 (2-3) (2010) 113 – 120; Maor E, et al, *PLoS ONE* Vol. 4, Issue 3 (March 2009) e4757. (abstr); Li W, *PLoS ONE*, Vol. 6, Issue 4 (April 2011), e18331. Note that these values were observed with different delivery parameters / waveforms.