Pulsed-Field Ablation: What Are the Unknowns and When Will They Cease to Concern Us?

Nathaniel Steiger[1] and Jorge Romero[1]

[1]Brigham and Women's Hospital/Harvard Medical School.

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Nathaniel A. Steiger* and Jorge Romero, MD*

**Cardiac Arrhythmia Center, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

Corresponding author:

Jorge E. Romero, MD, FACC, FHRS

Director, Arrhythmia & Electrophysiology Research

Associate Director, Ventricular Arrhythmia Program

Brigham and Women's - Heart & Vascular Center

Member of the Faculty at Harvard Medical School

Tel: (857) 307-4000 / Fax: (857) 306-1944

75 Francis Street, Boston, MA 02115

jeromero@bwh.harvard.edu

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Catheter ablation (CA) is the mainstay therapy for the maintenance of sinus rhythm in patients with paroxysmal and persistent atrial fibrillation (AF). Pulmonary vein isolation (PVI) has remained the most frequently used treatment strategy for this entity. Radiofrequency ablation (RFA), which has been in use for over 3 decades, is the most frequent energy source implemented for CA followed by cryoablation and laser, with alternative energy sources (including focused ultrasound, and microwave energy) used mainly in investigational studies with limited clinical applicability. The understanding of RF biophysics enables electrophysiologists to titrate tissue current delivery to control lesion surface area and depth. Nonetheless, in the case of PVI, RFA is associated with several potential complications or significant adverse events, including pulmonary vein stenosis, incomplete circumferential ablation, and thermal damage to adjacent structures (e.g., right phrenic nerve, esophagus), which limits lesion efficacy to maintain patient safety.

Although cryoablation was introduced as a faster and potentially safer alternative to achieve a complete PVI, it was also associated with a significant risk of phrenic nerve and esophageal injury and offers no real advantages in terms of arrhythmia recurrence (1). Use of direct current (DC) delivered through diagnostic catheters to elicit cellular destruction dates to the early days of CA. Nonetheless, the large amount of energy necessary to produce tissue destruction (up to 300 J - by what was considered to be "fulguration") was painful and the delivery of large monophasic unipolar defibrillation waveforms from small surface area diagnostic electrodes resulted in hazardous effects (2-4). These included the formation of gas vapor globe and arcing at the tip of the electrode, which produced barotrauma related complications including myocardial perforation and tamponade and formation of non-homogeneous lesions, which were proarrhythmic (5,6). The mechanism of lesion formation during DC ablation was later determined to be irreversible electroporation (IRE) (7,8). Subsequent studies used lower energy to achieve successful ablation with a reduced risk of adverse events (9-11). Nevertheless, before these improvements could be adopted, RFA became available and quickly achieved widespread acceptance given the ability to provide a controlled amount of energy, a greater effectiveness and a lower incidence of life-threatening complications compared to DC ablation.

Recently, ablation using electric fields generated by short pulses of high energy, known as pulsed field ablation (PFA), has shown promise by specifically targeting myocardium without generating heat or damaging adjacent tissue.

Membrane Electroporation Biophysics

Cell membranes are made up of a phospholipid bilayer that behave as a 2-dimensional aqueous solution and serve as a barrier to polar molecules. This stable structure protects the cell from its environment and is integral to the cell's function and survival. However, the stability of the phospholipid bilayer is reduced when exposed to external electric fields and leads to the formation of nanopores, which can allow transfer of ionic particles between the external environment and cell interior, known as electroporation. The lifetime of nanopores can range from milliseconds to minutes after the electric field is removed and is related to the electric field strength and duration (12). The cell may remain viable if the cell membrane recovery is rapid, termed reversible electroporation. However, if pores formed in the cell membrane are sufficient in number or have a long lifetime, this may lead to irreversible pore formation and cell death, termed irreversible electroporation (13).

Myocardial cells are uniquely sensitive to high voltage, short duration electric fields with electroporation thresholds of 268-375 V/cm compared to other tissue types including nerves, endothelium, smooth muscle (i.e., vessels, esophagus), and blood cells, all of which have electroporation thresholds of greater than 1600V/cm (figure 1) (14-18). However, these thresholds were evaluated with different experimental designs, and they may not be applicable with different pulse waveforms and electrode configurations. Furthermore, the threshold of reversible electroporation has not been well defined.

Pulse Waveform and Electrode Characteristics

The pulse waveforms used to generate an electric field can have many different characteristics including voltage amplitude, pulse width, cycle period, voltage polarity (monophasic vs. biphasic), electrode polarity (unipolar vs. bipolar), and number of pulses delivered in a train **(Figure 1**). There is limited data evaluating the impact of how each of these variables affect lesion safety and efficacy. The use of biphasic waveforms delivered with a high frequency pulse train have been found to have less skeletal muscle stimulation, which is highly desirable to avoid significant map shifts that may be uncorrectable. Nonetheless, biphasic waveforms may require a greater number of pulse trains to achieve a similar lesion size compared to monophasic pulses [19].

Furthermore, electrode polarity has an impact on lesion formation. The use of a unipolar configuration has been shown to create deeper lesions compared to a bipolar configuration in a vegetable model [20]. Similarly, the electrode shape can have an impact on electric field generation. A torus (surface generated by revolving a circle in three-dimensional space about an axis that is coplanar with the circle) may allow for reduced electric field attenuation and delivery of deeper lesions compared to standard ring electrodes

(two-dimensional object)**(Figure 1)** [21]. Future work is needed to better understand the implications of each of these parameters on patient safety and lesion efficacy.

In-Vivo Biphasic, Bipolar Pulsed Field Ablation Safety and Efficacy

In this issue of *The Journal of Cardiovascular Electrophysiology* , Hsu et al. evaluated the safety and efficacy of delivering PFA left atrial lesions in an *in-* vivo porcine model [22]. They delivered PFA with a novel 10-electrode irrigated circular catheter and pulse generator that is integrated with the CARTO mapping system (Biosense Webster, Irvine, California). PFA was delivered in 8 swine and included PFA delivered at (1) a PV ostium, (2) directly inside a PV to assess for stenosis, (3) over the phrenic nerve in the right atrium to assess for phrenic nerve injury, (4) lateral mitral valve annulus to assess for valvular damage, and (5) in the aorta adjacent to the esophagus to assess for esophageal injury. The swine were survived for 30 days and were remapped prior to being euthanized for histologic examination.

The pulse field waveform was delivered in a bipolar configuration alternating between different catheter electrodes in trains of biphasic pulses with a total application duration of approximately 250 msec. The authors report that the pulse generator was set to 1800V. However, it is not clear if this represents the amplitude for each electrode pair or if this is divided between multiple electrodes simultaneously. The pulse width, duty cycle, and the voltage amplitude of the waveform between each bipolar electrode pair are not described.

We congratulate the authors on this study, which adds to the growing body of evidence supporting the safety and efficacy of PFA. Hsu et al. showed that PFA did not cause collateral tissue damage acutely or at 30 days despite delivery of numerous PFA lesions to vulnerable areas. There was no pulmonary vein stenosis, phrenic nerve injury, mitral valvular damage, esophageal injury, or reduction in left ventricular function.

PFA lesions delivered at PV ostia demonstrated excellent efficacy with PV isolation acutely and durable isolation at 30 days in all swine and histology showing circumferential, transmural necrosis and repair.

Regarding safety, one of the potential issues with electroporation is the phenomenon of arcing, where energy above a given threshold results in rapid gas accumulation that results in a shock wave that can cause significant barotrauma [23]. The arcing threshold may be different for a given waveform and catheter design and should be carefully evaluated for each PFA system. In the current study by Hsu et al, there was no occurrence of thrombus and/or charring on the catheter tip, pericardial effusion and/or cardiac tamponade, steam pop events, or mural thrombus (on intracardiac echocardiography [ICE] during the procedure nor during gross pathology), no incidence of clinically significant mechanical tissue injury was noted from gross pathology, and no incidence of clinically significant thrombo-emboli was found in upstream and downstream organs nor within the heart. Silent cerebral infarctions (SCI) have been described in up to 67% of patients undergoing CA for AF and are defined as the presence of asymptomatic cerebral lesions detected with imaging (i.e., magnetic resonance imaging) studies (24). As PFA is associated with micro-bubble formation (probably due to electrolysis), there is a concern of SCI associated with these micro-bubbles. Nonetheless, a canine model failed to demonstrate SCI after PFA was administered in the ascending aorta (25). Moreover, Reddy et al failed to find SCI in the 13/81 patients who underwent cerebral MRI after PFA in the IMPULSE/PEFCAT trial (26). However,

using a lattice catheter, postprocedural brain MRI revealed diffusion-weighted imaging+/fluid-attenuated inversion recovery- and diffusion-weighted imaging+/fluid-attenuated inversion recovery+ asymptomatic lesions in observed in 9.8% and 5.9% of patients, respectively (27). Further studies and trials are needed to clarify this important dilemma.

The authors delivered supratherapeutic PFA lesions directly adjacent to the phrenic nerve from the endocardium. No acute injury was seen, nor was any injury found during gross pathology. This data is encouraging and may allow ablation of cardiac tissue that previously would have been prohibitively risky with RF, such as treating atrial tachycardias originating from the Crista terminalis, which frequently are near the right phrenic nerve. Currently, complex and risky procedures including epicardial access with devi-

ation/protection of the phrenic nerve using air, saline, deflectable sheaths and balloons are the only option for these patients.

There were no incidents of PV narrowing on the same day or 30 days post PFA application when

the vein was targeted for isolation via ablation delivered to the ostium, nor when ablation was performed directly inside of the vein, as demonstrated by X-ray, ICE, and by flow velocity data. This corroborates the work by Howard et al, hypothesized that pulsed field ablation (PFA) would reduce PV stenosis risk and collateral injury compared with irrigated radiofrequency ablation (IRF). A more precise method of evaluating PV stenosis was developed that includes the use of 3-dimensional modeling based on computed tomography angiography with triplicate measures of cross-sectional area at the distal PV and ostial ablation sites. PV measurements were made pre-ablation and at 2-, 4-, 8-, and 12-weeks post-ablation to provide a detailed time course of the progression of PV stenosis from radiofrequency ablations while showing negligible changes in dimensions in pulsed field ablation treated sites [28].

There was no evidence of esophageal injury despite delivery of supratherapeutic PFA lesions adjacent to the esophagus from the aorta. The esophagus in all animals showed no injury to the mucosa, muscularis or serosa on histology after surviving the animal for 30 days. This is consistent with prior *in vivo* studies showing no esophageal injury despite administering high doses of PFA adjacent to the esophagus and in human trials showing no evidence of esophageal lesions or enhancement on EGD or chest CMR (26, 29).

The Future of PFA

Thus far, published data has shown that PFA creates effective and durable lesions with a favorable safety profile that spares nerves, vasculature, and the esophagus. However, there are still many unknowns, and our understanding of electroporation biophysics continues to grow. Future work is needed to understand how pulse waveform parameters, electrode shape, polarity, and contact force impact myocardial lesion formation. Better understanding of these variables may allow the operator to titrate PFA energy to a desired lesion shape while limiting the risk of arcing. Furthermore, it is not clear if the irreversible electroporation threshold for the conduction system is different from myocardium. Understanding the reversible and irreversible electroporation thresholds for different myocardial tissues would be useful for delivering test lesions. The future of PFA is promising, yet it is important that we have a solid fundamental understanding of the biophysics before it becomes universally adopted as the next ablative energy, as "a matter that becomes clear ceases to concern us." – Friedrich Nietzche. A standardized way to report electrical pulse waveforms is eagerly awaited/needed so that different PFA strategies can be compared.

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