STATE-OF-THE-ART REVIEW

Catheter-Based Electroporation
A Novel Technique for Catheter Ablation of Cardiac Arrhythmias

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ABSTRACT

Catheter ablation of arrhythmias is now standard of care in invasive electrophysiology. Current ablation strategies are based on the use of thermal energy. With continuous efforts to optimize thermal energy delivery, effectiveness has greatly improved; however, safety concerns persist. This review focuses on a novel ablation technology, irreversible electroporation (IRE), also known as pulsed-field ablation which may be a safer alternative for arrhythmia management. Pulsed-field ablation is thought to be a nonthermal ablation that applies short-duration high-voltage electrical fields to ablate myocardial tissue with high selectivity and durability while sparing important neighboring structures such as the esophagus and phrenic nerves. There are multiple ongoing studies investigating the potential superior outcomes of IRE compared to radiofrequency ablation in treating patients with atrial and ventricular arrhythmias. In this review, we describe the current evidence of preclinical and clinical trials that have shown promising results of catheter-based IRE. (J Am Coll Cardiol EP 2023; - - - -) © 2023 by the American College of Cardiology Foundation.

Catheter-based irreversible electroporation (IRE) is a promising novel ablation energy source that has earned substantial attention in the past few years. For decades electroporation has been used as a treatment modality in various medical fields such as oncology and for drug therapy. Before radiofrequency ablation (RFA) was introduced in cardiac electrophysiology in the late 1980s, direct current catheter-based electroporation was used to treat cardiac arrhythmias. However, widespread use was limited due to several unintended consequences such as the creation of an electrically isolating vapor globe that caused sparking (arcing) followed by damaging pressure waves, barotrauma, and proarrhythmic side effects. Most of these issues were largely mitigated by the eventual adoption of RFA.

More recently, it has been shown that cautious use of lower-energy electroporation packets of short duration in multiple pulses can be used to produce effective ablation lesions while avoiding arcing and barotrauma. This stimulated interest and advancement in electroporation which may obviate the need for thermal ablation. As a result, various catheter platforms using IRE have been developed in hopes of fostering the future of catheter ablation. To that effect, several large pivotal trials of atrial fibrillation ablation are now being conducted with eventual approval in the United States. We review evidence from both preclinical and clinical research to drive...
future direction and possible implications of this novel technology.

**REVERSIBLE VS IRREVERSIBLE ELECTROPORATION**

The application of high-intensity pulsed electric fields to biological samples is commonly used to cause transient permeabilization of the cell membrane, a phenomenon known as electroporation. Cellular recovery is dependent on electrical pulse delivery settings such as pulse duration, voltage, and frequency. If cell defects reseal, reversible electroporation takes place, meaning the cell will survive because of re-establishment of plasma membrane integrity. However, if the cell is damaged beyond repair due to prolonged permeabilization, the cell dies, and IRE occurs. Since the 1980s, reversible electroporation has been commonly used as a method for gene insertion into cells and currently has important applications in the fields of biotechnology and electrogeneotherapy and for delivery of otherwise impermeable drugs into tumor cells (electrochemotherapy).6-8

IRE was deemed the upper limit of reversible electroporation and was typically avoided for the above purposes. Cells exposed to IRE were permanently damaged by exposure to strong electric fields above a certain threshold voltage. There has also been evidence of chromosomal DNA breakage in cells exposed to IRE which could be a strong indicator of late apoptosis.9

**BIOPHYSICS AND CELLULAR MECHANISMS OF IRE**

The application of IRE uses trains of high-voltage ultra-rapid pulses that result in destabilization of the cellular membrane by forming irreversible pores, resulting in cell death.10-13 In fact, electron microscopy studies have shown that permeability is governed by pore formation within the lipid bilayer of cellular membrane.13,14 The lipid membrane comprises 2 layers of phospholipid molecules where each molecule contains a hydrophilic head and a hydrophobic tail. This structure allows for water to diffuse through. However, charged ions and larger molecules are impermeable. The inner cell potential is usually more negative with respect to the outside. Thus, in eukaryotic cells, the resting transmembrane potential voltage (TMV) ranges from 40 to 70 mV. When the cell is exposed to an external electric field, an induced TMV is created as opposing charges gather on opposite sides of the cell membrane, leading to disruption of the physical integrity of the cell membrane. The induced TMV lasts only as long as the electric field is applied. Thus, membrane impermeability is compromised when a sufficiently strong electric field of sufficient duration is applied across the cell membrane and nanopores are formed.14,15 Tarek16 (2005) proposed a molecular dynamics model of pore formation that consists of 2 stages: 1) after electrical field application, water molecules organize in single file and penetrate the hydrophobic center of lipid bilayer; and 2) aquaporins continue to grow in size and expand into water-filled pores and are stabilized by the lipid head groups that relocate from the membrane-water interface into the middle of the bilayer. It is believed that nanopores form more rapidly as the magnitude of the electric field increases.16 The alteration in membrane properties caused by cellular swelling impedes the ability to maintain a molecular milieu vital to its homeostasis leading to cell death by necrosis.17

Pulsed electric fields also locally damage embedded proteins, alter tissue potential of hydrogen, cause lipid peroxidation, and induce production of reactive oxygen species and oxidative damage of unsaturated lipids that are critical to membrane permeability, thus resealing time, and cell integrity. Taken together, these intersecting pathways of cell injury overlap and induce other processes leading to cell death most notably through apoptosis.7,18,19

Electroporation is distinguished by the ability to titrate the applied electric strength at a tissue-specific threshold level which can result in selective cell death without damaging the surrounding tissue/or- gans.20,21 Such differential tissue sensitivity to
electrical fields, as well as the potential nonthermal mechanism of energy delivery, is an attractive alternative to conventional thermal energy sources and may be associated with a superior safety profile. In fact, thermal energy sources are associated with indiscriminate risk of collateral structure damage which remains a major challenge for electrophysiologists. In contrast, preclinical studies have shown that IRE can produce transmural lesions with minimal effect to surrounding structures such as the esophagus, phrenic nerve, pulmonary veins (PVs), and/or coronary arteries.29–24. Because of these aforementioned features and its unique safety profile, IRE offers the potential of a focused and secure alternative to conventional ablation technologies.

**ENERGY DELIVERY: OPTIMAL PARAMETERS**

Understanding the optimal energy delivery parameters will allow physicians to use this novel technology more efficiently and apply it with precision. The optimal parameters are not uniform and are different with each system. Nonetheless, the tissue characteristics and the general principles are similar.

**VOLTAGE.** The optimal goal of IRE is to deliver the highest energy possible to maximize the effect on target issue without causing thermal injury or affecting the adjunct structures. Tissues typically have distinct electroporation thresholds which are related to various interchanging cellular factors affecting the lipid bilayer such as the capacitance, dipole potential, and the nature of lipids hydrophobic tails. All these factors vary by tissue type resulting in tissue-specific electroporation thresholds.15. When an electric field is applied, electroporation will only occur if the magnitude of the field is large enough (above threshold).75,26. There is still no consensus defining the therapeutic spectrum of IRE application while avoiding thermal injury. What is known is that when applied in the atrium, atrial cardiomyocytes have lower electroporation thresholds (400 V/cm) than the esophagus, PV, and phrenic nerve (Table 1).

Theoretically any electric field strength between 400 V/cm and 1,200 V/cm is sufficient to induce electroporation while minimizing the risk of collateral damage. Work from Kaminska et al5 (2012) that studied neonatal H9C2 rat cardiomyocytes reported that electric field strength >375 V/cm resulted in significant IRE-induced cell death. A similar study by Hunter et al27 showed that a biphasic pulse of 400 V/cm resulted in 80% cell death in rat myoblasts. More recently, Montes et al28 (2022) showed that a 100-μs biphasic pulse at 500 V/cm resulted in 75% human AC16 cardiomyocytes death, in contrast to the Hunter et al27 study where a single pulse of 10 ms was used (5 ms for each phase).

The differences in the reported voltages are multifactorial and include: 1) study design—each study used different pre-specified values with variable increments (Kaminska: range 250–3,250 V/cm with variable increments; Hunter: range 200–500 V/cm with 100 V/cm increments; Montes: 250, 500, 750, and 1,500 V/cm). 2) Use of different species (2 studies used rat and one used human hearts); 3) Use of different systems with different catheters; 4) difference in pulse duration; and 5) different reported rates of cell death (the outcome that was measured to reflect myocardial threshold).

Nevertheless, increasing electric field strength to 1,200 V/cm can increase electroporation effect, thereby shortening the total duration of delivery. In one study, Yanpeng et al29 showed that by increasing the electric field intensity from 900 to 1,800 V/cm, electroporation effect occurred earlier (3.34 μs vs 0.74 μs). As such, one may argue that the esophagus and PVs are hypothetically at risk if certain conditions are met as stated above. However, Yue et al30 (2021) showed no evidence of esophageal injury when they directly applied a 2,000-V/cm electric field.

The possibility of thermal damage is a further argument against enhancing electric field strength. When applied with high enough voltage, electroporation will induce tissue heating according to Joule’s first law; the power of heating is proportional to the resistance and square of the current and directly proportional to the time that the current is applied (Heat = I^2 × R × t). This is overcome by delivering energy over short pulse duration (microseconds to nanoseconds). This results in dissipating any produced heat by the cooling effect of conduction and convection and the surrounding blood flow.10,25 Thus, when used with these parameters, electroporation’s cell-destruction mechanism does not rely on thermal damage, offering a significant advantage over other thermal ablation methods. Although some studies have shown that electroporation was associated with minor heating effects, most other studies that

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**Table 1**

**Electroporation Thresholds of Key Organs in Proximity of Atrial Tissue**

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<tr>
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measured direct temperature showed little or no increase. 31-33 Even when 2,100 V of energy was applied, tissue temperature remained below 45 °C.26,34,35 As detailed above, there is a certain threshold for thermal injury (Figure 1). So far, this threshold is yet to be determined because it is not solely dependent on the delivered voltage but also on other electric field parameters such as pulse duration, number of pulses, and pulse repetition rate (Central Illustration). Although published data are limited in terms of understanding the minimum or the maximum amount of energy that can be delivered without causing the undesirable effects of tissue heating, most studies that achieved adequate transmural cardiac tissue lesions reported no or minimal tissue heating while using 1,500 to 2,000 V/cm energy.

Therefore, as more systems and “recipes” are deployed with varying duration and energy intensity, it is important to test the safety of these systems with the aim of minimizing thermal damage and necrotic cell death while still stimulating therapeutic lesion formation and selective cell death.

PULSE DURATION. Another way of achieving optimal energy delivery is through increasing pulse duration. Increasing pulse duration will increase the magnitude of the electric field delivered and, hence, have a larger effect of electroporation on the cell.35,36 This is because longer exposure to an electric field will decrease the threshold membrane potential and will allow for increased cell apoptosis without the need to increase voltage delivery. Longer pulses require lower voltages to sustain the same number of electroporated cells in a nonlinear relationship.32 Zager et al33 showed that a longer pulse duration (100 µs vs 70 µs) is associated with larger myocardial volume reduction and, hence, electroporation effect. Also, the above-mentioned study from Montes et al28 (2022) has shown that when the pulse duration increased from 3 to 60 milliseconds, cell death increased from 15% to 80%. The overall prolongation of time is minimal and remains significantly shorter than with RFA even when prolonged pulses are used.

BIPHASIC VS MONOPHASIC PULSE DELIVERY. Energy can be delivered in either a monophasic or a biphasic fashion (termed high-frequency IRE). Monophasic energy delivery involves the use of bursts of unidirectional pulses (whether positive or negative), whereas biphasic energy delivery involves the use of bursts of bipolar bidirectional pulses (positive and negative) (Figure 2).37 Many studies have shown the advantage of applying biphasic pulses over monophasic pulse. During cardiac tissue ablation, biphasic energy is better able to penetrate epicardial fat cells and overcome fat tissue impedance.38,39 Contrary to biphasic energy delivery, the electric field is less contained in monophasic energy delivery; this can lead to substantial skeletal muscle and diaphragmatic engagement and pain, requiring general anesthetic

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**FIGURE 1** The Proportional Relation Between Pulse Width and Electrical Field Magnitude on Electroporation

Potential observed effect of electric pulse width, ranging from reversible to irreversible electroporation to thermal injury. The longer the pulse and greater the voltage, the more likely there will be irreversible injury and possibility of thermal injury. IRE = irreversible electroporation; RE = reversible electroporation; RFA = radiofrequency ablation.
and neuromuscular paralytics during operations.\textsuperscript{17} Additionally, although both energy waveforms have proven to create myocardial-specific lesions, biphasic waveforms have been associated with higher lesion durability during pulmonary vein isolation (PVI) than monophasic waveform.\textsuperscript{40} Consequently, the ablation protocol was subjected to consecutive evolutionary modifications (ie, from monophasic to biphasic pulses, and then optimizing the biphasic waveform morphology).

\textbf{NUMBER OF PULSES (FREQUENCY).} The role of pulse repetition in modulating IRE is still controversial and conflicting with the current limited data on the subject. A study by Yavin et al\textsuperscript{41} (2021) on an in vivo porcine model investigated the influence of IRE application repetition on lesion dimensions. The study included 12 swine applications of bipolar and biphasic waveforms (±1.3 to 2.0 kV, 4 seconds per application) using an 8-Fr lattice catheter with a compressible 9-mm nitinol tip with an IRE generator (Affera, Medtronic, Inc). Compared with single application, lesion width increased from 17.2 ± 2.9 mm to 22.7 ± 2.3 mm (\(P < 0.001\)) and lesion volume increased from 860 ± 362 mm\(^3\) to 2,383 ± 548 mm\(^3\) (\(P < 0.001\)) with 4 applications, suggesting that stacking of applications may lead to deeper lesions. This can be an advantage over RFA, where stacking multiple applications at a similar location has minimal effect on lesion depth while increasing the risk of steam pops.

Nevertheless, some studies have reported lower efficacy with increasing repetition rate, whereas others have suggested an increase that was limited due to saturation phenomenon, whereby an increase in the number of pulses does not result in an intensified effect as it becomes more difficult to induce TMV in an already permeabilized cellular membrane.\textsuperscript{42,43} For now, it is unclear whether a critical threshold exists for the number of pulses required to create permanent tissue damage.

\textbf{TISSUE CONTACT AND CONTACT FORCE}

Tissue contact is inevitably essential to achieve transmural lesion with RFA and cryothermal ablation.\textsuperscript{44} Although electroporation seems less reliant on degree of contact to achieve transmural lesions, studies have shown that tissue depth is markedly increased when electrode contact is present.\textsuperscript{45,46} This is because some of the energy transmitted by the electrodes will be lost as they are conducted through the blood leading to less energy delivery than
expected. Contact dampens the energy loss and leads to more electroporation effect. In one study by Hunter et al\textsuperscript{27} (2021), the investigators applied biphasic shocks with a fixed duration of 10 ms using a pair of 2 platinum wires separated by 1 mm. It was observed that conduction block occurred when 50% to 80% of the cells near the electrode were killed and required 400 ± 50 V/cm with the electrodes in contact in contrast to 690 ± 70 V/cm with the electrodes 1 mm above the cells \((P < 0.01)\). The degree of contact may also be important. Further study from Nakagawa et al\textsuperscript{47} has shown that, for the same electroporation dose intensity, lesion depth increases significantly with increasing contact force. However, more data are needed to explore the optimal contact force value that can produce consistent therapeutic lesions.

**CATHETER AND ELECTRODE DESIGN**

A list of the currently approved or under-evaluation IRE-based cardiac ablation systems is shown in Table 2.

Current conduction between electrodes is used to impart electroporation to tissues in either unipolar or bipolar arrangement. With a unipolar electrode arrangement, the electric field is generated between the catheter electrode and a dispersive electrode placed on the skin of the patient (usually back), while with bipolar delivery the electric field is generated between the bordering electrodes of the ablation catheter. Unipolar electrode configuration creates deeper lesions in thick tissue with less thermal-associated morbidity risks because it uses lower energy levels.\textsuperscript{17} This makes it well suited for thicker tissues (>2 mm), but at the expense of significant skeletal muscle contraction and pain because the electric field is less contained, which requires the use of general anesthesia.\textsuperscript{32} The optimal choice of electrode configuration should be tailored to the expected treatment outcomes. For example, unipolar electrode configuration can be more beneficial for thicker tissues such as in hypertrophic cardiomyopathy and ventricles in general.

Electrode geometry and dimensions (eg, material, shape, and surface area) remain one of the most important challenges in electroporation as they greatly influence the electric field in target tissues.\textsuperscript{10} Electroporation magnitude is measured by current...
density (current density = current/area). The smaller the exposed surface area of the catheter electrode’s active region, the greater the electroporation impact. To maximize the therapeutic impact of an IRE treatment, catheter electrode designs for IRE-based ablation strive to limit the active electrode contact area to create sufficient therapeutic lesions at the electrode-tissue interface.

Catheter shape is another important factor to optimize IRE delivery. To date, many experimental IRE ablation catheter and electrode designs have been applied in preclinical and clinical trials including balloon, basket, circular, and linear. A catheter with multielectrodes shaped in a circular pattern has an advantage over a catheter with a single electrode. Whereas the latter produces an exponential decay in current density as one moves away from the ablation electrode, a circular arrangement of electrically connected electrodes produces a torus-shaped electric field near and around the ablation hoop. The surface area of a torus is proportional to the torus’s size. As a result, as distance from the ablation hoop increases, current density decreases linearly rather than exponentially. Thus, lesion depth will be greater with such an ablation hoop than with a single ablation electrode.

Cell orientation influences electroporation in relation to the direction of the electric field. Electroporation is more pronounced when the electric field is perpendicular to the cell membrane rather than parallel. Therefore, a nonlinear design and rotational movement of the catheter also enhances the effect on cells as this can help compensate for variable cell alignment.

PRECLINICAL STUDIES

IRE FOR ATRIAL SUBSTRATE. The above-mentioned findings paved the way for further animal experiments as presented in Table 3 to further study and characterize the utility of electroporation in cardiac arrhythmia management.

The first in vivo experiment was reported in 2007 by Lavee et al where the investigators applied IRE ablation in 5 pigs using a handheld clamp containing 2 parallel electrodes. In this study, current pulses of 1,500 to 2,000 V were applied onto the left and right atrial appendages for a total of 10 ablations. Histopathological assessment showed a sharp demarcation line between the lesions and the surrounding normal myocardium, with no temperature change during the pulse sequence applications in any of the animals. Similarly, Hong et al was able to show that IRE can
TABLE 3 IRE Studies

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Methods</th>
<th>Follow-Up</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Preclinical</td>
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<tr>
<td>Lavée et al*55 (2007)</td>
<td>In vivo, 5 canines 1,500-2,000 V hand clamp</td>
<td>Acute model (24 h)</td>
<td>Complete transmural destruction of atrial tissue. No local temperature change.</td>
</tr>
<tr>
<td>Hong et al*58 (2019)</td>
<td>In vivo, 4 ovine 200 J Bipolar linear catheter</td>
<td>Acute model (24 h)</td>
<td>Well-demarcated lesion from unaffected tissue. Inflammatory reaction within the acute lesions was minimal.</td>
</tr>
<tr>
<td>Wittkampf et al*51 (2011)</td>
<td>In vivo, 10 swine Bipolar linear catheter</td>
<td>2 wks (pilot) to 3 wks (feasibility)</td>
<td>Low-energy IRE can create efficient lesions with high safety profile on the PV ostium.</td>
</tr>
<tr>
<td>Van Driel et al*52 (2014)</td>
<td>In vivo, 10 swine Bipolar balloon catheter</td>
<td>12 wks</td>
<td>IRE ablation in the PV ostia does not affect PV diameter. RFA in the PV ostia causes PV stenosis.</td>
</tr>
<tr>
<td>DeSimone et al*57 (2014)</td>
<td>In vivo, 4 canines Bipolar balloon catheter</td>
<td>Acute model (24 h)</td>
<td>Balloon catheter-based system can efficiently ablate cardiac tissue using RF or IRE energy. Enhanced drug delivery through porous configuration of the novel device.</td>
</tr>
<tr>
<td>Witt et al*58 (2018)</td>
<td>In vivo, 5 canines 100-200 V/cm Bipolar balloon catheter</td>
<td>7-44 d</td>
<td>Prototype balloon catheter successfully created transmural lesion inside the PV using IRE without stenosis nor esophageal injury.</td>
</tr>
<tr>
<td>Koruth et al*59 (2019)</td>
<td>In vivo, 14 canines 800-1,800 V Bipolar flower-shape catheter</td>
<td>63 d</td>
<td>Biphasic waveform induced significantly less skeletal muscle engagement with a higher durability of PV isolation than monophasic waveform.</td>
</tr>
<tr>
<td>Padmanabhan et al*55 (2019)</td>
<td>In vivo, 7 canines 1,000 V Bipolar linear catheter</td>
<td>113 ± 7 d</td>
<td>IRE energy can permanently ablate cardiac ganglia plexus with preservation of atrial myocordal. Cardiac ganglion plexus permanently damaged using DC for IRE without atrial myocordal damage and absence of inflammatory reaction and fibrosis.</td>
</tr>
<tr>
<td>Yavin et al*56 (2021)</td>
<td>In vivo, 25 swine 400 V/cm Bipolar lattice basket catheter</td>
<td>Acute model (n = 14) Chronic model 18-37 d (n = 7)</td>
<td>100% transmural lines with acute block in all atrial lines. IRE applied inside the esophagus produced mild edema compared to RFA which produced epithelial ulceration. IRE resulted in transient stunning of phrenic nerve (≤5 min) compared to RFA which produced complete paralysis.</td>
</tr>
<tr>
<td>Grimaldi et al*57 (2022)</td>
<td>In vivo, 10 swine Bipolar basket</td>
<td>Subchronic: 7 ± 3 d (n = 6); chronic: 30 ± 3 d (n = 4)</td>
<td>IRE catheter ablation showed well-demarcated lesions with preserved tissue architecture. The extent of postablation inflammation in the tissue is noticeable at 7 d and greatly reduced at 30 d.</td>
</tr>
<tr>
<td>Hsu et al*58 (2022)</td>
<td>In vivo, 8 swine 1,800 V (supratherapeutic) Bipolar basket</td>
<td>30 d</td>
<td>Supratherapeutic IRE energy successfully created durable lesions of cardiac tissue with no collateral damage to adjacent structures. High extent of cell necrosis around the circumference of the PV at 30 d after ablation.</td>
</tr>
<tr>
<td>Koruth et al*59 (2023)</td>
<td>In vivo, 29 swine 1.6-2 kV Multielectrode spherical mapping and ablation array with the ability to switch between RF and IRE energy</td>
<td>Acute model (RF arm: n = 6, IRE arm: n = 6); Chronic model (RF arm: 30 d, IRE arm: 14 d and 30 d)</td>
<td>Successful acute and durable isolation of the PVs in both arms with 97% to 100% transmurality. Linear and focal lesions displayed transmurality rates of 85% to 100% in the acute cohorts. Linear lesions created with RF, IRE &gt; RF, and IRE had no significant differences in depth or transmurality in the chronic cohorts. No evidence of collateral damage to any organs. IRE but not RF elicited bradycardia from ganglonated plexi stimulation.</td>
</tr>
<tr>
<td>Jian et al*60 (2013)</td>
<td>In vitro, HL-1 cell line 200 V/100 V/cm Bipolar</td>
<td>N/A</td>
<td>IRE is efficacious in creating lesions on HL-1 cell line (atrial cardiac muscle cell line). Electrode proximity to the target tissue is important for IRE efficacy. Cardiomyocytes are significantly more susceptible to damage from electroporation than esophageal smooth muscle cells or neurons.</td>
</tr>
<tr>
<td>Hunter et al*61 (2021)</td>
<td>In vitro, rat cardiomyocytes 100-700 V/cm Bipolar</td>
<td>N/A</td>
<td>Lesions at the PV ostia were up to 3.5 mm in depth with no evidence of PVS or phrenic nerve injury.</td>
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Continued on the next page
IRE FOR VENTRICULAR SUBSTRATE. Although there has been promising preliminary success with the application of IRE in atrial tissue, data regarding its application on ventricular myocardium are limited (Table 3). In fact, most of the preclinical studies examining the use of IRE on ventricular substrate are limited to epicardial ablation. Wittkampf et al was the first to investigate the utility of IRE on left ventricular (LV) tissue. IRE-based ablation was performed with 50, 100, and 200 J on the LV epicardium of an in vivo porcine model. At 3-week follow-up, histological analysis showed that the depth of ablation lesions is directly proportional to the strength of the current used for ablation.

**Table 3**

<table>
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<td>Preclinical ventricular studies</td>
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<tr>
<td>Wittkampf et al (2012)</td>
<td>In vivo, 5 swine 50, 100, and 200 J Bipolar circular catheter</td>
<td>3 wks</td>
<td>200-J applications yielded median continuous lesion depth of 5.2 ± 1.2 mm. Absence of electrically isolating gas bubbles and arcing. Absence of tissue heating. The depth of ablation lesions was directly proportional to the strength of current used for ablation.</td>
</tr>
<tr>
<td>Neven et al (2014)</td>
<td>In vivo, 6 swine 50, 100, and 200 J Bipolar circular catheter</td>
<td>12 wks</td>
<td>Lesion size, depth and width correlate to magnitude of energy used. Short-lasting (&lt;30-min) transient coronary spasm was noted, with no demonstrated spasm at follow-up.</td>
</tr>
<tr>
<td>Neven et al (2014)</td>
<td>In vivo, 5 swine 30, 100, and 300 J Bipolar linear suction device</td>
<td>12 wks</td>
<td>No long-term luminal narrowing was observed.</td>
</tr>
<tr>
<td>Neven et al (2014)</td>
<td>In vivo, 6 swine 200 J Bipolar circular</td>
<td>12 wks</td>
<td>31% of lesions were transmural. Short-lasting (&lt;30-min) transient coronary spasm was noted, with no demonstrated spasm at follow-up.</td>
</tr>
<tr>
<td>Zager et al (2016)</td>
<td>In vivo, 45 rats 50, 250, and 500 V Bipolar needle catheter</td>
<td>4 wks</td>
<td>Longer pulse duration is associated with larger volume reduction. More pulses are associated with larger volume reduction. Lower pulse frequency is correlated with harsher tissue damage.</td>
</tr>
<tr>
<td>Livia et al (2018)</td>
<td>Ex vivo, 8 canines 2,200 V Unipolar Nano knife catheter</td>
<td>Acute model</td>
<td>Abolishing Purkinje signals with IRE was associated with a decreased window of vulnerability toward ventricular fibrillation induction. No evidence of myocardial damage.</td>
</tr>
<tr>
<td>Koruth et al (2020)</td>
<td>In vivo, 4 swine 2,200 V Bipolar 4-spline multielectrode catheter</td>
<td>35 d</td>
<td>Endocardial IRE application can be successfully delivered to create homogenous myocardium-specific lesions. Fibrous tissue homogeneously replaced myocytes. Nerve fascicles and vasculature were preserved within surrounding fibrosis.</td>
</tr>
<tr>
<td>Yavin et al (2021)</td>
<td>In vivo, 12 swine 1.3 -2.0 kV Bipolar lattice basket</td>
<td>Acute model (n = 6) Chronic model: 23 ± 5.4 days (n = 6)</td>
<td>IRE-based ablation produced discrete lesions with well-demarcated borders. IRE effect is enhanced by repetition unlike RFA where stacking multiple applications at a similar location has minimal effect on lesion depth.</td>
</tr>
<tr>
<td>Im et al (2022)</td>
<td>In vivo, 10 swine Bipolar basket</td>
<td>Acute model</td>
<td>Endocardial delivery of focal IRE energy in infarcted LV myocardium is feasible and safe. IRE created greater lesion depth in infarcted myocardial tissue. IRE ablation spared arterioles, veins, and nerves in healthy and infarcted myocardium.</td>
</tr>
<tr>
<td>Kawamura et al (2022)</td>
<td>In vivo, 10 swine Bipolar lattice tip catheter</td>
<td>Acute and chronic models</td>
<td>IRE effect is increased by repetition. Epicardial IRE ablation creates lesions with comparable dimensions and architecture to endocardial IRE. IRE ventricular ablation is feasible with comparable efficacy to atrial ablation.</td>
</tr>
</tbody>
</table>

DC = direct current; LV = left ventricular; N/A = not available; RF = radiofrequency; RFA = radiofrequency ablation; other abbreviations as in Tables 1 and 2. 

The other PVs using 30-W applications via an irrigated 4-millimeters ablation catheter. PVs was documented with application of RFA which persisted at 3 months (despite increase in heart size). In contrast, using IRE, complete isolation was documented with preservation of the PVs. Witt et al confirmed these findings histologically with complete transmural lesions devoid of PVs or esophageal damage. All the other relevant animal studies on the atrial substrate are summarized in (Table 3).
Livia et al\textsuperscript{14} were the first to investigate the use of IRE as a potential ablative modality of Purkinje/fascicular fibers in an 8-canine heart ex vivo model. The investigators applied IRE current using the NanoKnife system and energy was delivered to tissue at 750 to 2,500 V in a train of 10 pulses at 1 Hz, with a pulse duration of 90 μs. They showed that IRE can ablate the Purkinje fibers in a dose-dependent manner while providing a safety advantage by reducing collateral damage. Consequently, the nonthermal energy delivery may also reduce the chance of stroke due to absence of tissue heating and the lack of coagulum formation, which is a common occurrence with RFA of ventricular arrhythmias.

Koruth et al\textsuperscript{15} investigated the use of IRE ablation delivered with a 12-F 4-spline multielectrode catheter (Farapulse Inc) under guidance of intracardiac echocardiography and electro anatomic mapping. Lesions were applied to the free wall, outflow tract, and septal regions of both ventricles. Postablation pacing threshold was used to assess the acute effect of IRE ablation. They described lack of capture despite maximal output (20 mA at 2.0 milliseconds) in 8 of 10 ablation sites from both ventricles. Repeat electro-anatomic mapping at 35.5 days confirmed areas of low voltage (<0.5 mV) corresponding to sites of IRE applications in both ventricles without any further inducibility of ventricular arrhythmias at the sites of prior IRE applications. Further histological assessment showed complete and homogeneous fibrotic replacement of the myocardium without involvement of the underlying vasculature consistent with the safety and specificity of IRE application.

The preceding work provides a solid foundation for efficacy and safety. The patients who are most likely to benefit from this evolving technology are those who have diseased hearts, where the performance of RFA is known to be limited as in the case of infarcted myocardium with endocardial scar. Im et al\textsuperscript{16} was the first to transition from a normal to diseased model. They investigated the application of IRE in ventricles in the presence of myocardial scar on a 10-swine model where a myocardial infarction was induced in the left anterior descending coronary artery and the swine were allowed to survive for 6 to 8 weeks (with 2 of 10 as controls). IRE was applied to the LV endocardium in regions of healthy myocardium or scar identified with electroanatomical mapping. Bipolar, biphasic energy was delivered using 2 different catheters (ie, linear quadrripolar [focal] or multispline 8-pole catheter [basket]). In myocardial scar, lesion depth did not differ significantly between the 2 IRE catheters ($P = 0.239$). However, lesion depth for IRE was significantly greater when compared with RFA (IRE vs RFA: $6.1 \pm 1.7$ mm vs $3.8 \pm 1.7$ mm; $P = 0.005$). Younis et al\textsuperscript{17} was able to confirm these findings in a
healed myocardium with anterior scar, and to elucidate the underlying mechanisms. Ablation with IRE resulted in transmural lesions and cell death deep to the scar, whereas RFA was restricted to the endocardial layer and was incapable of penetrating the scar. The reduced effect of RFA in eliminating viable myocardium separated from the catheter by collagen and fat was partially related to reduced tissue heating. In contrast to RFA (where the effect is mediated by heat), the effect of IRE is mediated by an electrical charge which is not limited by the insulating effects of collagen and fat within the scar.

**CLINICAL STUDIES**

Table 4 summarizes relevant clinical trials that were conducted and completed to date. The initial clinical experience with IRE-based catheter ablation for AF was performed in patients with paroxysmal AF and reported by Reddy et al. The pilot study was conducted at 2 European centers and included 22 patients with symptomatic paroxysmal AF. Ablation was performed using a monophasic waveform with either endocardial or epicardial approach. For the endocardial ablation group, PVI using a multispline IRE ablation catheter was successful in all 15 patients (100%), with an average of 3.26 ± 0.5 lesions per PV. For the epicardial ablation group, investigators reported surgical box lesions in 86% of patients. No procedural complications were reported during and up to 1-month follow-up.

In 2021, the patient cohort-of-interest was expanded to include persistent AF patients with drug refractory symptoms. A total of 25 patients were enrolled and followed-up for 75 days. IRE was performed using Farapulse (Boston Scientific Inc). Acute PVI (96 of 96 PVs) and left atrial posterior wall (LAPW) ablation were 100% acutely successful with IRE alone. Post-procedure esophago-gastroduodenoscopy and repeat imaging revealed no mucosal lesions or PV narrowing. Twenty-one patients underwent repeated invasive mapping at 75 days after the index procedure to assess durability. Durable PVI was documented in 96% of the PVs and LAPWs block was documented in 100% of the patients.

The multi-national survey on the methods, efficacy, and safety on the post-approval clinical use of pulsed field ablation trial (published in June 2022) is the largest cohort to date investigating real-world performance of the only commercially approved IRE catheter Farawave, Farapulse (Boston Scientific Inc). It included 1,758 patients from 24 clinical centers undergoing catheter ablation for AF. The major findings mirrored the preclinical studies in terms of efficacy (PVI was achieved in 99.9% of patients), fast procedure (65 minutes) and safety profile with a low rate of major complications (1.6%) largely due to pericardial tamponade and stroke. The pericardial tamponade was attributed to an extra stiff-straight guidewire that was used to deliver PFA catheter, inadvertently perforating the left atrial appendage when attempting to isolate the PVs. This was resolved by transitioning to a J-tip wire with no subsequent cases of tamponade. Stroke was attributed to suboptimal catheter exchanges and management of transeptal sheath, which required further recommendations of diligent saline aspiration/flushing to prevent inadvertent air or thrombus embolization. The overall freedom from AF after 1 year was 69% (73% in paroxysmal AF and 58% in persistent AF).

**SAFETY**

As discussed and elaborated above, IRE gained exponential interest during the last decade mainly due to its safety profile. In contrast to RFA in terms of thermal injury and nonselectivity, IRE produces durable effects on myocardial cells with minimum effects on the surrounding organs, particularly the esophagus, phrenic nerve, pulmonic veins, and the intramyocardial blood vessels.

Although rare, atrioesophageal fistula remains the most feared life-threatening complication of PVI which is caused by thermal energy (radiofrequency) application to the esophagus. IRE-based ablation has
been shown to cause minimal esophageal injury in preclinical models (Table 3). One study investigated the direct effect of IRE application on the esophagus. Direct IRE application within the esophageal lumen produced mild edema, whereas RFA produced epithelial ulceration (Figure 3).

Another safety issue is potential damage to the phrenic and vagus nerves. Several animal studies including direct comparisons between RFA and IRE were able to highlight the preferable safety profile of IRE over RFA (Figure 4). Phrenic nerve injury was reported to be transient when using IRE with normal phrenic function and histopathology on long-term follow-up (3-12 months) irrespective of the dose or repetition mode.

The risk of injury to the coronaries was investigated by Du Pre et al where direct IRE application over the coronary arteries did not result in significant narrowing (stenosis >50% of the lumen), or intimal hyperplasia. These findings suggest that IRE ablation can be applied safely near or even on coronary arteries. However, whether applying an inappropriately high dose/duration might result in transient or persistent coronary injury is yet to be investigated. In a case series of 20 patients who underwent PVI with IRE, 1 patient (with known ischemic coronary heart disease and existing stents) experienced coronary spasm during mitral isthmus line ablation. Another study by Neven et al (2014) reported intimal hyperplasia in 66 of 154 arteries (10% to 25% luminal stenosis) when IRE was applied.

One recent study by Ladeboji et al (2022) compared the effect of intracoronary electroporation versus epicardial electroporation on coronary arteries in a swine models. Intracoronary electroporation resulted both in significant coronary spasm and fixed coronary stenosis whereas epicardial electroporation, delivered at lower energy, resulted in reversible spasm but no fixed coronary stenosis. This further highlights the acute risk for transient coronary artery spasm during pulsed-field ablation. Furthermore, several clinical observations of coronary spasm were reported in the latest MANIFEST registry with 1 case of ST-segment elevation in 1 patient. Follow-up showed no incidence of arrhythmia or myocardial injury.

Future studies should investigate IRE-induced vasospasm to have a better understanding of the underlying pathophysiology and provide options of optimal prevention and management strategies.

Although the overall incidence is very low, procedure-related stroke remains one of the most disabling complications of AF ablation. Recently, 2 studies evaluated the effect of IRE on ischemic stroke and silent stroke (assessed by cerebral magnetic resonance imaging) after AF ablation. There were no events of clinical stroke in either study (the total for both studies was 111 patients). In 1 patient (<1%), a solitary 7-mm cerebellar lesion was observed. Follow-up cerebral magnetic resonance imaging scan performed 45 days following the procedure showed full regression of the lesion. These findings are similar to the low rates observed with RFA.

The response of the PVs is of particular interest in AF management. PVS remains one of the main challenges that face electrophysiologist during thermal ablation with a reported rate between 0.32% and
3.4%. RFA may result in various pathologic changes including intimal thickening, thrombus formation, endocardial contraction, and proliferation of elastic laminae. In contrast, IRE has been shown to spare including intimal thickening, thrombus formation, reduction in cross-sectional area with IRE, compared to current thermal modalities.94 Vascular beds and making it a compelling ablation concept that IRE has minimal damaging effects on with 46% reduction with RFA, further supporting the efficacy and the safety profile of IRE. 

**TABLE 5 Ongoing Pulsed-Field Ablation Trials Registered on ClinicalTrials.gov**

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Design</th>
<th>Estimated Enrollment</th>
<th>Anticipated Completion Date</th>
</tr>
</thead>
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<tr>
<td>NCT04198701</td>
<td>Pulsed Field Ablation to Irreversibly Electroporate Tissue and Treat AF (PULSED AF)</td>
<td>NRCT, single arm</td>
<td>418</td>
<td>November 2022</td>
</tr>
<tr>
<td>NCT05293639</td>
<td>Assessment of Safety and Effectiveness in Treatment Management of Atrial Fibrillation With the BWI IRE Ablation System (AdmIRE)</td>
<td>NRCT, single arm</td>
<td>362</td>
<td>January 2024</td>
</tr>
<tr>
<td>NCT04612244</td>
<td>The FARAPULSE ADVENT PIVOTAL Trial IRE System vs SOC Ablation for Paroxysmal Atrial Fibrillation (ADVENT)</td>
<td>RCT</td>
<td>900</td>
<td>June 2023</td>
</tr>
<tr>
<td>NCT05120193</td>
<td>Treatment of Persistent Atrial Fibrillation With Sphere-9 Catheter and Affera Mapping and Ablation System (SPHERE Per-AF)</td>
<td>RCT</td>
<td>477</td>
<td>November 2023</td>
</tr>
<tr>
<td>NCT05443594</td>
<td>A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects With Persistent Atrial Fibrillation (ADVANTAGE AF)</td>
<td>NRCT, single arm</td>
<td>339</td>
<td>August 2024</td>
</tr>
</tbody>
</table>

NCT = national clinical trial number; NRCT = nonrandomized controlled trial; RCT = randomized controlled trial; SOC = standard of care.

**PROCEDURE TIME**

Studies have shown that the procedure time for IRE ablation is significantly lower than for RFA. In 3 multicenter studies assessing PVI by IRE in more than 100 patients, the mean procedure timed was 96 ± 30 minutes, which is significantly faster than cryoablation or RFA (124 and 141 minutes, respectively).24,95 We anticipate that this advantage of IRE will continue to grow as operators gain more experience.

**CONCLUSIONS AND FUTURE PERSPECTIVES**

Catheter-based IRE is promising to be a much more favorable ablation energy source for arrhythmia management because of its improved efficacy and the better safety profile compared to existing cryo-/radiofrequency thermal-based ablations. Preclinical and clinical studies may ultimately establish IRE as an alternative to current thermal energy ablation, especially in AF ablation given the shorter procedure time, reduced risk of collateral injury, high selectivity, and possible improved long-term lesion durability. However, there are still several important unanswered questions concerning IRE. Although current data are based on healthy myocardial tissue or infarct-related scarred myocardium, the performance of this technology in nonischemic diseased myocardial models such as in the presence of sarcoidosis, amyloidosis, and other disease states remains unknown. The performance of IRE over previously ablated myocardial tissue is similarly unknown. This is important when considering redo ablation in cases of previously failed RFA or cryoablation. Moreover, as described in this review, there is significant heterogeneity in reporting of IRE parameters and electrode configurations because of proprietary concerns, which may limit operating physicians’ ability to modify and titrate energy delivery based on a specific clinical setting. Accordingly, it is possible that the efficacy and safety profiles of the different systems vary depending on the parameters discussed in this review and that the effects of this technology are driven by the specific ablation/mapping system rather than solely by the application of IRE energy. We hope that in the future these parameters are more readily disclosed to enable further progress in defining the optimal energy delivery settings similar to what clinicians are used to with the RFA systems. We are also uncertain whether the clinical benefit of IRE would outweigh the economic burden of replacing all the currently used clinical systems. Lastly, there are several ongoing US Food and Drug Administration (FDA)-mandated pivotal AF ablation trials that are in progress and
nearing completion with reporting as early as this year and potential FDA approval in 2024. A full list of current ongoing trials is available in Table 5. The efficacy and safety results will be important and will direct future adoption. Based on the preclinical work already done, there should be no hesitation to design and perform ventricular arrhythmia clinical trials.

IRE is a very encouraging development that will foster even more research into wider applications. We hope, given the safety profiles, that the efficacy will be reproducible and enable wide adoption. This will inevitably translate into better efficiency, better clinical results, and ultimately improve access to effective and safe ablation.

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76. Gunawardene MA, Schaeffer BN, Jularic M, et al. Pulsed-field ablation combined with ultrahigh-density mapping in patients undergoing catheter ablation for atrial fibrillation: practical


KEY WORDS atrial fibrillation, electroporation, catheter ablation, pulsed electric fields, pulsed-field ablation