

Advancements in irreversible electroporation ablation technology for treating atrial fibrillation

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Highlights

- Pulsed field ablation (PFA) demonstrates superior efficacy atrial fibrillation than traditional methods.
- Enhanced safety profile of PFA reduces complications in adjacent tissue damage.
- Optimized outcomes depends on key PFA parameters such as voltage, pulse width, and frequency.

Abstract

Pulsed field ablation (PFA), an emerging treatment method for atrial fibrillation, has demonstrated significant potential in arrhythmia therapy. PFA employs high-intensity, short-duration electric fields to induce irreversible electroporation in myocardial cells, disrupting abnormal cardiac rhythms, and restoring normal heart function. This technique exhibits high success rates and low recurrence rates in animal studies and early clinical trials, offering advantages over traditional methods by reducing damage to adjacent structures such as the esophagus, phrenic nerve, and pulmonary veins. This review examines PFA's application mechanisms, benefits, key operational parameters and the design and safety of related ablation devices. It emphasizes PFA's potential to enhance both the efficacy and safety of atrial fibrillation treatment and explores future research directions and technological developments.

Keywords: Irreversible electroporation, pulsed field ablation, atrial fibrillation treatment, ablation devices

Introduction

Irreversible electroporation (IRE) involves the formation of irreversible micropores in the cell plasma membrane when exposed to a strong electric field [1, 2]. These pores, termed irreversible electropores, induce cell apoptosis due to osmotic imbalance once their quantity on the cell membrane reaches a critical threshold. As an innovative medical intervention, IRE has shown tremendous potential in treating arrhythmias, especially atrial fibrillation (AF).

AF is a common cardiac disorder, primarily treated clinically through catheter ablation techniques [3]. Traditional catheter ablation methods, particularly radiofrequency ablation (RFA) and cryoballoon ablation, function by damaging abnormal cardiac cells through temperature

modulation [4, 5]. Although effective in some cases, these methods depend on efficient heat transfer from the catheter to the target tissue, necessitating substantial contact between the catheter and cardiac tissue. More importantly, the potential adverse effects of thermal action on cardiac cells and surrounding sensitive tissues, such as the esophagus, veins, and phrenic nerve can lead to adjacent tissue damage, complicating postoperative recovery and increasing risks.

To overcome these limitations, scientists have introduced treatment methods based on IRE technology. Unlike traditional thermal ablation methods, IRE-based treatments do not rely on thermal effects to eliminate cells, thereby significantly shortening treatment duration and accelerating the process [6]. Additionally, this

approach exploits the lower electric field tolerance threshold of myocardial cells compared to vascular tissues, allowing for more precise targeting of myocardial cells without damaging surrounding vascular structures [7-9]. This selectivity is crucial for protecting non-target tissues and provides a safer and more effective AF treatment option with the clinical application of IRE technology.

Technical advantages of IRE tissue selectivity

Pulsed field ablation (PFA) technology plays a crucial role in the selective damage cardiac tissues, while effectively avoiding damage to adjacent myocardial tissues such as the esophagus and phrenic nerve. This technology achieves electroporation effects by releasing high-intensity electric fields within a microsecond pulse width. When the electric field strength surpasses the irreversible damage threshold of specific cells, it can selectively affect these cells [9]. Studies have shown that the IRE damage threshold of myocardial cells is lower than that of adjacent esophageal and phrenic nerve tissues [7, 8]. Therefore, precise parameter adjustments make it possible to damage myocardial cells specifically while avoiding similar effects on adjacent tissues.

Initially verified through animal experiments by Koruth et al., this theory involved placing a mesh-like ablation catheter and a RFA catheter in the inferior vena cava, with the esophagus fixed behind it, using a particular device [10]. Post-ablation observations revealed that pulsed ablation technology did not cause damage to the esophagus, while RFA led to esophageal fistulas or ulcers [10]. Notably, although the smaller diameter of the mesh structure used in this study than the standard clinical size, resulting in a stronger electric field at the same voltage, the animal experiment results still confirmed the effectiveness of the tissue-selective damage mechanism.

Further clinical data supported these findings. In postoperative evaluations, certain patients showed no esophageal damage as assessed by enhanced magnetic resonance imaging examinations [11]. Besides, clinical trials identified two cases of persistent diaphragmatic nerve damage in the radiofrequency/cryoablation group, while no similar cases were recorded in the PFA group [12].

Ablation safety

IRE incites a markedly reduced inflammatory

response compared to radiofrequency/cryoablation, thereby diminishing the risk of pulmonary vein constriction. Unlike radiofrequency/cryoablation, which utilizes thermal conduction to inflict tissue damage, typically leading to coagulative necrosis, inflammatory responses, and fibrosis. PFA operates via an electroporation mechanism, leading cells to undergo apoptosis rather than necrosis, thus avoiding microvascular occlusion and intramural hemorrhage. This difference in mechanism is crucial for tissue recovery. Perioperative MRI detection indicates that myocardial areas treated with PFA demonstrate the potential for tissue tension recovery, a phenomenon not observed with RFA [13]. Research by Reddy et al., comparing the effects of the two techniques on pulmonary vein diameter, found PFA to be as efficacious as thermal ablation in maintaining vein diameter [12].

Impact of different pulse parameters on the treatment of AF

Understanding the operational parameters of IRE is vital for optimizing its application in treating AF. Pulse frequency, width, and duration are pivotal in determining treatment efficacy, influencing electric field interaction with cells and the extent of cell apoptosis.

Baena et al. demonstrates that apoptosis induction by pulsed electric fields (PEFs) correlates with field strength, pulse width, and duration [14]. Applying electric fields from 250 to 1000 V/cm to human myocardial cells, significant electroporation and cell death occurred at 750 V/cm, with a pulse width of 100 μ s, and of 3 ms. Effects were similar at a reduced field strength of 250 V/cm with a pulse duration extended to 60 ms. Additionally, short pulses of 2 and 5 μ s at field strengths above 1000 V/cm significantly induced apoptosis. Prado et al. noted that induce cell death with shorter pulse necessitates higher electric field strengths [15].

Jiang et al. suggested that the stochastic nature of IRE, indicating that not all cells undergo apoptosis under high electric field conditions if the pulse number or duration is insufficient [6]. Cardiac cell survival drops below 90% at field strengths above 750 V/cm. However, almost complete cell death (over 90%) is achievable at strengths above 1250 V/cm with adequate pulse numbers or duration. In the 750 to 1250 V/cm range, cells might be damaged without immediate death. Interestingly, increasing pulse numbers or duration does not enhance cell damage at low electric field strengths (below 500 V/cm), contrary to Rubinsky et

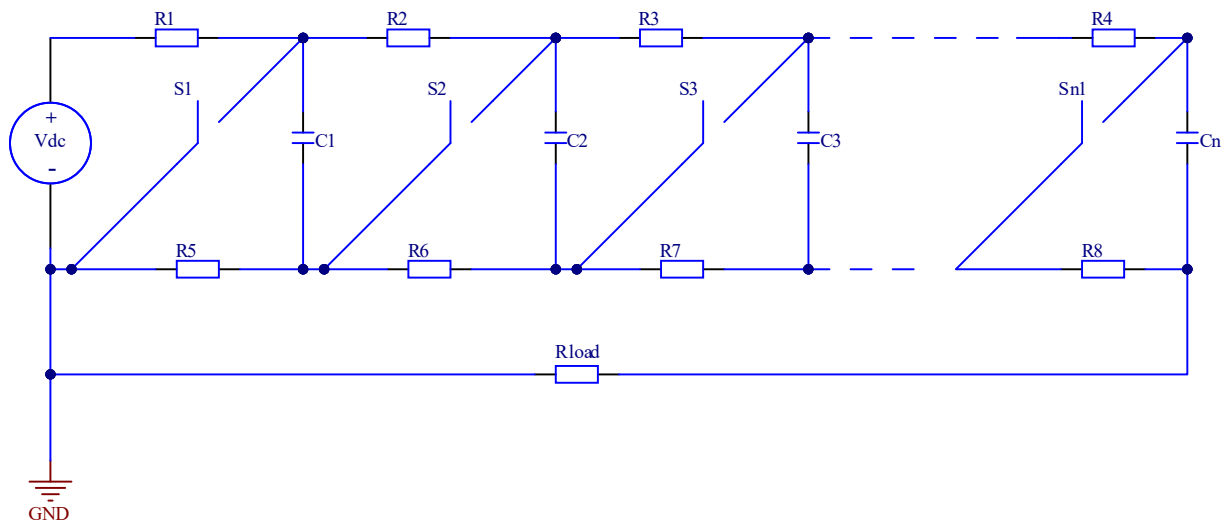


Figure 1. Basic topology of a Marx generator. Vdc, voltage direct current; GND, ground.

al., who achieved 100% cell death at 125 V/cm with significantly more pulses (up to 3840 compared to Jiang et al.'s maximum of 90) [16, 17]. Thus, investigating complete IRE-induced cell death with sufficient pulse numbers at low electric field strengths (below 500 V/cm) and its clinical relevance merits further research.

Miklovic et al. demonstrated that under constant electric field strength, pulse trains with wider pulse widths significantly enhance tissue ablation efficacy [18]. Specifically, a 50 μ s pulse train produced an ablation volume 7.2 times larger than a 1 μ s pulse train. However, they noted that extended pulse durations could induce severe muscle contractions, potentially leading to arrhythmias. An oversight in their report was the omission of pulse frequency, a critical parameter in IRE effectiveness. A study investigated the impact of various pulse frequencies on IRE treatment outcomes, employing pulse energies from 250 kHz to 2 MHz to [19]. The results indicated that, with all other parameters constant, a frequency of 250 kHz was most effective, with diminishing efficacy at higher frequencies. This trend may be attributed to the increase in high-frequency components which, according to bioimpedance theory, allow displacement currents at higher frequencies to penetrate cell membranes directly [20]. Thus, high-frequency pulses tend to affect internal cellular structures, like the nucleus and organelles, rather than the cell membrane's surface.

IRE ablation devices

Pulse power supply unit

The pulse power supply unit's primary function is to energize the pulse forming unit, a critical aspect influencing the entire system's perfor-

mance. This involves determining the energy storage module's charging speed in the pulse forming unit, which affects the system's maximum pulse frequency.

DC-DC high-voltage generation, pivotal in power conversion, offers notable stability in switching frequency and constant charging current. The LLC resonant circuit, used in high-voltage DC-DC converters, leverages inductance and capacitance resonance for, reducing switching losses and improving energy conversion efficiency. Azura et al. developed a DC-DC converter using LLC resonance, featuring a full-bridge inverter, an LLC resonant tank, a high-voltage transformer, and a full-bridge rectifier [21]. This converter, achieving ZVS through leakage energy and LLC resonance, showcased superior efficiency with a 300 V input to 3.5 kV/0.35A output, confirmed by design examples and simulations.

Pulse forming unit

The development of IRE ablation devices critically depends on the pulse forming unit, which utilizes high-voltage pulse generators, predominantly of the capacitor discharge type. This approach employs capacitors as energy storage, which are charged and then discharged through a switch to deliver high-voltage pulses. The Marx generators and H-bridge circuits are prevalent in capacitor discharge high-voltage pulse generation.

A Marx generator, with its simple structure and modest input power requirements, charges capacitors C_1 - C_n in parallel and discharges them in series to generate high-voltage pulses (Figure 1). Its ability to generate high voltages through cascading makes it a staple in pulse signal design. Advancements in switch technology have

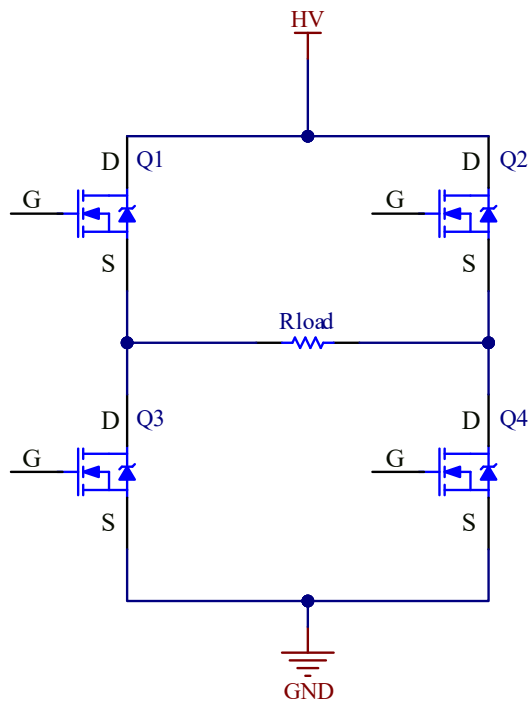


Figure 2. Basic topology of an H-bridge circuit. HV, high voltage; GND, ground.

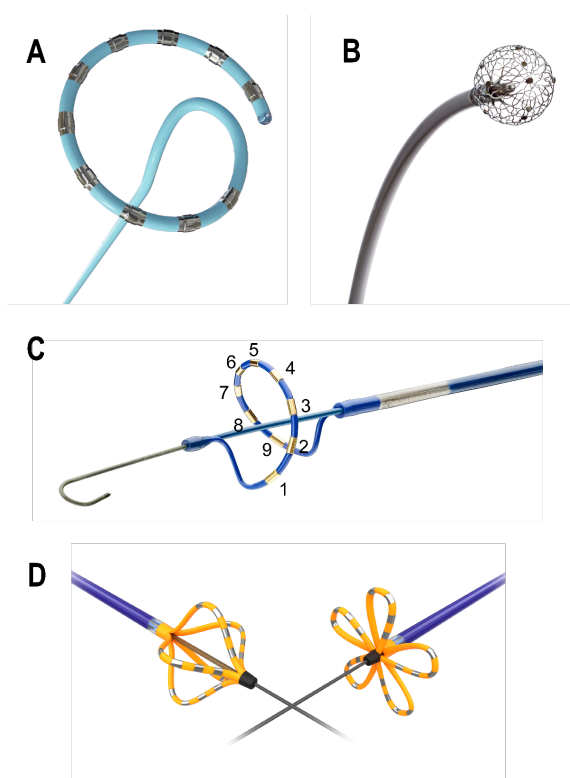


Figure 3. Different Types of PFA Electrodes. (A) VARIPULSE ablation electrode; (B) Sphere-9 catheter; (C) pulse select ablation electrode; (D) FARA-WAVE ablation electrode. The subfigures A, B, C, D were cited from [24], [26], [28], [31], respectively. PFA, pulsed field ablation.

made solid-state switches, such as MOSFETs, vital due to their compactness, controllability, and high repetition capabilities. Yao et al. replaced traditional spark gaps with MOSFETs in

a Marx generator, achieving pulse durations in the hundreds of nanoseconds, adjustable pulse widths from 200 to 1000 ns, rise times of 35 ns, and a frequency range of 1 to 1000 Hz, illustrating the potential for precise and efficient IRE ablation [22].

The H-bridge circuit, essential for generating positive and negative pulses, consists of four switching devices arranged in an “H” configuration (**Figure 2**). This setup enables control over the current flow direction by alternating the activation of these devices. Jiang et al. introduced a novel bipolar modular multilevel generator based on an H-bridge design, comprising a full-bridge module and multiple half-bridge modules [17]. This generator can produce up to 2000 V, 2 μ s nine-level step pulse waves, and adjustable square waves with 1-10 μ s pulse widths. Furthermore, Pirc et al. developed a device capable of emitting a maximum voltage of 4 kV and a maximum current of 131 A, with pulse durations as brief as 200 ns and a repetition rate up to 2 MHz [23]. This device produces asymmetric bipolar pulses, allowing independent adjustment of both pulse duration and amplitude.

IRE ablation devices: electrode needles

In the development of IRE ablation devices, the design of ablation electrode needles is equally crucial. The effectiveness and safety of the ablation treatment depend directly on these needles, as they deliver the PEF generated by the pulse forming unit to myocardial cells.

The VARIPULSE ablation electrode (Biosense Webster, California, USA), featuring a 7.5F diameter, incorporates 10 ring electrodes spaced 5 millimeters apart, each 2 millimeters in length [24]. This configuration allows for an adjustable diameter disk, varying from 25 to 35 millimeters, as seen in **Figure 3A**. This figure was cited from [24]. Such a design adapts to different pulmonary vein openings, offering flexibility in clinical applications. Additionally, the catheter also boasts bidirectional bending capabilities—up to 180° in one direction and 90° in the other—enhancing ease of use and precision in engaging with all pulmonary veins. Yavin et al. assessed the feasibility of using the VARIPULSE ablation electrode to create block lines from the superior vena cava to the inferior vena cava, examining its effects on cardiac lesions and esophageal and phrenic nerve tissues [25]. This comprehensive study included an atrial line model assessment and detailed analysis of PFA’s impact on the esophagus and phrenic nerve. Histopathological and statistical

analyses, conducted with Stata/SE software, confirmed that PFA could effectively establish continuous and transmural block lines in the atrium without causing significant harm to the esophagus and phrenic nerve.

The Sphere-9 catheter, also known as the Lattice-tip catheter (Affera, Nevada, USA) features an expandable spherical mesh tip, offering an effective area ten times larger than traditional 3.5 mm electrodes [26]. Its design enhances higher energy output while mitigating the risk of tissue overheating. The spherical ablation electrode is equipped with perfusion micro-holes and a central reference electrode for both measurement and ablation purposes, as seen in **Figure 3B**. This figure was cited from [26]. Capable of supporting both radiofrequency and PEF energy modes. In the study by Reddy et al. on 76 patients confirmed the system's safety and efficacy for pulmonary vein isolation and linear ablation tasks, with RFA/PFA and PFA/PFA strategies demonstrating solid acute efficacy and safety profiles [27].

The PulseSelect ablation electrode (Medtronic, Minneapolis, USA) features a catheter head with extendable electrodes forming a "disc-like" shape, 25 mm in diameter, where odd-numbered electrodes act as positive and even-numbered as negative [28]. The design, which includes a 20° forward tilt for ease of use, as shown in **Figure 3C**. This figure was cited from [28]. Stewart et al. carried out ablation experiments on pig hearts, showing that PFA effectively reduced local electrogram amplitudes and produced durable effects in AF treatment, surpassing RFA in lesion healing smoothness, without affecting surrounding tissues [29]. In a clinical study by Verma et al., all 38 patients achieved intraoperative PVI safely with the PFA system [30].

The FARAWAVE ablation electrode, also known as the petal-type ablation electrode (FARA-PULSE, Menlo Park, USA), uses a 12 F diameter design with 5 petal-shaped semi-rings, each containing 4 electrodes, presenting a basket-like structure when not fully expanded and a petal shape upon expansion., as shown in **Figure 3D**. This figure was cited from [31]. Reddy et al. evaluated its use in PFA for PVI and treating atrial flutter in 121 patients, highlighting PFA's rapid PVI achievement and low safety event rate (1.2%), with no observed pulmonary vein stenosis or damage to adjacent structures [32, 33].

Emerging insights on PFA in AF treatment

Reddy et al. pioneered the application of PFA in

treating atrial fibrillation in humans, detailing a study involving 22 patients [34]. Fifteen patients received endocardial PFA under general anesthesia, utilizing a petal-style electrode catheter guided to the pulmonary vein ostia with intracardiac ultrasound and fluoroscopy. This initial foray reported a 100% success rate in pulmonary vein isolation (PVI) via the endocardial route, with an 87.5% success rate for epicardial route ablations, without adverse events like malignant arrhythmias or ventricular dysfunction. Notably, right-side nerve function remained intact post-ablation.

A subsequent study of 81 patients, employing bipolar voltages between 1800 and 2000 V and unipolar voltages between 900 and 1000 V, recorded no acute adverse events, showcasing PFA's swift ablation and minimal fluoroscopy time. Three-month follow-up electrophysiological exams confirmed a 100% success rate in achieving circumferential PVI, with no significant damage to nerves or the esophagus, underscoring PFA's durability and safety [33].

More recently, Reddy et al. explored PFA's long-term efficacy in a trial with 121 patients, revealing a one-year atrial arrhythmia recurrence rate between 78.5%±3.8% and 84.5%±5.4% for the optimized PFA energy group, indicating effective long-term PVI and AF treatment [32].

Another innovative study utilized the Lattice-tip catheter for complex ablation treatments in 76 patients, incorporating both RFA and PFA [27]. Preliminary findings suggested enhanced treatment efficacy and reduced fluoroscopy time, with no perioperative device-related complications. Importantly, no thermal injury to the esophagus was observed, affirming PFA's safety.

While initial findings are promising, further research and long-term follow-up are essential to fully assess the clinical effectiveness and patient outcomes of PFA in treating AF. Future studies are critical for evaluating the sustained efficacy and therapeutic benefits of this combined treatment strategy, providing deeper insights into arrhythmia treatment.

Conclusion

PFA represents a burgeoning technology in the treatment of AF, showing considerable promise. Its distinct advantage lies in its targeted disruption of atrial myocardial cells, significantly reducing the risk of pulmonary vein stenosis and sparing adjacent structures such as the esophagus, autonomic nervous system, and

coronary arteries. Both animal studies and early clinical trials have attested to its viability and safety. Yet, the nascent state of current clinical research, characterized by limited sample sizes and brief follow-up durations, necessitates further investigation to corroborate and refine PFA's efficacy.

The success of PFA is contingent upon a multitude of factors, including voltage strength, pulse width, frequency, waveform, field intensity, and the pulse's vector direction, all of which influence the procedure's reach and impact. Therefore, identifying the optimal parameter configuration for specific clinical scenarios remains an area ripe for exploration. As medical device technology progresses, future evidence-based research is anticipated to bolster PFA's role in cardiac ablation, offering a more accurate and safer option for cardiac arrhythmia treatment.

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