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Review

Irreversible electroporation for the treatment of cardiac arrhythmias

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Abstract:

Introduction: Cardiac ablation is an established treatment modality for the management of patients with cardiac arrhythmias. Current approaches to cardiac ablation employ thermal based energy to achieve lesions (damage) within the heart. There are many shortcomings and limitations of thermal based approaches. Electroporation (DC energy) is a non-thermal alternative approach to ablation has shown significant promise in animal studies.

Areas covered: An extensive review of the literature on the application of electroporation for ablation (both cardiac and collateral cardiac tissue) was undertaken. This review explores irreversible electroporation as a cardiac ablation modality. Specifically, it focuses and explains the biophysics of electroporation, the limitations of current thermal based approaches and examines the current data published on electroporation cardiac ablation.

Expert commentary: Electroporation is a fast-growing novel ablation modality that has many advantages over current thermal based approaches. Current research in animal models shows its can be safely and efficaciously applied to the heart. Although further research is required, electroporation represents an appealing option for the ablation cardiac arrhythmias.

Keywords: electroporation, DC energy, cardiac ablation, atrial fibrillation, ventricular arrhythmias

1.0 Introduction

Cardiac ablation has experienced a remarkable evolution over the last 50 years and established itself as a fundamental treatment strategy in patients with arrhythmias. The goal of cardiac ablation is to apply energy to destroy the underlying tissue and create a permanent lesion that is both transmural and contiguous. Despite over 30 years of research focusing on ablation energy sources, the reliable creation of effective and durable lesions remains challenging. Historically, the primary treatment of cardiac arrhythmias (in particular refractory arrhythmias) was sympathectomy[1] which evolved into surgical approaches (simple ventriculotomy[2], ligation[3] or electrocautery of AV node[4], cryosurgical ablation[5]) and then to the appealing "closed-chest" (transvenous) approach. Initially, the transvenous approach employed large Direct Current (DC) energy for the creation of lesions.[6, 7] Although successful, it was inconsistency with tissue damage, recurrence of arrhythmias, as well as significant barotrauma that stimulated research into alternative ablative energies and techniques and ultimately paved the way for radiofrequency (RF) energy.[8] RF energy has spawned the revolution of catheter ablation, its initial application and success in the treatment of supraventricular tachycardias with accessory pathways and preexcitation syndromes lead to its application in atrial flutter[9], atrial fibrillation[10, 11] and ventricular arrhythmias.[12] Today it is the most commonly used energy source.

While RF can produce ablation lesions effectively, most RF catheters deliver energy at a single point and therefore creating a contiguous line of these points can be difficult and time-consuming. Further, there is growing recognition of shortcomings and complications from RF, which are fundamentally a consequence of thermal heat generation and collateral damage. This has seen a growth and desire to find and test alternate energy approaches. In particular, there has been a renewed interested in the application of DC energy for ablation. When DC energy is applied in a pulsed fashion (typically short pulses), tissue is exposed to an electric field. Exposure to this electric field causes electroporation to occur by inducing the formation of nano-scale defects or pores which lead to the permeabilization of cells. Depending upon the settings of the field (e.g., pulse duration, voltage, etc) this can be reversible or irreversible (**Figure 1**). As seen in Figure 1 the application of the electric field is on a continuum, with greater applications promoting longer pore opening, and this can lead to irreversible cell death (ablation) by apoptosis (**Figure 2**).

Irreversible Electroporation (IRE) is a well-established treatment modality for solid tumors[13, 14, 15, 16] and is particularly alluring as a method for cardiac ablation when compared to RF approaches as it can create lesions without the consequences of thermal heating and preservation of surrounding

structures (nerves, vessels).[17] The application of IRE to cardiac tissue is an area of exponentially increasing interest and to date has been successfully applied to a range of cardiac tissues in animal studies. (**Figure 3**). In this review, we will explain the biophysics of electroporation, discuss the limitations of current thermal based approaches and examine the current data published on cardiac ablation with irreversible electroporation to provide insight into this novel, innovative approach.

2.0 Electroporation

2.1 What is electroporation?

Electroporation is a process in which a cell membranes permeability to ions and molecules is increased when the cell is exposed to high electric fields. Usually, these electric fields are applied in the form of short Direct Current pulses with an increase in cell permeability attributed to the formation of nanometric pores in the cell membrane, hence the term electro-poration.[18]. Depending upon the electric field applied, the effect of electroporation can be transient and result in viable cells after electric field exposure. In this case, the term reversible electroporation is applied. On the other hand, when the cells die due to prolonged electroporation, either because of permanent permeabilization leading to cell lysis or severe disruption of cell homeostasis during transient permeabilization, the term irreversible electroporation (IRE) is applied.

Electroporation is widely employed in many sectors, not only medical. In vitro, reversible electroporation is used for gene transfection of cells in culture[19] whereas IRE is applied for cold pasteurization of liquid media and has multiple other applications in food industry.[20] In vivo, tissue electroporation is the basis of numerous clinical treatment modalities. Reversible electroporation is the basis of electrochemotherapy[21], and it is also the basis of gene electrotransfer, which is used for multiple therapies under clinical trials, including cancer treatments and vaccination.[22] Irreversible electroporation (IRE) is an established non-thermal ablation method for treatment of solid tumors.

2.2 How does electroporation destroy (ablate) tissue?

At a cellular level, the initiation of electroporation depends on the cell transmembrane voltage (TMV), with electroporation occurring when the externally applied electric field (DC energy) induces a TMV that overcomes a cell's threshold. The threshold value depends on the characteristics of the electric field, in particular, this would be the number of pulses, frequency, duration and shape of the pulses, and on how electroporation is assessed (e.g., by noticing an increase of membrane electrical conductivity, by

detecting intracellular contents release or by observing cell lysis). Most authors report TMV threshold values in the range from 200 mV to 1 V.

Once this threshold is overcome and electroporation begins, cell membrane permeabilization occurs (through the formation of nanopores) and increases during the electric field exposure and rapidly drops after exposure cessation but, in cells, the permeabilization remains significantly high for seconds or several minutes. Actually, since this recovery stage (or resealing of the pores) has a duration several orders of magnitude longer than that of the field exposure (typically much shorter than a second), most passive transport of ions and molecules across the membrane occurs after the exposure rather than during the exposure.

It is worthwhile to note that different competing theories have been proposed to explain electroporation at the molecular level[23, 24]. No theory is unanimously accepted. In particular, disagreement exists regarding the nature of the cell membrane perturbation that allows an influx of molecules and ions long after electric field exposure. It has been proposed that large and stable hydrophilic pores are formed during the exposure and that those remain opened after.[18] However, some researchers disagree with this explanation.[23] Reported pictures of large pores obtained by freeze-fracture electron microscopy [25] are attributed to artifacts of the technique[23]. Nevertheless, it must be noted that recent studies based on molecular dynamic simulations indicate that, after establishing the required TMV, aqueous pores are created in the lipid bilayer in a few nanoseconds[26] or less[27], provide convincing evidence that pores are the most probable mechanism of the initial membrane perturbation.

As mentioned, if the electric field exposure is prolonged this can lead to irreversible electroporation and cell death. The exact mechanism of death in electroporation is unknown, and the reports on the pathways that lead to cell death are somewhat contradictory.[28] It is commonly accepted that tissue destruction by IRE with microsecond, and longer pulses are predominantly necrotic.[29] On the other hand, other studies have also found evidence of apoptotic death.[30, 31] Interestingly, a recent experimental study with short (2 µs) pulses suggests that tissue damage is predominantly apoptotic at low electric field magnitudes whereas it is primarily necrotic at high field magnitudes.[32] In the case of sub-microsecond pulses, with the delivery of so-called nanosecond pulsed electric fields (nsPEFs), it appears that cell death is predominantly apoptotic.[33] In addition to direct electroporation effects on the cells that can lead to their death, it must be contemplated the possibility of indirect effects. One of

those effects may be ischemia. It has been indicated that ischemia may be a possible mechanism of cell damage in electrochemotherapy and IRE due to microvasculature disruption.[34]

2.3 Is electroporation non thermal?

Electric power is always dissipated as heat at any conductor. This is known as *Joule heating,* but it is also referred to as *ohmic heating* or *resistive heating* because of its relationship with Ohm's law. If one was to provide a single pulse of 100 μs at a magnitude of 1000 V/cm, the maximum temperature increase that must be expected to occur in living tissues is about 0.36 ℃.[35] For 2000 V/cm, the maximum increase would be about 1.44℃. Such increases in temperature are unlikely to produce any thermal effects on tissue considering the threshold for thermal injury is reported at 50℃. However, since IRE typically requires a series of those pulses not a single pulse, thermal damage may occur.[36] This issue was addressed in detail by Davalos when they first proposed IRE as an ablation method[37] with the main conclusion that non-thermal IRE was feasible. Of note, since Joule heating depends on the square of the electric field magnitude, field heterogeneities have a significant impact on heating. As a consequence, high electric fields around thin needle electrodes or at the edges of flat electrodes are likely to cause localized thermal burns[36, 38]. That said, the consensus is that IRE ablation is mostly non-thermal and that has prompted its emergence as a distinctive ablation method.

2.4 How can we create electric fields for electroporation?

Except recently reported studies indicating the possibility of performing electroporation by magnetic fields[39, 40] and radiated electromagnetic waves[41], the electric field required for electroporation is delivered by applying high voltages or currents across electrodes within or in contact with the tissue.

For simple electrode arrangements or idealizations of those arrangements, it is possible to find analytical expressions to calculate the field distribution.[42] However, in most cases, the use of numerical methods to simulate the electric field in computers is required. The IGEA and AngioDynamics systems described below are accompanied by basic software tools that allow predicting the treatment regions for some electrode arrangements under the assumption of tissue homogeneity. However, these tools are far from being patient-specific treatment planning platforms. Some efforts are being conducted towards the development of treatment planning tools similar to those used in radiotherapy.[43]

Currently, the only commercial generator intended for clinical IRE is the AngioDynamics NanoKnife™ ablation system. Other clinical systems designed for electrochemotherapy, such as the IGEA Cliniporator™, potentially can be used for IRE because they produce similar voltage signals. These devices can generate pulsed voltages up to 3000 volts. In essence, these systems are based on slowly charging at high voltage a capacitor and then partially discharging it, in a controlled manner, through the electrodes and the tissues.[44]

Defibrillators have been the mainstay IRE generators in studies of cardiac ablation. It must be noted, however, that defibrillators are not optimized for IRE. Instead of generating a sequence of short pulses, defibrillators generate a single relatively long pulse of a few milliseconds (compared with micro or nanoseconds), which is less effective for IRE and more likely to cause thermal damage (**Figure 1**) and arcing issues. Further, typically defibrillators do not control the applied voltage, but the total applied energy, which is likely to impact repeatability and reproducibility negatively.

2.5 What are the typical electroporation (electric field) settings used in clinical practice?

To create cell death, a typical IRE protocol consists in a series of 100 DC energy pulses of 100 µs at frequencies from 0.1 Hz to 10 Hz. For this sort of protocol, the field magnitude threshold for IRE in tissues is in the range from 0.5 kV/cm to 2.5 kV/cm, depending on the tissue and how tissue damage is assessed.[45] It is worth mentioning that electroporation efficacy does not seem to be directly related to the amount of delivered energy or charge. For instance, two 100 µs pulses of 1000 V/cm will be much more effective for IRE that a single pulse of 200 µs with similar energy and charge.

3.0 Current thermal energy modalities for ablation: shortcomings and limitations

In essence, the goal of catheter ablation is the destruction of cardiac tissue coupled with the creation of a durable, transmural and contiguous lesion. There is a multitude of ablative energy sources available in clinical practice including RF, cryothermal, microwave, ultrasound and laser. Clinical experience and success with each of these energy modalities vary with the greatest experience with RF energy.

3.1 Radiofrequency

RF is the most commonly used energy source and, while largely efficacious; RF has a multitude of significant shortcomings and limitations. Application of RF energy to tissues results in thermal ablation

through resistive heating of the tissue with subsequent heat conduction to deeper tissue layers. Successful ablation lesion creation relies on a multitude of factors; contact force (CF), power, impendence, temperature, duration. [46, 47] [48, 49] The proximity of the posterior atrial wall to the esophagus makes it a potential site of thermal injury. Thermal injury can cause ulceration formation or the creation of an atrial-esophageal fistula - a devastating consequence that is often fatal.[50, 51] Further concerns include collateral injury to phrenic nerve[52] as well as the vagus nerve and its branches.[53]

Coagulation and tissue necrosis induced by thermal energy in RF is associated with a risk of thrombus formation. In atrial ablations, the reported incidences of TIA and stroke are of 0.2% and 0.3%[54] and increase further when RF ablation is performed in systemic cardiac chambers (1.8% to 2.0%) and for ventricular arrhythmias(2.8%).[55] Although there has been a reduction in periprocedural TE events with the introduction of open-irrigated catheters and the use of early and aggressive heparinization, there is growing concern for silent cerebral infarcts/lesions and the long-term consequences of these.[56] Silent infarcts assessed by brain MRI have shown to be associated with dementia and cognitive decline.[57]

3.2 Cryothermal ablation

The mechanism of cryothermal ablation is contrastingly different to RF, as cryothermal aims to remove heat from tissues thereby lowering molecular movement and stored kinetic energy, which results in tissue cooling and ice formation.[58] Unlike RF ablations catheters, cryocatheters come in two forms: traditional tip ablation catheters used for focal ablation and expandable balloon for PV isolation. Cryothermal ablation, like RF, is also associated with significant complications including esophageal fistula[59], PV stenosis[60, 61], phrenic nerve palsy[62, 63], and potential lung hemoptysis[64, 65].

3.3 Microwave

Microwave energy is less commonly use and still undergoing clinical investigation. Therefore data is limited compared to RF and cryothermal. The source of heat for ablation is electromagnetic radiation – when high-frequency electromagnetic radiation stimulates the oscillation of dipolar molecules (water molecules) at high speed. This speed of vibration creates friction between water molecules that result in heat formation. Thermal lesion development results from radiant heating, and therefore there is no requirement for catheter contact. Moreover, microwave radiation is not absorbed by blood and has the benefit of limited heating of endocardial surface thereby limiting coagulum formation.[66] Initial results

with this energy have shown good penetration depth with delivery not limited to electrode size and contact.

3.4 Ultrasound

High-intensity Ultrasound can be applied to cardiac tissues both surgically and endocardially and causes injury by two mechanisms; thermal and mechanical energy.[67] Ultrasound does not require direct contact with the myocardium. Its fundamental capability of enabling focusing and minimization of collimation enables directed therapy towards distant deep tissue without collateral damage particularly the coronary arteries.[68] The ability to perform ablation on deep tissue is valuable for VT ablation.[69] Although upfront an attractive option it has had issues since its first inception, particularly in AF ablations (endocardial approaches) and at present is not safe for everyday clinical use.[70]

3.5 Laser

Laser ablation produces a vibrational excited state in molecules and can be delivered in a continuous or pulse mode to created tissue heating and lesion formation. Ablation is performed with a 980-nm diode laser, housed in the central lumen. While there were limitations with the 1st generation design, in particular compliance, and thrombus formation[71], the second generation design was more compliant with a bloodless interface[72] Generally, initial results have shown success however like most of the thermal energies efficacy still relies largely on good contact.[73]

4.0 Electroporation: overcoming thermal-based limitations and shortcomings

As discussed, there is a multitude of concerns with thermal based approaches in cardiac ablation. Based upon current animal studies to date, Electroporation offers a unique approach which addresses and avoids these limitations (Table 1).

4.1 Contact

The need for contact is a major limitation of RF, Cryoablation, and Laser. Although most data has employed a contact based approach for testing, preliminary animal data suggests that electroporation does not require direct contact with the destruction of cardiac conduction system and myocardium distant to the cardiac delivery catheter. [74]

4.2 Limited collateral damage

Electroporation can provide a targeted approach that can result in minimal collateral damage, truly making it a very appealing option. Remarkably electroporation has been shown in animal models not to injure the phrenic nerve, esophagus or coronary arteries – major concerns with thermal based approaches. [75, 76, 77]

4.3 Thrombus formation

Based upon preliminary animal data, it does not seem that electroporation causes significant thrombus

4.4 Efficiency

Other thermal ablation methods can be time-consuming, particular RF. Electroporation can be applied quickly, often in a few secs.

4.5 Tissue Specificity

A unique feature of electroporation is that for a specific tissue and a specific set of electric field features (e.g., number of pulses, frequency, duration and shape of the pulses); it is possible to define an electric field magnitude threshold for achieving reversible electroporation and, a higher one, for irreversible electroporation. How best to target the desired tissue by the manipulation of these parameters still needs to be studied. This enables treatment planning for electroporation-based treatments.[78] This is invaluable in the world of cardiology as unlike current other ablation therapies, except cryotherapy, reversible electroporation could test and ensure one is correctly targeting the arrhythmogenic substrate before permanently (irreversibly) affecting the tissue.

4.6 Lesion homogeneity

To date, histological evidence from animal studies suggests that IRE can produce homogenous cardiac lesions. Lesion homogeneity is likely a function of both the electric field (i.e., strength, direction, pulse width, pulse shape) and underlying tissue properties when exposed to this field. As more research is performed, further information will enable these initial observations to be confirmed.

5.0 Current use of cardiac irreversible electroporation

As mentioned, the first experience with the application of DC energy was in the 1980s however there were significant complications from arcing and barotrauma from both a catheter and defibrillator that were not designed for effective IRE ablation. Since this time there has been significant advancement in both technology (such as catheter design and electroporation delivery tools) and understanding (such as the impact of field manipulations) that has made IRE an appealing ablation modality. As highlighted in **Figure 3**, it has many potential applications including, pulmonary veins cardiac muscle, Purkinje fibers and cardiac ganglia.

5.1 Cardiac tissue

The spark that spurred the revival of electroporation as a potential ablation energy source occurred in 2007, where IRE was successfully tested surgically as a method to perform epicardial atrial ablation.[79] In this study, the right and left atrial appendages were ablated with subsequent gross histological analysis showing a clear demarcation line between ablated and normal tissue. It was further noted, there was no charring and histology showed complete transmural destruction of atrial tissue at the site of the electrode application. Hong furthered these initial findings in 2009 when he applied electroporation epicardially at multiple locations in the heart and showed that many of the ablation lesions were transmural (a key element to an effective ablation lesion).[76]

On the foundation of this, Wittkampf[80] in the pursuit of a better energy modality for AF ablation applied electroporation directly to pulmonary vein ostia. At this time the recognition of the limitations of RF ablation was growing, particularly regarding pulmonary vein stenosis (a consequence of direct RF application to the PV ostia). His results remarkably not only demonstrated safety but showed a lack of histological changes associated with PV stenosis after three weeks that would be expected in RF ablation. These results were subsequently further validated in a long-term study using RF energy as a comparator.[81] Our group has also shown that we can delivery DC energy directly to the pulmonary veins without any stenosis.[82] Wittkampf further examined the relationship between delivered energy and lesion size by application of IRE to the myocardium epicardially and proposed that lesions deep enough for electrical PV isolation potentially could be created with a single 200J application of a few milliseconds in duration.[83]

As discussed above, RF energy cannot be applied to coronary arteries without significant consequences. Both du Pré[84] and Neven[75] published both short term and long term data (respectively) on the

safety of electroporation over coronary vessels and reported that no short-term (3 weeks) or long-term (3 months) luminal narrowing was seen. Further, deep myocardial lesions were created without the cost of major damage to the coronary arteries and notable advantage over current RF energy.

Zager[85] meticulously evaluated for a graded effect of different electroporation protocols on in vivo myocardial tissue. Results from their study showed IRE has a graded effect on the myocardium and that the extent of ablation can be controlled by changing pulse length, frequency and number, as well as by changing electric field intensity. Ultimately, greater field strength (voltage) and longer pulse duration resulted in greater myocardium ablation. More recently our group has published data on a novel prototype catheter that can perform IRE in pulmonary veins/atrial tissue.[86] All our treated pulmonary veins showed marked EGM amplitude reduction (61.2% on average) with all lesions transmural and histological analysis showing loss of cardiomyocytes with preserved structural collagen. Further, there was no significant PV stenosis detected on either CT scan or histology.

5.2 Esophageal

Esophageal injuries are a major concern in thermal approaches to cardiac ablation, particular when ablations are performed on the posterior wall of the atrium. There has been a drive in innovative devices and procedural techniques in an attempt to minimize this with varied results.[87, 88] Electroporation treatment is advantageous in that it has been shown in preliminary studies not to injury esophageal tissue both directly when applied to the esophagus and indirect through ablation in the left atrium. Hong[76] targeted the esophagus directly with electroporation and showed in contrast to RF ablation which compressed the esophageal wall and destroyed the epithelial, muscular layers, and the adventitia the IRE lesions were restricted to the muscle layer with the luminal epithelial layer and the delicate Lamina muscularis mucosae left without pathological changes. This was further validated by Neven[89] who showed that esophageal architecture remains unaffected two months using an energy level capable of creating ≈7-mm deep lesions.

5.3 Autonomics/nerves

Electroporation has also shown to have beneficial outcomes in relation to nerve damage. Outside of the cardiac field, the results of nerve sparing with electroporation have been largely positive, particularly in local treatment of tumors bordering nerves. Early studies showed no effect on the neurovascular bundle of canine prostates[90], which was supported by subsequent studies.[91, 92] However some studies have demonstrated axonal injury in the sciatic nerves with full recovery within seven weeks.[93, 94]

Regarding specific cardiac studies there is limited but early positive data, Neven showed that electroporation ablation applied at an energy level to created myocardial lesions did not damage histological or functionally of the phrenic nerve.[77]

The heart is richly innervated by autonomic nerves and activation of the autonomic nervous system (ANS) has been implicated in the genesis and propagation of AF[95]. Modulation of the ANS by targeting cardiac ganglionated plexus (GP) with endocardial ablation [96, 97] or surgical approaches [98, 99] has shown some benefit in AF treatment. However, as the GP are located predominantly in the fat pads on the epicardial surface of the heart, current approaches involve either significant invasive surgery or extensive endocardial ablation which can cause unnecessary myocardial damage. Our group has highlighted that GP electroporation is feasible and safe, with electroporation at 500–5,000 μA is moderately effective in abolishing the response to local application of acetylcholine and results in less atrial myocardial injury compared to RF.[100] Further data by our group (unpublished) confirms these findings and shows augmentation with the addition of Botox. Further, we have also shown (unpublished) that electroporative ablation is sustained and has minimal collateral damage.

5.4 Vessels

Direct application of radiofrequency ablation to cardiac vessels presents significant limitations. On the other hand, IRE by DC pulses has shown considerable promise in this regard, and it has been a topic led largely by the work of Maor[101, 102, 103, 104]. The effects of IRE were studied on the carotid artery or the iliac artery, with all studies showing that the connective matrix of the blood vessels remained intact and the number of vascular smooth muscle in the arterial wall decreased with no evidence of an aneurysm, thrombus formation or necrosis. Although further work is needed, these studies are preliminary indicative of the safety of treatment concerning the application of IRE near blood vessels.

5.5 Purkinje fibers

Purkinje system has been implicated in the genesis of primary VF[105, 106], with ablation of focal Purkinje triggers successfully treating the arrhythmia.[106, 107] Preliminary data from our group has shown the ability to manipulate the electric field to acutely eradicate Purkinje potentials without significant injury to the underlying myocardium.[108]

6.0 Electroporation challenges

Based upon current animal studies to date IRE is a cardiac ablation modality that has unique features which suggest the potential to be advantageous over current thermal based approaches. That said, there are several challenges facing this technology before it fulfills its promise and is adopted as the preferred cardiac ablation energy source in the clinical setting.[109]

6.1 Device design and innovation

IRE technology poses novel challenges for device design. The ideal ablation modality must be compatible with catheters in a wide variety of configurations and possess steerability, which will permit energy delivery to a variety of intra and extra-cardiac anatomical structures. The currently available irrigated and non-irrigated catheters may not be ideally suited for electroporation delivery. Catheters designed specifically for electroporation are under development, with models including circular epicardial, linear epicardial, and balloon endocardial devices.[82, 110] Further research into the impact of catheter diameter, geometry and profile will help design electroporation catheters of the future. The electric field intensity may vary with differences in catheter size and tip configuration (flat plate-like versus linear), and a better understanding of the electroporative capabilities of these will allow us to exploit these differences for clinical use.[111]

A dedicated generator system that can perform a wide range of electric field intensities and pulse width durations will allow flexibility and dose titration of energy delivery. Current cardiac IRE research involves a wide range of energy sources from adapting FDA approved technology (NanoKnife TM) to using external defibrillators.[86, 112], There exists a need for a concerted effort to develop generators capable of DC energy delivery across a wide range of voltage and pulse width duration; and the ability to power multiple catheters simultaneously. Ease of integration with currently available electroanatomic mapping and signal processing systems will assist in the adoption of IRE in contemporary labs.

6.2 Avoiding muscle and nerve stimulation

IRE protocols typically consist of series of direct current (DC) pulses with lengths ranging from 10 µs to 100 µs. Unless preventive measures are taken, these pulses are likely to cause acute pain and strong muscle contractions due to the capture of nearby efferent and afferent nerves. This is particularly relevant when monopolar electrode configurations are attempted due to the wider “antenna” inherent to monopolar stimulation.[113]

A commonly used workaround includes administration of local and general anesthesia along with muscle relaxants or neuromuscular blockade.[114] This leads to an increase in the complexity of the whole clinical procedure that may limit the applicability of electroporation-based treatments. To overcome this drawback, Davalos proposed a novel IRE pulsing protocol consisting of bursts of short (1 µs to 5 µs) bipolar square pulses.[32, 114] This protocol, labeled High-Frequency Irreversible Electroporation (H-FIRE), very substantially reduces muscle contractions, hence preventing the need for neuromuscular blockade. However, this protocol has not been studied for cardiac ablation.

6.3 Risk of ventricular fibrillation

Another adverse consequence of electroporation delivery is the risk of triggering ventricular fibrillation (VF) or other cardiac arrhythmias.[115] Fortunately, a solution was envisioned quite early in the field of electrochemotherapy: pulses can be synchronized with the electrocardiogram (ECG) signal so that they are delivered when all myocardium cells are in the absolute refractory period. Currently, all IRE treatments near the heart are delivered with ECG synchronization. This was concluded to be a safe procedure.[116]

6.4 Collateral heating

The tissue temperature required for thermal ablation is estimated at 50 degrees Celsius based on prior in vivo data.[117] As discussed previously, the Joule heating effect caused by IRE is considered to be negligible based on mathematical modeling.[118] Inferential data from in vivo experiments using conventional or specially designed IRE catheters suggests the absence of thermal ablation.[119]

In contrast, in vivo experiments with needle electrodes demonstrate significant Joule heating effects at extremes of electroporation settings.[120] Mathematical modeling as well as in vivo experiments by van Gemert et al. also found evidence of tissue temperatures exceeding 50 degrees Celsius.[121] Furthermore, esophageal temperatures much lower than 50 degrees Celsius and as low as 40 degrees Celsius are associated with the formation of esophageal ulcers, a precursor to atrioesophageal fistula, after atrial fibrillation ablation.[122] Direct measurement of tissue temperature while utilizing contemporary cardiac IRE protocols has not been performed. In vivo data studying multiple configurations of catheters coupled with different field strengths and pulse widths are critical to the identification of Joule heating thresholds and could determine non-thermal thresholds for cardiac electroporation.

7.0 Conclusion

Cardiac ablation is an established and important pillar in the treatment of patients with cardiac arrhythmias. Current approaches to ablation rely on thermal energy to create lesions, with RF the most popular modality. While thermal ablation overall is reasonably effective, it harbors significant limitations and complications. In particular, dependence on contact for effective lesion creation, collateral damage to nerves, myocardium, and blood vessels as well as thrombus formation raises the risks and complications associated with thermal ablation. Electroporation offers a non-thermal ablation strategy which has the potential to solve these issues, but further human clinical studies are required. Current animal data on irreversible electroporation shows significant promise for cardiac ablation should we address the challenges it faces.

8.0 Expert commentary

Evolution and innovation in cardiac ablation, particular regarding ablation energy modalities, tracks a truly remarkably course over the last 50 years. Today, radiofrequency (RF) is the most applied energy modality, but its significant limitations and shortcomings fuel the search for a superior modality. Attempts with other modalities to improve ablation risks and outcomes, such as with microwave and laser, have been somewhat unsuccessful to date, as they not been able to achieve the same efficacy and safety as RF. The primary concern with currently available energy modalities is the dependence on and consequences of thermal energy for lesion formation, which causes many complications, including collateral damage and thrombus formation. The ability to ablate with a non-thermal ablation modality would be paradigm shifting.

Irreversible electroporation is a non-thermal cardiac ablation modality that shows true promise. With alluring results from preclinical studies to date. Early results are optimistic, and early studies show an excellent safety profile with limited reported adverse events (which bodes well for future human use). As summarised in table 2 at present a large majority of cardiac IRE is based upon acute models; there is a need to increase chronic studies to examine the long-term effects of IRE with a particular focus on the durability of lesions and untoward effects on cardiac muscle and function. While further chronic studies are needed, before IRE can be truly established in human practice there are some challenges which need to be addressed (as discussed in the article). One particular challenge, which we feel is extremely important, is the development of a method to reduce or involve no pain with the delivery of IRE. Traditional IRE protocols, especially in the tumor field, require general anesthesia and deep muscle relaxants to limit muscle contractions during delivery. Techniques to circumvent this are been developed like nanosecond pulses or H-FIRE, but research with these techniques for cardiac ablation is sparse to date. Further studies are required in this regard.

Additionally, as cardiac innovation with IRE cultivates; we envisage translation of cardiac-based designs to tumor treatments, particularly balloon based designs. At present many of the tumor approaches are percutaneous – the experience with balloons in the cardiac IRE field may open up new horizons for transvenous tumor treatments.

9.0 Five-year view

In the next five years, as there is continued drive and innovation in the field of electrophysiology, there will be constant growth, application and understanding of irreversible electroporation (IRE) as an ablation modality. The major improvement we envisage is the development of IRE protocols for tissue specificity and the application of new IRE techniques to reduce muscle contraction. Further, we hope to see IRE employed in clinical trials (humans) as an AF ablation modality and close to application for the treatment of ventricular arrhythmias.

10.0 Key issues

- Electroporation is a process in which a cell membranes permeability to ions and molecules is increased when the cell is exposed to high electric fields. Usually, these electric fields are applied in the form of short Direct Current pulses. This effect can be reversible or irreversible and lead to cell death.

- Irreversible electroporation is an established ablation modality in solid tumors and has growing interest as cardiac ablation tool.

- Current approaches to cardiac ablation employ thermal energy, and although reasonably efficacious, thermal heat has significant drawbacks including thrombus formation, collateral damage, and the reliance on contact.

- Irreversible electroporation offers many advantages over current thermal based approaches; most importantly it is nonthermal, avoids collateral damage and can target specific tissue (tissue specificity).

- Early preclinical data shows significant promise of IRE as an ablation modality with an attractive safety profile.

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Declaration of interest

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Papers of special note have been highlighted as:
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*** of considerable interest*

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Figure legends

Figure 1 – Depiction of the impact of pulse duration and electric field strength on the observed impact, ranging from reversible electroporation to irreversible electroporation to thermal damage. The longer the pulses and the greater the voltage, the more likely there will be irreversible damage and the possibility of thermal damage.

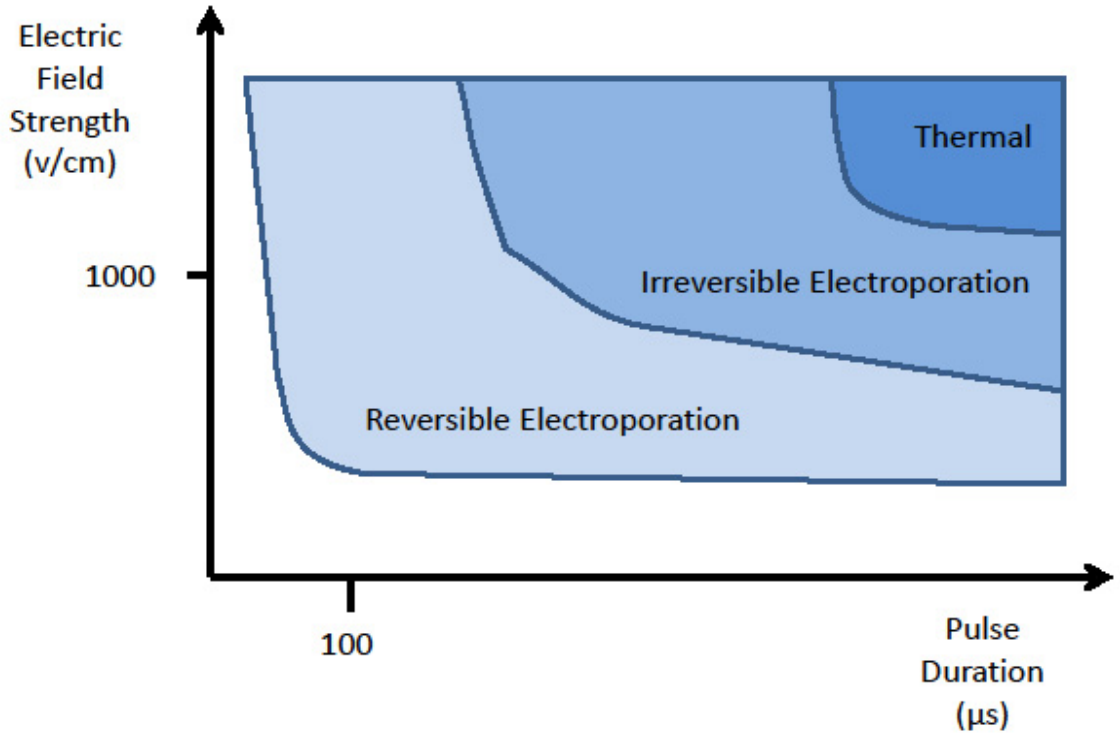

Figure 2 - Irreversible cell death by apoptosis

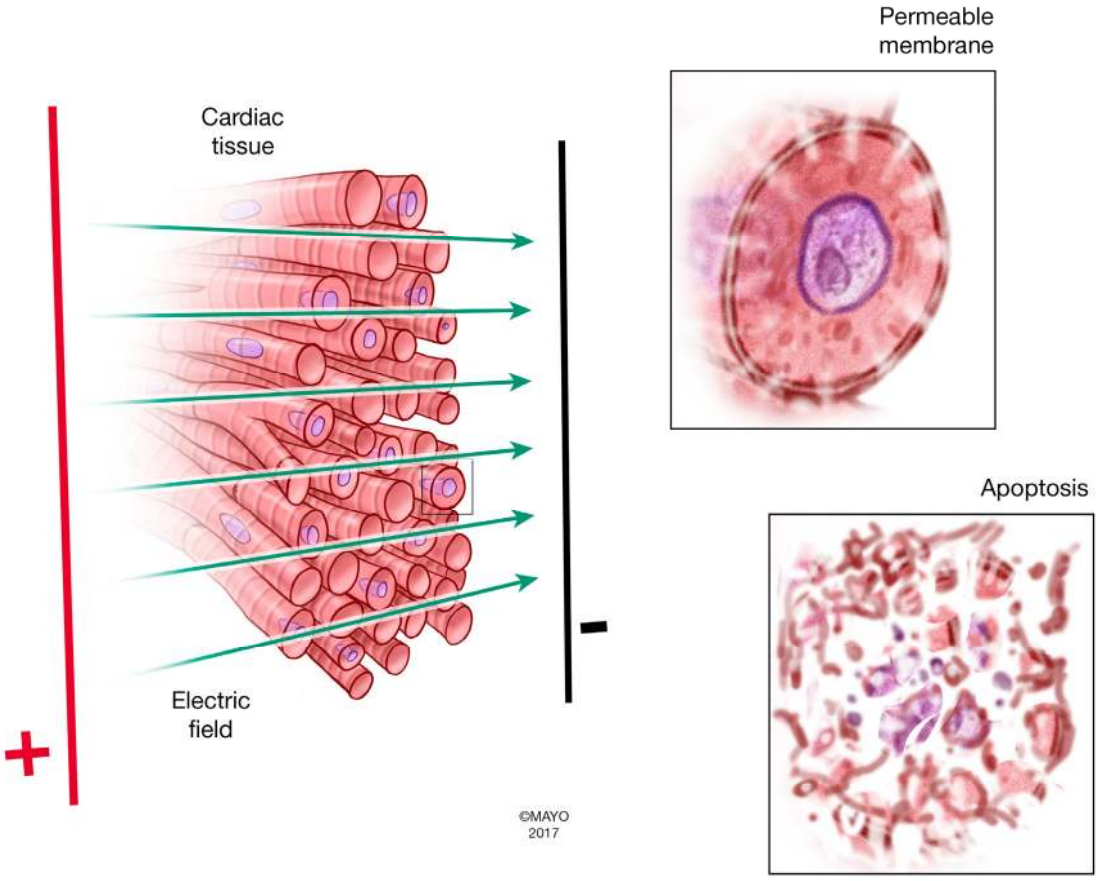

Figure 3 – To date, irreversible electroporation has been successfully applied to these areas of cardiac tissue.

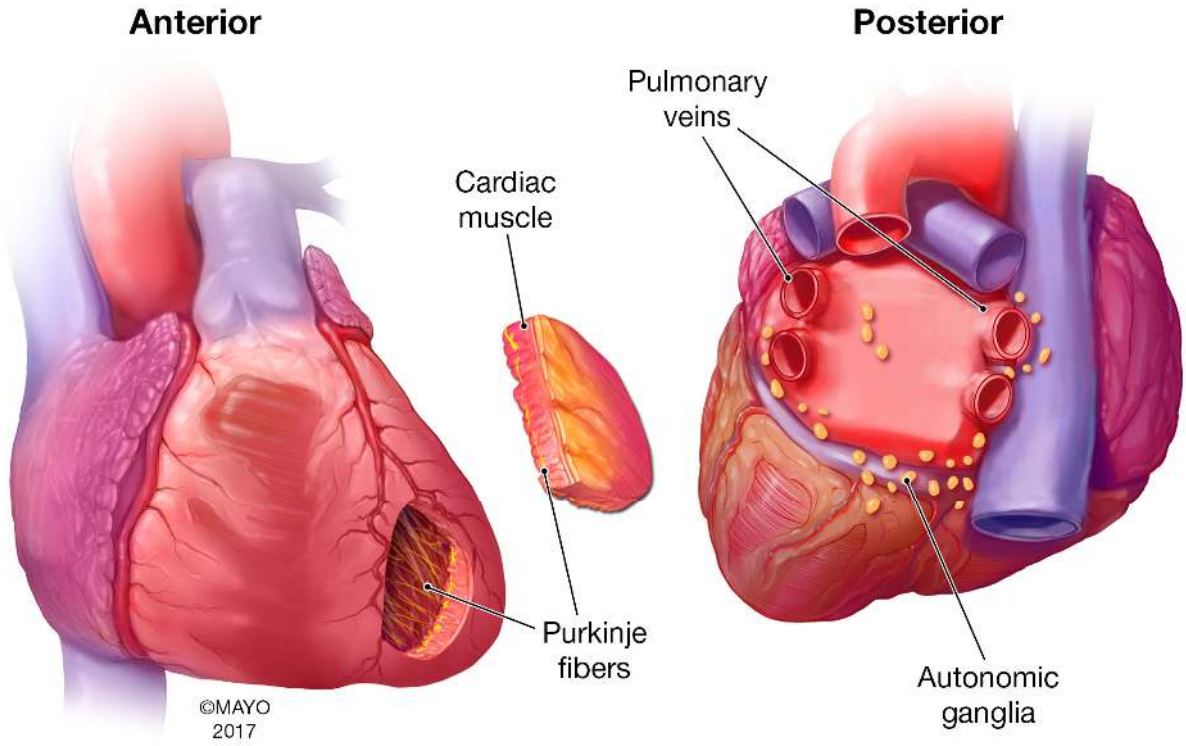

Table 1 – Comparison of Different Energy Sources for Ablation.

	Radiofrequency	Cryothermal	Microwave	Ultrasound	Laser	Electroporation (DC energy)*
Contact	Dependent	Dependent	Independent	Independent	Dependent	Independent
Collateral damage	Yes	Yes	Yes	Yes	Yes	No
Esophagus	++	+	++	+++	++	-
Phrenic nerve	++	++	++	++	++	-
Vagal nerve	++	++	~	~	~	-
Coronary Artery	++	-	++	-	++	-
Thrombus	++	+	-	-	+++	-
Tissue Specificity	-	-	-	-	-	+++
Reversibility Potential	-	++	-	-	-	+++

~ Unknown at present

*Based upon animal data published to date

Table 2 – Electroporation Targets and Limitations

Potential Cardiac Ablation Targets
- Atrial Fibrillation
- Ventricular Arrhythmias
- Ganglia
- Septum (for septal ablation)
Current Limitations
- Testing has been largely in preclinical models with limited human application
- Ideal electrical field parameters still need to be examined
- Method to reduce muscle contraction
- Long term studies need to address safety and efficacy