Electroporation
Past and Future of Catheter Ablation

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Successful catheter-based management of cardiac arrhythmia involves accurate identification of the arrhythmogenic substrate and complete, permanent elimination of that substrate without collateral injury. Despite >30 years of intensive research and innovation that has included novel energy sources, the seemingly straightforward objectives have been elusive. Limited advances have translated to clinical practice, including improved methods of delivering existing energy sources (irrigated catheters, balloon technology, and assessment of contact), but a permanent and effective energy source with efficient tissue specificity to eliminate the possibility of unnecessary collateral damage has not surfaced.

In this issue of *Circulation Arrhythmia & Electrophysiology*, Neven et al and van Driel et al from the laboratory of Wittkampf report 2 separate studies involving the use of irreversible electroporation (IRE) for cardiac ablation. They report in the first article the relative effects of IRE versus radiofrequency energy on the risk of pulmonary vein stenosis. In the second article, they examine the ability to create transmural lesions with IRE applied epicardially in the left ventricle with minimal collateral damage, specifically the potential for an ablation source to create transmural lesions without 2 of the most worrisome complications associated with thermal injury (scar leading to pulmonary vein stenosis and coronary arterial trauma).

Electroporation

Electroporation should be considered in the historical context of direct current (DC) ablation, the beginnings of catheter ablation. Direct current energy may produce effects by affecting the cell membrane, thermal injury, or barotrauma.3-5 In addition, nonhomogenous DC ablation lesions may be proarrhythmic.6 The relative merits of radiofrequency and DC ablation were studied extensively in the early 1980s and suggested better safety and efficacy with radiofrequency ablation.7,8

The term electroporation can be thought of more traditionally in the context of DC ablation that was performed in the early days of catheter-based ablation. Direct current energy produced cell damage by directly affecting the cell membrane although the amount of energy delivery required was often painful to the patient, thus requiring general anesthesia, and could result in barotrauma because of explosive gas formation at the catheter tip.3-5 Furthermore, because of nonhomogeneous lesion formation, DC ablation was also thought to result in proarrhythmia.6 The advantages of radiofrequency energy over DC ablation were studied extensively in the early 1980s and suggested that both efficacy and safety were much increased using radiofrequency energy.7,8

The concept of electroporation refers to applying an external electric field to a cell, resulting in an increase in electric conductivity and permeability of the cell plasma membrane.9-11 This is a dynamic phenomenon and has been implemented in a variety of biological systems—most commonly for transfection of cells in vivo or in vitro—and is potentially reversible (ie, the cells may reconstitute their membrane integrity). However, higher voltages used during electroporation, rather than transiently disrupting the cell membrane, have also been shown to be capable of destroying target cells within a discrete lesion, while leaving neighboring cells unaffected.9-12 This concept underlies the theory of IRE, wherein via nonthermal effects, a permanent effect on the cell membrane integrity via the creation of permanent nanopores that cannot be repaired leads to cell death. The cutoff between reversible and IRE is dependent on the electric field threshold of the tissue. When the electricity applied is below the cells’ threshold, the cells can repair their phospholipid bilayer and can restore the separation of charge across the membrane. However, when above the threshold, the pores formed are beyond the ability of the cells to repair themselves. Studies using nonthermal IRE have been done using both unipolar bursts of electricity at low frequency (which carries the risk of electrically depolarizing surrounding tissues, such as skeletal muscle) and bipolar bursts of electricity at high frequency (which eliminates the need for a paralytic agent during energy delivery).13

Early electrophysiologic ablation was in effect an early attempt at electroporation. However, the true potential of this technology was severely limited by specific energy delivery options and resulted in the multiple risks and complications mentioned above. Neven et al and van Driel et al report their work where these potential negatives were overcome, in part, by applying a novel catheter design using a circular arrangement of electrically connected electrodes to create a torus-shaped electric field rather than applying a single point of direct current energy.

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Tissue Specificity: The Key to Increase Efficacy and Improve Safety Simultaneously

The composition of a proximate tissue affects the electric field thresholds. Thus, the potential for controlled delivery of electroporation energy pulses may allow for preferential effects on certain tissues (eg, myocardium) by avoiding a similar effect on other also nearby tissue (eg, coronary arteries).

Pulmonary Vein Stenosis

Present radiofrequency ablation procedures for atrial fibrillation involved circumferential atrial ablation with meticulous care to avoid energy delivery into the pulmonary veins, so as to prevent the seriously lifestyle-limiting occurrence of pulmonary vein stenosis. The downside to wide area circumferential ablation is that a single area of recovery along the circle would then reconnect the vein completely. Desirable, perhaps, is ablation of the pulmonary vein myocardium itself so that even if recovery were to occur, only a small percentage of the arrhythmogenicity of the vein would reappear but can pulmonary vein ablation be performed without risking pulmonary vein stenosis? van Driel et al2 ablated up to a centimeter inside the pulmonary vein ostia with IRE and found no severe pulmonary vein stenosis and even an increase in the ostial diameter when compared with radiofrequency energy. This effect may be related to the relative tissue specificity of IRE affecting fibrogenic endothelium versus myocardium, which may become dilated or aneurysmal after ablation.

Esophagus and Phrenic Nerve

The present studies do not specifically shed light on whether IRE can be manipulated to avoid collateral damage to skeletal muscle, smooth muscle, or neural tissue.

Autonomic Tissue and the Retroatrial Ganglia

Ablation approaches have specifically attempted to target the pericardial autonomic ganglia to render the heart less likely to initiate or remain in atrial fibrillation. Whether electroporation can specifically affect the cardiac ganglia, which are encased within epicardial fat, without affecting the surrounding myocardium remains unknown.

Transmurality

For ventricular tachycardia ablation, an elusive goal is transmural ablation when a linear ablation approach is used to connect scars and anatomic obstacles. Furthermore, the true arrhythmogenic substrate may be embedded within fibrous/scar tissue. In addition, epicardial circuits are notoriously difficult to target from either an endocardial or epicardial approach because of the surrounding epicardial fat, phrenic nerve, and the coronary arteries. IRE has been shown previously, when treating tumors, that specific tissue injury to cancerous cells may occur with relative sparing of bystander tissue, such as the arteries or normal parenchymal tissue. Neven et al1 successfully demonstrate that transmural lesions can be reproducibly applied epicardially with a direct relationship between the amount of energy applied and the lesion size, and importantly without affecting the coronary arteries.

Remaining Needs and Unanswered Questions

There is a recognized risk of inducing ventricular arrhythmias during direct current energy delivery, including electroporation. Although methods to minimize the risk of ventricular fibrillation during electroporation delivery have been developed, an approach that completely eliminates this possibility is necessary before clinical implementation.

Although IRE was applied in the pulmonary vein,2 myocardium may extend beyond a centimeter into the vein, and ablation for the epicardial autonomic nerves may require even deeper energy application. The risk of stenosis developing at these sites requires investigation.

Although the data of Neven et al1 begin to reassure us that coronary artery damage will not occur with epicardial IRE, there was no purposeful targeting of the arteries to investigate worst case scenarios, particularly when the arteries themselves are diseased or flow limited. Coronary vasospasm, while not severe in the present study, can be difficult to manage in the electrophysiology laboratory. Finally, the principal potential merit of IRE—tissue specificity—is likely related to specific parameters and ranges of the IRE output, waveform, frequency, etc, and the precise methods on how best to target the desired tissue and pathological substrate by manipulating these parameters need to be worked out.

Summary

Professor Wittkampf had previously introduced and taught us about the value of open irrigation with ablation,26 and now his group reports on findings that highlight the potential advantages of IRE. The probable reason why this renaissance of DC as an energy source stems from existing experience in noncardiac fields (solid tumor oncology) is the potential tissue specificity and its corollary, tissue-sparing effects. Additional study that defines the exact energy delivery characteristics to exploit the possibly tissue-specific properties of IRE is needed fully.

Disclosures

Dr Asirvatham receives no significant honoraria and is a consultant with Abiomed, Attricure, Biosense Webster, Biotronik, Boston Scientific, Medtronic, Spectranetics, St. Jude, Sanofi-Aventis, Wolters Kluwer, Elsevier. Dr Asirvatham is a named inventor on a patent application covering electroporation technology. Neither Mayo Foundation nor Dr Asirvatham has received any compensation for the patent application to date but may do so in the future. The other authors report no conflicts.

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