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Electroporation: The 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 more than 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*, van Driel et al and Neven et al from Professors Wittkampf's laboratory report two separate studies involving the use of irreversible electroporation (IRE) for cardiac ablation.[1, 2] They report in the first paper[2] the *relative* effects of IRE versus radiofrequency energy on the risk of pulmonary vein stenosis. In the second paper,[1] 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 two 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 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, non-homogenous DC ablation

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lesions may be proarrhythmic.[6] The relative merits of RF and DC ablation were studied extensively in the early 1980s and suggested better safety and efficacy with RF 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, though the amount of energy delivery required was often painful to the patient, thus requiring general anesthesia, and could result in barotrauma due to explosive gas formation at the catheter tip.[3–5] Furthermore, due to non-homogeneous 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 electrical conductivity and permeability of the cell plasma membrane.[9–11] This is a dynamic phenomenon and has been implemented in a variety of biologic systems – most commonly for transfection of cells *in vivo* or *in vitro* – and is potentially reversible (i.e., 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 cells' membrane integrity via the creation of permanent nanopores that cannot be repaired leads to cell death. The cutoff between reversible and irreversible electroporation 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 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 EP 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. Van Driel et al and Neven 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 electrical field rather than applying a single point of direct current energy.[1, 2]

Tissue Specificity – The Key to Simultaneously Increase Efficacy and Improve Safety?

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

Pulmonary vein stenosis

Present RF 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 resurface, but can *pulmonary vein* ablation be performed without risking pulmonary vein stenosis?[14] Van Driel et al 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 osteal diameter 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 following 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 pericardiac autonomic ganglia to render the heart less likely to initiate or remain in atrial fibrillation.[15, 16] Whether electroporation can specifically impact 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. Further, 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.[17] IRE has been shown previously, when treating tumors, that specific injury to cancerous cells may occur with relative sparing of bystander tissue, such as the arteries or normal parenchymal tissue.[18, 19] Neven et al 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 prior to 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.

While Neven et al's[1] data 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 EP 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 needs to be worked out.

Summary

Professor Wittkampf and colleagues – who introduced and taught us the value of open irrigation with ablation – report their findings that highlight the potential advantages of irreversible electroporation. 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. Further study that defines the exact energy delivery characteristics to fully exploit the possibly tissue-specific properties of IRE is needed.

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