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Electroporation and Its Relevance for Cardiac Catheter Ablation

Fred H.M. Wittkampf, PhD,[a] René van Es, PhD,[a] Kars Neven, MD, PhD[a,b,c]

ABSTRACT

Irreversible electroporation can be used as a nonthermal energy source to ablate tissue. Cardiac catheter ablation by irreversible electroporation may be a safe and effective alternative for thermal ablation techniques such as radiofrequency or cryoablation. Total applied current, not delivered power (watts), energy (joules), or voltage, is the parameter that most directly relates to the local voltage gradient that causes electroporation. Electroporation can be achieved with various modalities: direct current, alternating current, pulsed direct current, or any combination of these. Experimental cardiac and noncardiac studies have demonstrated tissue specificity with survival of arteries and nerves in large lesions. In addition, porcine data suggest that application inside a pulmonary vein does not lead to pulmonary vein stenosis and that the esophagus is remarkably insensitive to electroporation. Therefore, irreversible electroporation is a very promising technique for cardiac catheter ablation and especially for electrical pulmonary vein isolation. (J Am Coll Cardiol EP 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

In the last decade, we explored electroporation as a novel energy source for cardiac catheter ablation. This project was triggered by the observation that internal cardioversion eliminated the left atrial electrograms recorded via a cardioversion catheter in the coronary sinus. As was discovered after starting this project, the same observation and even lesion analysis had already reported by Wijffels et al. (1).

RELEVANT ELECTRICAL PARAMETERS

During cardiac stimulation, defibrillation, radiofrequency (RF) ablation, as well as during electroporation, an electrical voltage is applied between at least 2 electrodes in contact with tissue. This results in a current flow that depends on the magnitude of applied voltage and total electrical resistance. The latter is affected by the size, shape, and surface structure of the electrodes, distance between electrodes, and the resistive properties of all structures between electrodes.

Within the target tissue, the local effect of the application directly depends on the strength of the local electrical field. However, the relationship between applied voltage and local field is rather complex. Simply dividing applied voltage by distance between electrodes yields 1 uniform value for the electrical field strength v (V/cm) within all targeted tissue. Such calculation is only valid for the exceptional case of a homogeneous current density in tissue sandwiched between 2 parallel plate electrodes.

With unipolar and bipolar catheter ablation, however, the applied current spreads out from the application electrode(s). This creates a spatially dependent local current density i (A/cm^2) through tissue that

From the [a]Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands; [b]Department of Electrophysiology, Alfried Krupp Krankenhaus, Essen, Germany; and the [c]Witten/Herdecke University, Witten, Germany. Dr. Wittkampf is consultant for Abbott and St. Jude Medical; and is a coinventor of circular electroporation ablation and receives royalties from its commercial use. Dr. van Es is a coinventor of circular electroporation ablation and receives royalties from its commercial use. Dr. Neven is a consultant for Abbott.

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ABBREVIATIONS AND ACRONYMS

DC = direct current

PV = pulmonary vein

RF = radiofrequency

usually decreases with the square of distance from the electrode(s). The current density creates a local electrical field across targeted cells according Ohm law in 3-dimensional space: field strength $v = i \times r$, with r (Ω cm) being the local specific resistance. Local current density and thus also field strength both relate linearly to total ablation current: Everywhere in the tissue, local current density and field strength increases by a factor of 2 when total ablation current is doubled.

Conversely, the relationship between applied voltage and local field strength across a targeted cell membrane is rather complex. The resistance of the indifferent electrode is part of total ablation resistance. A higher indifferent electrode resistance causes a smaller total applied current and thus a smaller local current density and field strength. Consequently, local field strength may differ despite a constant applied voltage. Using applied energy as ablative parameter is even more erroneous. Energy is the product of applied voltage, current, and duration of the application. Doubling of ablation current and thus doubling of local current density and electrical field strength will require doubling of applied voltage and thus 4 times more energy! In other words, an increase in applied energy by a factor of 2 only increases local current density by a factor of $\sqrt{2} = 1.4$.

With a given electrode configuration and tissue contact, total applied current therefore is the parameter that most directly relates to the strength of the local electrical field that may lead to electroporation (2–4). A future generator should therefore allow for control of delivered current strength, not voltage or energy.

ELECTROPORATION THRESHOLD

Electroporation current can be achieved with various modalities: direct current (DC); alternating current; pulsed DC; or a combination of these (5–10). Published data about the critical magnitude of the required field strength for permanent electroporation range from a few hundred millivolts across single cell membranes to values in the 500 to 1,000 V/cm range for a suspension of living cells and tissue (11–16). Data of linear epicardial electroporation ablation with a linear suction device allow for an estimation of the threshold current density for permanent electroporation using a single monophasic application with a duration of a few milliseconds (17). The suction device ensures that all delivered current will be forced through myocardial tissue and the half-circular cross-sectional shape of these lesions allows estimation of the outer lesion surface area where current density must have reached lesion threshold level. This calculation suggests a current density threshold level of 1.7 A/cm^2. For a specific myocardial impedance of 158 Ω cm, as reported for healthy sheep myocardium, this would correspond to an electrical field strength of 268 V/cm (18).

TISSUE SPECIFICITY

As explained, local current density creates an electrical field, expressed in volts per centimeter, and the logical consequence is that the voltage across each tissue cell will be proportional to its diameter measured in the axial direction of the electrical current. Cell size may thus be among the factors that determine tissue specificity of electroporation (13). Cell membranes have a much higher electrical resistance than the extra- and intracellular fluid and therefore the voltage across each cell is roughly divided over the 2 membrane sections that are perpendicular to the direction of current flow. Both these sections are thus exposed to approximately one-half the voltage gradient across the complete cell and are the most likely sites where pores will be created (8,19) (**Figure 1**).

The estimated permanent electroporation threshold of 268 V/cm is much lower than what has been reported for other tissue types. However, our impulse waveform also is very different from the pulse trains that have been applied in almost all noncardiac studies. Therefore, these values cannot be used to explain selective myocardial ablation.

BLOOD VESSELS

Various studies reported blood vessels to appear unaffected after electroporation ablation. Motivated by the anticipated use electroporation for treatment of tumors near large blood vessels, the carotid artery has been directly targeted in rats using a bipolar clamp around the artery. Histology, 4 weeks after the procedure, showed that the connective matrix of the artery remained intact with no evidence of aneurysm, thrombus formation, or necrosis (20).

In a porcine study, histological analysis 14 days after pancreatic electroporation ablation revealed patent vascular structures in targeted areas despite significant destruction of pancreatic tissue (21). In the same species, an electroporation study targeting lung tissue with 4 weeks survival demonstrated mild chronic inflammatory changes and hemosiderin deposition, but otherwise intact vessels without