REIVEW ARTICLE

Clinical Usage of Tissue Electrical Conductivity during the Electroporation: An Essential and Useful Factor

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Abstract

Electric field intensity at each point is responsible for pore creation in the cell membrane during the electroporation process. These pores can increase the tissue electrical conductivity in the electroporation. Changes in electrical conductivity through the electroporation is a useful factor for imaging and tracking of electroporation inside the body. Electrical conductivity is set to become a vital factor for accurate estimation of the electric field and cell kill probability distribution in the course of electroporation for treatment planning purposes. Therefore, for more accurate treatment, tissue electrical conductivity changes due to electroporation should be considered in the treatment planning system. This paper describes the advantages of tissue electrical conductivity as a useful factor in the clinic.

Keywords: Electroporation; Electrical Conductivity; Electric Field; Numerical Modeling.

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1. Introduction

Electroporation is a physical process that used electric pulses [1]. This process has application in the treatment of cancerous tumor and macromolecule transport to the cells [2, 3]. During the electroporation, pores were created in the cell membrane [3–5] (Figure 1). The resulting pores can be temporary or permanent [6]. If transient pores were constructed, the resulting process was called reversible electroporation [7] (Figure 1). Irreversible electroporation is the outcome of the fabricates of permanent pores [8].

Reversible electroporation provides a powerful tool for gene delivery and chemotherapy agent delivery (Electrochemotherapy (ECT)) into the cell [9–15] (Figure 1). However, irreversible electroporation has the potential for killing the tumor cells and was used as a new ablation technique without Joule heating with the minimum invasive process [16–21] (Figure 1). Electric field intensity is the main cause of pore creation on the cell membrane. It is generally accepted that electric field intensity inside the tissue is the most critical factor during the electroporation [22–24]. Electric field intensity and distribution inside the tissue depend on pulse parameters, electrode parameters, and tissue parameters [25–28]. Pulse dependent parameters include pulse shape, frequency, voltage, duration, etc. [29]. Electrode parameters are electrode type, distance, number, insertion depth, electrode geometry, etc. [25, 30]. The most critical tissue parameter is electrical conductivity. Electrical conductivity at any point can affect the electric current and electric field intensity at the desired point. A growing body of literature has evaluated the electrical conductivity during the electroporation process [31–39].

This paper is an overview of electrical conductivity during the electroporation and use of this parameter in the clinic for different purposes (Table 1). This paper is divided into three sections. The first section gives a brief overview of the models used for calculating the electric conductivity change and expresses the relationship between electric conductivity and electric field intensity in the electroporation procedure. The second section analyzes the conductivity change during the electroporation. In the third section, the clinical use of conductivity change during the electroporation is presented. The aim of this review is to evaluate the impact of electrical conductivity on the electroporation process and investigate the usage and effectiveness of this parameter in the clinic.

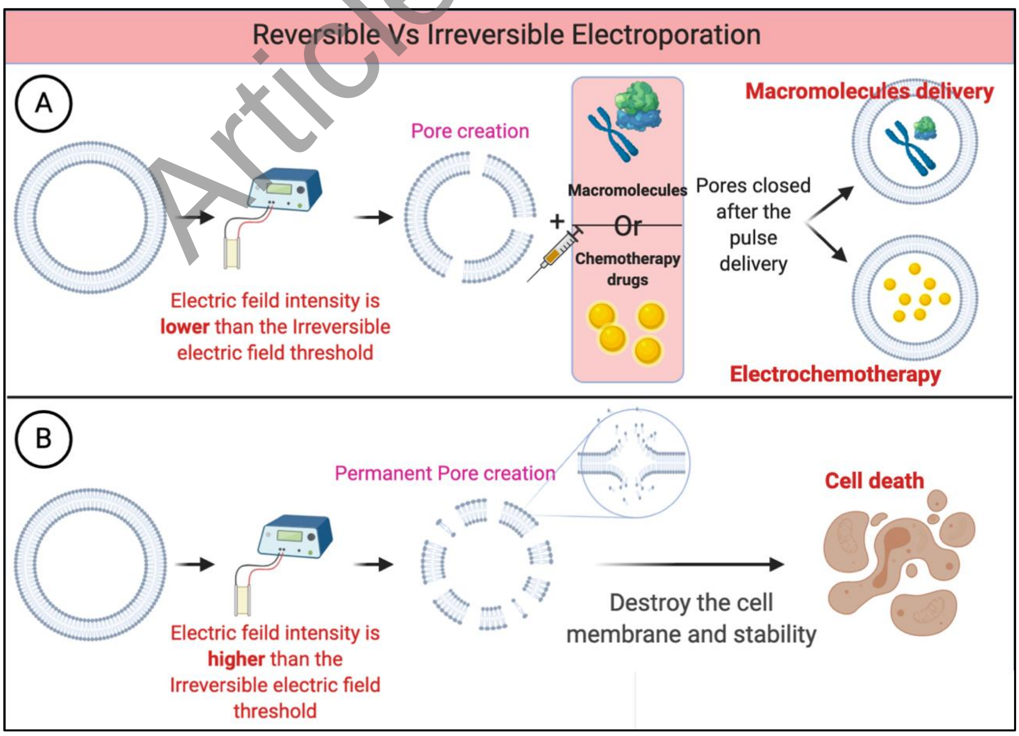

Figure 1. Electroporation use in the clinic. A-Reversible Electroporation (RE) is used for macromolecules and gen delivery to the cells and Electrochemotherapy. B- Irreversible Electroporation (IRE) is used for killing undesirable cells and tumor treatment

Table 1. Summary of the usage of electrical conductivity changes in the clinic

References	Year	Journal	Purpose
Sel *et al.* [40]	2005	*IEEE Trans. Biomed. Eng.*	Calculating the conductivity and electric current in the electroporation.
Garcia *et al.* [41]	2010	*J. Membr. Biol.*	Considering the dynamic electrical conductivity of the tissue and electric field for the treatment planning system in electroporation.
Ivorra *et al.* [31]	2007	*Bioelectrochemistry*	Calculating the conductivity change in electroporation in liver tissue.
Pliquett *et al.* [32]	2009	*IEEE Trans. Dielectr. Electr. Insul*	Calculating the conductivity change in electroporation.
Khorasani *et al.* [33]	2017	*Iran. J. Med. Phys.*	Calculating the conductivity change during the irreversible electroporation with the plate electrode and high-frequency pulses.
Khorasani *et al.* [34]	2019	*Polish J. Med. Phys. Eng*	Calculating the conductivity change during the irreversible electroporation with needle electrode and high-frequency pulses.
Moisescu *et al.* [35]	2013	*Biochim. Biophys. Acta (BBA)-Biomembranes*	Calculating conductivity change in electroporation
Ben-David *et al.* [42]	2013	Radiology	Studying the effects of the tissue parameters and the surrounding electrical microenvironment on the outcome of Irreversible Electroporation (IRE) ablation
Pliquett *et al.* [43]	1995	Biochim. Biophys. Acta (BBA)-Biomembranes	Calculating the electrical parameters of human stratum corneum due to electroporation
Ivorra *et al.* [46]	2009	*Phys. Med. Biol.*	Correlation between treatment outcome and electric conductivity change in the electroporation process
Garcia *et al.* [45]	2012	*Annual International Conference of the IEEE Engineering in Medicine and Biology Society*	Calculating the pre and post treatment tissue electrical conductivity and analyzed for estimation of electric field intensity and treatment output
Ivorra *et al.* [48]	2009	*World Congress on Medical Physics and Biomedical Engineering*	Impact of conductivity change in electroporation on the electroporated area and electric field intensity
Khorasani *et al.* [47]	2018	*mdrsjrns*	Effect of conductivity change on electric field distribution in electroporation with low-frequency pulses
Corovic *et al.* [49]	2013	*Biomed. Eng. Online*	Impact of electric conductivity in electric field intensity and distribution

References	Year	Journal	Purpose
Khorasani [42]	2020	*Polish J. Med. Phys. Eng*	Effect of tissue electrical conductivity on cell killing probability distribution inside the tissue with needle electrode by a finite element analysis
Davalos *et al.* [50]	2002	*IEEE Trans.Biomed.Eng.*	Use of electric impedance tomography (EIT) for monitoring the electroporation process
Kranjc *et al.* [51]	2014	*Physiol. Meas.*	Use magnetic resonance imaging electrical impedance tomography (MREIT) to reconstruct conductivity images during the electroporation process.

2. Main Text

2.1. Mathematical Model for Conductivity Change during Electroporation

To calculate the tissue electrical conductivity during the electroporation, different models are introduced. By using these models, we were able to calculate electrical conductivity quantitatively in the electroporation process. Some preliminary models and work were listed below.

In their groundbreaking paper, Sel *et al.* [40] introduce a sigmoid model for calculating electrical conductivity in the electroporation process.

$$\sigma(E) = \frac{\sigma_1 - \sigma_0}{1 + De^{-\frac{E-A}{B}}} + \sigma_0 \qquad (1)$$

$$A = \frac{E_0 + E_1}{2} \qquad (2)$$

$$B = \frac{E_1 - E_0}{C} \qquad (3)$$

Where $\sigma(E)$ is the electrical conductivity, σ_1 is maximum electrical conductivity during the electroporation, σ_0 is the base-line of electrical conductivity before the pulse delivery to the tissue, E is electric field intensity at each point inside the tissue, A, B, D, E_1, and E_0 are the constant values for each tissue type. This model has been demonstrated to be useful for predicting the conductivity change and volume of permeabilized tissue in electroporation. The main limitation of Equation 1 is ignoring the effect of temperature. Garcia *et al.* [41] calculated the electrical conductivity during the electroporation by a numerical model for the treatment planning system. In this model, temperature and electric field intensity dependency were considered.

$$\sigma(\mathrm{E,T}) = \sigma_0 * \left(1 + flc2hs\left(E - E_{delta}, E_{range}\right) + \alpha * (T - T_0)\right) \qquad (4)$$

Where σ_0 is base-line conductivity of the tissue before the treatment, E is the electric field intensity, E_delta is the electric field threshold, E_range is the electric field range, α is temperature coefficient, and T and T_0 are the temperature and initial temperature of the tissue, respectively. flc2hs, is a smoothed Heaviside function in COMSOL Multiphysics software. Having Equation 4 enabled us to calculated electrical conductivity more precisely. Different studies were used Equation 4 for calculating conductivity change [34, 42, 43].

2.2. Conductivity Changes during the Electroporation

There is a considerable amount of literature on tissue electrical conductivity during the electroporation process [31–35, 40]. They point out that because of the large electric field intensity, the tissue electrical conductivity was increased at the time of sending the electroporation pulse during the electroporation process. In their analysis of tissue electrical conductivity changes in the electroporation phenomenon, Ivorra *et al.* [31] highlight that the increase in tissue electrical conductivity in irreversible electroporation was more significant than in reversible electroporation.

They point out that, due to larger electric field intensity in irreversible electroporation compared with reversible electroporation, the increase in tissue electrical conductivity in irreversible electroporation was more tremendous. Eliel *et al.* [44] demonstrated that irreversible electroporation is highly sensitive to the target tissue and the surrounding's electrical conductivity, which influences the treatment results. Several studies, for example, [33, 34], have been carried out for comparison of the change in tissue electrical conductivity with different electrode types. Different electrode types such as needle, plate, and single bipolar electrode with different configurations are used for pulse delivery in the electroporation process. It has been shown that the changes in tissue electrical conductivity with needle electrodes were more prominent than the plate electrodes [34]. The reason for the more considerable conductivity changes in the electroporation process with needle electrodes related to plate electrodes can be attributed to the larger current density at the tip of needle electrodes. Several studies have calculated the conductivity changes in different points inside the tissues during the electroporation [33, 34]. They conclude that the electrical conductivity increase in the region near the tip of electrodes was more considerable compared to other points inside the tissue. It has been suggested that in the vicinity of the electrodes, especially in the tip of electrodes, during the electric pulse delivery, the electric field intensity was more significant than in comparison with points in the tissue which are far away from the electrodes. An increasing number of studies have found that the tissue electrical conductivity during the electroporation increased with the voltage of electric pulses [33, 34, 40, 45]. The electric field intensity inside the tissue increased with the voltage of electric pulses in the electroporation process. And this increase in electric field intensity inside the tissue is responsible for the rise in tissue electrical conductivity in the electroporation phenomenon.

2.3. Clinical Use of Conductivity Change during the Electroporation

In the previous section, demonstrated in the electroporation process, conductivity was increased. So, electrical conductivity rise could be used in the clinics to predicate the outstanding treatment, accurate electric field intensity, cell killing probability distribution for treatment planning, and imaging and monitoring the electroporation process (Figure 2).

2.3.2. Impact of Conductivity Change on Electric Field Intensity and Distribution

Ivorra *et al.* [48] reported on by taking into account electrical conductivity change during the simulation, the error in the electroporated area went down from 30 % to 3 % and concluded that for successful treatment,

2.3.1. Conductivity Change as a Prediction Parameter

The most remarkable result to emerge from previous papers is that, in the electroporation, tissue electrical conductivity was increased significantly. So electroporated regions inside the tissue can be detected by measuring conductivity changes.

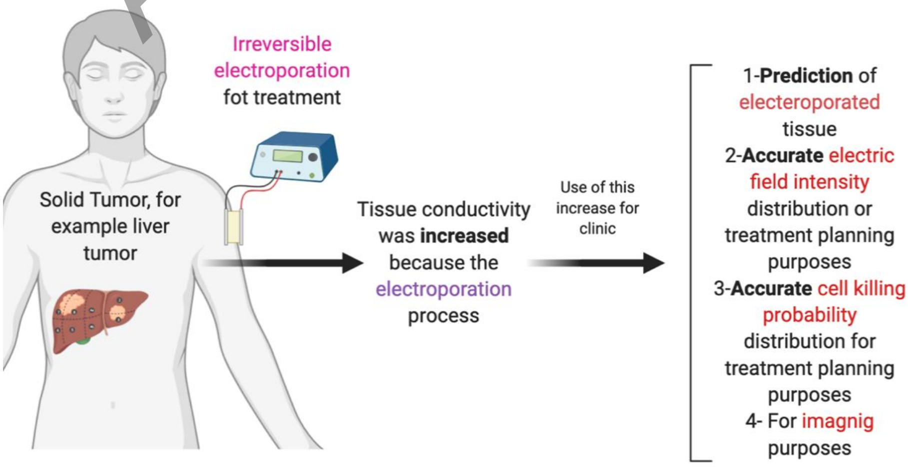

Figure 2. Use of tissue electrical conductivity in the clinic after the electroporation procedure was done

Ivorra *et al.* [46] developed methods for detecting electroporation and concluded that by measuring the tissue electrical resistance and tissue electrical conductivity, we could predict the electroporation occurrence. They have measured the electrical conductivity of target tissue in mice before, within the pulses, and for up to 30 mins after electroporation treatment pulse delivery. There was a significant correlation between post-treatment tissue electrical conductivity with treatment outcome. In [47] the ratios pre and post-treatment of tissue electrical conductivity were used to predict of electric field intensity distribution and treatment volume and presented a model based on the electric conductivity of the tissue.

the electrical conductivity increase due to electroporation must be considered. Khorasani *et al.* [43] calculated the impact of conductivity changes on electric field distribution in the electroporation. They have used a finite element simulation in two groups of simulations to calculate the electric field intensity and distribution inside the target tissue in their study. One group simulated the electroporation process by considering the constant value for the electrical conductivity of liver tissue. Another group used the variable electric conductivity during the pulse delivery in the electroporation process. And they make a comparison with the results of these two groups of simulation. The analyses highlighted the impact of change in tissue electrical conductivity during the electroporation on the electric field intensity and distribution inside the tissue. They claim that in the electroporation process for accurate estimation of electric field intensity and distribution, we should consider the impact of conductivity change on electric field distribution inside the tissue. In a major advance in 2013, Corovic *et al.* [49] investigated the tissue response to the electroporation when the increase of tissue electrical conductivity was taken into account. They reported on a different electrode type and tissue modeling in comparison with [43]. They underline that for more precise prediction of tissue volume, which was effectively electroporated, the increase in tissue electrical conductivity through the electroporation must be taken into account.

2.3.3. Impact of Conductivity Change on Cell Kill Probability in Electroporation

The aim of irreversible electroporation is to destroy undesirable cells and maximum damage to the tumors with minimum damage to the surrounding healthy tissues. To achieve this goal, we can use a treatment planning system. Initial work in this field focused on treatment planning systems based on electric field intensity and distribution, which is difficult and incomprehensible for clinical use. Instead of electric field intensity, we can use cell killing probability. The different cell killing models exist. One of the vital models is the Peleg-Fermi model, which is an electric field intensity-dependent model.

The first study on the influence of conductivity change on cell killing probability distribution through irreversible electroporation was conducted in 2020 by Khorasani [42]. He used the Peleg-Fermi model with needle electrodes to calculate cell killing probability. Peleg-Fermi model is an electric field and pulse number dependent mathematical model for calculating cell killing probability at each point. It has been demonstrated that by bearing in mind the effect of the increase of tissue electrical conductivity on cell kill probability, we can achieve more accurate treatment planning.

2.3.4. Electrical Conductivity Change for Imaging Purpose

The results of previous studies indicated that tissue electrical conductivity increased during the electroporation, as described in the previous section. We can use this increase in tissue electrical conductivity for imaging purposes to monitor and follow-up the treatment procedure. So, tissue electrical conductivity in the electroporation phenomenon is a useful factor for imaging purposes.

Electrical Impedance Tomography (EIT) is a non-invasive imaging modality. In this modality, the electrical conductivity and impedance of the body were measured by surface electrodes, and the tomographic images were reconstructed based on the electrical properties of tissue. In the literature, which is given in the previous section, several studies have been published in tissue electrical conductivity increased in the electroporation procedure [31–35], [40]. So EIT can be used as an imaging modality for monitoring of electroporation.

In their cutting-edge paper, Davalos *et al.* [50] have shown the EIT images of electroporated tissue. Kranjc *et al.* [51] reported new imaging methods with Magnetic Resonance Imaging (MRI) for imaging of the electroporated region. They used Magnetic Resonance imaging Electrical Impedance Tomography (MREIT) for the reconstruction of conductivity images during the electroporation. They suggest that we would be able to use MREIT as an electrical conductivity imaging utility for electroporation detection and monitoring.

3. Conclusion

Electrical conductivity is a tissue parameter that can affect the electroporation process. This paper has investigated the importance of electrical conductivity during the electroporation as an essential and attractive parameter for clinical use.

Much work has demonstrated that the tissue electrical conductivity increased in the electroporated regions inside the tissue because of pore creation in the technique. The evidence from this study implies that tissue electrical conductivity change in the electroporation process can be both beneficial and harmful in electroporation's clinical use. The positive aspect of conductivity change in the electroporation is using this change for medical imaging, monitoring, and prediction of electroporated tissues. This finding highlights the usefulness of the combination of electroporation method with imaging modalities such as MREIT and EIT for the detection of electroporated area and tracking and monitoring of the electroporation process. On the other hand, electrical conductivity affects the electric field's magnitude and distribution in the tissue. In the clinic, physicians used the electroporation treatment planning system to show the electroporated regions and electric field and cell killing probability distribution and choose best electrode and electric pulse parameters for maximum damage to the target tissues and minimum damage to the normal tissues. Bodies of literature point out that electric field and cell killing probability distribution and intensity changed by considering electrical conductivity changes in the electroporation method. I believe that in order to have precise and proper treatment planning results and treatment outcomes, electrical conductivity changes during the electroporation should be considered in the treatment planning systems.

I have obtained satisfactory results from other studies, proving that the electrical conductivity is a useful and vital factor in the electroporation process and in the clinic to achieve the best treatment outcome, for monitoring and imaging of the electroporation procedure, and for electroporated tissue prediction, must be considered and must be used.

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