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Conductivity change with needle electrode during high frequency irreversible electroporation: a finite element study

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Abstract

Irreversible electroporation (IRE) is a process in which the cell membrane is damaged and leads to cell death. IRE has been used as a minimally invasive ablation tool. This process is affected by some factors. The most important factor is the electric field distribution inside the tissue. The electric field distribution depends on the electric pulse parameters and tissue properties, such as the electrical conductivity of tissue. The present study focuses on evaluating the tissue conductivity change due to high-frequency and low-voltage (HFLV) as well as low-frequency and high-voltage (LFHV) pulses during irreversible electroporation. We were used finite element analysis software, COMSOL Multiphysics 5.0, to calculate the conductivity change of the liver tissue. The HFLV pulses in this study involved 4000 bipolar and monopolar pulses with a frequency of 5 kHz, pulse width of 100 µs, and electric field intensity from 100 to 300 V/cm. On the other hand, the LFHV pulses, which we were used, included 8 bipolar and monopolar pulses with a frequency of 1 Hz, the pulse width of 2 ms and electric field intensity of 2500 V/cm. The results demonstrate that the conductivity change for LFHV pulses due to the greater electric field intensity was higher than for HFLV pulses. The most significant conclusion is the HFLV pulses can change tissue conductivity only in the vicinity of the tip of electrodes. While LFHV pulses change the electrical conductivity significantly in the tissue of between electrodes.

Key words: irreversible electroporation; electric conductivity; high frequency; low voltage; finite element.

Introduction

Electroporation is a phenomenon in which cell membrane permeability to ions and macromolecules is increased by exposing the cell to short, high electric field pulses [1]. This process is related to the creation of nano-scale defects or pores in the cell membrane [2]. Membrane permeabilization can be either permanent or temporary, termed irreversible electroporation (IRE) or reversible electroporation (RE), respectively [3].

In RE, temporary pores are formed. This process is used for the introduction and transfer of macromolecules, such as DNA and proteins, into cells. But, after the end of the electric pulses, the pores close and the cells remain viable [4].

Under some conditions (e.g., extremely large electric field magnitude), permanent pores are formed and IRE occurred. The IRE is used for inducing cell death of undesirable cells. Recently, IRE has been used as a minimally invasive ablation tool [5-7].

There are two groups of IRE pulses, high-frequency and low-voltage (HFLV) and low-frequency and high-voltage (LFHV). The LFHV pulses can lead to patient pain. Pain can be caused by muscle contractions during each pulse [8]. The threshold for nerve stimulation, which causes muscle contraction, increases as the pulse frequency is elevated [9]. So, the HFLV pulses generate a lower temperature in the tissue and eliminate the patient's pain during clinical applications [8,10]. For this reason, we have used HFLV pulses in our study.

There are some factors that affect the electroporation process such as electric field magnitude, pulse frequency, period, duration, pulse shape, number of electric pulses, and electric field distribution [11]. The electric field distribution and magnitude inside the tissue depend on electric pulse parameters and tissue properties, such as tissue electrical conductivity [12]. Electrical conductivity is an important factor, which affects the electric field and temperature distribution in the tissue [13]. Different studies have shown an increase in conductivity in IRE [14-16]. The measurement of tissue electrical properties (such as electrical conductivity) may optimize the efficiency of electroporation protocols and predictions of the electroporation process [17-19]. Electroporation was performed with plate electrodes for surface application and with needle electrodes for deeper application [20]. In the previous study [21], we were calculated the conductivity change of liver tissue created with plate electrodes. Some researchers prepare to used needle electrodes for their flexibility in placement and ability to treat superficial and deep-tissue [22]. For these reasons, we studied

the effect of needle electrode on tissue conductivity change during IRE electroporation. With this background, the main focus of this study was to evaluate the conductivity change with needle electrodes due to HFLV and LFHV pulses during irreversible electroporation.

Materials and methods

Finite element model

This study was used by finite element analysis software, COMSOL Multiphysics 5.0, to calculate a finite element model. The liver tissue was modeled as a cube geometry. The liver diameters are 32*32*17 mm. We have used 6 needle electrodes in our simulation. We have arranged these electrodes in 2 rows. Which each row of electrode contains 3 electrodes. These geometries were represented in **Figure 1a**. The diameter of each needle is 0.43 mm, while the distance between 3 electrodes in a row is 2.5 mm and the distance between two rows of electrodes is 8.66 mm. The model was performed with triangular mesh that contained 126169 mesh nodes. In COMSOL Multiphysics software, in order to reduce the simulation time, we can use the symmetric model. For this reason, the geometry was created in the symmetric model (**Figure 1b**).

Parameter model

In this study, we have used two electric pulse parameters, high-frequency and low-voltage (HFLV) as well as low-frequency and high-voltage (LFHV) pulses. According to the literature, the IRE is achievable by using HFLV pulses [23,24]. The HFLV pulses involved 4000 bipolar and monopolar pulses with a frequency of 5 kHz, the pulse width of 100 µs, and electric field intensity from 100 to 300 V/cm with steps of 50 V/cm. The difference between monopolar and bipolar pulses is in bipolar pulses, the maximum applied voltage is less than monopolar pulses; i.e., $-V_{max}/2$ to $+V_{max}/2$ Vs. 0 to V_{max}.

On the other hand, the LFHV pulses included 8 bipolar and monopolar pulses with a frequency of 1 Hz, the pulse width of 2 ms and an electric field intensity of 2500 V/cm as representative pulse sequence of classic IRE with low frequency.

The electric and thermal properties of the liver and stainless-steel electrodes are listed in **Table 1** [25,26].

Table 1. The electric and thermal properties of the liver and stainless-steel electrodes

	Electrical conductivity (S/m)	Thermal conductivity (W/m.K)	Density (kg/m^3)	Heat capacity (J/kg.K)	reference
electrode	1.398*10^6	16.3	7800	490	[25,26]
liver	0.067 (initial)	0.512	1050	360	[25,26]

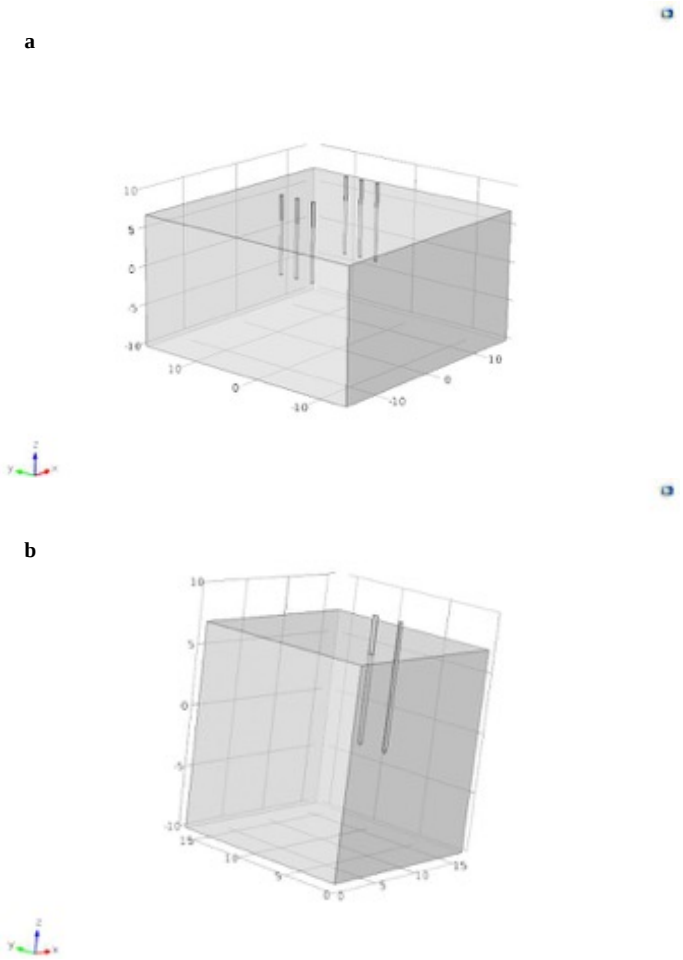

Figure 1. The geometry of numerical modeling

Calculating method

The electric field and electric potential distribution inside the tissue was obtained by Laplace's equation:

$$\vec{\nabla} \cdot \left(\sigma \cdot \vec{\nabla}\varphi\right) = 0 \qquad \text{Eq. 1}$$

Where σ and φ are tissue conductivity and electrical potential, respectively. Heat transfer in the tissue was estimated using Penne's Bioheat equation:

$$\nabla \cdot (k\nabla T) + \sigma|\nabla\varphi|^2 + q''' - W_b c_b T = \rho c_p \frac{\partial T}{\partial t} \qquad \text{Eq. 2}$$

Where φ is electrical potential, T is temperature, q''' is the heat produced by metabolism, $W_b c_b T$ is the heat produced by perfusion, ρ is density, and c_p is a specific heat capacity of tissue. The conductivity changes in the IRE inside the tissue was calculated as [25,26]:

$$\sigma = \sigma_0 * (1 + flc2hs(E - E_{delta}, E_{range}) + \alpha * (T - T_0)) \qquad \text{Eq. 3}$$

Where σ_0 is initial conductivity of the tissue, E is the electric field, E_{delta} is an electric field threshold, E_{range} is electric field range, α is temperature coefficient, and T and T_0 are the temperature and initial temperature of the tissue respectively.

Additionally, to ensure the convergence of the numerical solution, flc2hs function was used. flc2hs, a smoothed Heaviside function in COMSOL, is characterized by changing from zero to one while $E - E_{delta} = 0$ is over the range E_{range} [25]. The parameters used in **Equation 3** are listed in **Table 2** [25,26].

The electrical boundary condition at the active row of electrodes was set to be $\varphi = V(t)$. Where V(t) were pulses with time-varying voltage. Another row of electrodes was set at $\varphi = 0$. The remaining boundaries were considered as electrical insulation.

Result

Simulation results for conductivity change in LFHV

The conductivity changes of LFHV pulses during pulse transmission time are presented in **Figure 2**. This pulse consists of 8 monopolar pulses. Conductivity changes of the 8 LFHV bipolar pulses are presented in **Figure 3**.

Figure 2a illustrates the conductivity changes of the tip of the middle electrode in one row, where LFHV pulses were applied across the electrodes.

While **Figure 2b** presents the conductivity change in point of between two rows of electrodes. **Figures 3a** and **b** present these results for bipolar LFHV pulses. According to the results, tissue conductivity in the transmission time of pulses was increased (**Figure 2,3**). The conductivity changes occurred when the intensity of the electric field in the point of interest was higher than the threshold.

The maximum conductivity changes in the tip and between of electrodes with monopolar LFHV pulses were 0.385 and 0.16 S/m respectively. While these changes for bipolar LFHV pulses were 0.17 and 0.14 S/m respectively.

Regarding our results, conductivity changes in monopolar LFHV pulses were greater than bipolar LFHV pulses. According to **Figure 2** and **3**, conductivity changes in the tip of electrodes was higher than the between of electrodes row.

Table 2. Parameters used in simulation

Variables	Variable values	reference
σ_0	0.067 (S/m)	[25,26]
E_{delta}	580 (V/cm)	[25,26]
E_{range}	(120, -120) (V/cm)	[25,26]
α	0.015 ($℃^{-1}$)	[25,26]
T_0	37 (℃)	[25,26]

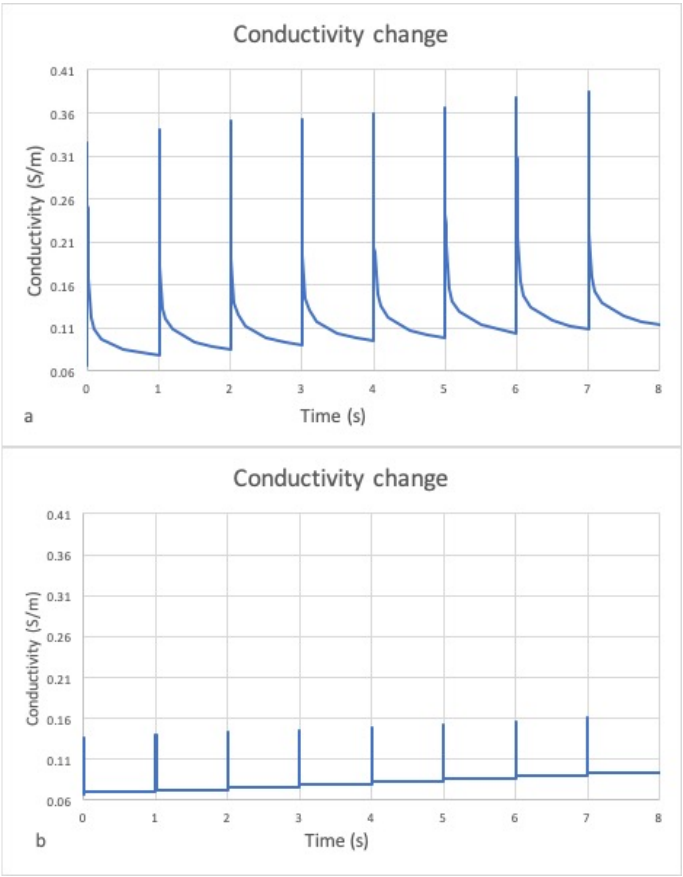

Figure 2. Conductivity changes for eight monopolar pulses with the frequency of 1 Hz, the pulse width of 2 ms, and electric field intensity of 2500 V/cm a) in the tip of needle electrodes b) between the needle electrodes row

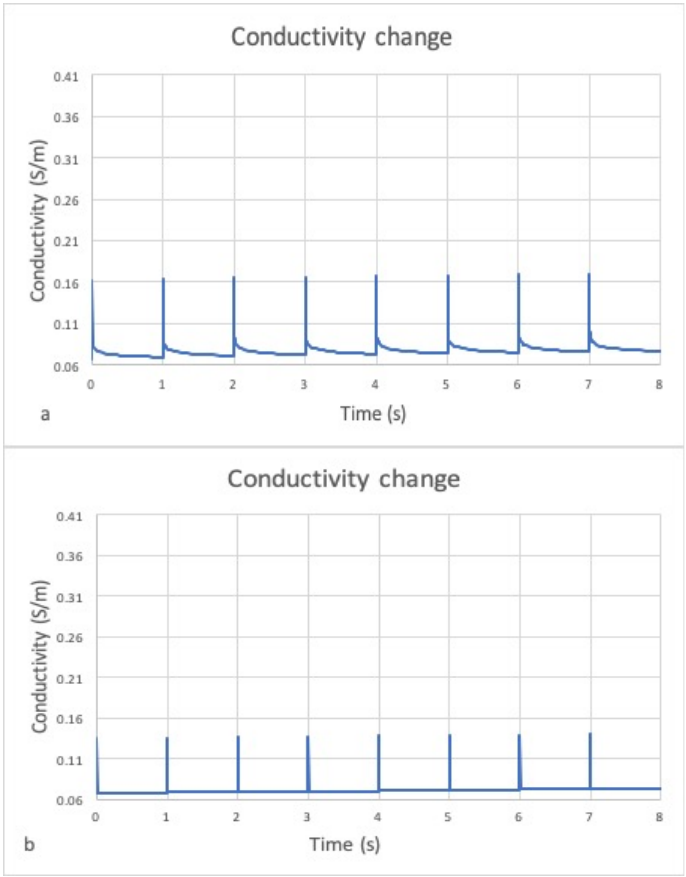

Figure 3. Conductivity changes for eight bipolar pulses with the frequency of 1 Hz, the pulse width of 2 ms, and electric field intensity of 2500 V/cm a) in the tip of needle electrodes b) between the needle electrodes row

Simulation results for conductivity change in HFLV

We have used 4000 monopolar and bipolar pulses with a frequency of 5 kHz, pulse width of 100 µs, and electric field intensity of 100-300 V/cm as HFLV electric pulses. **Figure 4** presents the conductivity changes of monopolar HFLV pulses with the electric field intensity of 300 V/cm, during pulse transmission time. The conductivity changes at the time of the last pulse (4000^{th}) with different electric field intensity are given in **Table 3**.

Table 3. Conductivity change in the tip of and between the electrodes at the time of the last pulse with 4000 monopolar and bipolar pulses with the frequency of 5 kHz, pulse width of 100µs, and electric field intensity of 100-300 V/cm

Pulses	Electric field intensity (V/cm)	Conductivity changes in the tip of the electrode (S/m)	Conductivity changes of between the electrode (S/m)
Monopolar	100	0.132	0.067
	150	0.144	0.067
	200	0.151	0.068
	250	0.161	0.069
	300	0.172	0.071
Bipolar	100	0.130	0.067
	150	0.136	0.067
	200	0.138	0.067
	250	0.141	0.067
	300	0.144	0.068

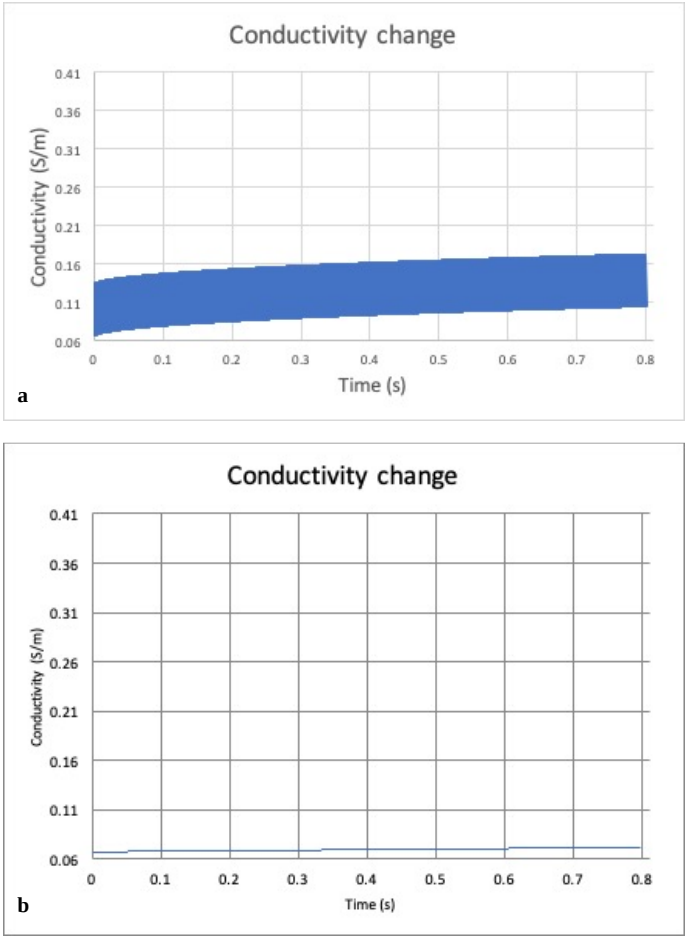

Figure 4. Conductivity changes for 4000 monopolar pulses with the frequency of 5 kHz, the pulse width of 100µs, and electric field intensity of 300 V/cm a) in the tip of the needle electrodes b) between the needle electrodes row

Discussion

Conductivity changes in IRE with LFHV pulses

The conductivity of tissue increases immediately after electroporation pulses then slowly returns to its original value [14-16,27]. Tissue conductivity also increases pulse after pulse (**Figures 2** and **3**). This phenomenon is linked to the closing of transient pores. Due to higher electric field intensity at the electrode tip, changes in conductivity at the tip were larger than conductivity changes in the space between electrodes (**Figures 2** and **3**). In 2014, Miklavcic et al. calculated conductivity changes in liver tissue and reported similar findings to those of our study [28]. With bipolar pulses, the maximum applied voltage is less than monopolar pulses; i.e., $-V_{max}/2$ to $+V_{max}/2$ vs. 0 to V_{max}. For these reasons, the conductivity changes following monopolar pulses were greater than those generated with bipolar pulses.

Conductivity changes in IRE with HFLV pulses

Exposing tissue to electrical pulses as a therapeutic treatment has been previously considered. Such electrical pulses can change tissue conductivity [14-16,27]. Indeed, our current data demonstrate that the conductivity of the tip of the electrode changed significantly (**Table 3**, maximum change was calculated using the factor of 2.57 for a 300 V/cm monopolar pulse). According to our data, the electrical conductivity of the space between electrodes does not change following HFLV pulses (**Table 3**, changes were less than 10%).

Our study provides additional support for an electric filed intensity relationship with conductivity change. According to our results, tissue conductivity was increased with electric field intensity for both HFLV and LFHV pulses. This matches well with [29].

Our simulation results are in line with our previous study [21]. Which we were calculated conductivity change in IRE with plate electrodes. The evidence from the current study in comparison with our previous study [21] has shown that conductivity change with needle electrode in both point of tip and between of electrodes is greater than the plate electrode when used as an electrode for IRE treatment.

One of the possible explanations for these results is, in the needle electrode due to lower electrode surface contact with the tissue, electric current density is greater than the plate electrode. So, electric field intensity and consequently conductivity change were greater for needle electrodes for all

pulses which we have used in our studies. These findings correlate fairly well with Berkenbrock al.'s [30] and Lacković et al's [31] and further support the role of greater electric field intensity and temperature for needle electrodes in comparison with plate electrodes.

The main focus of this study was to evaluate conductivity changes due to HFLV pulses during IRE. The results demonstrated that LFHV pulses generated larger conductivity changes than HFLV pulses due to the greater intensity of the electric field. As expected, increasing the pulse voltage generated increased levels of electrical conductivity due to the higher electric field intensity during each pulse. These data are in agreement with our previous study [21].

Conclusion

The most significant conclusion that can be drawn from this study is the HFLV pulses can change tissue conductivity only in the tip of electrodes. While LFHV pulses change the electrical conductivity significantly in the tissue of between electrodes. The change in conductivity due to electroporation may have a significant effect on temperature and electric field distribution and treatment outcome [13,28]. So, for accurate treatment outcome, we must consider the impact of tissue conductivity change due to IRE on electric field distribution and temperature when we used LFHV pulses. Therefore, it can be concluded that the use of HFLV pulses produces lower temperature and eliminate muscle contraction and ignoring the influence of the conductivity change on the electric field and temperature distribution would be associated with fewer errors. In fact, data from the present study suggest that in the clinic we can use HFLV pulses as electrical pulses for irreversible electroporation as a treatment modality for cancer treatment.

Acknowledgements

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