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Study of irreversible electroporation by pulse field of a biological object

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Abstract. The paper presents the results of computer modeling of the ablation process (irreversible electroporation) of the myocardium with a pulsed electric field and a full-scale experiment (in vivo) on a large laboratory animal using a prototype device with the following characteristics: voltage 500-1500 V, pulse duration 100 μs with a pause of 12 ms, with a number of pulses of 1–50 per 1 s, a bipolar system of two electrodes was used. A study was conducted of the influence of voltage amplitude and geometric dimensions of the electrode system on the distribution of electric and temperature fields in the myocardium; it was shown that the time of safe exposure of the pulsed electric field to the myocardium depends on the energy of the pulsed field and the temperature of the electrodes. Mathematical modeling makes it possible to predict the process of irreversible electroporation in the myocardium and accelerate the introduction of the technique into clinical practice for the treatment of various cardiac arrhythmias.

Keywords: irreversible electroporation, myocardium, bipolar electrodes, pulsed electric field.

1. Introduction

Irreversible electroporation is a new ablation technique based on the effect of high-voltage pulsed electric fields on biological membranes, which leads to a rapid and large increase in their electrical conductivity and permeability.

For cardiac applications, irreversible electroporation (IRE) offers several advantages over thermal methods in terms of safety and efficacy due to minimal thermal energy transferred to target tissues, thereby increasing the susceptibility of myocardial cells to electric fields.

The effect of a strong electric shock during electroporation has been demonstrated both on isolated cells [1] and on cardiac tissue preparations [2–4]. Studies using a simplified suspension culture electroporation model to study IRE thresholds for cardiac applications have shown that IRE causes significant cell death at field strengths greater than 1000 V/cm for at least 50 pulses [5], while the electrical properties of cells may vary nonlinearly and change over time of electroporation [6].

Although many variations have been reported in vitro and preclinical literature regarding the effective voltage threshold for cell damage, understanding the optimal threshold for irreversible electroporation is vital to achieve a safe destruction method without any adverse effects on nearby cells. Questions remain about the localization and spatial extent of electroporation in the intact heart, as well as about optimal parameters (electric field, number and duration of the pulse).

A clearly defined boundary of the damage zone during irreversible electroporation allows planning the procedure using mathematical methods. To predict the process of propagation of a pulsed field in the myocardium and select the optimal modes of electrical influence on biological objects, it is advisable to use computer modeling.

The purpose of the work is to develop a three-dimensional mathematical model of the ablation process (irreversible electroporation) by a pulsed field of a biological object (myocardium) and a numerical study of the influence of the amplitude-frequency characteristics of the voltage source and the geometric dimensions of the laboratory electrode used in a full-scale experiment on a large laboratory animal (in vivo) to study a distribution of the electric field in tissues, dynamics of the temperature field and duration of safe exposure.

2. Methods

2.1. Experiment

In laboratory experiments with animal myocardium in vivo, a bipolar system of two electrodes was used (Fig. 1), diameter d = 3 mm and electrode length of 45 mm was used, the distance between their axes of symmetry was 20 mm. The biological object was the myocardium, the external environment was air.

Characteristics of the voltage source: voltage amplitude U = 500–1500 V, pulse duration (monophasic and biphasic) t_{imp} = 20–100 μs with a pause between them t_{br} = 12 ms, number of pulses per second N = 1–50.

a b

Fig. 1. Bipolar two-electrode system: 1- air, 2 – electrode, 3 – biological object.

During the experiment, current I and voltage U were measured. At voltage amplitude values (N = 10, t_{imp} = 100 μs) U = 500, 1000 and 1500 V, the current for two options of electrode arrangement (Fig. 1a and 1b) is equal to: I = 10, 11 and 11 A (Fig. 1a) and I = 3, 5 and 4 A (Fig. 1b), respectively. The absence of a pattern in the change in current with increasing voltage is most likely due to the fact that each time a new place on the heart was chosen.

2.2. Model

The computer model was developed using the COMSOL Multiphysics software package. In a three-dimensional cylindrical simulation area (R×H = 80×120 mm), taking into account various properties of the medium (myocardium, air or blood), the location of the electrodes relative to the surface of the myocardium (Fig. 1) and the depth of their immersion corresponded to the experiment.

The physical and mathematical model includes a multiphysics problem associated with quasi-static electrical conductivity (Laplace's equation) and thermal conductivity of living tissue:

$$-\nabla\sigma\nabla U = 0,$$

$$\rho c\frac{\partial T}{\partial t} + \nabla\left(-k\nabla T\right) = \rho_b c_b \omega_b \left(T_b - T\right) + Q,$$

where U is voltage, σ is specific electrical conductivity S/m, ρ is tissue density, ρ_b is blood density, c is tissue heat capacity, c_b is blood heat capacity, T is tissue temperature, k is tissue thermal conductivity, ω_b is blood perfusion index, T_b is the arterial blood temperature, Q is the power density of the electric field.

The conservation equation for current is solved based on Ohm's law using the scalar electric potential as the dependent variable. The electric field is determined in accordance with the Poisson equation $E = -\Delta U$, the current density $j = \sigma E$ in conducting media is calculated under the conditions that inductive effects can be neglected at frequency of 10 Hz (the skin depth is much greater than that of the device under study). The physical interface for modeling heat transfer by conduction takes into

account that thermal effects are inertial and the heating power density σE^2 in the frequency domain $t_a = N(t_{imp}+t_{br})–t_{br}$ is equivalent to a constant averaged power density.

Parameters of the computational experiment: diameter of bipolar electrodes d = 1–3 mm, distance between the axes of the electrodes h = 14–20 mm, voltage amplitude U = 500–1500 V. Initial temperature of the myocardium T_m and blood T_0 = 37 °C, air 25 °C , convective heat exchange between the myocardium and (air) blood with a heat transfer coefficient at the myocardium-blood interface of 2000 W/(m^2·K) and 1000 W/(m^2·K) myocardium-air. Thermophysical parameters c = 3077 J/(kg·deg), ρ = 1080 kg, k = 0.525 Watt/(m·kg).

3. Results of numerical calculations

An estimate of the myocardial electrical conductivity of 0.33 S/m was obtained taking into account experimental measurements of current and voltage (1000 V) for both electrode placement options (Fig. 1). Fig. 2 shows the distribution of the electric field strength along the Y coordinate axis at different depths from the lower boundary of the electrodes (plane z = 0 on which the electrodes are located). The electric field is concentrated near the electrodes (~ 10 mm), which decreases with distance from the metal surface by ~$1/r^2$. The electric field strength at the end of the electrode (Fig. 2a) is 2 times higher than with a horizontal arrangement of the electrodes (Fig. 2b) (in the middle of the electrodes).

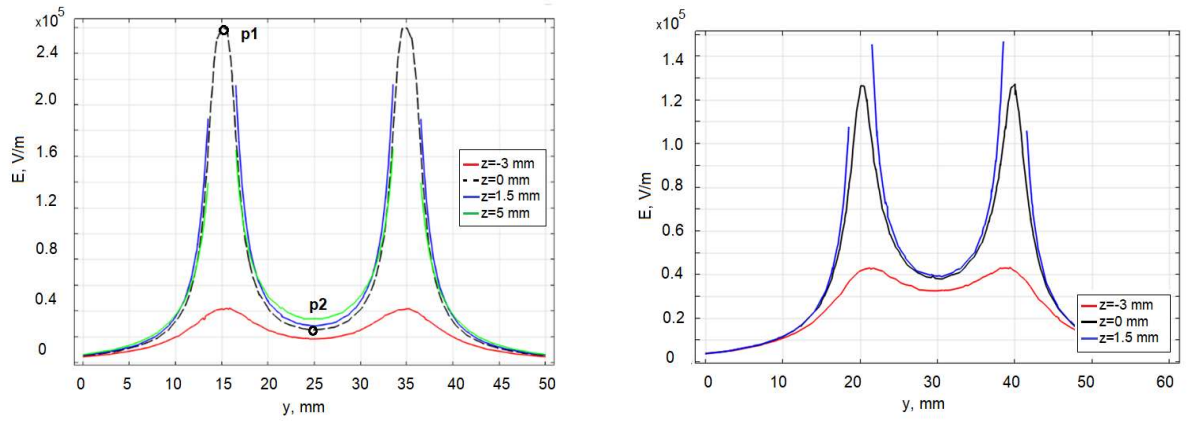

Fig. 2. Distribution of electric field strength along the Y axis: a – vertical (Fig. 1), b – horizontal (Fig. 1b) arrangement of electrodes.

The electric field strength E depends on the geometric factor (the diameter of the electrodes and the distance between them) and the voltage amplitude U. Figure 3 shows the dependences of E on voltage at two points p1 (0.10, 0) at the end of the electrode and p2 (0, 0, 0) between the electrodes (Fig. 1a) for two values of electrode diameters d = 3 and 1 mm and the distance between electrode axes h = 20 and 14 mm. The electric field strength increases linearly with increasing voltage amplitude U (E = -ΔU) and at the end of the electrodes (point p1) is significantly higher than between them (point p2). This leads to an uneven distribution of current density and, accordingly, temperature along the electrode.

The dissipation of a high-intensity electric field energy due to the release of Joule heat leads to an increase in tissue temperature; when a critical value is exceeded, thermal damage process occurs. The estimated time t is limited by reaching the temperature T_{cr} = 40 °C, i.e. heating is carried out at ΔT = 3 degrees. During pulsed field exposure, the change in myocardial temperature on the electrode surface increases linearly with time $\Delta T(z,\ t) \sim \sigma EUt/c\rho$. Between applications, a decrease in temperature occurs due to thermal diffusivity $a = \lambda/c\rho$ and convective heat exchange with the external

environment (blood, air), as shown in Fig. 4 shows the temperature dynamics at 4 points (x, y, z) for a two-electrode system (Fig. 1a) at U =1000 V, N = 2, myocardium/blood system, T_m=T_{el}.

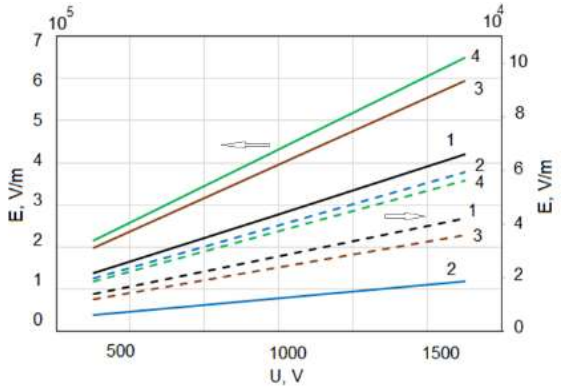

Fig. 3. Dependence of the electric field strength on the voltage U, point p1– solid lines, p2 –dashed lines (Fig. 2a); 1 – d/h = 3/20, 2 – 3/14, 3 – 2/20, 4 –2/14

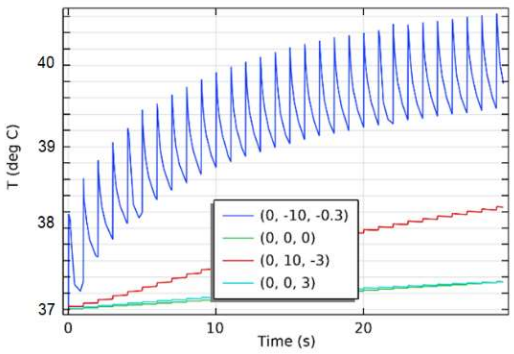

Fig. 4. Temperature change over time at points (x, y, z) for a two-electrode system Fig. 1a, U =1000 V

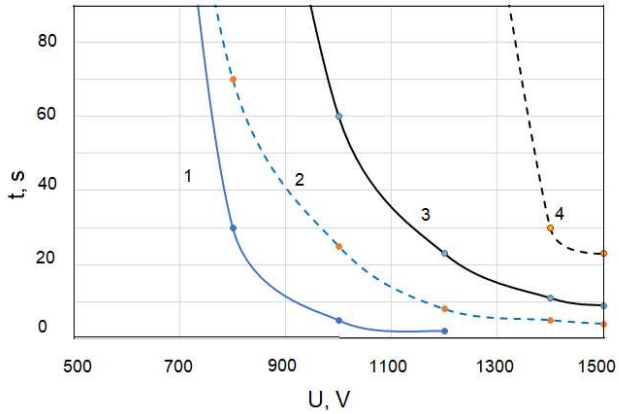

Fig. 5. Dependence of time t (T = 40 °C) of exposure to a pulsed field on voltage amplitude U; 1, 3 – N = 10, T_{el} = 25; 2, 4 – N = 2, T_{el} = 37 °C; two-electrode system: 1, 2 – (Fig. 1a), 3, 4 – (Fig. 1b).

The duration of safe pulsed exposure to the electric field depends on the thermophysical characteristics, the number of pulses, voltage amplitude and the temperature difference between the myocardium and electrode T_m-T_{el}. Figure 5 shows the functional dependence of t = t(U) on the voltage amplitude U, which was obtained when the temperature reached T_{cr} = 40 °C, the temperature of the electrodes (and medium) T_{el} = 25 and 37 °C, the number of pulses N = 2 and 10, safe voltage areas are located to the left of the t(U) curves. When the temperature difference T_m-T_{el} = 12 °C and N = 2, heating does not reach a critical value in the voltage range under consideration (500–1500 V), a stationary temperature $T < T_{cr}$ is established. The area of safe voltages decreases with increasing exposure energy (increasing the number of pulses at the same density), so for N = 10 with a vertical arrangement of electrodes U < 800 V, with a horizontal arrangement – U < 1000 V (Fig. 4, curves 1 and 3). At the same temperature of the myocardium and electrode (and medium) T_m=T_{el} =37 °C, the range of safe accelerating voltages is reduced due to an increase in the heating rate, which can be compensated by a decrease in energy (number of pulses): so for N=2 with a vertical arrangement of electrodes U < 850 B, with a horizontal position – U< 1350 V (Fig. 4, curves 3 and 4). The time of safe exposure to a pulsed electric field is t(T=Tcr) ~$c\rho$ and therefore can increase in the presence of local inhomogeneity of density and heat capacity.

4. Conclusion

The mathematical model describes the process of propagation of electric and thermal fields when exposed to pulsed voltage on the myocardium. Numerical experiments were carried out in accordance with the measured electrical characteristics (voltage and current) in vivo using a bipolar system of two electrodes (Fig. 1). It was found that the electric field depends linearly on the amplitude of the external field and decreases from the metal surface of the electrode at a distance of ~ 10 mm. The temperature of the electrode and the external environment significantly influence the time of safe exposure to the pulsed field. The time required for the temperature to reach a critical value depends on the amplitude-frequency characteristics of the voltage source, the geometry of the electrodes, as well as the temperature of the electrodes and the external environment. There is an optimal range of parameters (voltage amplitude, frequency and number of pulses in the application, electrode geometry), in which damage to tissues located under the electrodes is minimized, and the determination of the boundaries of which is influenced by the correspondence of the computer model parameters (electrical conductivity, thermophysical coefficients) to the full-scale experiment.

It is expected that the mathematical model will be validated during a full-scale experiment on a large laboratory animal using a prototype device and taking material for histological examination to confirm the area and volume of damage. It is also planned to record signals from the surface of the myocardium using the electrode from which the shock is applied or other electrodes that may be located in close proximity to the damaged area and the use of electrical stimulation of the damaged area.

Mathematical modeling makes it possible to predict the process of propagation of a pulsed field in the myocardium, and when conducting experiments on laboratory animals, it allows us to improve the selection of optimal parameters for more successful and safe use on biological objects and accelerates the introduction of the technique into clinical practice for the treatment of various cardiac arrhythmias.

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