International Journal of Heat and Mass Transfer 72 (2014) 66–74

Contents lists available at ScienceDirect

International Journal of Heat and Mass Transfer

journal homepage: www.elsevier.com/locate/ijhmt

Three-dimensional analysis of irreversible electroporation: Estimation of thermal and non-thermal damage

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ARTICLE INFO

Article history:
Received 20 July 2012
Received in revised form 29 October 2013
Accepted 26 December 2013
Available online 25 January 2014

Keywords:
Irreversible electroporation
Finite element analysis
Electric-field distribution
Joule heating
Temperature rise
Tissue ablation

ABSTRACT

Irreversible electroporation (IRE) is a novel method to ablate abnormal cells by applying a high voltage between the electrodes punctured in abnormal tissues. The cell membrane exposed to the potential difference above a certain threshold is permanently disrupted, which consequently induces cell necrosis. One of the advantages of the IRE is that the extracellular matrix (ECM) can be kept intact, which is favorable for healing. Thus, it is important to determine an optimal condition of electric pulses and electrode configuration prior to a clinical application so that a proper volume of the targeted tissue is ablated without thermal damage resulted from the Joule heating. The aims of this study were, therefore, to estimate the possible temperature rise during the IRE by a nondimensional 3-D analysis, and to reveal the risk of ECM denaturation caused by the IRE parameters such as electrode dimension, the distance between two electrodes, and the applied voltage. The heat conduction equation and the Laplace equation in non-dimensional forms were solved numerically using the finite element method for the IRE with a pair of rod-shaped electrodes placed in a simulated tissue. Numerical analysis clarified that concentration of electric current induced local heat generation, which resulted in the formation of hot spots near the base and the tip of electrodes. The highest temperature rise occurred at the base of electrodes adjacent to the insulated surface. The result was significantly different from a two-dimensional (2-D) analysis due to end effects, suggesting that the 3-D analysis is required to determine the optimal condition. The region of ablated tissue and its volume were also shown as a function of IRE parameters. This provides useful information for a preoperative simulation of the IRE. Finally, the accumulation of the thermal damage was estimated for three kinds of tissue, *i.e.,* epidermis, aorta, and skin collagen. Although the IRE usually uses a short electric pulse duration from several ten to hundred microseconds, our study demonstrated that even the short pulses in the order of hundred microseconds have a risk for the thermal denaturation depending on tissues and the pulse magnitude.

1. Introduction

Electroporation is a technique to perforate the cell membrane by applying a pulsed voltage to cells. Since there is no obvious evidence supporting the existence of the electropores in the cell membrane, some researchers preferably use the term “electropermeabilization” instead of “electroporation” [1]. Whatever it is called, the application of electric pulses in an appropriate condition can temporarily increase the permeability of the cell membrane, which allows the cells to incorporate a variety of exogenous substances such as proteins, DNA, organelles and pharmaceutical agents [2–5]. The permeabilized membrane is then resealed by self-assembled repair process and returned to its original state within a few minutes [6]. This technique, which is called “reversible electroporation”, has currently become an essential part in the field of plant breeding [7,8], biomedicine [9–11], and biotechnologies [12].

The irreversible breakdown of the cell membrane has been thought as an unfavorable side effect in electroporation because it critically reduces the electrotransfer efficiency of the cells. However, this side effect has begun to get a lot of attention since it was introduced as a novel method to treat tumors [13]. An overdose of electric pulses brings irreversible change to the cells. The cells cannot successfully accomplish their repairing process after the pulse application due to the excess damage, and thereby inducing cell death. Rubinsky and his coworkers have called this method “irreversible electroporation (IRE)” and showed that the IRE could

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http://dx.doi.org/10.1016/j.ijheatmasstransfer.2013.12.065

Nomenclature

A	frequency factor (1/s)	T_0	initial temperature (K)
C	non-dimensional heat capacity	t	time (s)
c	specific heat capacity (J/(kg K))	V	applied voltage between two electrodes (V)
d	diameter of electrode (m)	W	non-dimensional ablated tissue volume
E_a	activation energy (J/mol)	Φ	non-dimensional electric potential
F_O	Fourier number	ϕ	electric potential (V)
H	non-dimensional length of electrically conductive surface of electrode	Λ	non-dimensional thermal conductivity
h	length of electrically conductive surface of electrode (m)	λ	thermal conductivity (W/(m K))
J	non-dimensional electric current density	Θ	non-dimensional temperature
j	electric current density (A/m^2)	P	non-dimensional density
L	non-dimensional distance between the electrodes	ρ	density (kg/m^3)
l	distance between the electrodes (m)	Σ	non-dimensional electrical conductivity
$N(\tau)$	amount of undamaged tissue molecules at time τ	σ	electrical conductivity (S/m)
P	predicted tissue damage possibility (%)	Ω	thermal damage index
R	universal gas constant (J/(mol K))		
r_t	radius of tissue as the solution domain (m)	*Subscripts*	
T	temperature (K)	e	electrodes
		t	tissue

ablate tumors while preserving blood vessels and nerve system around the affected area [13]. The IRE would be similar to the electrochemotherapy for the point that both methods utilize the electric pulses for a treatment. However, the IRE necrotizes the targeted cells directly by much intensive electric pulses without any kinds of chemotherapeutic drugs, whereas the electrochemotherapy kills the cells by the help of electro-transferred agents [14].

The most significant advantage of the IRE is that it affects only the cell membrane and keeps the extracellular matrix (ECM) around the targeted cells intact by reducing the Joule heating for maximizing the benefits of this non-thermal mode of tissue ablation. Thus, a successful IRE without the thermal effect leads to a promotion of quick tissue regeneration because the intact ECM can provide a favorable scaffold for cell migration and proliferation immediately after the IRE treatment. However, during the IRE, a train of electric pulses of a few kilovolts is commonly applied between electrodes that are percutaneously inserted into abnormal tissues, and therefore possibly produces a thermal effect on the surrounding tissues. To maximize the benefits of the IRE therapy, optimal conditions of the electric pulses and electrode configuration must be determined prior to a clinical application.

Numerical analysis is one of the methods that give us an estimation of the IRE outcome. A number of numerical solutions to 3-D problems were applied to treatment planning electrochemotherapy [15–23]. Most of them however demonstrated distribution of electric field instead of thermal effects. Electrochemotherapy eliminates tumors by means of cytotoxic drugs that incorporated into the cells by electroporation. Since relatively moderate pulse conditions are used in the electrochemotherapy compared with the IRE, less attention has been paid to the Joule heating during electroporation. Regarding the IRE, only a few studies have looked at the temperature rise due to the Joule heating [24–26]. For instance, Garcia et al. developed a 3-D numerical model of canine brain with a pair of blunt-ended electrodes, and examined the effect of different patterns of electric pulses on the temperature rise as well as the ablated volume in the brain [24]. However, the risk of the local temperature rise caused by the electrode geometry was not discussed enough although the electric fields at the electrode tip or the base adjacent to the insulated surface are expected to be considerably different from that at the midshaft. Moreover, the previous study provided an easily comprehensible explanation for a choice of IRE parameters because it assumed the specific case of intracranial disorders in canine and solved dimensional equations. However, nondimensional analysis would be much preferable to generalize the IRE model, to elucidate the effects of the IRE parameters on the therapeutic efficacy, and to utilize them for various clinical applications.

The aims of this study are, therefore, to estimate the possible temperature rise during the IRE by a non-dimensional 3-D analysis, and to reveal the risk of ECM denaturation depending on the electrode geometry. The heat conduction equation and the equation of electric field in non-dimensional forms were solved numerically using the finite element method for the IRE with rod-shaped electrodes placed in a simulated tissue. We also evaluated the volume where the irreversible cell breakdown was achieved as a function of the electric potential and the electrode interval. Additionally, accumulation of the thermal damage that depends on the pulse duration was evaluated by adapting non-dimensional results to different types of tissues.

2. Model and method

Configuration of the analytical model is described in 3-D Cartesian coordinate system in Fig. 1. A pair of electrodes with a diameter of d is placed in a simulated tissue, separated by a center-to-center distance of l. The length h from the tip of the electrodes is electrically conductive, and the voltage V is applied between the electrodes.

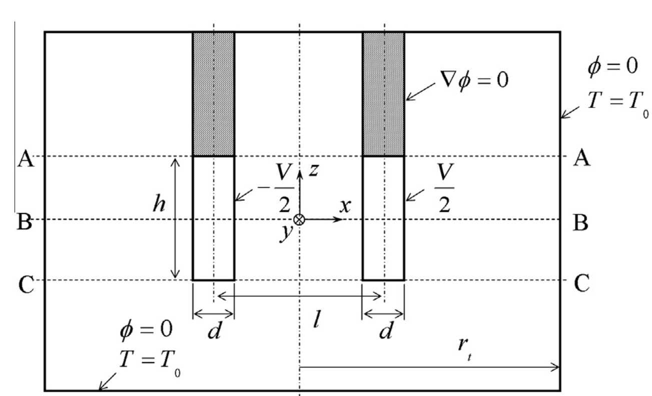

Fig. 1. Physical model and coordinate system.