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Visualization of electroporation-induced temperature rise using temperature-sensitive ink

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ABSTRACT

Irreversible electroporation (IRE) is attracting attention as a new technique to treat tumors, in which electric pulses over a certain threshold perforate the cell membrane and induce necrotic cell death. Since the electric pulses potentially generate the Joule heating around electrodes, successful IRE needs to apply a pulsed voltage high enough for the irreversible perforation yet minimizes the thermal effect on the extracellular matrix in the surrounding tissue. The temperature rise around the electrodes is therefore one of the most important concerns in the IRE. However, no experimental evidence has been reported for the temperature rise because of extremely short pulses used in the IRE. The aim of this study was therefore to establish a new method to detect the temperature rise during the IRE. A key technique is to use temperature-sensitive ink to visualize in situ instantaneous temperature rise. Chromatic change of the ink that depends on the temperature was preliminarily calibrated by a transient short-hot-wire technique combined with color analysis of the ink, and then utilized to determine the temperature distribution after electroporation. The maximum temperature rise was thus successfully visualized after the electroporation using agar gel as a tissue phantom. Our method is useful for direct evaluation of a risk of thermal damage and provides experimental evidence for theoretical study.

1. Introduction

Electroporation is a technique to perforate the cell membrane by external field pulses. The cells are subjected to reversible or irreversible perforation depending on a transmembrane potential difference. Generally, the critical potential to induce a breakdown of the plasma membrane is assumed to be approximately 1 V at room temperature [1–3]. When the transmembrane potential difference exceeds this threshold, the perforated membrane will not be spontaneously repaired, resulting in necrotic cell death. This is called irreversible electroporation (IRE), distinguished from reversible electroporation that is used for induction of macro molecules into cells, and is attracting much attention because of its potential use for a less-invasive treatment for tumor. The IRE can necrotize the tumor cells by using a pair of percutaneous electrodes inserted into an abnormal tissue [4–6].

The great advantage of the IRE over any other methods of treatment is that the extracellular matrix (ECM) in the treated tissue is kept intact, which is favorable for healthy tissue regeneration. To avoid thermal damage resulted from the Joule heating is therefore one of the most important concerns in the successful IRE.

The temperature rise during the IRE has been examined by numerical simulations. For instance, Davalos et al. have used a two-dimensional (2-D) model and examined the effect of electrode diameter, distance between electrodes, pulse duration, and a magnitude of voltage on the temperature distribution in the tissue [7,8]. The result that the Joule heating could significantly increase the tissue temperature indicated that these parameters should be determined appropriately prior to the IRE treatment. Nomura et al. have also shown the effect of electric field on the temperature rise during the IRE [9]. They found with a 3-D model that the temperature rise at the tip of the electrode and the base adjacent to the insulated surface was much higher than that of the 2-D model.

Although the potential temperature rise around the electrodes has been estimated by numerical simulations, it has not been validated experimentally. This is because the IRE uses the extremely short electric pulses from several ten to hundred microseconds. Neither thermocouples nor any other temperature sensors are available for measuring such a short temperature rise in situ around the electrodes. The only study that has tried to measure the IRE-induced temperature rise was that used a fiber optic probe in combination with a temperature sensitive phosphorescent element [10]. The temperature was successfully recorded for a 5-min IRE treatment at a frequency of 2 Hz, but only at two

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locations near the electrode. No paper has therefore reported yet on the measured distribution of the temperature rise around the electrode that was inserted into a tissue. The aim of this study was therefore to establish a new technique to detect temperature rise during the IRE. A key technique employed here is to use temperature-sensitive ink to visualize in situ instantaneous temperature rise. Chromatic change of the ink depending on the temperature was preliminarily calibrated by a transient short-hot-wire technique combined with color analysis of the ink, and then utilized to determine the temperature distribution around the electrodes.

2. Experiments

2.1. Temperature-sensitive ink

Temperature-sensitive ink was collected from an erasable ballpoint pen (FriXion Erasable Rollerball Pen, PILOT Corporation, Tokyo, Japan). The ink contains small microcapsules of color formers and developers (Fig. 1). They are chemically coupled at room temperature producing a color, while they decouple each other and loose the color once the temperature exceeds a certain threshold.

2.2. Calibration of the temperature-sensitive ink

An experimental setup of the transient short-hot-wire method was utilized to examine the thermal characteristics of the temperature-sensitive ink. It was originally proposed for the measurement of thermal conductivity and thermal diffusivity of liquids by Fujii et al. [11]. They submerged a short platinum wire in a liquid sample and heated with a DC voltage impression. Transient increase of the wire temperature was then measured from electrical resistance. To determine the thermal transport properties of the sample, they compared the measured temperature rise with that obtained by a numerical analysis. Here in our study, we used a gel sample with known thermophysical properties. We can therefore estimate the transient temperature increase in the sample around the wire from a numerical analysis.

Fig. 2 shows the transient short-hot-wire equipment used in this study. A short platinum wire, 50 μm in diameter and 13 mm long, was welded at both ends to a platinum lead terminal with a diameter of 1.5 mm. The terminal was supported with a ceramic block and connected to lead wires. The ceramic block was fixed to a cylindrical test vessel approximately 250 ml in volume. The data acquisition system is schematically shown in Fig. 3. It consisted of a DC power supply (R6245, ADVANTEST Corporation, Tokyo, Japan) and a couple of digital multimeters (2002, Keithley Instruments Inc., Cleveland, OH). One was used for measuring the electric potential difference between two ends of the short-hot wire, and the other was used with a 10-Ω standard resistor to determine the electric current through the circuit. The electrical resistance and the heat generation in the wire were calculated from the measured potential difference and current. The power supply and the multimeters were connected to a personal computer through the GP-IB interface and automatically controlled by a sequential program. Prior to the experiment, the relationship between the electrical resistance of the wire and temperature was calibrated. Contribution of the electrical resistance within lead terminals was also took into account assuming no temperature increase due to their large heat capacity.

Agar gel containing the temperature-sensitive ink was used in the present study as a tissue phantom. Agar powder was dissolved in a 0.9% NaCl aqueous solution at 80 °C to the final concentration of 4% (w/v). When the agar solution was cooled down to approximately 50 °C, the temperature-sensitive ink was added at a concentration of 1% (v/v). The mixed solution was poured into a test

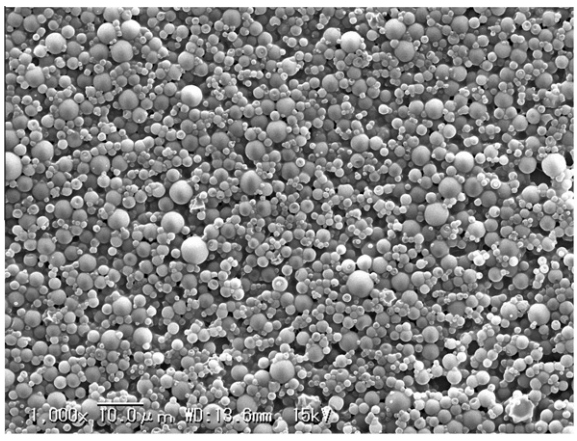

Fig. 1. Scanning electron micrograph of the temperature-sensitive ink.

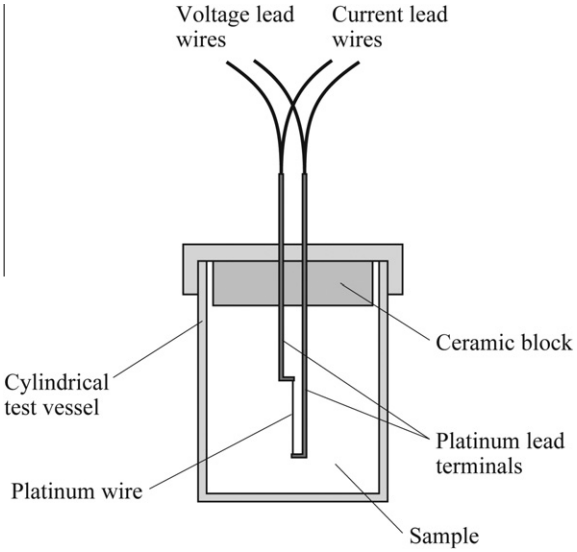

Fig. 2. Experimental setup for the short-hot wire method.

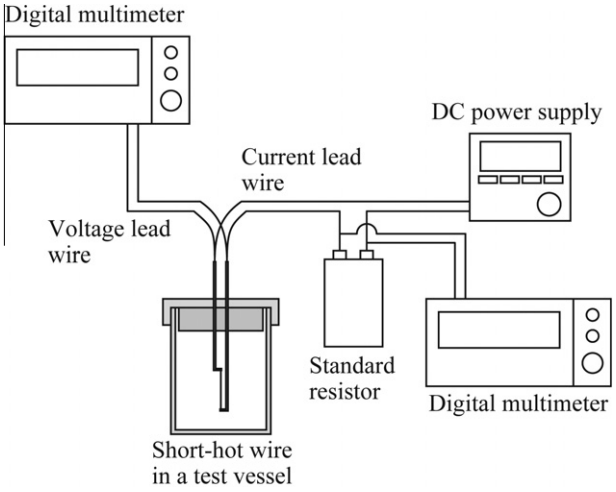

Fig. 3. Data acquisition system for the short-hot wire experiment.