Electrolytic Ablation Dose Planning Methodology

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Abstract— **Electrolytic ablation (EA), a medical treatment increasingly used in solid tumor ablation, consists in the passage of a low direct electric current through two or more electrodes inserted in the tissue thus inducing pH fronts that destroys the tumor. The combined use of EA with a recently introduced one-probe two electrode device (OPTED) results in a minimally invasive tissue ablation technique. Despite its success related to low cost and minimum side effects, EA has drawbacks such as the difficulty in determining the current and time needed to assure total tumor ablation while avoiding healthy tissue intrusion. Here we introduce a realistic dose planning methodology in terms of the coulomb dosage administered and the associated pH tracking, that predicts an optimal EA/OPTED protocol treatment for a given tumor size, that is, the current and exposition time necessary to succeed in eliminating all the tumor mass while minimizing healthy tissue damage.**

Keywords— **tumors, electrolytic ablation, electrochemical treatment, in silico model, in vitro model, pH front tracking**

I. INTRODUCTION

Electrolytic ablation (EA) also called electrochemical treatment of tumors (EChT) is a non-thermal method of tissue destruction that has been progressively used as a medical treatment for tumor ablation. It consists in the passage of a low direct electric current through two or more electrodes inserted in the tissue inducing pH fronts thus, tumor destruction. EA was pioneered by Nordenstrom [1] in the late seventies, since then it has been widely used in China with good clinical results [2]. The effects of EA, either alone or with the use of chemotherapy, on tumors in mice was studied in [3]. During the last decade, pulsed electric fields were explored in local tumor treatment based upon electroporation (EP), a technique in which pulsed electric fields are employed to perturb cell membrane permeability. Among them, electrochemotherapy (ECT) combines reversible EP with poorly-permeant anticancer drugs to potentiate their entry to the cell thus their intrinsic cytotoxicity. Since its beginnings in the late 1980s, ECT has evolved into a clinically verified efficient cytoreductive treatment for cutaneous and subcutaneous tumor nodules of different origin in Europe [4]. Recently, it was shown in [5] that combining electrolysis with reversible EP yields a significant increase in the extent of tissue ablation in comparison to that obtained with EA alone. A possible explanation is that reversible EP potentiates the entrance of toxic electrolytic products into the cell causing more effective tissue destruction. Some of the advantages of EA are its simplicity, effectiveness, low cost and negligible side effects.

Tissue destruction in EA is mainly produced by necrosis. This is because during electrolysis, electrochemical reactions take place at the electrodes. At the anode mainly oxygen, chlorine and protons are produced, while hydrogen and hydroxide ions are released at the cathode. It is the presence of strong pH changes that causes necrosis. Concomitantly, there is a migration displacement of water from the anode to the cathode causing dryness at the anode and hydration at the cathode. Part of the gases released at the electrodes remain in the medium participating in other chemical reactions with tissue components [6].

Dose planning methodology is mandatory for treatment replication with predictable results. Since the late seventies coulomb dosage according to tumor size was the guideline for optimal choice of electric parameters [6]. The dose-response relationship between the applied current, treatment time, coulomb dosage and tissue destruction was later investigated by various authors for optimal planning methodology. Some of them found a linear relationship between tissue destruction and coulomb dosage (see[6] and references cited there); they also found no differences using lower or higher currents at a given coulomb dosage. However, other authors [6] found tissue destruction to be related, not only to coulomb dosage, but to the way at which it was administered. Low current and longer treatment times yielded higher destruction, compared with higher current and shorter treatment time [2].

In the classical EA method, the distance between the two electrodes is in the order of centimeters. This is due to the general belief that there is an optimal distance between electrodes and that if they are placed too close to each other, chemical reactions between the different electrode reaction

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products are possible; moreover, the effect of clinical treatment, has not been as good as in those cases where the separation was large enough to avoid overlapping of destruction zones [6]. At variance with this belief, in [7] a one-probe two-electrode device (OPTED) containing the cathode and the anode with a separation of 10^{-3} m between each other, was introduced; its main advantages being the insertion of one applicator rather than two or more (thus minimizing tissue intrusion, for instance, in zones where nervous fibers are present). Clearly, OPTED improves the ability to reach tumors beyond capabilities of conventional surgery improves and minimizes electric current circulation through the treated organ. Experiments in [7] show that upon application of the EA/OPTED protocols in a 3D gel model, two half-spherical pH fronts, one basic and the other acid (from cathode and anode, respectively), expand towards the periphery configuring a distorted full sphere. Between electrodes, the fronts collide and vanish due to neutralization.

The efficacy of the EA/OPTED protocol was assessed by measuring the extent of the volume which in turn is determined by the pH fronts scanned volume through a pH front tracking using the color change of pH indicators. It was suggested in [8] that the necrotized area is a function of the coulomb dosage applied. It follows that for optimal EA/OPTED protocols is needed to find an optimal coulomb dosage that would succeed in eliminating all the tumor mass while minimizing healthy tissue damage.

In this context, *in silico* modeling validated with *in vitro* and *in vivo* measurements can greatly contribute to the EA/OPTED protocol optimization. In a pioneering series of papers [6] *in silico* modeling of an EA protocol applied to a tumor tissue was presented. The tissue matrix was seen as an electrolyte consisting of an aqueous solution of sodium chloride at pH = 7, and ion transport around both electrodes was analyzed. In [9] a new model was presented consisting in the 1D Nernst–Planck equations governing ion transport in a four component electrolyte under galvanostatic and electroneutral conditions. Results showed that since necrotic areas correlated well with zones covered by alkaline and acid fronts advance, pH front tracking could be effectively used to predict the extent of tumor destruction and thus, the assessment of EA effectiveness.

Here we introduce a more realistic theoretical model describing two-dimensional pH fronts interaction in a tissue under an EA/OPTED protocol and its validation with *in vitro* measurements. The main goal is to introduce a dose planning methodology for predictable and reproducible EA/OPTED protocol for a given tumor size, that is, to find a coulomb dosage that eliminates all its mass while minimizing healthy tissue damage.

II. MATERIALS AND METHODS

In vitro modeling of the EA/OPTED protocol in a 3d gel cube is described in detail in [7]. Here we present a summary. The tissue is represented by a gel cube consisting of 1% agar-agar in distilled water, with NaCl at physiological concentration. The OPTED, composed of two solid platinum needle electrodes is, inserted in the middle of the back face of the cube and a current is passed through the electrodes during 1200 s. Each electrode has an exposed area of $1.5\ 10^{-7}$ m^2 and its separation is 10^{-3} m. In its maximum diameter the OPTED reaches $5\ 10^{-3}$ m. pH front advance was tracked via an optical absorption technique [7] using phenolphthalein (transition pH range 8.0 - 9.62) and methyl red (transition pH range 4.8 - 6.2) as basic and acid indicators, respectively. Electric current circulation between the two electrodes in an electrolyte produces bubbles. If the electrodes are close enough, bubbles between them act as an electric insulator. These diminishes the effective area through which electric current flows, thus current density increase in each electrode.

The mathematical model describing the EA/OPTED protocol is presented in full detail in [10]. It describes the evolution of a four-component electrolyte which represents biological tissue or gel. It is based on the Nernst-Planck equations for ion transport with Butler-Volmer boundary conditions and electroneutral conditions (details of the equations and boundary treatment are presented in [10]).

EA/OPTED therapy is an evolutionary process determined by the pH fronts emerging from the products of the electrolysis process. During its evolution all the variables intervening in the electrolysis and in the generation of electrolytic products are modified. Clearly, pH fronts advance, thus EA/OPTED therapy, is a highly nonlinear process strongly dependent in the transport of ions and in the electrochemical reactions.

III. RESULTS AND DISCUSSION

Numerical results of ion transport mimicking the EA/OPTED protocol previously discussed are shown next. For brevity, we only present model predictions of pH and electrostatic potential to show the complex interaction and evolution during the electrolysis process. Ion transport is determinant for obtaining pH fronts, which in turn is essential for reliable necrotic area prediction. In biomedical terms, during electrolysis the extent of necrotic tissue is related to the amount of tumor ablation covered by the pH front, also scaling with the total amount of electric charge or coulomb dosage pumped into the system.