EVALUATION OF DC CURRENT THERAPY IN MAMMARY CANCER TUMOR

MARCOS TELLÓ PUCRS, AV. IPIRANGA, 6681 CEP: 90619-900

LUCIANA OLIVEIRA DE OLIVEIRA UFRGS – AV. PAULO GAMA 110 CEP 90040-060

ROSEMARI TERESINHA DE OLIVEIRA UFRGS – AV. PAULO GAMA 110 CEP 90040-060

GUILHERME DIAS PUCRS, AV. IPIRANGA, 6681 CEP: 90619-900

ADROALDO RAIZER UFSC, POSTAL CODE 5024 CEP 88040-970

Abstract

The aim of this paper is to present the results attained by our research group from the clinical applications of DC current in dogs presenting mammary tumors. Indeed, it is important to point out that the cytopathological exams, attained from the treated mammary glands, indicate that the macrophage cells appear in all treated tumors after some application sessions.

Keywords – ElectroChemical Therapy, DC current, mammary glands, cancer.

I. Introduction

The DC current applied to treat tumors use the BCEC (Biologically Closed Electric Circuits) concept [1]. Conceptually, all kinds of electrical current (or ions) flowing in the closed pathway into biological matter or the existence of current loops within the body forms the BCEC. Fig. 1 shows an example of the BCEC, where ions flows among vessels and interstitial regions forming a closed pathway. Therefore, several kinds of BCEC can be establish inside biological matter [2].

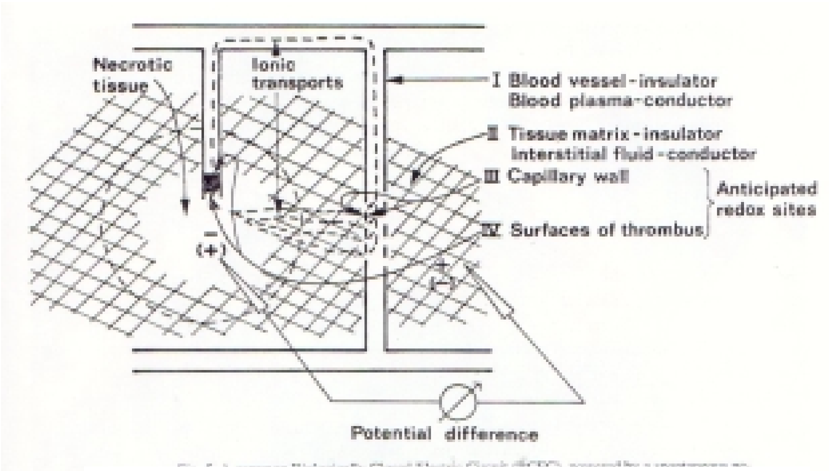

Fig. 1. Vascular-interstitial closed circuit forms a BCEC [1].

The treatment of cancer using the BCEC is shown in Fig.2. In this figure a DC current is injected through electrodes in cancer area forming an artificial BCEC. The existence of the closed circuit transport of ions inside the tumor promotes structural modifications in it. The therapy in Fig. 2 is known by EChT (Electro Chemical Therapy).

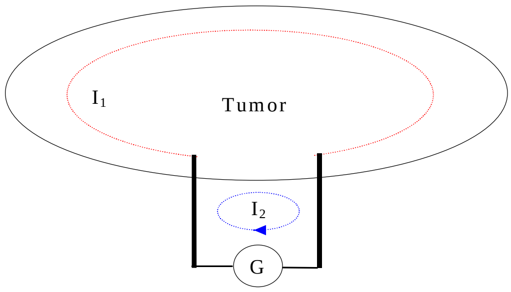

Fig 2. EChT.

EChT consist in the circulation of DC current in the tumor region through electrodes (anodic and cathodic electrodes) implanted directly inside the tumor region [3], [4]. The flow of DC current into the tumor start an eletrolytic process, where positively charged ions (H^+, Na^+, K^+) migrate to the cathode and negatively charged ions (Cl-) migrate to the anode. The area around the cathode becomes alkaline and around the anode becomes acid. The acidity and the alkalinity together electrochemical reactions that take place in the tissue have a destructive effect over tumor. Fig. 3 shows the transport of ions through a cellular membrane under an externally applied DC current.

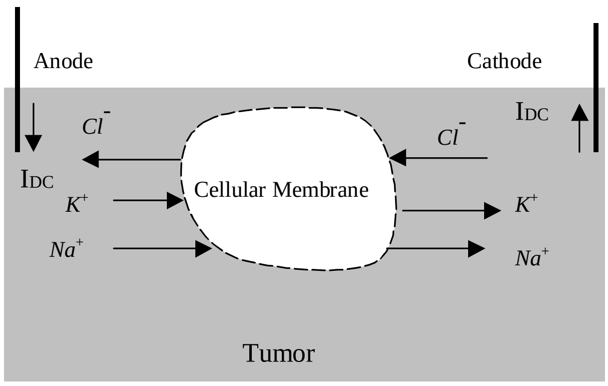

Fig. 3. EChT applied in target volume (tumor region).

At this moment, we are applying a DC current in dogs and evaluating the response of this treatment. It is important to say that the partial results are as expected.
We applied the EChT in a clinically healthy mammary gland of a dog with the objective of compare the results between this healthy mammary gland and the cancerous mammary glands. 4.90 mA DC current is applied in a healthy and in a sick mammary glands of two different dogs. The mammary glands are in the same position in both dogs (healthy and sick).
Our preliminary results suggest that each type of tumor has a different value of threshold current which promote a beneficial effect. These values of current were not established yet. We assume that EChT application can be reduced to a simple electrical circuit that describe both the transient and steady-state periods obtained from experimental data. In our conceived model there are a nonlinear relationship between the imposed DC current source and the verified voltage among anodic and cathodic electrodes. The equivalent circuit comprise a nonlinear resistor, which is time-dependent, in parallel with the DC current source. The nonlinear resistor is composed by a variable resistor in series with constant resistor. Knowing the tumor resistance value is possible to determine the power density imparted into the target volume (cancer area) by DC current source.

II. Materials and Methods

1.Animals

Three adult female mongrel dogs were used for this experiment. The dogs were provided by the Municipal Kennel and were housed individually at the Veterinary Hospital of Federal University of Rio Grande do Sul.
The dogs were placed under general anesthesia for application of continuous current.

2.Equipment

Electronic device was used to apply the DC current into the target volume (tumoral area). Basically, the apparatus consist of a injection DC current system which the desired value of current is previously adjusted. Indeed, the device is galvanically isolated at to uncouple the animal under treatment from the power supply. When the DC current flows into the tumor the electrical parameters of the tumor changes. During a section of EChT in the occurrence of the tumor electrical parameters variation, the electronic device keeps the previously adjusted value of the DC current. The current available values of the DC current are in the range of 0.0 mA to 15.0 mA.

3.EChT Procedure

Continuous current was applied (4.90 mA) during 20 minutes (total charge 5.88 Coulombs) through two electrodes inserted 2.0 cm apart in a healthy mammary gland of one dog. The dog was evaluated clinically after the treatment by visualization, palpation and size of the gland and measurement of body temperature.
Two dogs presenting mammary tumors (dog number 1 and dog number 2) were clinically examined, location and size of tumors were recorded and the mammary masses were submitted to aspirative needle biopsies. Thoracic radiographs were taken.
The tumoral glands were treated in two sessions weekly. Positive electrode (anode) was introduced at the center of the lesion and negative electrode (cathode) 2.0 to 3.0 cm away. Application consisted of 5.0 mA of continuous current for a period of 60 minutes. Treatment was performed in one mammary gland of dog number 1 and in two mammary glands of dog number 2.
Follow-up physical examinations and evaluation of lesions were conducted before each session. Any event occurring at the mammary gland during or immediately after the treatment was recorded. Aspirative needle biopsies were taken after each four applications of current or with 15 days intervals after the final of the treatment.
Treatment was stopped when cytopathological exams of the treated glands showed normal gland cells or absence of tumoral cells.

4.Results

All three dogs tolerated well the sessions of anesthesia and treatment. Anesthetic recoveries were uneventful. The dogs were submitted to general anesthesia because of the excited temperament of the dogs and the difficulty in evaluating pain in animals.

A. Healthy mammary gland

At the end of the application of continuous current, the treated mammary gland had increased volume and created a serous secretion. There was no evidence of alterations in the other mammary glands of the dog.

At the first day post-treatment, the gland presented a firm mass measuring 1.5cm of diameter. The dog had normal body temperature and normal behavior. The mass created in the mammary gland diminished gradually. At the 9^{th} day after the treatment, two small firm nodules (less than 0.5cm of diameter) were remaining at the site of application of the electrodes. Cytopathological exams of this animal were not taken. One month later, the nodules regressed and the dog was clinically normal.

B. Dog number 1

The dog presented malignant mixed tumor at the fourth mammary gland at the left mammary chain. The lesion was firm, encapsulated, irregular, ulcerated, measuring approximately $45.23cm^3$. Exact volume of the tumor was difficult to obtain due to the irregular shape of the lesion. Metastasis was not visualized in thoracic radiographies.
Application of direct current consisted of 5.0 mA during 60 minutes through two electrodes positioned 3.0 to 4.0 cm apart in the tumoral mass. Ten applications of current were necessary for treatment of the mammary gland.
After the first sessions of application of current, tumor volume enlarged and small points of necrosis appeared on the ulcerated surface. Production of gas during the applications of current started after the third session. After the 7^{th} application, started the production of purulent material in the mass. After the 10^{th} application, tumor volume diminished to approximately half of initial volume.

C. Dog number 2

The **first tumor treated** was the fourth mammary gland of the left mammary chain. The mass was firm, irregular, measuring 3.0 x 2.3 x 2.0 cm. Cytopathological exam revealed malignant mixed tumor. Five applications of continuous current were performed. Secretion of purulent material occurred since the first application of continuous current. Initially the tumor enlarged. After five sessions of treatment, necrotic cells appeared and the neoplasm progressed to a fibrous mass that was slowly being reabsorbed. At the 10^{th} day after the final of the treatment, only mammary duct cells were found on cytopathological exam and the mass was reduced to a firm nodule of 1cm of diameter.

The **second neoplasm treated** was located between the first and second mammary gland of the left mammary chain. The mass was irregular, firm, with multiple nodules, measuring 8.5 x 5.5 x 3.0cm. Exact volume of the mass was difficult to obtain due to the irregular shape of the lesion. Result of the cytopathological exam was adenocarcinoma. After the first application the tumor enlarged. Necrotic cells were present at cytopathological exam after the second application. Production of gas at the tumor started during the second application. After seven applications, the left axillary lymph node enlarged. Needle biopsy diagnosed reactional hiperplasia, that can be considered part of the inflammatory response to the treatment imposed. During the course of treatment, the tumor acquired a softer consistency at the central area. After ten sessions, ulceration of the tumor occurred. After 19 sessions, tumoral cells are still present at cytopathological exams, the dog is still under treatment.
Metastasis pretreatment were not revealed in thoracic radiographies.

5.Discussion

Possible hazardous effects of the treatment with continuous current in health mammary tissue were not found.
After an initial increase of the mass presumably due to edema, foci of necrosis and liquefaction of the neoplasm occurred. Decrease of tumoral mass occurred gradually, caused by inflammation, macrophage cells and necrosis induced in the tumor by the continuous current treatment. Destruction of tumoral cells was confirmed through cytopathological exams at the end of the treatment.

III. Theoretical Analises

All conducted applications using EChT showed a voltage profile having a decaying exponential waveshape. Our principal aim is to represent the electrode/material (electrode system/ tumor tissue) by electrical circuit and to determine the delivered energy to the tumor by DC current source. The most convenient form to express the referred decaying exponential waveshape is in terms of the total input impedance variation (of the tumor) as function of time.
The electric circuit conceived model represents the impedance (in macroscopic sense) that describe how the ions behavior when flows inside the tumor. The value of time-dependent resistance varies according chemical process that occur inside the tumor when DC current flow in the cancer area.

III.1 Model Parameter Estimation

Circuit model parameters were estimated from the experimental data.
Time-dependent resistance of the tumor is not constant in each session of EChT application. Tumor has time-dependent resistance *R(t)* which can be defined by the following expression:

$$R(t) = Ae^{-\xi t} + B \tag{2}$$

where, A, ξ and *B* are constants obtained from *Vxt* curves in each application session. The first term in right side of the expression (2) represent a variable resistance. The second term in the above expression represent a constant resistance. Indeed, both resistances are connected in serie. So, this time-dependent resistance, *R(t)*, arises when a DC current flows between the cathode and the anode electrodes through the extended region of the tumor.
We describe the electrical circuit model used to represent the tumor when DC current is applied into the target volume. The verified nonlinear resistance seems correct, because the transport equations which governs the motion of charges in a liquid (or solid) are nonlinear [5].

III.2 Discussion of the Conceived Model

Fig. 4 shows the general equivalent circuit used to represent the electrical response of the tumor when DC current is applied. The electrode impedance is modeled by a parallel RC circuit [6]. The C_{dl} is the capacitive double layer between the electrode metal and ions in the biological tissue (tumor). In the adopted model C_{dl} is assumed an open circuit. The resistor R_{electr} characterizes the charge transfer between electrode and the biological tissue [7]. For the derivation presented in Section III.1, we assume that the tumor (and associated electrodes) can be reduced to a simple nonlinear resistance connected to a DC current source. In our resistive model exist a nonlinear relationship between the imparted DC current and measured voltage among electrodes.

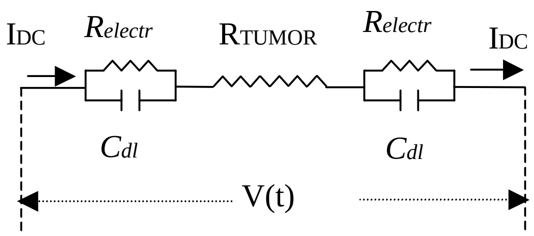

Fig. 4. Electrical circuit model of the tumor when DC current is applied in it.

The obtained resistance expression exhibits two components. The first component we can to relate with the transient change in the resistance and the second component is characterized by a steady state where the value of resistance is practically constant. Initially, the passage of DC current changes the tumor composition. Ion exchange and electron exchange (electrodes) are processes that generates a voltage difference.
The passage of DC current changes the composition of the medium (tumor), or we can say, that the changes in the tumor resistance occur due to the electrochemical reactions inside the treated area when DC current is applied. Indeed, the resistance represents the charge transferred between electrodes and tumor.
The total energy delivered by EChT to the target volume, E_{del}, can be calculated as:

$$E_{del} = \int_0^{t_1} \left(I_{DCsource}\right)^2 R(t)dt \tag{1}$$

where, $R_S(t)$ represent the effective time-dependent resistance seen by the DC current source, $I_{DCsource}$ is the DC current that circulate among electrodes and t_1 is the time application of the EChT in each application session.

IV.Conclusions and Open Questions

The relationship between treatment by EChT and biological response in our experiments is limited by the destruction of tumoral cells confirmed by cytopathological exams. The immune cells of the dogs under treatment, e. g. macrophages cells, that is the “police” of the body, are activated by EChT. We present simple analytical expression to the nonlinear resistance value of the tumor under EChT and the experimental procedure that support the referred analytical results. The apply DC current changes the concentration of ions, which in turn leads to a change of the membrane potential affecting, of this manner, certain ionic flows (Na^{+}/K^{+} pumps, Ca^{++}, Cl^{-}, etc.). In summary, there still much to be learned about the EChT and improvements can be expected.

References

[1] Nordenström, B. E. W., **Biologically Closed Electric Circuits – Clinical, Experimental and Theoretical Evidence for an additional circulatory system**, *Nordic Medical Publications*, Sweden, 1983.

[2] Nordenström, B. E. W., **Survey of Mechanisms in Electrochemical Treatment (ECT) of Cancer**, *The European J. of Surgery* , 1994; Suppl 574: 93-109

[3] Telló, M., Dias, G. A. D, Cardona A. V., Raizer, A., **Tumor Compression Due Application of DC Current**, IEEE Transactions on Magnetics, Vol. 37, NO. 5, September 2001, pp. 3753-3756.

[4] Nordenström, B. E. W., **An Additional Circulatory System: Vascular-Interstitial Closed Electric Circuits (VICC)**, *J. of Biol. Phys*., Vol 15, 1987, pp. 43-55.

[5] Macdonald, J. R., Franceschetti, **Theory of small-signal ac response of solids and liquids with recombining mobile charge**, J. Chem. Phys., VOL. 68, NO. 4, February 1978, pp. 1614-1637.

[6] Weiland, J. D., Anderson, D. J., **Chronic Neural Stimulation with Thin-Film, Iridium Oxide Electrodes,** IEEE Transactions on Biomedical Engineering, VOL. 47, NO. 7, July 2000, pp. 911-918.

[7] Mundt, C. W., Nagle, H. T., **Applications of SPICE for Modeling Miniaturized Biomedical Sensor Systems,** IEEE Transactions on Biomedical Engineering, VOL. 47, NO. 2, February, pp. 149-154.