Selective Electroporation of Liver Tumor Nodules by Means of Hypersaline Infusion: a Feasibility Study

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Abstract—**Spread tumors in liver are not suitable to be treated with local treatments, such as conventional surgery or radiofrequency ablation, thus entailing a poor prognosis. Electroporation-based therapies imply the delivery of pulsed high electric fields and currently are performed in a local fashion using needle or plate electrodes. Here, however, it is proposed a novel electroporation paradigm in which field delivery is not local. All the tumor nodules will be selectively treated using large plate electrodes at both sides of the liver. By infusing an hypersaline solution of high electrical conductivity through the portal vein, the electrical conductivity of healthy tissues and tumor nodules will be made significantly different so that the electric field will be focused on the undesirable tissues. Numerical simulations were used to evaluate the feasibility of the proposed technique. In addition, an in vivo procedure was carried out to assess whether it is possible and practical to significantly modify the conductivity of the liver tissue by hypersaline infusion. Both the numerical simulations and the in vivo procedure provided encouraging results.**

Keywords— **Electroporation, Liver, Spread tumors, Disseminated nodules, Hypersaline.**

I. Introduction

Electroporation is the phenomenon in which cell membrane permeability is increased by exposing the cell to high electric field pulses. Two electroporation-based therapeutic technologies are used for destroying tumors. *Electrochemotherapy* uses electroporation to cause reversible permeabilization of cell membranes which then facilitates anticancer drugs to penetrate within tumor cells. Non thermal irreversible electroporation (NTIRE) is a different technique that causes a permanent permeabilization inducing the final death of the undesired cells [1].

Liver tumors are often present in a spread fashion resulting in multiple tumor nodules (Fig. 1). In this case, patients usually have a poor prognosis because surgery cannot be employed to ablate adjacent tumors to principal blood vessels. Moreover, the removal of healthy tissue associated with collateral damage from surgery would be too large for the patient's survival [2].

Liver has a characteristic blood supply structure. Blood gets inside through two pathways. About 70% of the blood comes from the portal vein, whereas the remaining 30% comes from the hepatic artery. This blood flows through the hepatic sinusoids supplying nutrients throughout the parenchyma. However, the tumor nodules have a disorganized vascular structure and abnormal blood supply pathways: the lack of sinusoids implies that tumors are only supplied with blood from the hepatic artery [3]. This fact is currently used for identifying tumors by the injection of contrast agents during medical imaging (Fig. 1). Radiologists introduce the contrast solution by arterial infusion. Approximately 30 seconds after infusion the solution reaches the liver via portal vein (portal phase). Tumor nodules appear in the image as dark areas since the highlighting only affects at the healthy liver tissue.

Taking advantage of this fact, and inspired by our previous studies on the use of conductive fluids to modulate the electric field during electroporation [4], here it is proposed infuse hypersaline solution (with a high electrical conductivity) through the portal vein for selectively electroporating tumor nodules when the electric field is applied through the whole liver parenchyma. The hypersaline solution would cause an increase in the conductivity of the healthy tissue so that, when potential difference is applied between opposite sides of the liver, the electric field magnitude in the tumors would be significantly larger than in the rest of the tissue. Therefore it would be possible cause electroporation in the tumor cells avoiding the phenomenon in the healthy hepatic cells.

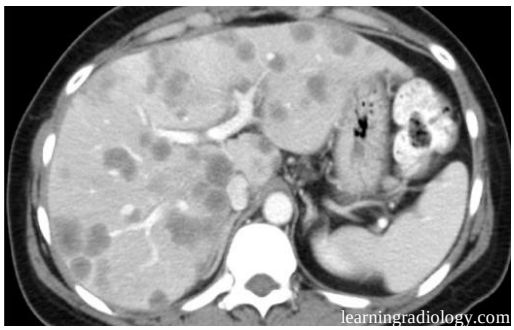

Fig. 1 Transversal section at liver with multiple tumor nodules. Healthy tissue enhancement by contrast introduced through portal vein.

This novel electroporation technique could be employed in irreversible electroporation therapies and also in electrochemotherapy. In the last case, the additional chemotherapeutic agent would be injected through hepatic artery so that, thanks to the characteristic blood supply distribution of the liver, a larger concentration of the drug would be present in the tumor regions thus increasing the efficacy of the method.

II. Materials and Methods

A. Numerical study on treatment feasibility

Numerical simulations were carried out with a geometrical model (Fig. 2) which represents a cylindrical portion of liver (radius 15 mm and height 30 mm) in which three tumor nodules are represented as spheres (radius 3 mm). High voltage was applied between parallel plates located at the top and bottom of the liver.

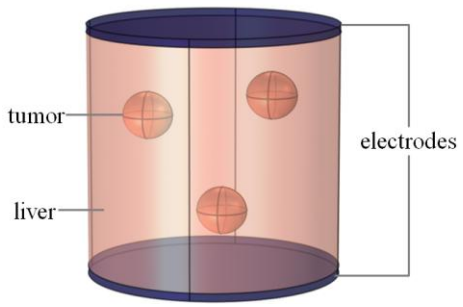

Fig. 2 Geometrical model used in the numerical study. The model included three different elements: metallic electrodes, hepatic tissue, and tumor tissue.

Reported healthy liver conductivities goes from 0.03 S/m [5] to 0.12 S/m [6]. At the same time is commonly reported a significantly higher conductivity of tumor than healthy one. Taking into account the liver conductivity obtained during in vivo experiments, the values previously reported in [6] were used (Table 1). With these values is possible to calculate the electric field distribution within the model when a certain electric potential is applied between both electrodes. A constant conductivity i.e. non-dependent on electric field magnitude was used for facilitating computation. The problem was solved numerically using the finite element method (FEM) by means of COMSOL Multiphysics 4.3a (COMSOL, Stockholm, Sweden).

Table 1 Properties of the materials used in the theoretical model

Tissue/material	Electrical Conductivity (S/m)
Electrode	7.4×10^{6}
Liver	0.12
Tumor	0.27
Infused liver	0.3, 0.6, 1.2

Numerical simulations of irreversible electroporation treatment were performed. The relative amounts of treated tumor volume and also of the treated healthy tissue were assessed applying voltages from 0 V to 3000 V. Treatment was consider effective when the electric field magnitude surpassed the reported irreversible electroporation threshold for liver tissue (680 V/cm) [7].

B. In vivo hypersaline infusion

With the aim of quantifying the conductivity changes in liver due to hypersaline infusion, a single procedure was performed in a healthy female Landrace pig under general anesthesia. The procedure was approved by the Ethical Commission of the Universitat Autònoma de Barcelona.

Through midline laparotomy, extrahepatic portal vein catheterization was performed in order to deliver 200 ml of 20% NaCl with an electrical conductivity of about 19 S/m. In order to minimize a possible ionic and osmotic imbalance at the rest of the body, distilled water was simultaneously injected through an additional catheter at cava vein.

The conductivity changes were monitored in real time using a two electrode setup. This setup consists of two PCBs with round gold electrodes on them (radius 10 mm). The PCBs are mounted on a pincer so that the electrodes are securely paced at opposite sides of a hepatic lobule (Fig. 3). Impedance was measured using a 1 V amplitude sine wave at 5 kHz excitation signal by means a custom developed impedance meter.

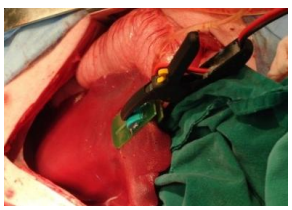

Fig. 3 Probe used to measure conductivity changes in liver.

Finally, the animal was stabled during a month. After that it was sacrificed to obtain histological samples of the liver.

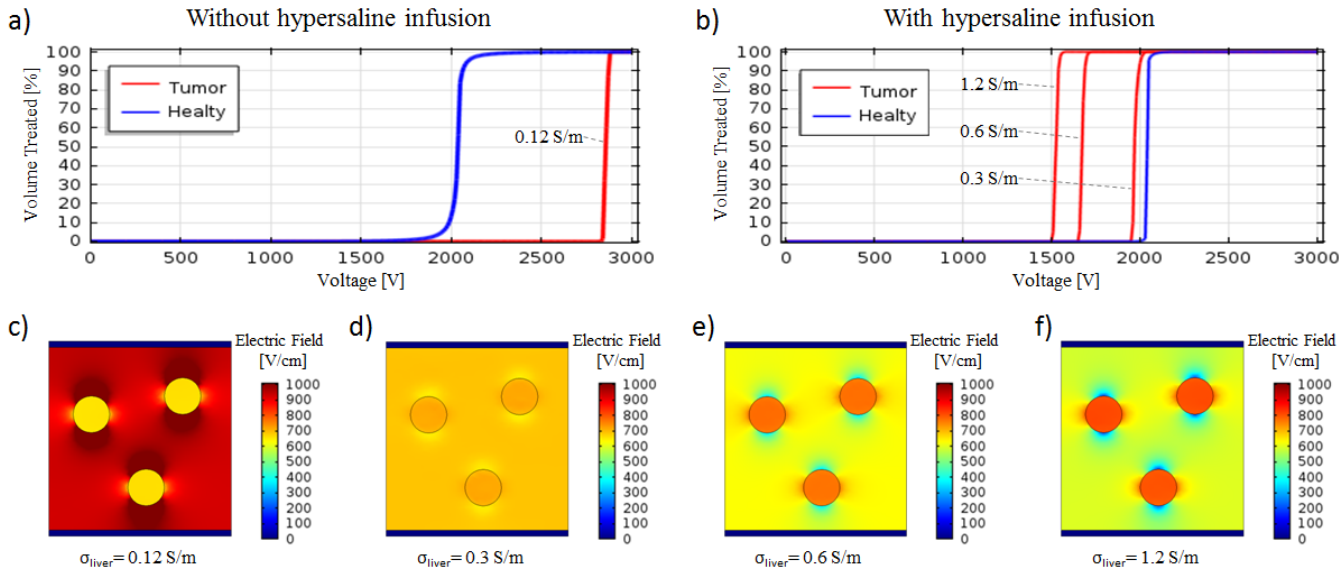

Fig. 4 Numerical simulation results. a) Relative volume of tissue irreversibly treated by electroporation in relation to the voltage applied between electrodes without hypersaline infusion. (σ_{liver} = 0.12 S/m). b) Relative volume of tissue affected by electroporation according to voltage applied between electrodes after hypersaline infusion. Effects for 0.3, 0.6 and 1.2 S/m liver conductivity are represented at the same time. c) Electric field distribution within liver applying 2750 V between electrodes (σ_{liver} = 0.12 S/m). d) Electric field distribution within liver with a high conductivity applying 2050 V between electrodes (σ_{liver} = 0.3 S/m). e) Electric field distribution within liver with a high conductivity applying 1880 V between electrodes (σ_{liver} = 0.6 S/m). f) Electric field distribution within liver with a high conductivity applying 1790 V between electrodes (σ_{liver} = 1.2 S/m).

III. Results

A. Numerical results

Depending on electric potential applied between electrodes, the electric field generated within the tissue will cause the irreversible electroporation effect at certain tissue volume (Fig. 4a).

According to the initial conductivities of healthy and tumor tissue, the sufficient voltage to produce irreversible electroporation of the whole tumor tissue (2750 V), also would suppose the overtreatment of the whole healthy tissue (Fig. 4c).

Observing the outputs of relative volume treated after hypersaline infusion (Fig. 4b), with a liver conductivity of 0.6 S/m it exists a certain range of treatment intensity from 1740 V to 2000 V that affects the whole tumor tissue but not healthy one. With a higher electrical conductivity of the healthy tissue, the voltage drop in the tumor is higher due to its lower conductivity. With hypersaline infusion, applying a voltage within the previous range higher electric field will be focused on tumor areas (Fig. 4e).

B. Experimental results

Infusion of a high-conductivity solution through portal vein produces a rapidly increase of the whole conductivity of the liver. In the in-vivo experiment carried out a conductivity value above 0.6 S/m was observed after infusion of hypersaline solution (Fig. 5).

Histopathologic examination of samples obtained from sacrificed animal does not show damage due to procedure.

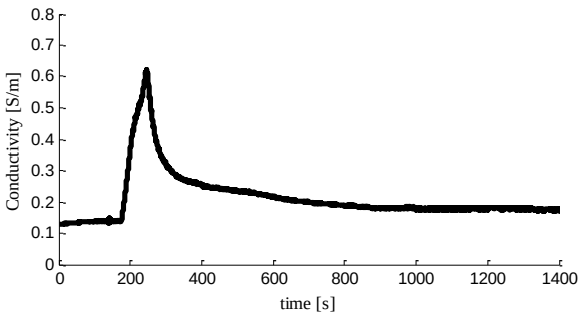

Fig. 5 Electrical conductivity during hypersaline infusion.

IV. Discussion

The results obtained using numerical simulations show that within a certain range of applied voltage the tumor nodules will be treated whereas most of the healthy tissue will be spared. As expected, the voltage range in which treatment is effective (tumor nodules are effectively treated) but no overtreatment occurs (healthy tissue is spared) increases as the difference in conductivity between the healthy liver and the tumor nodules increases. Thereby it is desirable to maximize the ratio of conductivities in order to increase the safety of the treatment.

The in vivo experiment shows a liver electrical conductivity peak value over 0.6 S/m. As numerical simulation shows, this value would provide a safe potential range of 280 volts (a 15% of applied voltage) which appears high enough. Nevertheless, the limitations of the model must be pointed out. There are some uncertainties about electroporation thresholds and the basal conductivities for tumors and healthy tissues. In addition, tumor shapes cannot be considered as perfect homogeneous spheres. Therefore, higher conductivity contrast may be actually necessary.

It is also convenient to point out that the impact of electroporation on microvasculature could demand a modification the approach described above. Actually, it would imply to infuse the hypersaline solution through the hepatic artery rather than through the portal vein. Briefly: the difference in conductivity between blood and endothelia causes an electric field concentration in the vessel walls [8]. As a consequence, thin vessels are likely to be disrupted during any tissue electroporation treatment. This fact most likely provokes the observed disruption of microvasculature flow after electroporation treatments [9], [10] which results in ischemia. Increasing the conductivity of tumor blood could facilitate the destruction of its microvasculature applying lower treatment intensity.

V. Conclusions

Here it is presented the first step towards the development of a new therapeutic approach able to broaden the use of electroporation therapies for treating hepatic tumors. Despite of being a high invasive treatment, against the trend towards minimally invasive approaches, this technique could offer a new opportunity for current untreatable cases were multiple tumor nodules are present.

The results presented in this study indicate that by means of hypersaline solution infusion it may be possible to produce selective electroporation focused on tumor tissue.

Acknowledgments

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. A. Golberg and M. L. Yarmush, (2013) Nonthermal irreversible electroporation: fundamentals, applications, and challenges. IEEE Trans. Biomed. Eng., vol. 60, no. 3, pp. 707–14. doi:10.1109/TBME.2013.2238672.
2. J. S. Bolton and G. M. Fuhrman, (2000) Survival after resection of multiple bilobar hepatic metastases from colorectal carcinoma. Ann. Surg., vol. 231, no. 5, pp. 743–51.
3. A. Kitao, Y. Zen, O. Matsui, T. Gabata, and Y. Nakanuma, (2009) Hepatocarcinogenesis: multistep changes of drainage vessels at CT during arterial portography and hepatic arteriography--radiologic-pathologic correlation. Radiology, vol. 252, no. 2, pp. 605–14. doi:10.1148/radiol.2522081414.
4. A. Ivorra and B. Rubinsky, (2007) Electric field modulation in tissue electroporation with electrolytic and non-electrolytic additives. Bioelectrochemistry, vol. 70, no. 2, pp. 551–60. doi:10.1016/j.bioelechem.2007.02.001.
5. S. Laufer, A. Ivorra, V. E. Reuter, B. Rubinsky, and S. B. Solomon, (2010) Electrical impedance characterization of normal and cancerous human hepatic tissue. Physiol. Meas., vol. 31, no. 7, pp. 995–1009.
6. D. Haemmerich, S. T. Staelin, J. Z. Tsai, S. Tungjitkusolmun, D. M. Mahvi, and J. G. Webster, (2003) In vivo electrical conductivity of hepatic tumours, Physiol. Meas., vol. 24, no. 2, p. 251.
7. R. V. Davalos, L. M. Mir, and B. Rubinsky, (2005) Tissue Ablation with Irreversible Electroporation, Ann. Biomed. Eng., vol. 33, no. 2, pp. 223–231. doi:10.1007/s10439-005-8981-8.
8. G. Sersa, T. Jarm, T. Kotnik, a Coer, M. Podkrajsek, M. Sentjurc, D. Miklavcic, M. Kadivec, S. Kranjc, a Secerov, and M. Cemazar, (2008) Vascular disrupting action of electroporation and electrochemotherapy with bleomycin in murine sarcoma., Br. J. Cancer, vol. 98, no. 2, pp. 388–98.
9. J. Gehl and P. F. Geertsen, (2006) Palliation of haemorrhaging and ulcerated cutaneous tumours using electrochemotherapy., Eur. J. Cancer Suppl., vol. 4, no. 11, pp. 35–37. doi:10.1016/j.ejcsup.2006.07.007.
10. E. Bellard, B. Markelc, S. Pelofy, F. Le Guerroué, G. Sersa, J. Teissié, M. Cemazar, and M. Golzio, (2012) Intravital microscopy at the single vessel level brings new insights of vascular modification mechanisms induced by electropermeabilization., J. Control. Release, vol. 163, no. 3, pp. 396–403.

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