PRELIMINARY IN-VIVO PROBE MEASUREMENTS OF ELECTRICAL PROPERTIES OF TUMORS IN MICE

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Abstract

The induction of hyperthermia into neoplastic tissues using electromagnetic radiation depends significantly upon the electrical properties of the tissues of interest. An in-vivo measurement probe based upon an antenna modelling theorem was designed and a measurement system that is capable of performing accurate in-vivo measurements has been developed and tested on several standard materials. This measurement probe and system were used to perform dielectric measurements on normal and neoplastic tissues from 0.01 to 2.0 GHz. The preliminary results of measurements performed on six malignant tumor types in mice are compared with results obtained on normal muscle tissue and on phantom modelling materials. The trends of the in-vivo measurements show differences that indicate the possibility of using such data and techniques in various types of future cancer research.

Introduction

Knowledge of the electrical properties (dielectric constant and conductivity) of malignant tissue is necessary in any well-founded effort that utilizes electromagnetically induced hyperthermia (electrohyperthermia) as an adjunct to cancer treatment. Without this knowledge, neither the heating pattern developed in the tissue nor the design of applicators that efficiently couple electromagnetic (EM) energy into the tissue can be accurately determined on an a priori basis. The EM heating techniques that have been used in previous electrohyperthermia investigations have not taken into account the in-vivo electrical properties of the tissue being heated. In particular, these techniques have either employed in-vitro electrical properties of normal tissues such as muscle or given no consideration to tissue electrical properties.

The adequacy of in-vitro electrical property measurement techniques is limited because of the need to excise the tissue in order to perform measurements from which the electrical properties can be determined. Not only are the possible effects of the circulatory system not taken into account, but the electrical properties of the excised sample can further deteriorate from the in-vivo values during sample preparation. An instrument that can be employed to quickly and accurately measure these in-vivo electrical properties in a clinical situation would therefore have great utility in biomedical research.

A measurement system that may be utilized to determine the in-vivo electrical properties of both malignant and normal tissue is presently being developed[1,2]. The measurement concept is based on an antenna modelling theorem which states that the change in free space terminal impedance of an antenna inserted into a lossy medium is related to the electrical properties of that medium[3]. If an analytical expression for the impedance of an antenna is known, in both the reference medium and the medium under study, this modelling theorem may then be used to determine the electrical properties of that medium[4]. Because the impedance of a very short monopole is easily described analytically, this antenna may be used as a small probe that can be inserted into living tissue and thereby permit measurement of electrical properties. Measurement equipment required for use with the probe consists of a signal source, reflectometer, network analyzer, and data recording equipment. This measurement system yields probe impedance in the form of a complex reflection coefficient which is subsequently converted to dielectric constant and conductivity data via a computer algorithm.

Initial efforts with this probe system involved determining measurement accuracy. This was accomplished through a series of electrical property measurements using standard reference materials. Once the accuracy of the measurement system had been established, measurements were performed on canine muscle, kidney, and fat tissue as well as phantom modelling material. These measurements were followed by preliminary electrical property measurements of six tumor lines in mice.

Theoretical Basis

By measuring the impedance of a short monopole antenna inserted in living tissue, it is possible to determine both the relative dielectric constant (K') and loss tangent (tanδ), and hence, the power which would be absorbed in the tissue. This is achieved by employing an antenna modelling theorem[3] which relates the impedance of a short monopole antenna in air to its impedance in a lossy dielectric medium. For biological materials, the permeability μ of the medium is essentially that of free space and, in this case, the theorem is expressed mathematically as

$$\frac{Z(\omega,\varepsilon)}{\eta} = \frac{Z(n\omega,\varepsilon_o)}{\eta_o} \qquad (1)$$

where $\omega = 2\pi f$ is the angular frequency,

$\eta = \sqrt{\mu_o/\varepsilon}$ is the intrinsic impedance of the medium,

$\eta_o = \sqrt{\mu_o/\varepsilon_o}$ is the intrinsic impedance of free space, and,

$n = \sqrt{\varepsilon/\varepsilon_o}$ is the index of refraction of the medium to that of air.

To employ this modelling theorem, an analytical expression of the probe impedance in the medium under study is needed. In the case of a short monopole antenna, this impedance can be expressed as

$$Z = A\omega^2 + \frac{1}{jC\omega}, \qquad (2)$$

in which A and C are constants that are determined by the dimensions of the specific probe under consideration[5]. In order to characterize the electrical properties of the medium under study in terms of the relative dielectric constant and loss tangent, the complex index of refraction is defined as

$$n = \sqrt{\varepsilon/\varepsilon_o} = \sqrt{K'(1 - j\tan\delta)} \qquad (3)$$

where $\varepsilon = \varepsilon' - j\varepsilon''$, $K' = \varepsilon_r = \varepsilon'/\varepsilon_o$, $\tan\delta = \frac{\sigma}{\omega\varepsilon'}$, and σ is the conductivity. Utilizing the form of the antenna impedance given in Equation (2) in the modelling theorem of Equation (1) yields

$$Z(\omega,\varepsilon) = A\omega^2\sqrt{K'(1 - j\tan\delta)} + \frac{1}{jC\omega[K'(1 - j\tan\delta)}, \qquad (4)$$

This equation can be presented in the form $Z = R + jX$, which reduces to two real equations to give

$$R = \frac{\sin 2\delta}{2K'\omega C} + A\sqrt{K'}\,\omega^2\sqrt{\frac{\sec\delta + 1}{2}}, \qquad (5)$$

and

$$X = \frac{\cos^2\delta}{K'C} + A\sqrt{K'}\,\omega^2\sqrt{\frac{\sec\delta - 1}{2}}. \qquad (6)$$

The parameters R and X are the measured impedance, A and C are physical constants of the probe, and all other parameters are known except K' and δ, for which an iterative solution is obtained.

Experimental Technique

Several probe configurations were initially investigated during the development of a suitable measurement system. The probe ultimately selected was constructed by cutting away a short section of the outer conductor of a length of semi-rigid coaxial cable, thus exposing a portion of the center conductor. A small ground plane was also affixed to the base of this probe. The exposed section of the center conductor behaved electrically as a short antenna , and the ground plane served to insure that the terminal impedance of the probe was described accurately by the expression in Equation (2). The system employed to measure the impedance of the probe consisted of a reflectometer in conjunction with a network analyzer as depicted in Figure 1. By employing this system to measure the complex terminal impedance of the probe when radiating into a lossy medium, it was possible to experimentally determine the dielectric constant, loss tangent, and conductivity of the medium from the relationships given by Equations (5) and (6).

Experimental Results

The measurement accuracy of the probe system was initially determined through measurements on a number of standard materials. Water and ethylene glycol were included in these standard materials because their electrical properties have been well documented by other researchers[6,7]. Results of measurements for water and ethylene glycol are shown in Figures 2 and 3, and, as depicted by these results, the probe system yields good correlation with reference data. These measurements on standard materials indicate that the probe is potentially useful at frequencies up to at least 8 GHz. However, measurements of muscle-equivalent phantom modelling materials and tissue were performed only up to 2.0 GHz because of procedural limitations.

Preliminary dielectric constant and conductivity measurements have been made in-vivo on canine thigh muscle tissue and six different types of malignant tumors in mice. The tumor types included Lewis Lung Carcinoma, Melanotic Melanoma B16, Barrett Mammary Adenocarcinoma (MA), Mendecki Mammary Adenocarcinoma (MA), Glioblastoma, and Ependymoblastoma. These preliminary measurements were made over a 0.01 to 2.0 GHz frequency range. The in-vivo values of dielectric constant and conductivity measured on Lewis Lung and B16 type tumors are shown relative to the canine thigh muscle tissue and the muscle-equivalent modelling material in Figures 4 and 5. Figures 6 and 7 present in-vivo values of dielectric constant and conductivity measured for the Barrett and Mendecki mammary tumors, again relative to muscle tissue and muscle-equivalent modelling material. The measured results for the Glioblastoma and Ependymoblastoma are presented in Figures 8 and 9. Although (1) only a limited number of tumor samples were measured, (2) the measurement effort was preliminary in nature, and (3) the protocols were developmental, the resulting dielectric constant and conductivity values appear reasonable in relation to in-vivo values previously measured using normal tissue. In addition to the knowledge of relative electrical property values provided by these preliminary measurements, information regarding improved measurement procedures was also obtained. For example, initial procedures for positioning the animal during the measurement sequence, providing suitable contact pressure between the probe tip and the tissue, and maintaining the necessary moisture on the tissue surface were developed. Also, in order to accommodate in-vivo measurements, the center conductor of the probe was slightly extended, thereby insuring good electrical contact with the tissue. These procedures, the probe modifications, and the correlation of electrical properties of these tumors with observed physical characteristics will be described during the paper presentation.

Conclusions

The probe system, measurement procedures, and preliminary data presented in this paper represent an important advancement in the ability to define electrical properties of living tissue. From these preliminary results, it is evident that a need exists to know, for each individual case, not only the electrical properties of the tumor line, but also the properties of adjacent normal tissue. Further improvements in the probe system and measurement procedures are still being developed. This system, once automated with a swept frequency capability and an increased sensitivity, could represent a potentially useful diagnostic tool for differentiating between normal and malignant tissues. Once the probe system and measurement procedures are developed over their full range of frequency capability, extensive in-vivo measurements will be undertaken to define the electrical properties of malignant tissues. Accurate knowledge of these properties can then be used to significant benefit in efforts where electrohyperthermia is used as a cancer treatment modality.

Acknowledgements

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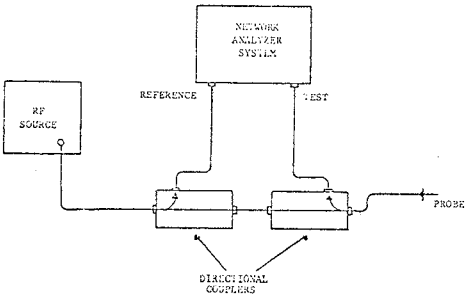

FIGURE 1. BLOCK DIAGRAM OF IN-VIVO PROBE MEASUREMENT SYSTEM AND PROBE.

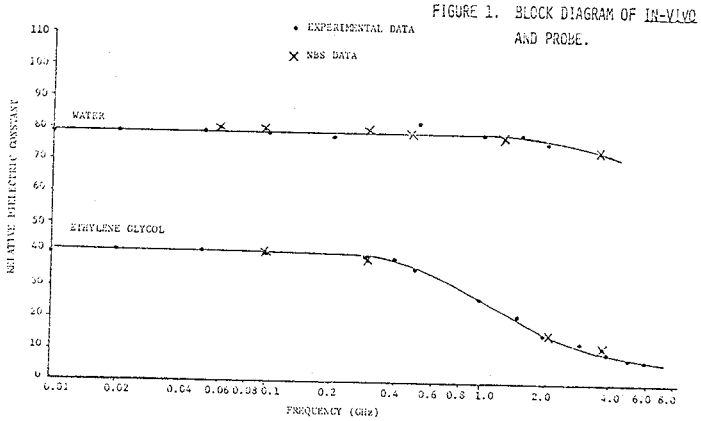

FIGURE 2. MEASURED DIELECTRIC CONSTANT OF WATER AND ETHYLENE GLYCOL AT 23°C COMPARED TO NBS STANDARDS DATA.

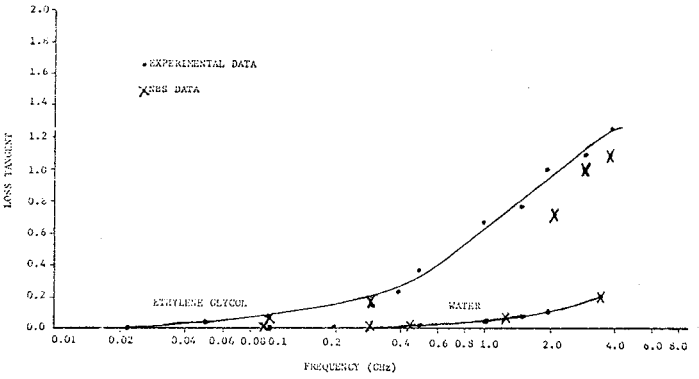

FIGURE 3. MEASURED LOSS TANGENT OF WATER AND ETHYLENE GLYCOL AT 23°C COMPARED TO NBS STANDARDS DATA.

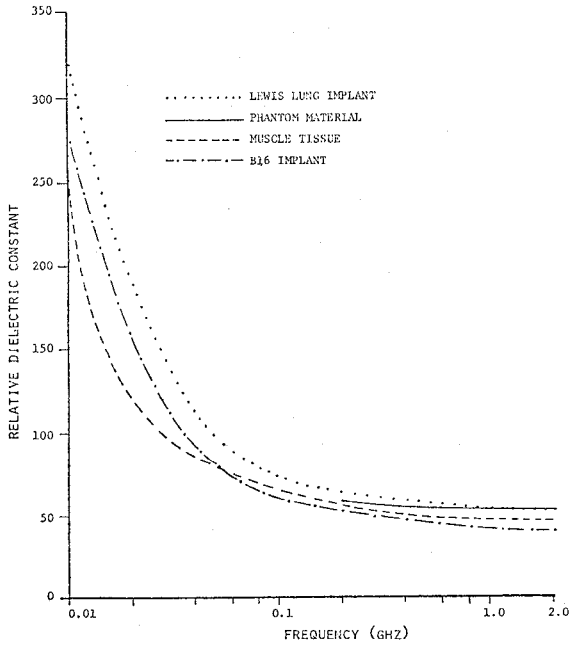

FIGURE 4. MEASURED DIELECTRIC CONSTANT OF LEWIS LUNG AND B16 TUMORS COMPARED TO THAT OF CANINE MUSCLE AND PHANTOM MODELLING MATERIAL

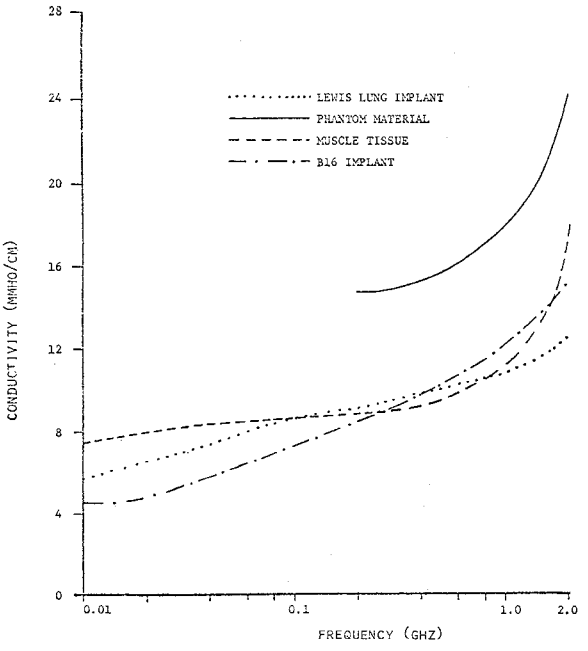

FIGURE 5. MEASURED CONDUCTIVITY OF LEWIS LUNG AND B16 TUMORS COMPARED TO THAT OF CANINE MUSCLE AND PHANTOM MODELLING MATERIAL.

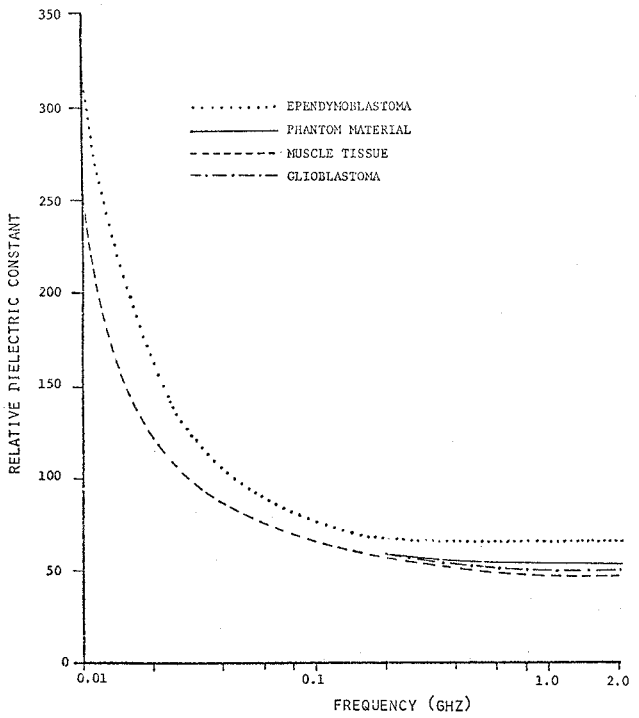

FIGURE 6. MEASURED DIELECTRIC CONSTANT OF GLIOBLASTOMA AND EPENDYMOBLASTOMA COMPARED TO THAT OF CANINE MUSCLE AND PHANTOM MODELLING MATERIAL.

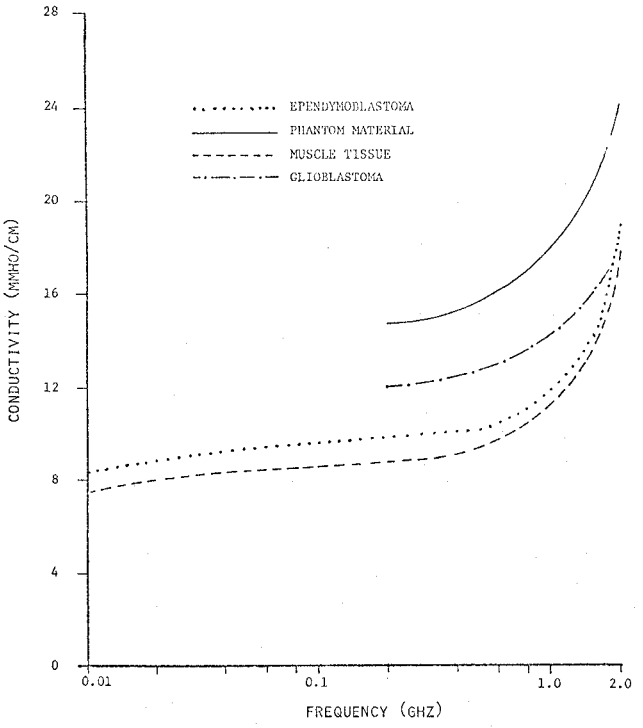

FIGURE 7. MEASURED CONDUCTIVITY OF GLIOBLASTOMA AND EPENDYMOBLASTOMA COMPARED TO THAT OF CANINE MUSCLE AND PHANTOM MODELLING MATERIAL.

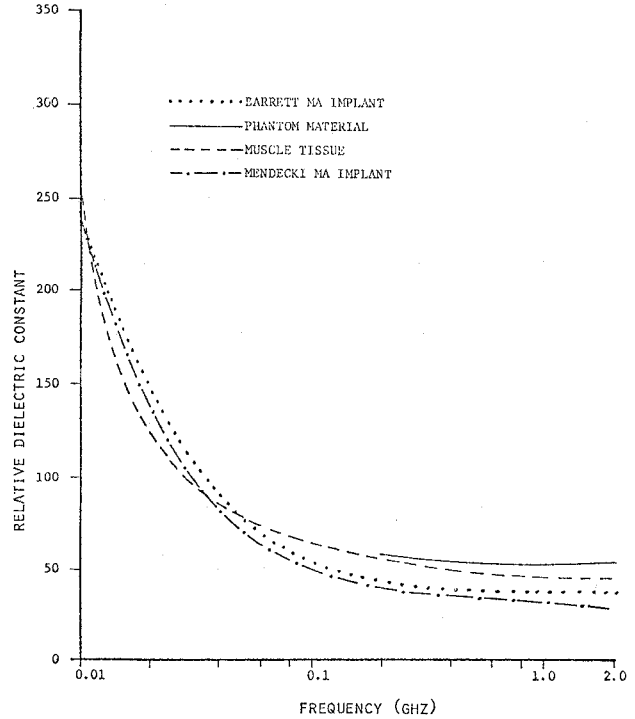

FIGURE 8. MEASURED DIELECTRIC CONSTANT OF BARRETT MA AND MENDECKI MA COMPARED TO THAT OF CANINE MUSCLE AND PHANTOM MODELLING MATERIAL.

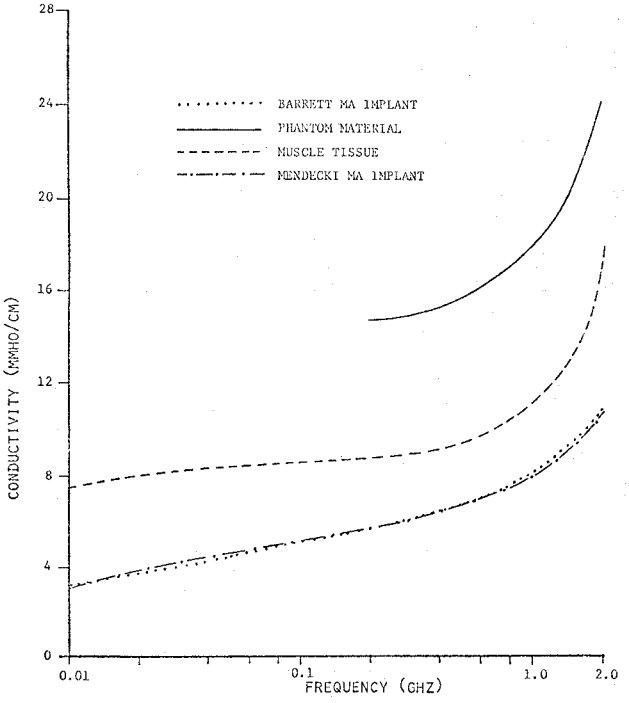

FIGURE 9. MEASURED CONDUCTIVITY OF BARRETT MA AND MENDECKI MA COMPARED TO THAT OF CANINE MUSCLE AND PHANTOM MODELLING MATERIAL.