NON-INVASIVE *IN VIVO* TEMPERATURE MAPPING OF ULTRASOUND HEATING USING MAGNETIC RESONANCE TECHNIQUES

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Abstract-A major problem with conventional methods of measuring heating *in vivo* is that they are invasive and therefore interfere with heat propagation. A sensitive *non-invasive* method for temperature measurement using *in vivo* magnetic resonance spectroscopy (MRS) of the temperature dependent chemical shift of the cobalt(III) nucleus has been developed. Initial experiments demonstrate that this technique can be used to measure ultrasound induced temperature changes in the liver. Tris(ethylenediamine) cobalt(III) trichloride was encapsulated in liposomes and injected into seven rats. Heating was performed using a calibrated unfocused transducer operating at 3.41 MHz. After 5 minutes of CW ultrasound exposure, the chemical shift of the cobalt complex indicated that the temperature rise within the liver was 2.0±1.2 °C. This was seen to return to normal upon cessation of heating. The acoustic power was determined in a water bath using a calibrated hydrophone. Theoretical calculations based on the transducer calibration characteristics using the monopole-source solution for estimating tissue temperature increase yielded 2.0 °C based on steady state conditions. These results indicate that experimental values agree with the heating theory.

I. INTRODUCTION

The hypothesis behind this research is that tissue temperature rise from ultrasound exposure can be accurately calculated using the monopole-source method, and that these calculations can be verified using non-invasive magnetic resonance techniques. Measurement of heating produced by ultrasound has direct relevance to hyperthermia therapy. Elevation of the local temperature to between 42 and 45°C has been shown to kill cancer cells. Monitoring of the temperature in both the tumor and surrounding healthy tissue is of vital importance since changes of less than 1°C within the tumor have large effects on the efficacy of treatment. Increases in the temperature of healthy tissue have been shown to cause serious injury (Corry et al., 1984).

Existing methods for thermal mapping using magnetic resonance have generally used protons as the observed nucleus. There are potentially four magnetic resonance parameters which can be used to measure temperature rise: the proton density (Alexander et al 1994), the spin-lattice (T_1) relaxation time (Parker 1984, Matsumoto et al 1992), the self-diffusion coefficient of water (Lebihan et al. 1989, Zhang et al. 1992, Samulski et al. 1992), and the chemical shift of the water peak (De Poorter et al. 1994, Macfall 1994). These methods have many desirable characteristics, but are susceptible to physiological changes induced by temperature, and also motion artifacts.

The approach in this research is to use new MR imaging agents based on the direct detection of the cobalt resonance. The temperature dependence of the chemical shift is 100-300 times greater than that of the water protons. This nucleus is 100% naturally abundant and has a gyromagnetic ratio approximately one quarter that of the hydrogen nucleus. Cobalt is a quadrupolar nucleus (I= 7/2) and subsequently the NMR lineshape is considerably broadened by interaction of the electric field gradient with the nuclear quadrupole moment. This problem can be overcome, however, with a symmetric chemical environment around the central cobalt nucleus. The temperature dependence of the chemical shift arises from the relationship between the diamagnetic shielding constant and the crystal field splitting, which is affected by temperature (Freeman et al. 1957, Proctor 1951).

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II. MATERIALS & METHODS

A. Calculation of Temperature Rise

The monopole-source solution for an unfocused transducer is used to calculate heating in the rat liver (Ellis and O'Brien, 1994). Briefly, the point-source solution to the linear bio-heat transfer equation is used to calculate the axial steady-state temperature increase for focused and unfocused circular apertures. To determine tissue heating, the monopole-source solution used two independent procedures. The first procedure is to determine the acoustic pressure field generated by an ultrasonic transducer. The second process consists of using the acoustic pressure field to determine the temperature increase at any point in the medium. Using the monopole-source solution it is possible to determine the temperature increase profile at any location in the medium.

To calculate the temperature rise in rat liver due to ultrasound heating, the acoustic power of the transducer is measured following the AIUM Acoustic Output Measurement and Labeling Standard (AIUM 1992). The acoustic power was establish by measuring the spatial characteristics of the ultrasound field produced by the transducer. The same electronic equipment and transducer used for the ultrasound heating experiment described in the following methods section are used for the exposimetry measurement. To mimic the heating conditions described in the following section, the transducer and standoff were mounted 5 cm apart in an anechoic tank of degassed water at room temperature. A polyvinyl difluoride bilaminar membrane hydrophone (GEC Marconi, Y-33-7611) was mounted in front of the standoff and maneuvered using a automated positioning system. The acoustic power which was measured to be 4.3 W. Using an ultrasonic absorption coefficient 0.5 dB/cm-MHz for liver (Pohlhammer et.al, 1981) the monopole-source solution for estimating tissue temperature increase predicted 2.0^{o}C based on 5 minutes for the change in temperature to reach steady-state conditions.

B. Measurement of in vivo Temperature Rise

Seven female Sprague-Dawley rats weighing 200.0±10.0g were anaesthetized using ketamine/xylazine (0.1ml/100g). Tris(ethylenediamine) cobalt(III) trichloride encapsulated in liposomes was injected (0.29mM/kg) into a rat via the tail vein. $Co(en)_3Cl_3$ was encapsulated in liposomes prepared using the reverse evaporation phase process (Szoka and Papahadjopoulos, 1980) as modified by Magin and Weinstein (1984). The liposomes are subsequently taken up by the macrophages of the liver and spleen. The abdominal area of each rat was clipped with an electric shaver and the hair removed with a depilatory agent (Nair®) to minimize air entrapment.

The experimental set-up for ultrasound exposure of the rat is shown in Figure 1. Ultrasound heating was performed using an unfocused PZT-4 transducer, diameter 3.8 cm, operating in continuous-wave mode at a frequency of 3.41 MHz. The water filled standoff utilized a loose fitting thin flexible latex window which could easily mold to the abdominal area of the rat. The transducer was submerged in the degassed water filled standoff 5 cm from the abdomen of the rat. Ultrasound gel (Parker Laboratories, Inc.) was used on the abdomen of the rat to ensure contact to the latex window of the standoff. The RF coil was placed against the rat abdomen beneath the standoff. All ultrasound exposures were performed inside the magnet.

Magnetic resonance experiments were carried out at a magnetic field strength of 4.7 Tesla, using a 33 cm bore horizontal superconducting magnet from Spectroscopy Imaging Systems Corporation (SISCO), Freemont, CA. The two turn 4 cm diameter RF surface coil, tuned to 47.8 MHz, was used for both transmission and reception. The T_1 value of the cobalt complex was 7 ms, the and the T_2 value 4 ms. Spectra were acquired using a standard pulse and acquire sequence, TR=36ms, pulse width=180 μs. The linewidth was 140 Hz and the signal to noise was 15:1 for 1024 transients.

Control spectra of the liver of each rat were collected for 5 minutes prior to the first ultrasound exposure. Five minutes is the required time for the temperature increase to

reach steady-state. No MR temperature measurements were performed during the application of ultrasound inside the magnet. After 5 minutes of ultrasound exposure an elevated temperature was observed. The return of tissue temperature to the initial value was monitored by collecting spectra for 11 minutes at 1 minute intervals. Two more ultrasound exposure followed by MR temperature measurements were performed before the rat was removed from the magnet.

III. RESULTS

The temperature vs chemical shift conversion factor has been determined experimentally to be 67 ± 10 Hz/°C (Niesman et al. 1994), which gives a temperature resolution of ± 0.1°C. For all seven rats studied the temperature measurements within the liver displayed similar temperature increases after heating, and cooling during the time that the ultrasound was turned off. However the initial internal temperature of the liver differs between rats due to biological variations and differences in the ambient temperature at the time of the experiments. The results in Figure 2 graph the change in temperature, averaged over all seven rats, from the initial pre-exposure value. The average temperature rise was 2.0 ± 1.2 °C for the rat liver, and the temperature returned to its original baseline after 5 minutes. The temperature resolution of the MR data was ± 0.1°C with a temporal resolution of 15 seconds per spectrum over a volume of approximately 8 cm^3.

IV. DISCUSSION

Theoretical calculations for the ultrasound heating are in excellent agreement with the experimentally determined values and show the validity of the monopole-source method for calculating temperature changes *in vivo*. The particular agent used to measure experimentally the temperature rise avoids the problems of tissue perfusion and physiological changes which are encountered by T_1 and diffusion measurements, and the sensitivity of the chemical shift to temperature is two orders of magnitude greater than that of the proton chemical shift. However, the need for an exogenous agent removes, to some extent, the "non-invasive" character of the method, and more importantly limits the use to tissues which can be targetted, in this case liver, spleen, and specific tumors. This agent is therefore likely to find most use in the deep-heating of hepatic tumours, where heating times of the order of 1-2 hours are common, thus reducing the need for high temporal resolution.

Future work will compare the monopole-source solution of ultrasonic induced tissue heating generated from focused and phased-array transducers with experimental results using magnetic resonance. In addition improvements in signal to noise will be sought through improved coil designs such as separate transmit and receive coils and increasing the encapsulation efficiency of the liposomes. Spectral localization techniques are also under investigation in order to improve the spatial resolution of the method.

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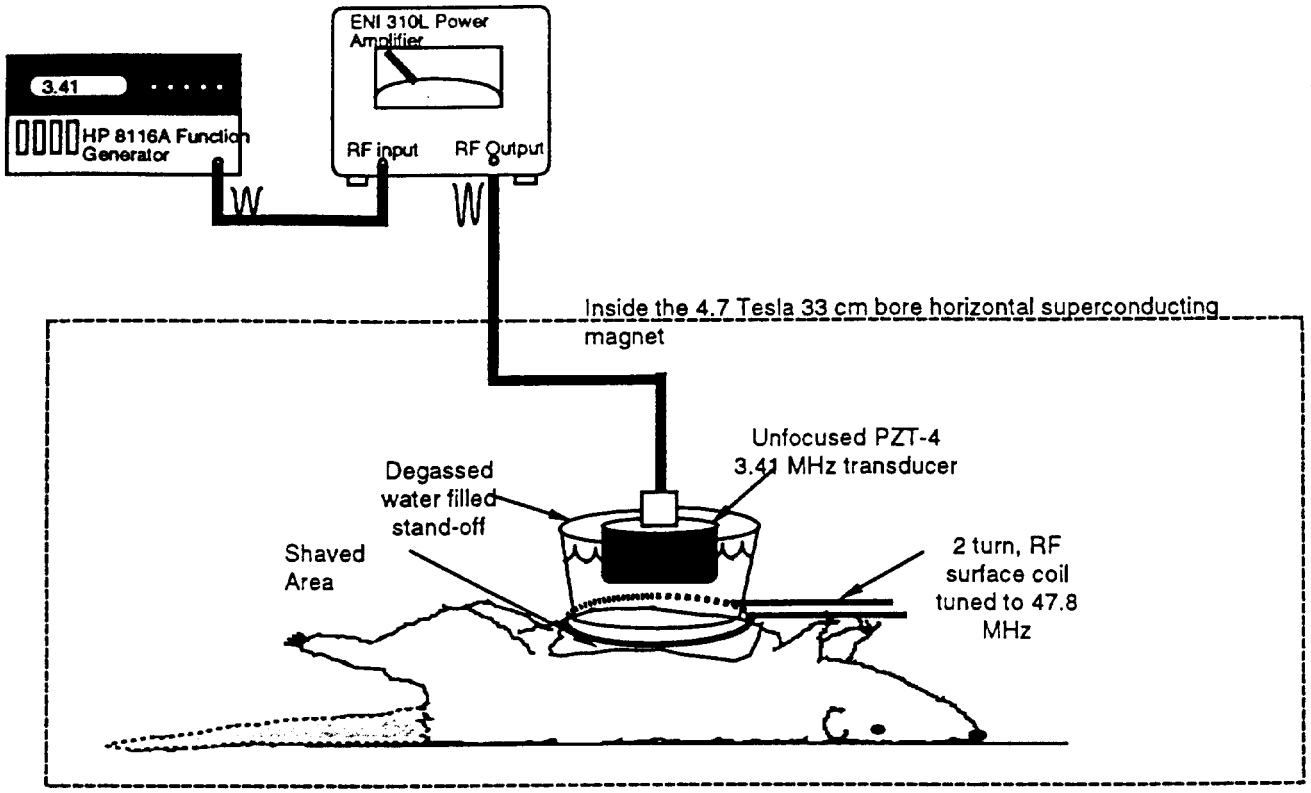

Figure 1. Block diagram of the experimental set-up used to expose the rat liver to ultrasound heating and measure the temperature rise from the chemical shift of the cobalt complex. Due to physical restraints of the magnet, the anaesthetized rat needed to be exposed in the supine position.

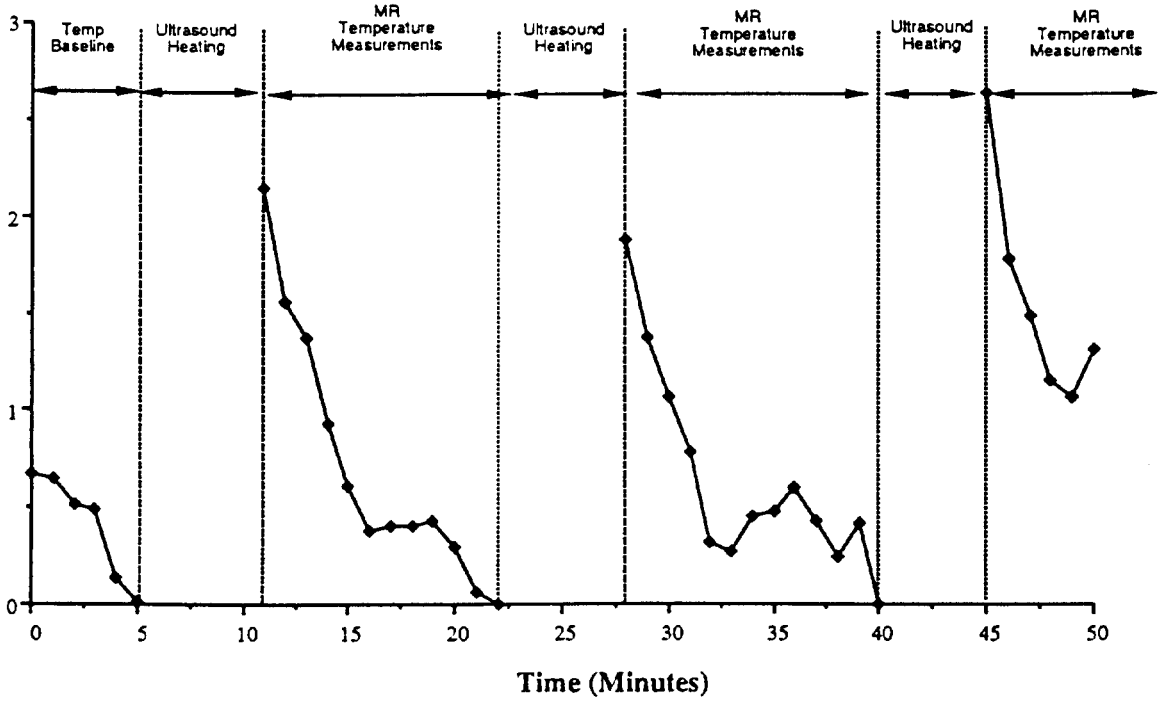

Figure 2. Experimental results of the temperature rise versus time in rat liver due to ultrasound heating from an unfocused 3.41 MHz PTZ-4 transducer. Magnetic resonance spectroscopy was used to measure the temperature dependent chemical shift of the encapsulated cobalt taken up by the liver. The temperature rise results shown is averaged from the 7 exposed rats.