Letters

Experimental Verification of Theoretical *in vivo* Ultrasound Heating Using Cobalt Detected Magnetic Resonance

Nadine Barrie Smith, Andrew G. Webb, D. Scott Ellis,
Lisa J. Wilmes, and William D. O'Brien Jr.

***Abstract*—Conventional methods of measuring heating *in vivo* are invasive and therefore interfere with heat propagation. For the first time, ultrasound-induced temperature increases in living specimens have been estimated theoretically and measured experimentally using a noninvasive technique. *In vivo* ultrasound-induced temperature increases in the livers of rats show consistent results between: (1) a theoretical ultrasound point-source solution for a measured ultrasound source power of 4.3 W (2°C) and (2) a sensitive *noninvasive* magnetic resonance method with the cobalt (III) nucleus as a probe (2.0 ± 1.2°C).**

I. Introduction

The purpose of this paper is to show that *in vivo* rises in tissue temperature resulting from ultrasound exposure can be accurately predicted using the monopole-source solution, and that these calculations can be experimentally verified using *non invasive* magnetic resonance (MR) techniques. Previous studies have used invasive thermal monitoring e.g. thermocouples [1]. Measurement of heating produced by ultrasound has direct relevance to hyperthermia therapy where elevation of the local temperature to between 42 and 45°C has been shown to kill cancer cells, but can also cause serious injury in healthy tissue [2].

Existing MR techniques for measuring temperature have used the proton density [3], the proton spin-lattice relaxation time [4]–[6], self-diffusion coefficient [7]–[9], and the chemical shift of the water peak [10], [11]. These methods have many desirable characteristics, including high spatial and temporal resolution, but can be susceptible to physiological changes induced by temperature, and also to the effects of respiratory and bulk motion. As an alternative approach we have used an MR imaging agent, developed recently in this laboratory, based on measurement of the temperature dependent chemical shift of the cobalt nucleus [12], [13]. This phenomenon arises from the relationship between the diamagnetic shielding constant and the temperature dependent crystal field splitting [14], [15]. Cobalt-59 is 100% naturally abundant and has a gyromagnetic ratio approximately one quarter that of protons. It is a quadrupolar nucleus and subsequently the NMR lineshape is 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 such as is found in the compound used for these studies, tris(ethylenediamine) cobalt (III) trichloride.

Manuscript received December 21, 1994; revised March 13, 1995. This work was supported in part by the National Center for Supercomputing Applications and NIH Grants HD21687 and CA09067.

N. B. Smith, D. S. Ellis and W. D. O'Brien, Jr. are with the Bioacoustics Research Laboratory, Department of Electrical and Computer Engineering, University of Illinois, Urbana, IL 61801 USA.

A. G. Webb and L. J. Wilmes are with the Magnetic Resonance Engineering Laboratory, Department of Electrical and Computer Engineering, University of Illinois, Urbana, IL 61801 USA.

IEEE Log Number 9411950.

II. Calculation of Temperature Rise

The monopole-source solution [16] was used to calculate the axial steady-state temperature increase for a 3.8 cm diameter, unfocused circular transducer operating in continous wave (CW) mode at 3.41 MHz. This procedure considers the acoustic source to be the superposition of a number of acoustic monopoles. The monopole-source solution to the Helmholtz equation gives rise to an outgoing spherically symmetric wave. The transducer's ultrasound power is required to estimate temperature rise using the theoretical ultrasound point-source solution technique. Using established measurement procedures [17] with a polyvinyl difluoride bilaminar membrane hydrophone (GEC Marconi, Y-33-7611) and an identical set-up to that for the *in vivo* experiments (detailed later in the text), at a distance of 5 cm from the face of the transducer the acoustic power was measured to be 4.3 W. From the two dimensional lateral cross section of the beam, shown in Fig. 1, the axial temperature increase can be calculated. Using the point-source solution [18] to the bio-heat transfer equation, the steady state temperature increment is calculated by summing the increase from every heated point-source location [18]. Using an ultrasonic absorption coefficient of 0.5 dB/cm-MHz for liver [19], the monopole-source solution predicted an average temperature rise of 2.0°C, with a maximum value of 2.8°, based on 5 min of CW heating in order for steady-state conditions to be established.

III. Measurement of *in vivo* Temperature Rise

Six female Sprague-Dawley rats weighing 200±10 g were anesthetized using ketamine/xylazine (0.1 mL/100 g). Tris(ethylenediamine) cobalt(III) trichloride was encapsulated within liposomes and injected (0.29 mmol/kg) into a rat via the tail vein. The liposomes are subsequently taken up by

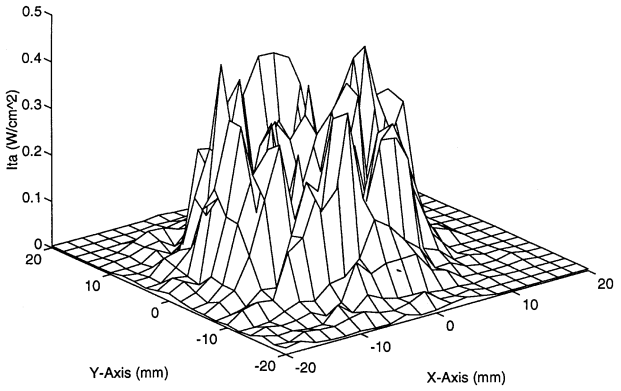

Fig. 1. At a distance of 5 cm from the face of the transducer the acoustic power was measured to be 4.3 W from the two dimensional lateral cross section of the ultrasound field used in the *in vivo* ultrasound exposure.

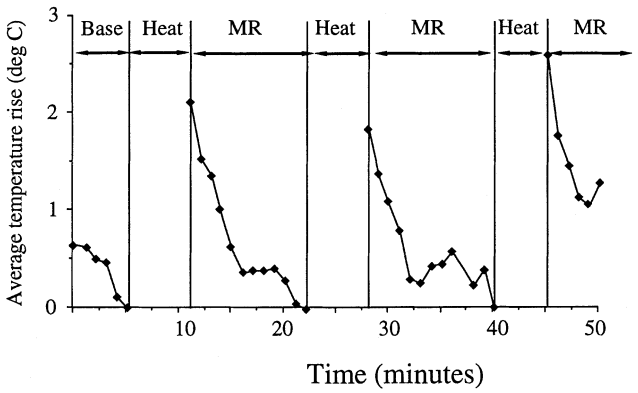

Fig. 2. *In vivo* experimental results of the temperature rise versus time in rat liver due to ultrasound heating from an unfocused 3.41 MHz PZT-4 transducer. Magnetic resonance spectroscopy was used to measure the temperature dependent chemical shift of the liposome encapsulated cobalt complex taken up by the liver. Each point on the graph represents the average of six exposed animals.

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 to minimize air entrapment. Ultrasound heating was performed using an unfocused PZT-4 transducer, diameter 3.8 cm, operating in CW mode at a frequency of 3.41 MHz. The low level RF signal is supplied by the HP 8116A pulse/function generator, and signal amplification performed by a 50 dB gain, ENI 310L RF power amplifier. A degassed-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 standoff 5 cm from the abdomen of the rat to minimize magnetic susceptibility effects which would broaden the MR spectral lineshape. Ultrasound gel (Parker Laboratories, Inc.) was used on the abdomen of the rat to ensure contact between the animal and the latex window of the standoff. The RF coil was then placed against the rat abdomen beneath the standoff.

Magnetic resonance experiments were carried out at a magnetic field strength of 4.7 Tesla, using a 33 cm bore horizontal superconducting magnet. The two turn 4 cm diameter RF surface coil, tuned to 47.8 MHz, was used for both transmission and reception. Cobalt spectra were acquired using a standard pulse and acquire sequence, with an interpulse repetition time of 36 ms. Using 1024 transients per acquisition resulted in a signal to noise of 15 : 1 for a total data acquisition time, and hence temporal resolution, of approximately 40 sec.

Spectra of the liver of each rat were collected for 5 min prior to the first ultrasound exposure. After 5 min of ultrasound exposure an elevated temperature was observed. Interference from the broad-band transducer meant that no MR temperature measurements were performed during the application of ultrasound. The return of tissue temperature to its initial value was monitored by collecting spectra for 11 min at 1 min intervals. Two more ultrasound exposures followed by MR temperature measurements were performed before the rat was removed from the magnet.

IV. Results

The temperature versus chemical shift conversion factor for the tris(ethylenediamine) cobalt (III) trichloride complex has been determined previously to be 67 Hz/°C [10]. For all six rats studied the temperature measurements within the liver displayed similar behavior after heating and subsequent cooling. However the initial internal temperature of the liver differs between rats due to biological variations and differences in the ambient temperature in the magnet at the time of the experiments. The results in Fig. 2 therefore graph the change in temperature, averaged over all six rats, from the initial preexposure value. The average temperature rise over a volume of approximately 8 cubic centimeters was 2.0 ± 1.2°C The relatively large standard deviation is in part due to the small sample size, as well as inter-experiment variations in transducer placement and magnet bore temperature. Bartlett's test for homogeneity of variances for the three temperature rises from each animal, measured immediately after cessation of heating, showed that differences among the standard deviations of the temperature rises was not significant ($p = 0.61$). This indicates that the analysis of variance (ANOVA) is an appropriate statistical test. The ANOVA analysis demonstrated that the variation among the three sets of temperature rises was not significantly greater than expected by chance ($p = 0.71$) i.e. there was no difference between the three data sets for the six animals studied. Repeated measures (paired) ANOVA test suggested that each experimental run was very significant ($p = 0.0064$) i.e. each of the six experiments yielded consistent results.

V. Discussion

Theoretical calculations for the ultrasound heating have been shown to be consistent with the experimentally determined values of temperature rise, and show the validity of applying the monopole-source method for calculating temperature changes *in vivo*. This study represents one of the first *in vivo* comparisons between theory and a noninvasive experimental procedure for ultrasound heating. The particular MR 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. Since the attainable signal-to-noise ratio is well above

the detection limit, the spatial resolution could potentially be reduced to 2–3 cubic centimeters. However, the need for an exogenous agent removes, to some extent, the "noninvasive" character of the method, and more importantly limits the use to tissues which can be targeted, in this case liver, spleen, and specific tumors. We are therefore currently investigating the use of the proton chemical shift imaging technique to obtain full two-dimensional temperature maps, and to compare these with calculations from the monopole-source solution.

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