NON-INVASIVE *IN-VIVO* TEMPERATURE MAPPING OF ULTRASOUND HEATING USING FLUORINE-BASED MAGNETIC RESONANCE IMAGING AGENTS

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ABSTRACT

The aim of this study was to investigate the feasibility of using fluorine based magnetic resonance to measure accurately hepatic heating from a focused ultrasound transducer in rats. This new method uses the temperature dependence of the difference in fluorine chemical shifts within a single molecule to provide internal compensation for complicating physiological effects. Female Sprague-Dawley rats were exposed to 5 minutes of CW irradiation at 1.37 MHz from a focused transducer. Theoretical calculations based on the monopole source solution to the bio-heat transfer equation gave a volume-averaged temperature rise of 2.1 °C. Preliminary experiments using protein encapsulated perfluoro-octylbromide targeted to the liver gave an empirical rise of 2.0 ±0.4 °C.

I. INTRODUCTION.

A number of proton magnetic resonance imaging (MRI) techniques have been developed to map temperature: the relevant parameters being the chemical shift of the water peak (1), the proton T_1 relaxation time (2), and the diffusion coefficient of the water protons in tissue (3). Liposome encapsulated cobalt complexes have also been shown to be effective *in-vivo* (4). *In-vitro* results using phase transition compounds (5) and liquid crystals (6) have also been reported. The main advantages of the MRI techniques are their non-invasive character, and the high spatial and temporal resolution attainable. Using such MRI methods, the field of mapping temperature *in-vivo* has shown a recent rapid expansion. The proton based methods of mapping temperature are particularly suited to studies of muscle and other relatively stationary organs. In contrast, we are interested in the reticuloendothelial system (RES) which presents particular problems due to motion artifacts and local changes in magnetic susceptibility due to respiration. Relaxation time and diffusion mapping require a number of images to be acquired. Motion artifacts can be reduced by using high-speed imaging techniques such as echo-planar, but these require specialized hardware. The proton reference frequency method can also be affected by motion.

Our new approach here is to use an internal reference such that motion or changes in magnetic susceptibility are internally compensated. In order to achieve this we use an agent which contains two chemical shifts, where the difference in chemical shifts is temperature dependent.

II. MATERIALS & METHODS

A. PERFLUOROCARBON PROPERTIES

Perfluorooctylbromide (PFOB) has been used as a blood-substitute, and as an imaging agent in MRI, ultrasound and CT. For MRI there is no fluorine background signal, an increased echogenicity gives contrast for ultrasound imaging, and the electron-rich bromine group results in attenuation of x-rays. Here, we use the

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temperature dependent chemical shift of the CF_3 and terminal CF_2-Br groups to measure temperature. Figure 1 shows a calibration curve of the temperature dependence of the difference between the two chemical shifts.

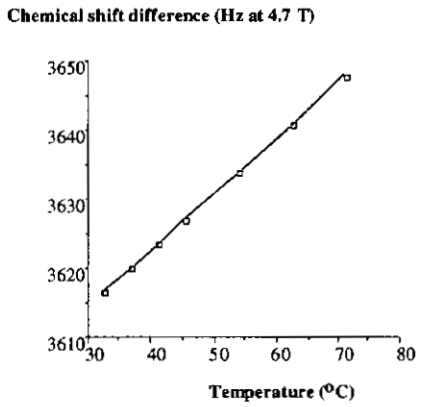

Figure 1

The problem with temperature mapping techniques based on chemical shift changes is that an apparent thermal change can be induced by a change in the local magnetic susceptibility due to, for example, inhalation. A 10 Hz shift would correspond to an apparent 5°C change using the proton resonance frequency at 4.7 Tesla. However, by using the difference in chemical shifts of the two fluorine nuclei, the effects of susceptibility changes are canceled out. In order to demonstrate this, a sample of PFOB was held at constant temperature, and the shim currents varied as a function of time to simulate changes in magnetic susceptibility. Figure 2 shows the built-in compensation of measuring the difference in chemical shift rather than the absolute value.

B. ENCAPSULATION PROCEDURE

In order to target the PFOB to the RES, we use a proteinaceous encapsulation technique. Ultrasound irradiation at the interface of an aqueous protein solution and a non-polar liquid has been shown to produce proteinaceous microspheres at high concentrations with narrow size distributions (7). The protein forms a thin shell surrounding the encapsulated non-polar liquid.

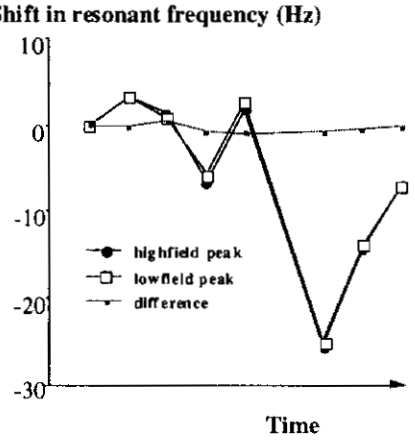

Figure 2

Microencapulation was carried out using high-intensity ultrasound irradiation of a 1:2 (v/v) mixture of PFOB with 5% (w/v) aqueous bovine serum albumen (BSA) solution. The BSA solution was layered over the mixture at an initial temperature of 23°C and pH 7.0. With a titanium acoustic horn positioned at the organic-aqueous interface, the mixture was irradiated for 3 minutes at an acoustic power of approximately 150 W/cm^2. The microspheres remained as a suspension in the native protein solution. In order to separate the microspheres from the non-reacted protein, a centrifuge filter with a molecular weight cut-off of 100 kD was used. Centrifugation was done at 5000 G for 5 minutes, the microspheres were then resuspended in buffer. This process was repeated five times. Particle size distribution was determined with an Elzone particle counter and confirmed by light microscopy. Analysis showed that the purified microspheres have a Gaussian-like size distribution with mean diameter 2.5 ± 1 μm. We have shown previously (5) that these microspheres efficiently target the RES with a uniform distribution throughout the liver, and result in high intensity two- and three-dimensional magnetic resonance images.

C. MONOPOLE SOURCE SOLUTION

The monopole-source solution for an unfocused transducer is used to calculate heating in the rat liver (8). 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 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 (9). The acoustic power was determined 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 7.7 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 an automated positioning system. At a distance of 7.7 cm from the face of the transducer the acoustic power was measured to be 725.5 mW. The two dimensional lateral cross section of the ultrasound field is shown in Figure 3. Using an ultrasonic absorption coefficient of 0.5 dB/cm-MHz for liver (10) the monopole-source solution for estimating tissue temperature increase predicted 2.1°C based on 5 minutes heating for the change in temperature to reach steady-state conditions.

Two dimensional lateral cross section of the ultrasound field.

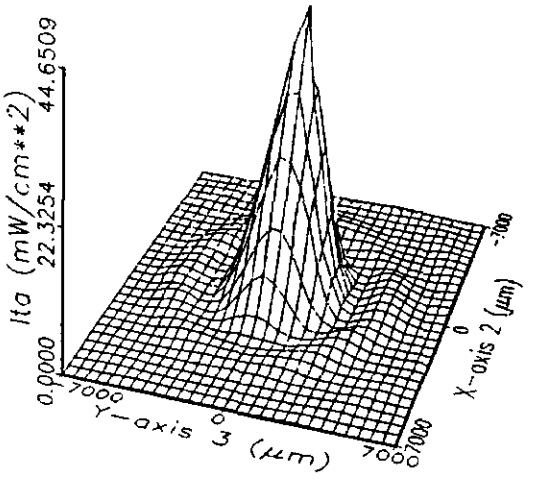

Figure 3

D. MAGNETIC RESONANCE

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 188 MHz for fluorine, was used for both transmission and reception. Spectra were acquired using a standard pulse and acquire sequence, TR=2s, 8 scans, digital resolution 0.4 Hz. A gaussian shaped "soft" pulse envelope of 120 ms was used for selective excitation of the two upfield peaks of the PFOB, thus enabling a smaller spectral width to be used and a higher resulting signal-to-noise ratio.

E. EXPERIMENTAL PROCEDURE

Sprague-Dawley rats (200-300 g) were anesthetized with ketamine/xylazine. The abdomen was shaved, and hair remover applied to reduce any effects of trapped air. The microspheres were injected via the tail vein. These spheres have a half-life in the bloodstream of 2.5 minutes. Thirty minutes

after injection, the heating protocol was begun. 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 10 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

Three rats have been studied so far. Based on the chemical shift difference of the two peaks, a temperature rise of 2.0 +/- 0.4 °C has been experimentally determined. The frequency shifts were calculated using a Hankel single value decomposition line-fitting routine. These results are in good agreement with the theoretical value obtained using the monopole source solution (2.1 °C).

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