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Temperature-dependent MR signals in cortical bone: Potential for monitoring temperature changes during high-intensity focused ultrasound treatment in bone

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Abstract

Purpose—Since existing MR-thermometry techniques do not provide temperature information within the bone, high intensity focused ultrasound (HIFU) exposures in bone are monitored using temperature changes in adjacent soft tissues. In this study, the potential to monitor temperature changes in cortical bone using a short TE gradient echo sequence is evaluated.

Methods—The feasibility of this proposed method was initially evaluated by measuring the temperature dependence of the gradient echo signal during cooling of cortical bone samples implanted with fiber-optic temperature sensors. A subsequent experiment involved heating a cortical bone sample using a clinical MR-HIFU system.

Results—A consistent relationship between temperature and the change in magnitude signal was observed within and between cortical bone samples. For the 2D gradient echo sequence implemented in this study, a least-squares linear fit determined the percentage change in signal to be $(0.90 \pm 0.01)\%/^{\circ}\text{C}$. This relationship was used to estimate temperature changes observed in the HIFU experiment and these temperatures agreed well with those measured from an implanted fiber-optic sensor.

Conclusion—This method appears capable of displaying changes related to temperature in cortical bone and could improve the safety of MR-HIFU treatments. Further investigations into the sensitivity of the technique in vivo are warranted.

Keywords

MR-HIFU; thermometry; cortical bone

Introduction

Magnetic resonance imaging guided high-intensity focused ultrasound (MR-HIFU) therapy is a non-invasive image-guided treatment for soft tissues and bone. Ultrasound energy is used to generate a region of thermal coagulation in tissue under real-time monitoring and control of heating with MRI. This technology has been translated to human studies for a variety of benign and malignant conditions including uterine fibroids (1-3), prostate cancer (4, 5), breast cancer (6-8), and essential tremors (9, 10). Recently, it has been demonstrated that MR-HIFU is effective at alleviating pain associated with metastatic and benign bone tumors (11-13). This indication has been approved for clinical use in a number of jurisdictions for patients whose tumors are non-responsive to radiation therapy.

During a typical sonication of bone with MR-HIFU, ultrasound energy passes through subcutaneous fat, soft-tissue, and is rapidly absorbed at the proximal surface of the bone. Temperature elevations occur in all of these tissue components. Soft-tissue thermometry is commonly performed with MRI using the proton resonance frequency (PRF)-shift method, which is based on measuring phase changes in gradient echo MR images caused by heating (14, 15). This technique is quantitative and provides a precision of approximately 1°C in vivo with a spatial resolution of 1 mm and a temporal resolution of a few seconds (16). Unfortunately, the technique is unable to measure temperature changes in bone, due to a high fat concentration in the marrow, and the fact that the short T2 of cortical bone results in an absence of signal on most conventional MR imaging sequences. Consequently, temperature monitoring in bone is currently not possible during MR-HIFU treatments, and practitioners rely on monitoring temperature changes in adjacent soft tissues using conventional PRF-shift methods.

A number of attempts have been made to characterize temperature changes in bone and marrow with MRI. One approach involves measuring the spectral frequency difference between fat and water to calculate the absolute temperature (17-20). This approach can be used to measure temperature in fatty marrow located within bones (21). Ultra-short echo time (UTE) imaging has been shown to recover the signal from short T2 species like cortical bone (22, 23), and initial investigations demonstrate a temperature dependent signal that can be measured during heating (24, 25). Unfortunately, most existing UTE sequences are 3D acquisitions with long acquisition times, and further development is required to adapt these techniques for dynamic real-time monitoring during MR-HIFU. Furthermore, a detailed correlation of these signals with physical temperature measurements has not been conducted.

Although monitoring soft tissue temperature adjacent to bone has enabled MR-HIFU to proceed to clinical practice, the safety of these treatments would be greatly improved if robust methods for real-time thermometry of both bone and soft-tissue were available. In the case of soft-tissue HIFU treatments (brain, prostate, uterine fibroids), bone is often located

in the path of the ultrasound beam, and can be a site of rapid heating and potential damage to surrounding sensitive tissue structures such as nerves, vessels, and gray matter (26, 27). Monitoring temperature changes in bone could enable the detection of heating in bone prior to soft tissue to improve the safety of these treatments. In the case of HIFU treatments targeting bone itself, there is often uncertainty related to the extent of heating within osteolytic versus osteoblastic tumors. Direct visualization of heating in the bone itself would provide insight into the effectiveness of ultrasound penetration into this tissue and would inform the delivery of energy to the target.

In this study we investigated the temperature dependence of MRI signal within cortical bone for short echo time acquisitions. Also evaluated was the potential of a multi-echo gradient echo sequence to monitor thermal effects in both soft tissue and bone during heating. Our hypothesis was that a dual echo acquisition with a short (~1ms) echo plus a more conventional long echo time (~10 ms) could be used to perform simultaneous bone and soft-tissue thermometry respectively. As gradient echo acquisitions are currently used clinically for MR-HIFU therapy and have been validated extensively for tissue thermometry, we anticipate that this technique may be rapidly translated to improve temperature feedback during MR-HIFU ablation in patients.

Methods

Ex vivo bone cooling experiment

An initial set of experiments was performed to investigate the temperature dependence of cortical bone signal for a short TE gradient echo imaging sequence. Fresh beef shanks (n=3), approximately 1 inch in length, were obtained from a local supermarket and stripped of flesh, marrow and connective tissue on the day of the experiment. Fiber-optic temperature sensors (Neoptix, Quebec, Canada) were inserted into three 1 cm deep holes drilled into the cortical bone from the end of the sample (ie. along the long axis of the bone). The bone sample (with embedded fiber-optic sensors) was placed in a plastic bag to keep it dry and submerged in a beaker of hot water until the sensors and water reached an equilibrium temperature (approximately 80°C in 7-10 minutes). The bone was then quickly transferred into a 3T MR imager (Achieva, Philips Healthcare, Netherlands) for continuous imaging and monitoring of fiber-optic sensor temperature while the sample cooled down to room temperature. Gradient echo images were continuously acquired coplanar with the fiber-optic sensors during cooling using an 11 cm diameter flexible surface receive loop coil (SENSE-FLEX-S, Philips Healthcare). A fourth sensor was embedded in an unheated bone sample that served as a reference sample, and a syringe of water in the field of view ensured successful pre-scan quantification of the central frequency of water. A schematic of the experimental setup is shown in Figure 1a. The bone samples typically cooled from 60 °C to approximately 25 °C during 25-30 minutes of continuous imaging using a single slice 2D gradient echo sequence with RF and gradient spoiling, TR/TE/flip = 10.9 ms/1.05 ms/ 30°, slice thickness = 4.0 mm, FOV = 160 mm, number of averages = 8, voxel size = 1.00 × 1.00 mm², image acquisition time = 7.02 s. Dynamic stabilization was used in these experiments to update the center frequency regularly, thus reducing field (B₀) drift. This option operates by acquiring a few lines of k-space prior to each image acquisition, and adds 11.7 ms to each

acquisition. Part way through the experiment, the fan within the magnet bore was turned on to accelerate cooling. The normalized change in the signal magnitude was calculated using the average of the first two images in each experiment as a reference. The behaviour of this normalized signal change was examined as a function of time and temperature using the average values within 3×3 ROIs which were centered on the locations of each of the fibre-optic sensors. Least squares linear fitting was performed in an effort to quantify the relationship between the normalized magnitude signal change in bone and the temperature change registered by the fiber-optic sensors. Fitting was done with data from each bone separately, as well as with data from all bones combined.

MR-HIFU Heating Experiments

The ability to monitor spatially localized temperature changes was evaluated using a high-intensity focused ultrasound (HIFU) therapy system (Sonalleve V2, Philips Healthcare). A fresh beef shank (prepared as described above in the bone cooling experiments) was embedded in a cylindrical Gellan gum (Gelrite, CP Kelco, Atlanta, GA, USA) phantom and positioned on the MR-HIFU system above the transducer. The transducer had an operating frequency of 1.2 MHz, a focal length of 140 mm, and the distance between the focal spot and the proximal bone surface was ~ 1 cm. Four fiber-optic temperature sensors (Neoptix, Quebec, Canada) were inserted into pre-drilled holes in the bone, with sensors 1 and 2 in the proximal side of the bone in the path of the ultrasound beam, and sensors 3 and 4 in the distal side of the bone. A single flexible surface receive loop coil (SENSE-FLEX-S, Philips Healthcare) was placed around the bone for imaging. A schematic of the experimental setup is shown in Figure 1b. High resolution 3D T1-weighted images were acquired to guide the positioning of the transducer focus on the inner surface of the bone between sensors 1 and 2. The location of the focus was known in the 3D T1-weighted images since the location of the transducer relative to isocenter was calibrated upon installation of the HIFU system. Three successive sonications of 30 second duration each were performed using acoustic powers of 20, 40, and 60 W respectively, with approximately 150-200 seconds of delay in between each exposure for cooling. Before, during and after these sonications, continuous imaging with a dual echo, single slice, 2D spoiled gradient echo sequence was performed with dynamic stabilization enabled. The parameters of this sequence were: TR/TE1/TE2/flip = 7.2 ms-16.2 ms/1.04 ms/6-15 ms/20°, slice thickness = 10 mm, voxel size = 1.33 × 1.33 mm², FOV = 96 mm, number of averages = 4, image acquisition times 2.11-4.74 s. As in the cooling experiments described above, the normalized change in the signal magnitude for the short TE echo was calculated using the average of the first two images in each experiment as a reference. The linear fit parameters derived from all three bones used in the cooling experiments (last line of Table 1) were combined with this normalized signal change to obtain local temperature change estimates for the HIFU experiment. Temperature changes estimated by this method in a 3×3 ROI in the proximity of fiber-optic sensor 1 were compared with temperature changes measured directly by that sensor over the length of the experiment. As well as this novel analysis of the short TE magnitude signal, the phase images associated with the longer TE were processed using a typical PRF shift algorithm to obtain temperature maps in the supporting Gellan gum gel as a function of time.

Results

Ex vivo bone cooling experiment

Figure 2a shows a gradient echo image through a typical cortical bone sample, depicting the ROIs (3×3 pixels) selected for comparison with the fiber-optic sensor information and indicating the position of the MRI coils. Fiber-optic sensors 1-3 were embedded in the cooling bone and sensor 4 in the control bone. The fiber-optic sensor temperatures as function of time for bone 2 are shown in Figure 2b. Although the reference bone was initially at room temperature, its close proximity to the heated bone caused a slight elevation in its temperature for the first 700 s of the experiment. Figure 2c shows the variation of the mean normalized signal change in the ROIs as function of time, again for bone 2, with the error bars representing the standard deviation of the signal magnitude within these ROIs. The normalized change in magnitude signal decreased monotonically over time for the three ROIs in the heated bone, while increasing slightly over time in the reference bone. The rate of decrease before and after the magnet fan was turned on is different, as is observed for the fiber-optic temperature sensors (Fig.2b) as well. Phase differences were also monitored during cooling, but the phase changes observed were similar in the heated and reference bones, and no correlation was observed between the phase changes and fiber-optic sensor temperatures. The graph in Figure 2d depicts the relationship between the normalized change in signal magnitude and the fiber-optic temperature change for the three cortical bone samples that were analyzed. In this plot, data from sensors 1-3 were combined for each bone, and for ease of viewing, data points were averaged into 0.5 °C bins. Error bars indicate the standard deviation of signal change data within these temperature intervals.

All data points associated with sensors 1-3 and having temperature changes between 0 and -33 °C were included in least squares linear fitting. The results are summarized in Table 1. The R^2 values for all fits exceed 0.85, indicating good correlation between changes in temperature and changes in the normalized magnitude difference signal. The slopes vary from 0.68 to 1.07 percent change per degree Celsius. The 95% confidence intervals on the fitted slope values for each bone sample were smaller than the range of slopes observed across the samples, suggesting that a truly universal relationship may not exist.

MR-HIFU heating experiment

Figure 3a shows a typical gradient echo image of the Gellan gel with embedded bone, as well as the relative positions of the MRI coils and ultrasound transducer. The proximal region of the bone, indicated by the red oval, was locally heated by ultrasound. In Figure 3b, the temperature change measured by fiber-optic sensor 1 located in the heated area of the bone is shown in blue for an experiment with $TR/TE1/TE2 = 7.2\text{ms}/6.0\text{ms}/1.0\text{ms}$ and an acquisition time of 2.11 s. The red curve depicts the estimated temperature in a 3×3 ROI in the vicinity of sensor 1 (white square in Fig 3c), calculated from the mean normalized magnitude signal change in that ROI and the linear relationship derived from the cooling experiments (see Table 1). The agreement of these two temperature measurements is excellent throughout three cycles of heating and cooling, and is well within the error estimated for the red curve (indicated by the representative error bar in Fig. 3b). An estimated temperature change map based on the magnitude signal change at the time of

maximum heating, indicated by an asterisk in Fig. 3b, is shown in Fig. 3c. Although noisy, high temperature changes similar to those recorded by the fiber-optic sensors are seen in the heated part of the bone proximal to the ultrasound transducer, whereas little or no temperature change is seen in more distal parts of the bone. For comparison, the PRF temperature map in the Gellan gel is shown in Fig. 3d on the same temperature scale. Although temperature changes observed in the Gellan gel are lower than those in bone due to the small ultrasound absorption coefficient of the material, this image clearly shows temperature elevations in parts of the gel contiguous to the areas of bone showing elevated temperatures in Fig. 3c.

Discussion

This preliminary ex vivo study describes a quantifiable, positively-correlated change in the magnitude signal with temperature change for a standard SPGR sequence with TE ~ 1.0 ms, TR = 10.9 ms and a flip angle of 30°. In the central experiment described in this report, the change in the normalized SPGR (TE ~ 1 ms) magnitude signal was observed as a function of temperature change while a pre-heated cortical bone sample was cooled. Over a temperature range of 35 °C, the signal from all sensors in a given bone decreased monotonically with temperature, falling, within error bars, on a single curve. For three different bone samples, linear least squares fitting yielded fits with R² values ranging from 0.85 to 0.92, indicating a strong correlation between changes in temperature and changes in the magnitude signal change. The slopes of the linear fits indicate the signal change per unit temperature is in the range of 0.68-1.07 %/°C for the three bones tested.

In a second related experiment, a cortical bone sample embedded in Gellan gel was heated repeatedly using a clinical MR-HIFU system and allowed to cool between exposures. Implanted fiber-optic sensors tracked cortical bone temperature throughout, while both short (TE ~ 1 ms) and long (TE = 6-15 ms) SPGR images were acquired. By using the rate of magnitude signal change as a function of temperature change derived from the cooling experiments, it was possible to calculate a spatial temperature map in the bone using the short echo data (TE ~ 1 ms). This temperature map showed a spatially localized heating pattern in the proximal part of the bone, such as would be expected from focused ultrasound heating. It was also observed that the temperature change estimates based on changes in the short echo magnitude signal in the vicinity of the fiber-optic sensors closely matched the temperature changes recorded over time by the sensors.

Since there is not sufficient SNR to perform conventional PRF-shift thermometry in cortical bone, this phenomenon has the potential to add considerably to the safety and reliability of HIFU treatments of bone itself as well as surrounding tissues where there is risk of inadvertent bone heating. The short acquisition times for standard SPGR sequences make them an attractive choice for high temporal resolution monitoring of temperature changes.

A potential clinical application of this phenomenon would be as part of a dual echo SPGR sequence with a short echo at TE ~ 1 ms and a longer echo at 6-20 ms. The magnitude signal change at the shorter echo time could be used to estimate the temperature in bone, while longer TE phase images could be used to generate typical PRF-shift temperature maps of

surrounding soft tissue. Multiple-echo gradient echo sequences have been proposed in the past for absolute thermometry (17, 20) but there have not been any investigations to our knowledge that have tried to utilize a specific short echo to track temperature dependent signal changes in cortical bone. The proposed pipeline to produce a composite thermal map of soft tissue and bone is through the combination of a magnitude subtraction of the short echo time image with a phase subtraction of the long echo time image, as depicted in Figure 4. The HIFU heating experiments described in this report serve to illustrate the feasibility of this idea. In those experiments, the longer TE phase images were processed to produce PRF shift temperature maps of the Gellan gel, which depicted an area of increased PRF temperature in the gel, contiguous with the area of increased estimated temperature within the bone.

The primary advantages of a dual echo approach are its simplicity, and its potential for immediate translation. Dual echo acquisitions can be performed with existing MR thermometry sequences on clinical scanners with no modification. The two images are inherently registered, and are acquired simultaneously, making it straightforward to overlay and display the thermally-related changes in bone and tissue. The time required to process and overlay signal magnitude changes in cortical bone with PRF temperature maps is not significant and would not impact existing monitoring efficiency of MR thermometry. Finally, previous studies have demonstrated the potential for spectral techniques to measure bone marrow temperature using a multi-echo sequence, pointing to the possibility to extend this approach to provide simultaneous temperature measurements in the marrow as well (18, 20, 21).

Although this study demonstrates that changes in cortical bone SPGR magnitude signal at low TE are positively correlated with temperature changes, there are a series of technical issues to be addressed before the method can be applied clinically. The small size of the ex vivo samples in these experiments permitted the use of small surface coils, which enabled good spatial resolution, high signal to noise ratios, and reasonable acquisition times. In a clinical setting, imaging conditions would not be as optimal, and the SNR would likely drop below an acceptable limit. To mitigate this issue and recover signal in vivo, a shorter TE could be used. Although the Cartesian gradient echo sequence used for imaging in this study was restricted to a minimum TE of 1 ms, alternative approaches using modified RF pulses and radial acquisitions would enable reductions of TE well below this value. Another potential issue in vivo will be the presence of marrow, whose large signal can overwhelm the cortical bone signal unless fat suppression techniques are applied. This issue was avoided in the current study since the marrow was removed from the cortical bone samples. Further studies are necessary to investigate impact of marrow on this technique.

The relationship between magnitude signal changes and temperature changes was not quantitatively consistent across the three bone samples investigated. Our belief is that this was due to experimental factors present in the ex vivo samples; however it could also be related to variable water fraction or porosity in the samples and requires further study. Nonetheless, even a qualitative confirmation of heating in cortical bone would have value in thermal therapies where these tissues are exposed to heating. Finally, a wide range of temperatures were used in this study, including temperatures above and below the

denaturation temperature of proteins. From previous studies (28), protein denaturation often results in a change to the temperature dependence of relaxation parameters. Further experiments with careful cooling and heating of these samples are necessary to investigate whether protein denaturation within cortical bone affects the temperature dependence of the MRI signal.

The fundamental mechanisms contributing to the observed signal changes in cortical bone during heating/cooling were not addressed in this study. One topic for further research is an explanation of these temperature dependent signal changes, in terms of MR relaxation times and their affect on the SPGR signal equation. There is very little (if any) information in the literature about the temperature dependence of T1 and T2* of cortical bone. In general, T1 of soft tissues increases with temperature, which for an SPGR sequence, would lead to a signal decrease with increasing temperature. Note that this negative correlation was seen in the gel surrounding the bone in the heating experiments done in this study. However the opposite trend was observed in the cortical bone samples. Hence, if the signal changes seen in cortical bone are due to T1 changes, cortical bone T1 must be different than other tissues and decrease with increasing temperature. On the other hand, the SPGR signal equation predicts a signal increase with increasing T2*, so a T2-based explanation would require T2* of cortical bone to increase with temperature. A more detailed treatment of this topic is planned for a future study by our group.

At a microscopic level, cortical bone has a complex structure and the protons which are the source of the MRI signal are known to exist in a variety of different environments, each with its own relaxation parameters. Examples of possible hydrogen pools within bone include macromolecular hydrogen in collagen itself (T2<100 μ s), collagen bound water (T2 ~ 400 μ s), pore-bound water and lipid hydrogen (~ 1 ms) (29). Separating the contributions of these pools is not straightforward, especially in GRE sequences where susceptibility effects and other imperfections play a significant role, leading to overlap of T2* values for collagen- and pore-bound water. Although considerable work has been done to measure the relaxation parameters of these pools and thus identify how they contribute to the MRI signal in various experiment contexts (29, 30), there has been little work on the effect that temperature change might have. Future research could involve determining which hydrogen pools are responsible for the observed temperature dependent signal change, perhaps using the methods of Horch et al (31) to distinguish between pore- and collagen-bound water.

The focus of this investigation was to establish first whether there was a detectable temperature-related signal change at short TE's in cortical bone. Given the positive outcome of initial experiments described here, further in vivo studies are warranted to optimize image acquisition in a more realistic environment. This will include efforts to unravel the temperature dependence of relaxation parameters in this tissue, and the design of low-TE, high-SNR 2D SPGR sequences using shorter RF pulses and/or radial readouts.

Conclusions

The present ex vivo study demonstrates a simple method for monitoring thermal changes simultaneously in cortical bone and soft tissue using a dual echo gradient echo sequence.

Signal magnitude changes observed on a short echo image (TE = 1 ms) correlated with changes in cortical bone temperature, while phase changes on a longer echo image (TE = 10 ms) reflected soft tissue temperature changes. This acquisition strategy can be easily translated onto existing MR imaging systems for monitoring thermal changes in bone and soft tissue during thermal therapies such as MR-HIFU.

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FIG. 1.

Schematics of the two experiments performed in this study. **a:** In the cooling experiments, a cortical bone sample was heated uniformly outside the magnet bore and then imaged in the scanner during cooling. **b:** In the heating experiments, a focused ultrasound transducer was used to heat a small segment of the bone sample during concurrent MR imaging. Fiber-optic thermal sensors were inserted in the bone samples to measure temperature changes in both cases.

FIG. 2.

a: A gradient echo MR image showing the experiment geometry for the cooling experiments, including the ROI's used to characterize the signal change in bone as a function of temperature. Each ROI is centered at the position of a sensor and the associated colors correspond with the temperature plots in **b** and normalized signal changes in **c**. The white horizontal bar indicates 1 cm. **b:** Temperature versus time at three fiber-optic sensors implanted in a pre-heated cortical bone sample and another in a reference bone sample, as depicted in **a**. Data shown here and in **c** were obtained from the second of three bones analyzed. **c:** Normalized change in the magnitude signal over the course of cooling, as a function of time. **d:** Normalized change in the magnitude signal as a function of temperature change during cooling for each of three cortical bone samples tested.

FIG. 3.

a: Experiment geometry for a cortical bone heating experiment using a clinical MR-HIFU system. A region circled in red (~1 cm) of the bone proximal to the ultrasound transducer was heated by ultrasound. **b:** Temperature change as measured by a fiber-optic sensor embedded in the cortical bone sample, and as estimated from signal magnitude changes within an ROI (3×3) in the vicinity of this sensor (white square in **c**). The latter estimate of temperature change was based on a linear fit of the cooling data (Fig 4). A typical error bar for the estimated temperature is shown in black. **c:** Estimated temperature distribution (calculated from the magnitude signal change in the short echo image) within the cortical bone at the time when the peak temperature was measured in the fiber-optic sensor (shown as * in **b**). **d:** PRF-shift temperature change in the gel surrounding the cortical bone at the same time point as **c**.

FIG.4.

A processing pipeline that could be used to create a simultaneous composite thermal map of soft tissue and bone. A short echo time ($TE < 1$ ms) acquisition is used to monitor bone thermal changes through a magnitude difference, while a longer echo time is used to measure tissue temperature through a phase subtraction (i.e. the PRF method). The spatial information from bone and soft tissue can be overlaid to produce a composite thermal map.

Table 1
Results of Least Squares Linear Fitting for Cortical Bone Cooling Experiments

The results of least squares linear fitting of the normalized change in magnitude signal vs change in fiber-optic sensor temperature. Results are shown for each of three cortical bone specimens as well as for the data from all the bones combined. The bracketed figures indicate 95% confidence intervals.

	Slope ($^{\circ}\text{C}$)	Intercept	R²
Bone 1	0.0068 (0.0066, 0.0070)	0.0129 (0.0089, 0.0169)	0.90
Bone 2	0.0089 (0.0087, 0.0091)	0.0198 (0.0152, 0.0243)	0.90
Bone 3	0.0107 (0.0105, 0.0110)	0.0630 (0.0579, 0.0680)	0.92
All Bones	0.0090 (0.0089, 0.0092)	0.0327 (0.0295, 0.0359)	0.87