MRI-controlled focused ultrasound hyperthermia in bone for thermally mediated drug delivery

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INTRODUCTION: Thermosensitive liposomal drug carriers provide a method for triggering the rapid release of high drug concentrations in a targeted region [1]. In patients with painful bone metastases, this could increase the effectiveness of thermal approaches to pain palliation by increasing cell kill in treatment margins, and reducing the required energy deposition, potentially reducing treatment time and the potential for normal tissue damage. MRI-controlled focused ultrasound can achieve noninvasive heating in a number of soft tissues, but temperature control in bone is made difficult by the inability of PRF thermometry to measure temperature in bone, and due to preferential heating at the bone interface due to high ultrasound absorption of bone. While chemical shift imaging techniques for bone marrow thermometry have been described [2], conventional PRF thermometry can be used to maintain desired temperatures in bone by controlling the treatment based on temperatures measured in the soft tissue immediately in front of the bone interface, as temperatures here are expected to be similar to those in the bone [3]. *The objective of this work is to demonstrate the feasibility of MRI-controlled FUS hyperthermia in bone, and its potential use in localized drug delivery from thermosensitive liposomes.*

METHODS: MRI-controlled focused ultrasound heating of 10mm diameter regions in the femur of five New Zealand White rabbits was achieved by positioning the animal's leg such that ultrasound could be focused through the muscle, at the muscle-bone interface. MRI temperature measurements in the muscle just below the bone interface, acquired in a plane perpendicular to the acoustic field, were then used to control temperature elevations created by scanned focused ultrasound [4], with a target temperature of 43°C to be maintained for 20 minutes.

Anaesthetized rabbits had their thighs shaved and depilated, and were placed in the lateral decubitus position on a stage above the degassed water tank of an MRI-compatible focused ultrasound system in the bore of a clinical 1.5T MRI (Signa, GE) (Figure 1). Heat was delivered by continuous sonication with a spherically focused, air-backed piezoceramic transducer (f_5 = 2.787 MHz, f# = 2, OD = 5 cm), driven by a computer-controlled arbitrary waveform generator (33250A, Agilent, USA) and a radiofrequency power amplifier (NP2912, NP Technologies Inc., USA). The transducer was integrated into an MRI-compatible 3-axis positioning system [5] programmed to move along a 10-15 mm diameter circular trajectory at a speed of 1 revolution per second.

A single-loop RF receive coil with a square opening in the middle was designed to fit underneath the animal for optimal SNR in the targeted region during simultaneous mechanically-scanned FUS heating and MRI thermometry using the PRF technique (FSPGR, TE = 10 ms, TR = 38.6 ms, 30° flip, 128 x 128 matrix, BW = 31.25 kHz, FOV = 16 cm, slice thickness = 5 mm, slices = 3, NEX = 1, acquisition time = 5 s, PRF coefficient = -0.010 ppm/°C). Coronal temperature images were acquired in a control plane prescribed in the muscle immediately superficial to the femur, as well as in non-control planes through the bone and in the muscle closer to the skin. A real-time image acquisition interface was used to transfer raw k-space data to a control computer to reconstruct temperature maps in all three planes, using a baseline temperature measured by a fibre-optic temperature probe in the rectum, correcting for magnetic field drift by adding the temperatures measured in an oil reference phantom in the plane, and averaging over a 30 second sliding window to reduce the effect of periodic susceptibility-related phase shifts caused by circular transducer motion during imaging. For the control plane image acquired at time t_n, temperatures at 8 control points around the scanned circular trajectory ($T_{1..8}$) were used in 8 independent proportional-integral controllers to define a list of output powers ($P_{1..8}$) to be applied as the focus crossed each region. Modulation of function generator amplitude occurred at a frequency of 8 Hz during circular scanning at 1 Hz and temperature imaging at 0.2 Hz.

Lyso-thermosensitive liposomal doxorubicin (LTLD, Celsion) was infused into the ear vein at a doxorubicin dose of 2.5 mg/kg over 8 minutes during MRI-controlled FUS using an MRI-compatible injection system (Spectris Solaris, MEDRAD), starting when target temperatures reached 43°C. After heating, T2 and contrast-enhanced T1-weighted images were acquired to assess tissue damage. Two hours after treatment, unabsorbed liposomes were flushed from the vasculature by perfusion with saline, and samples of bone, marrow, and surrounding muscle were harvested from the heated and unheated thighs. Drug concentrations were measured by the fluorescence intensity of doxorubicin extracted from homogenized tissue [6].

RESULTS: MRI-controlled focused ultrasound was able to achieve stable heating of a 10mm diameter region of thigh at the bone interface to 43°C for 20 minutes. Figure 2 shows spatially uniform temperature distributions in coronal slices taken 15 minutes after the start of heating (a) in the control plane defined in muscle beneath the bone and (b) in the plane of the bone. Temperature control across all experiments is summarized in Table I. Closed-loop control of FUS hyperthermia using MRI thermometry achieved temperature distributions with median, T_{90}, and T_{10} of 43.1°C, 41.6°C and 44.4°C across the 10 mm diameter target, varying ±0.9°C (SD) over 20 min.

Table I. Summary of MRI-controlled focused ultrasound bone heating & drug delivery.

Results (n = 5 rabbits)		Mean ± SD
Temperature control at muscle-bone interface		
Mean ± SD T_{50}, muscle	(°C)	43.1 ± 0.3
Mean ± SD T_{90}, muscle	(°C)	41.6 ± 0.4
Mean ± SD T_{10}, muscle	(°C)	44.4 ± 0.4
Thermal dose in muscle (CEM43)		26.4 ± 5.3
Drug delivery		
[DOX] unheated muscle	[ng/mg]	1.7 ± 0.9
[DOX] heated muscle	[ng/mg]	27.2 ± 8.9

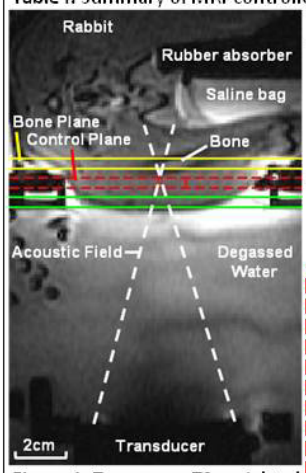

Figure 1. Transverse T2-weighted image of experimental setup for MRI-controlled scanned focused hyperthermia in rabbit bone. Coronal imaging planes used for temperature control in muscle (red, dashed) and monitoring in bone (yellow, solid) are shown.

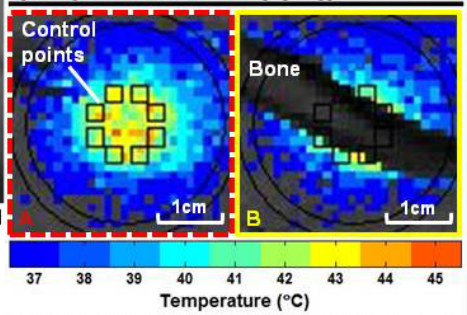

Figure 2. Temperature images acquired during MRI-controlled FUS heating in (a) control plane in muscle immediately beneath the bone, and (b) in bone.

Table I shows the mean ± SD tissue drug concentration in heated muscle sampled at the heated bone interface from the targeted femur and the unheated contralateral side. Doxorubicin concentrations in heated regions were, per animal, 18.4 ± 9.2 (SD) times higher than in the unheated contra-lateral thigh.

CONCLUSION: The results demonstrate the feasibility of using MRI-controlled focused ultrasound to achieve mild hyperthermia in bone, and suggest the potential of its combination with thermosensitive liposomes for localized drug delivery near bone.

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