Localized hyperthermia in rodent models using a MRI-compatible high-intensity focused ultrasound system

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Introduction: The use of temperature-sensitive drug carriers allows a rapid release of high concentrations of active drug within a region of localized heating[1]. Magnetic resonance guided high-intensity focused ultrasound (MR-HIFU) can create controlled heating within tissue using active temperature feedback. These characteristics make it a strong candidate for triggering release from temperature-sensitive carriers, and promising results have been demonstrated using thermosensitive liposomes (TSLs) encapsulating doxorubicin[2]. The goal of this study was to 1. develop a platform for performing localized hyperthermia in rodent models, and 2. evaluate image-guided drug delivery from novel antimicrobial (ciprofloxacin) encapsulated TSLs using MR-HIFU for targeted therapy of localized chronic infections.

Methods: The hyperthermia platform consisted of an MRI-compatible small animal HIFU system (RK100, FUS Instruments, Canada), a custom-made receive coil for high signal to noise (Clinical MR Solutions, USA), and a 3T MR imager (Ingenia, Philips Healthcare, Netherlands). Custom MATLAB software was developed utilizing a real-time transfer library matMRI[3] to acquire images during heating, process temperature maps, and adjust power based on a proportional-integral-derivative (PID) feedback control algorithm. A photo of the system is shown in Fig.1. Preliminary studies were performed in a tissue-mimicking phantom with implanted fiberoptic temperature sensors (Neoptix, Canada) to verify the accuracy of the temperature maps calculated by the MATLAB software. Single point heating in the vicinity of the sensors was performed and the temperatures calculated by the software were compared with the values recorded by the sensors. In a second set of experiments, single point hyperthermia was performed in the thigh of Sprague Dawley rats (n=2, male, 300-350g). All *in-vivo* experiments were approved by UT Southwestern Institutional Animal Care and Use Committee. The rat was prepared and stabilized on the HIFU system with one side of the thigh facing the transducer. Ultrasound gel was applied for coupling. The heated region was selected in the thigh muscle, shown in Fig.2A. Target temperature was set to be 42℃ and 10 minutes hyperthermia treatment was performed followed by a 5-10 min cooling procedure. During the treatment, a 4mm diameter circular ROI was assigned in the heated region for the PID controller. Temperature measurements and output power were logged using the MATLAB software.

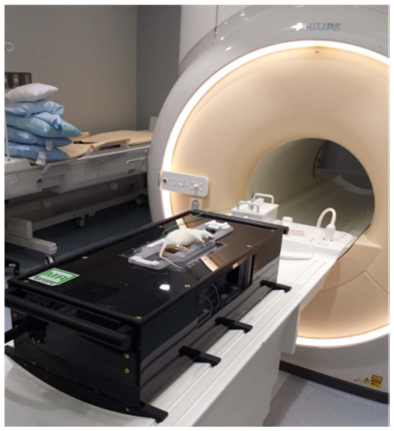

Fig.1. System setup for *in-vivo* experiment.

Results: The region of localized heating produced in the rat thigh is shown in Fig.2B mid-way during treatment when a stable temperature was achieved. Fig.3 shows the phantom validation results acquired with two fiberoptic sensors during a 10min hyperthermia treatment. Excellent agreement between the MR-derived temperatures and the sensors was observed. Fig.4A shows the mean temperature in the 4mm ROI over the course of treatment. A mean temperature of 42.2±0.5°C was achieved within 1.2 minutes, and maintained for 10 minutes. The cooling rate after heating was approximately 0.8°C/min. Fig.4B shows the output power (Watts) as a function of time that was applied to the transducer to achieved the desired temperature profile in tissue. A PID controller with k_p=0.8, k_i=0.04, and k_d=1.6 was implemented for this experiment. Other parameters were investigated in gel phantoms and exhibited slower rise times, or oscillations in the temperature.

Conclusions: An MRI-compatible system for small animal hyperthermia was developed and tested. Results from phantom tests confirmed the accuracy of temperature maps calculations in the software. The feasibility of using the system to perform controlled hyperthermia in a rat thigh was also demonstrated with a target temperature of 42.2±0.5°C and maintained for 10 minutes at the focus of the ultrasound beam. The extent of heating was well localized within the rat thigh and suggests this configuration is suitable for further studies. The PID parameters selected from the initial gel phantom tests worked well in the first pilot animal studies, but further studies are required to understand the inter- and intra- animal differences in heating and PID tuning.

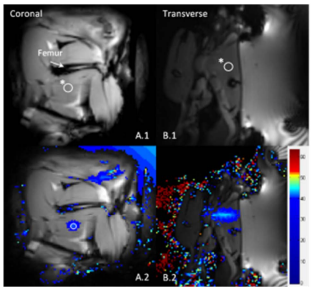

Fig.2 Treatment planning and corresponding temperature overlay. *: heated region

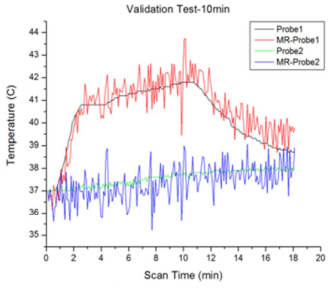

Fig.3 Phantom validation results with two fiberoptic temperature sensors.

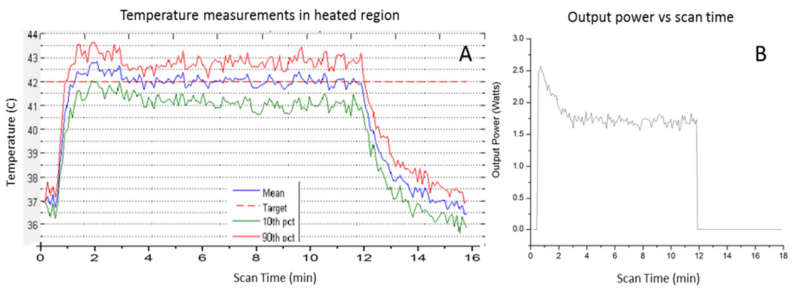

Fig.4 Temperature and output power as a function of time. Temperature is well controlled with PID controller. Panel B plots the output power as a function of time.

Reference:

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2. Hijnen, N. et al., *Magnetic resonance guided high-intensity focused ultrasound for image-guided temperature-induced drug delivery*, Adv Drug Deliv Rev, 72, pp.65-81, 2014

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