A Temperature Dependent Perfusion Rate Model for Simulating Temperature Evolution in Tissue for Magnetic Resonance Imaging guided High Intensity Focused Ultrasound (MR-HIFU) Therapy: Initial Experience in a Pig Model

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Introduction: MR-HIFU is clinically used for non-invasive thermal ablation of tumor tissue based on the absorption of focused ultrasound energy in the target region. The responses of perfusion rate and tissue thermal properties to local heating will determine the temperature distribution during sonication and thus affect the effectiveness of the treatment. While it is well known that both the tissue thermal conductivity and the blood perfusion rate increase under hyperthermia treatments (<45^{o}C) [1], their behaviors in the small focused volume under extreme temperature (>60^{o}C) conditions prevalent during HIFU surgery are largely unknown. We simulate the spatio-temporal temperature distribution of pig muscle tissue treated by MR guided HIFU *in vivo* using three models with various assumptions about tissue thermal conductivity and perfusion rate. We find that a fast temperature-dependent perfusion rate is necessary to account for the time evolution of the temperature of the entire HIFU treatment.

Methods: *Animal Care:* The study was approved by the Institutional Animal Care and Use Committee (IACUC). The animals were sedated throughout the volumetric MRgHIFU procedure, and sacrificed immediately thereafter under Institutional guidelines. Thermal ablation of thigh muscle were performed in five pigs (50~65 kg). *MR-HIFU procedure*: All ablations were done on a Philips 1.5T MR scanner (Achieva) with a 256 channel spherical shell HIFU transducer (frequency range 1.2-1.4 MHz), and an integrated receiver coil for signal reception. The spatio-temporal temperature evolution in volumetric sonication was recorded in real-time using a multi-shot echo planar imaging (EPI) technique [2].

Simulation of blood perfusion rate response: The spatio-temporal temperature evolution of HIFU treatment was modeled using bio-heat transfer equation [3]. Three models were used for simulation: 1) Both the thermal conductivity and perfusion rate were constant; 2) Thermal conductivity was assumed to be a linear function of temperature and blood perfusion rate was fixed at normal perfusion rate for muscle (6.71×10^{-4} s^{-1}); 3) The blood perfusion rate in the simulation was assumed to be a temperature dependent parameter. It is linearly increased from normal perfusion rate with the temperature rise followed by a more rapid linear decay with the temperature decrease (Figure 1). The evolution of blood perfusion rate *versus* time was shown in Figure 1. All simulations were performed in MATLAB™ (MathWorks Inc., MA, USA) and Comsol 3.5a (COMSOL, Inc., MA, USA).

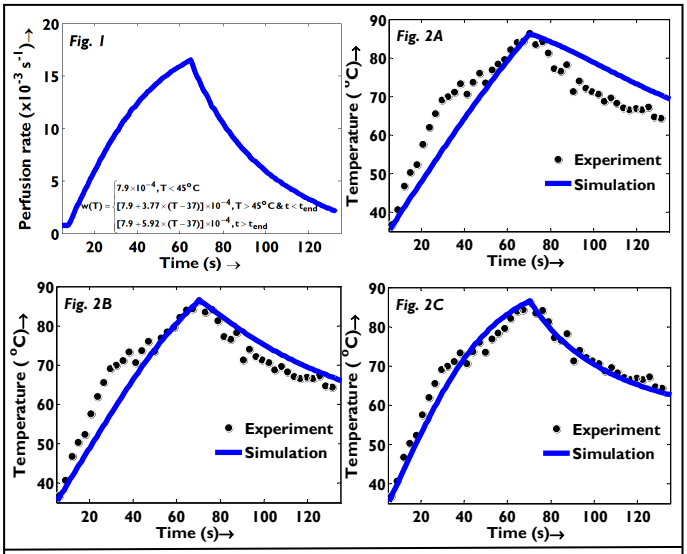

Fig. 1: Perfusion rate *vs* time. T is temperature, t is time and t_{end} is the time when sonication was stopped. Fig 2: Temperature evolution at cell center were plotted using model 1 of constant thermal conductivity and perfusion rate (Fig. 2A), model 2 of temperature dependent thermal conductivity and constant perfusion rate (Fig. 2B) and model 3 of constant thermal conductivity and temperature dependent perfusion rate (Fig. 2C) and corresponding HIFU experimental data.

Results: Nine ellipsoidal cells with diameter of 8 mm, 12 mm, 16 mm were successfully treated at different depths (3.7 cm - 5.4 cm) on the thigh muscle. The thermal conductivity of 0.54±0.05 W/(m*K) used in model 1 and 3 were extracted from the spatio-temporal temperature distribution of treated pigs muscle using the method described previously [4]. Perfusion rate in models 1 and 2 were 6.71×10^{-4} s^{-1} for normal muscle tissue reported in the literature. Specific heat, tissue density of both muscle and blood, and blood temperature in all three models were 3600 J/(kg*K), 1060kg/m^3, and 37^{o}C respectively. The acoustic power input for each model was estimated based on the peak temperature measured experimentally (86.5 °C), and was 3.25×10^{6} W/m^3, 3.46×10^{6} W/m^3, and 4.52×10^{6} W/m^3 for models 1 through 3 respectively. Temperature evolution at the center of a 16 mm cell simulated using model 1 through 3 is shown in Figure 2A through 2C, respectively. Sonication duration was 65s followed by equal amount of time for cooling. The simulation based on the 1st model of constant thermal conductivity and perfusion rate can not describe the temperature evolution both before and after sonication (Figure 2A); While model 2 appears to match experimental observation, the thermal conductivity needed to be increased up to 1.2 W/(m*K), which is well beyond the thermal conductivity for soft tissue. In contrast, model 3 (Figure 2C) matched the experimental data both in heating and cooling period. The perfusion rate went up to 20 times of that of the normal perfusion rate which is similar to that observed in the hyperthermia treatments [1]. However, it should be noted that, unlike hyperthermia where the tissue response time is on the order of tens of minutes, the time scale of tissue response for HIFU treatment is on the order of tens of seconds. It is worth pointing out that, the third model also has the ideal characteristic that the perfusion rate decreases faster during the cooling period than the rising period due to the lesion created after sonication.

Conclusions: The results from this preliminary theoretical and experimental study suggest the following: (i) Temperature dependent perfusion rate is needed to properly describe the local physiologic response of tissue to HIFU treatment; (ii) Local blood perfusion rate responses are much faster than that have been reported in hyperthermia treatment; (iii) Fast blood perfusion increases with increasing local temperature should be considered in clinical HIFU therapy planning and optimization.

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