Real-time Monitoring of Temperature and Magnetization Transfer during HIFU Transmission and Long-term Follow-up of Magnetization Transfer Effect : in vivo rabbit investigations

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Introduction: The development of high intensity focused ultrasound (HIFU) technology has offered a potentially new approach to the local ablation of cancer [1]. In previous study, temperature measurement using phase mapping was developed based on the temperature dependence of the water proton resonance frequency (PRF) shift [2]. In addition, the changes in magnetization transfer (MT) contrast of tissues after heat treatment was also evaluated in a previous study [3]. Moreover, the histologic evolution over time of rabbit thigh muscle after HIFU ablation has been examined with pathology after sacrificing the animals [4]. In our previous study [5], a sequence which can simultaneously monitor temperature change and magnetization transfer effect during HIFU heating was demonstrated on *ex vivo* porcine muscle tissue. In this study, we apply this method to rabbit thigh muscle *in vivo* to investigate long-term follow-up, with usage of the MT effect to evaluate the evolution of ablated spots after HIFU sonication.

Methods and Materials: A single-element focused piezoelectric transducer (central frequency 1.85 MHz, 10 cm diameter, 12.5 cm curvature, Imasonic, Besancon, France), used as the source of sonication, was immersed in 37 °C degassed water. Continuous wave HIFU pulses with power of 40 Watt were applied on the thigh muscle tissue of 5 adult New Zealand White rabbits (2.8~3.2 kg) for 38 sec (in total 10 heated spots). Rabbits were sedated using isoflurane and was placed in a right- or left-lateral position. Serial MR images were acquired at pre-heating (t=0~19sec), heating (t=20~58sec) and post-heating time (t=59~622sec). All MR images were acquired on a 3T clinical imager (Siemens Trio, Erlangen, Germany). The pulse sequence used a dual gradient-echo design, with ON and OFF of the MT pulse interleaved [5], such that the phase images from the two gradient echoes could be used to estimate PRF shift in response to temperature change, and the first echoes from two consecutive TR could be used to derive MT ratio (MTR = 1-(M_{MT}/M_0), where M_{MT} and M_0 are the signal intensity of magnitude images with and without off-resonant MT pulse, respectively) on a pixel-by-pixel basis. Imaging parameters were TR=27 msec, TE=3.61/7.55 msec, flip angle=20°, FOV=240x240 mm², matrix size=128x96, slice thickness=3 mm, off-resonance frequency of MT pulse = −1200 Hz. Temporal resolution of about 2.4 sec for monitoring temperature change and observing MTR change was achieved simultaneously. To further enhance visualization of the heated spots, we subtracted the baseline MTR values, which were calculated from the mean of all pre-heating MTR maps, from the instantaneous MTR values to yield series of ΔMTR maps. To characterize the time courses of temperature and ΔMTR with respect to the heating time, two ROIs were selected in the heated and non-heated regions (2 cm from the heated spot) from the ΔT map (dotted lines in Fig. 1a). For long-term follow-up, T2 weighted images (TR/TE=2500/45 msec), fluid attenuation inversion recovery (FLAIR) images (TR/TE=7000/79 msec), and 3D MT images (parameters as above) were acquired.

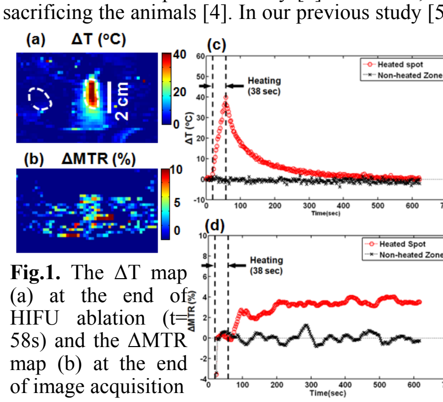

Fig.1. The ΔT map (a) at the end of HIFU ablation (t=58s) and the ΔMTR map (b) at the end of image acquisition were shown. ROIs (white dotted lines) selected in the heated and non-heated regions (2 cm from the heated area) from the ΔT map were shown. The time courses of temperature change and ΔMTR within the two ROIs were shown in (c) and (d). The mean ΔMTR from t=550s till the end of acquiring images for these two regions were 3.62%±0.10% and 0.12%±0.27%, respectively. The two vertical lines shown in (c) and (d) denote the heating duration.

Results: The ΔT map at the end of HIFU transmission (t=58s) and the mean ΔMTR map at the end of image acquisition (t=610s-622s) were shown in Fig.1(a,b). The time courses of temperature change and ΔMTR in the heated and non-heated regions for one rabbit were shown in Fig.1(c,d). The mean temperature change within the heated region reached a peak at 40 °C at the end of heating. As shown in Fig. 1d, ΔMTR in the non-heated zone was varying slightly around 0%. In the heated region, ΔMTR first decreased during the HIFU transmission. After turning-off the HIFU pulses, ΔMTR increased gradually to 4%, which was distinguishable from that in the non-heated zone. The mean ΔMTR from t=550s till the end of acquiring images for these two regions were 3.62%±0.10% (mean±standarder deviation) and 0.12%±0.27%, respectively. Fig.2 shows the follow-up images of T2WI, FLAIR, and MTR maps for Day1, Day15, and Day22, respectively. In T2WI and FLAIR images, the heated regions were surround by hyper- to iso-intense tissue which may obscure visualization of the area of heated spots. As for MTR maps, the heated spots with higher MTR values were surrounded by tissue with lower MTR. The histology on Day22 of one of the rabbits were shown in Fig.2b. The follow-up of mean MTR values within ROIs of heated spot and surrounded tissue of 5 rabbits were shown in Fig.3. The mean MTR of heated spots were kept at 28~32% during the three weeks of follow-up. As for the surrounded tissue, the MTR values were 12~17%.

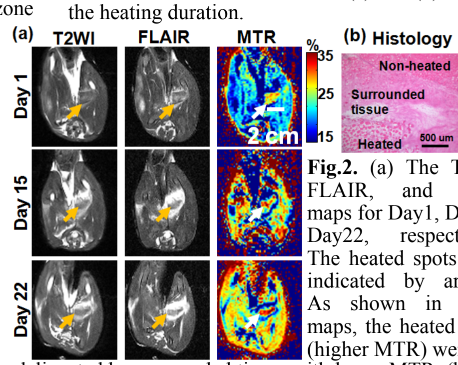

Fig.2. (a) The T2WI, FLAIR, and MTR maps for Day1, Day15, Day22, respectively. The heated spots were indicated by arrows. As shown in MTR maps, the heated spots (higher MTR) were delineated by surrounded tissue with lower MTR. (b) The histology of heated spot, surrounded tissue, and non-heated tissue was shown in (b).

Discussion and Conclusions: Monitoring temperature change and magnetization transfer in response to tissue damage under HIFU treatment is crucial to the evaluation of treatment efficiency, as they provide complimentary information regarding temporary and permanent thermal alterations of tissue characteristics, respectively [5]. The *in vivo* feasibility of simultaneous MR measurement of temperature change and MT effect during HIFU procedures on rabbit thigh muscle was verified. The ΔMTR first decreased during HIFU transmission, which was somewhat different from *ex vivo* findings [5], suggesting possible temperature dependency of the MTR derivation which needs to be further investigated. Nevertheless, the follow-up (Day15, Day22) of MT effect showed persistently increased MTR values in heated spots, demonstrating the value of MT effect monitoring in HIFU treatment. In conclusion, MRI with simultaneous temperature and MTR mapping is potentially an effective technique to evaluate tissue damage upon HIFU treatments *in vivo*, as demonstrated on rabbit thigh muscle. The immunity to phase variations and off-resonance effects (in contrast to temperature mapping derived from phase images) plus the unique capability clearly distinguishing heated spot and non-heated region (Fig. 1b) after turning-off HIFU pulses suggests that the simultaneous temperature and MTR mapping technique should worth further explorations. Moreover, the surrounded tissue with low MTR, delineating clearly the extent of heated region, underlines the advantage of long-term follow-up with usage of MT effect to evaluate the efficacy of HIFU treatment. In the future work, contrast-enhanced T1 weighted images should be acquired to compare with MTR maps for the investigations of long-term follow-up after HIFU treatment.

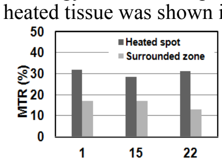

Fig.3. The follow-up (Day1, Day15, Day22) of mean MTR values within ROIs of heated spot and surrounded tissue of five rabbits were shown. The mean MTR of heated spots were 28~32% during the three weeks of follow-up. As for the surrounded tissue, the MTR values were 12~17%.

References: 1. Cheng et. al, J Cancer Res Clin Oncol 1997, 123: 219-223. **2.** Ishihara et. al, Mag Reso Med 1995, 34: 814-823. **3.** Graham et. al, Magn Reson Med 1999, 42: 1061-1071. **4.** Solomon et. al, Invest Radiol 2003, 38:293-301. **5.** Peng et. al, J Magn Reson Imaging 2009, 30: 596-605.