Thermal Responses of MRI Contrasts in ex vivo Tumor and Muscle Tissue

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Purpose: Longitudinal relaxation time (T_1), transverse relaxation time (T_2), chemical shift (CS), and apparent diffusion coefficient (ADC) are imaging parameters that change with temperature [1-4]. It is challenging to use all these descriptors to measure temperature because the way they change is very tissue dependant. T_1 relaxation tends to decrease with increasing temperature given that molecules in imaging experiments have a rotational correlation time in the picosecond regime [2]. T_2 and ADC have also been shown to increase with increasing temperature [2,4]. The temperature-dependent CS change in water leads to the well-known proton resonance frequency shift (PRFS), used as a popular means of MR thermometry (MRT) for non-invasive temperature monitoring [3]. Once most tissues go above a threshold temperature of ~45°C there is usually an irreversible change in the tissues' relaxation parameters due to a permanent change in tissue structure [5]. This must be taken into account if using T_1/T_2 for hyperthermic temperature monitoring. Here we use T_1, and T_2 to determine salient characteristics of *ex vivo* tumor and muscle tissue when it is held at steady-state temperatures from 0°C to 22°C. We look for the accuracy and repeatability in measuring relaxation parameters, and evaluate if these heat-induced contrast mechanisms can be used to add information to conventional MR imaging contrast types for better characterization of tumors from surrounding tissues.

Methods: Rat breast adenocarcinoma (RBA), and rat prostate carcinoma (RPC) cells were cultured and used to inoculate female Fischer 344 rats and male Copenhagen rats respectively. Tumors were grown on the rat flanks and excised when they reached a size of 2-3cm. Imaging tests were performed on the *ex vivo* tissue samples of RBA tumor (tumor 1), muscle tissue excised directly surrounding RBA tumor (muscle 1), RPC tumor (tumor 2), and muscle tissue excised directly surrounding RPC tumor (muscle 2). All tissues were placed in sample tubes as shown in Fig. 1a. Sample tubes were cooled in an ice-water bath (Fig. 1b) for ~3 hours to ensure a steady 0°C temperature was reached. Samples were then allowed to equilibrate to room temperature through thermal interaction with the air. Two cycles of cooling and warming were performed. T_1 data sets were acquired during both cold and warm periods using a 2D coronal inversion recovery (IR) sequence at the following TI values: 3500, 1150, 950, 750, 550, 350, 200, 50 with all times in ms. Other parameters included flip angle (θ) = 180°/90°, TR = 5000ms, TE = min, FoV = 19, matrix 128 x128, NEX = 1, 1 slice, 5 mm thick. T_2 data sets were acquired using a 2D coronal spin echo (SE) sequence with the following TE values: 300, 200, 150, 100, 50 ms (θ = 90°/180°, and same parameters as IR). All images were acquired on a 3T GE MR750 scanner (GE Healthcare, Waukesha, WI). T_1 and T_2 fitting was done in Matlab (Mathworks, Natick, MA) using an in-house developed fitting algorithm performed per-pixel, or for select regions of interest.

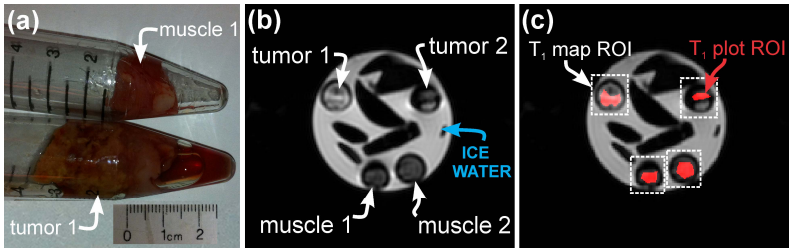

Fig. 1 *(a) Sample tubes containing rat breast adenocarcinoma (RBA) tumor, labeled as "tumor 1", and muscle directly surrounding the RBA tumor labeled as "muscle 1". (b) Coronal IR image showing general sample locations in the ice-water bath. (c) Coronal IR image showing approximate ROIs used for T_1 plots in Fig. 2, and T_1/T_2 maps in Fig. 3.*

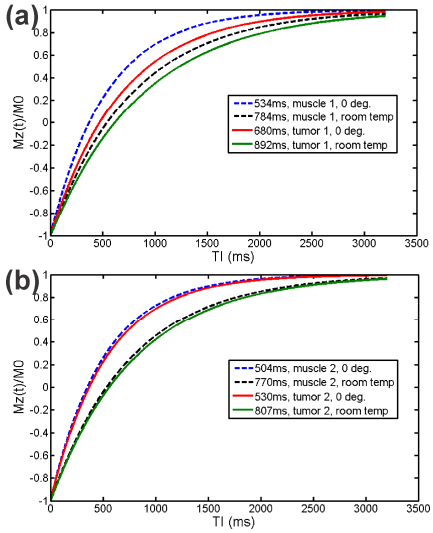

Fig. 2 *(a) Inversion recovery plots for tumor 1 and muscle 1 at 0°C and 22°C. (b) Inversion recovery plots for tumor 2 and muscle 2 at 0°C and 22°C. Signal intensity (S) from mag.images were plotted for ROIs in Fig. 1c as a fn of inv. time (τ) and fit to* $S(\tau) = S_0(1-2\cdot e^{-\tau/T_1})$.

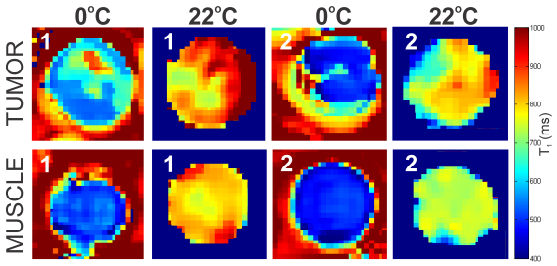

Fig. 3 *Coronal T_1 maps of tumor 1 and 2, and muscle 1 and 2, at 0°C and 22°C. The approximate regions of interest used for these images can be seen in Fig. 1c. Here signal intensity (S) was fit per pixel to* $S(\tau) = S_0(1-2\cdot e^{-\tau/T_1})$ *where (τ) is the inversion time.*

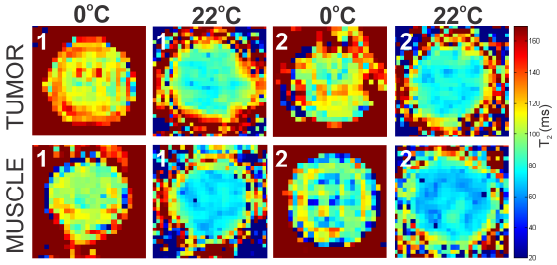

Fig. 4 *Coronal T_2 maps of tumor 1 and 2, and muscle 1 and 2, at 0°C and 22°C. Here signal intensity (S) was fit to* $S(\tau) = S_0 \cdot e^{-\tau_E/T_2}$ *where (τ_E) is the echo time.*

Results: The plots in Fig. 2a-b show the inversion recovery relaxation curves for all tissue samples at 0°C and 22°C. Here we see a T_1 change of 2.1%/°C, 1.4%/°C, 2.4%/°C, and 2.4%/°C for muscle 1, tumor 1, muscle 2, and tumor 2 respectively. Results were fully reversible. Data was also processed to give T_1 maps as shown in Fig. 3. The T_1 maps give good contrast showing the T_1 contour in regions where tissue was heterogeneous. T_2 maps indicate a change of ~ 2.3%/°C, 2.5%/°C, 3%/°C, and 2.3%/°C for muscle 1, tumor 1, muscle 2, and tumor 2 respectively, as shown in Fig. 4. **Conclusions:** All tissue samples show repeatable (<2% change) relaxation parameter measurement over a range of 0-22°C. In addition we see a distinct difference in T_1 for tumor/muscle 1, but not tumor/muscle 2, and vice versa for T_2. These findings indicate a link to improved MR imaging visualization or characterization of tumors with heat-induced T_1/T_2 relaxation contrast types. Extensions to use these techniques to assess similar *in vivo* human tumor-tissue thermal response are underway.

References: [1] Bloembergen et al. Phys Rev 1948;73:33, [2] Parker DL IEEEBME 1984;31:161-7, [3] Riecke et al. JMRI 2008;27:376-90, [4] Chenevert et al. JMRI 2011;34:983-7, [5] Wu et al. Radiology 2009;253:297-31