Parametric MRI for Muscle Degeneration and Regeneration

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Introduction

Magnetic resonance imaging (MRI) based on changes in spin-spin relaxation time (T2) is currently the clinical standard to assess a wide variety of pathology in muscles and soft tissues. In addition to T2, MRI is rich in many other imaging parameters that can be potentially utilized as additional tools to further understand the processes in muscle changes due to muscle damage, degeneration and recovery. In this study we used four MR imaging parameters to investigate muscle damage and repair over time subsequent to myotoxin injection. The MRI parameters include muscle volume measurement using 3 dimensional imaging, T2, apparent diffusion coefficient (ADC) and magnetization transfer (MT) suppression ratio values and are correlated with histology findings conducted for selected time points. Our goal was to develop noninvasive biomarkers using MRI and MRS for the process of muscle changes including edema, inflammation, damage and recovery.

Methods

MRI was conducted on a Bruker 4.7 T horizontal bore magnet equipped with Varian INOVA spectrometer. A ^{1}H volume coil (25 mm inner diameter volume coil from Doty Scientific Inc., Columbia, SC) was used to acquire MR images. Normal mice were used for MR imaging the 4.7 T MR scanner with 4 pulse sequences: with and without magnetization transfer, single echo multi-slice sequence for T2 measurements with three TE values (13, 30 and 60 ms), diffusion weighted imaging sequence to measure ADC values with three b values of 0, 573 and 1123 s/mm^2 and a gradient echo sequence for 3 dimensional images.

To induce local muscle damage in mouse muscle, we injected myotoxin ($BaCl_2$, 50 mL 1.2 % by weight) on the lower gastrocnemius of one leg for each normal 8 week old mouse while the other leg was uninjected and served as a control. Six mice were used for longitudinal MRI conducted for the total of 3 weeks

Results and Discussion

Figure 1 shows longitudinal measurements of multi-parameters demonstrating that different phases of muscle change are observed for different imaging parameters acquired for mouse lower leg muscles. ADC, T_2 and MT suppression maps shown in Figs. 1A-C were cropped to visualize cross sectional views of both legs on day 3 post $BaCl_2$ injection. The histology images for the similar slice to the MR images are presented in Figs. 2D-G: macrophage infiltration is clearly observed in two expanded Hematoxylin and eosin (H&E, Fig. 2E) and Masson's Trichrome (Fig. 2G) stained images. As shown in Fig. 2H, the maximum level of swelling was observed 1 – 2 days (day 1 or 2 on the graph) after the injection. The tendency of diffusion variation is similar to that of the swelling effect as seen in Fig. 2I. T_2 values were maximized on day 3 after injection and decreased to normal values in three weeks (see Fig. 2J). MT suppression ratios reached the maximum values on day 4 or 5; then the values were gradually decreased afterwards.

The exciting results obtained show it is possible to distinguish underlying pathology as a function of time, as indicated by the arrows in Figure 1. Acute damage and necrosis is evident with 1 – 2 days (changes in volume and diffusion), followed by macrophage infiltration (day 3 – 4), then followed by onset of regeneration (day 6 – 8) followed by recovery by the third week.

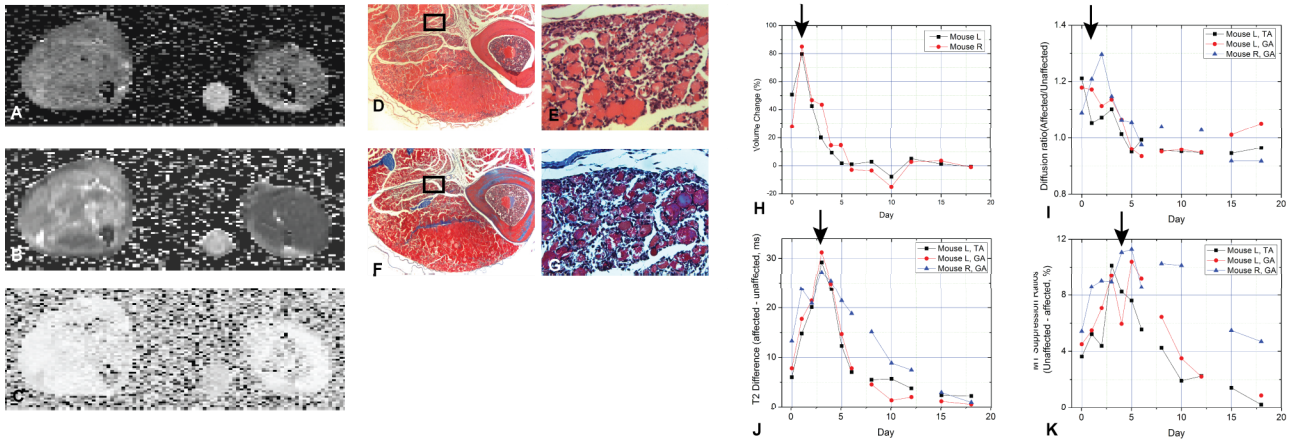

Figure 1. ADC map (A), T2 map (B) and MT suppression ratio map (C) calculated by T2 weighted, ADC weighted and MT weighted images for mouse leg *in vivo* on day 3 post BaCl2 injection onto the left leg. A similar slice from the damaged left leg was prepared for H&E (D and E) and Masson's Trichrome staining (F and G) with their expansion scales of 4x and 40x (a region marked by a rectangle for a corresponding 4x image), respectively. Time course changes of muscle volume and imaging parameters including volume (H), ADC (I), T2 (J) and MT suppression ratios (K) after a left lower leg muscle injected with BaCl2.

Conclusions

We demonstrated that noninvasive MRI would be a valuable tool to monitor muscle changes over time and that the MRI results were well correlated with histological findings. Our approach can provide a systematic way to monitor muscle degeneration and regeneration, which is potentially used to monitor the progression of a variety of muscle disorders and responses to therapeutic treatments for the muscle disorders.

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