Monitoring exercise-induced muscle changes using Diffusion Tensor Imaging, with and without caffeine

Conrad Rockel[1,2], Andrew Davis[2,3], Greg Wells[4], and Michael Noseworthy[1,2]

[1]*School of Biomedical Engineering, McMaster University, Hamilton, Ontario, Canada,* [2]*Imaging Research Centre, St Joseph's Healthcare, Hamilton, Ontario, Canada,* [3]*Medical Physics and Applied Radiation Science, McMaster University, Hamilton, Ontario, Canada,* [4]*Faculty of Physical Education and Health, University of Toronto, Toronto, Ontario, Canada*

Introduction: Diffusion tensor imaging (DTI) is an MRI technique that uses the restriction of hydrogen proton mobility within tissues to assess tissue microstructure, and allows rotationally-invariant quantification of fiber orientation and fluid dynamics. Diffusion has been shown to increase in skeletal muscle following bouts of exercise **[1]** and to vary with workload **[2].** Studies of post-exercise diffusion time course have presented increased values following exercise in comparison to resting values, followed by gradual decline **[3,4]**. However, these studies used diffusion MRI techniques known to have less absolute quantitative value than DTI **[5].** Caffeine (trimethylxanthine) is a substance known to cause peripheral vasodilation **[6]** and stimulation of the central nervous system **[7],** although there is considerable debate with respect to its ergogenic benefits**.** Caffeine has been shown to increase endurance during exercise **[6,8]**, as well as stimulate leg contraction in paraplegic individuals **[9].** However, reviews have found mixed results regarding the benefit of caffeine on speed and force output, as well as wide variations in individual responsiveness to caffeine **[6,10].**

Purpose: To investigate the DTI response to exercise in skeletal muscle across time immediately following exercise, and whether the presence of caffeine would influence measures of diffusivity within muscle tissue.

Methods: Three healthy male volunteers (mean age 34.6 years) underwent two trials on separate days, each trial consisting of 2 bouts of exercise one hour apart **[Fig 1].** Exercise consisted of 2.5 minutes of plantar flexion (0.5 Hz) at 50% of individual right leg maximum load using a custom-built MRI-compatible ergometer. One trial involved the oral administration of 200 mg of caffeine following the first bout of exercise (Caff), while the other did not (NoCaff). DTI data (GE 3T, b=400s/mm^2, 15 dir, 4mm slice, 16 slices, 64x64) was obtained from the thickest cross-section of the right calf. Eight DTI volumes were collected consecutively prior to and following each exercise session. Each DTI excitation represented approximately a 2 minute time period. Regions-of-interest (ROI) were drawn on the gastrocnemius (medial and lateral combined) and soleus muscles, and registered to each consecutive DTI volume. DTI indices such as mean diffusivity (MD) and individual eigenvalues were calculated for each ROI across time.

Results: A notable increase in gastrocnemius MD and eigenvalues was observed between the first and second post-exercise DTI volumes in all trials, after which diffusivity declined across excitations **[Fig 2].** MD and eigenvalues preceding and following the second bout of exercise were equivalent to those preceding and following the first bout. In the soleus, a slight post-exercise increase was seen in MD and eigenvalues which appeared relatively stable across time, although slightly higher at the first time point compared with subsequent time points. There was no difference between Caff and NoCaff post-exercise conditions in either muscle.

Discussion: The magnitude of gastrocnemius MD increases following exercise are consistent with previously published studies, as is the time course of gradual decrease towards resting values **[3,4]**. However, contrary to previous studies, the present study found that diffusion for the two minutes immediately post-exercise appears to resemble that of pre-exercise and increases in the subsequent two minutes, rather than displaying increased diffusivity immediately after exercise cessation. Also of note is the similarity of peak post-exercise diffusion values across all conditions, indicating the repeatability of diffusion induced by the current exercise protocol. Further research is needed to determine whether this peak signifies maximum diffusion in muscle tissue, and whether peaks of lower magnitudes would be repeatable with lesser workloads. The increased diffusivity seen with exercise has been attributed to water shifts as well as temperature **[11].** Considering that exercising muscles generate heat, it is surprising that diffusion immediately post-exercise remain at pre-exercise levels. It is possible that the spike seen at the second post-exercise time point is the result of reactive hyperemia, as relaxing muscle removes vascular occlusions that occur in muscle contraction, and blood is allowed to reperfuse into the tissue. The differences in diffusion between gastrocnemius and soleus could be due to the present exercise protocol (supine plantar flexion with 0 degree knee angle) isolating the gastrocnemius, and thus less contractive occlusion is experienced in the soleus. However, these differences could also be due to the heavily-vascularized soleus being able to maintain consistent blood flow throughout the exercise, resulting in little change in tissue fluid levels. It was hypothesized that the presence of caffeine would increase

Figure 1. Schematic of a single trial comprised of two exercise sessions, with approximately one hour rest between exercise. Star indicates where dosage of caffeine would occur in the Caffeine condition.

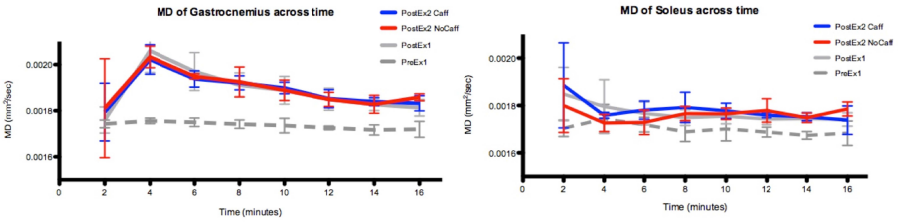

Figure 2. MD values across 8 sequential DTI acquisitions, showing pre-exercise and post exercise values across time in the gastrocnemius (left) and soleus (right). Timepoint reflects acquisition of diffusion information for the two minutes preceding the time point. Post-exercise acquisitions began immediately following cessation of exercise.

diffusion due to its vasodilatory properties. However, no diffusion differences were found between Caffeine and NoCaffeine trials, unlike the effect seen in BOLD studies of muscle **[7]**.

Conclusions: (i) DTI can be used to provide a detailed analysis of exercise-induced changes in fluid dynamics within muscle tissue. (ii) Caffeine does not affect diffusion within skeletal muscle tissue before or after exercise.

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