Co-localized Post-Contractile BOLD and 31P-MRI in Muscles of the Lower Leg

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TARGET AUDIENCE: Those interested in muscle physiology, muscle bioenergetics and microvascular function.

PURPOSE: To acquire co-localized post-contractile blood-oxygen-level-dependent (BOLD) and phosphocreatine (PCr) imaging data and quantify metabolic and micro-vascular function in the lower leg muscles of healthy subjects.

BACKGROUND: Defects in muscle efficacy can result from reduced blood supply, tissue oxygenation, and/or mitochondrial dysfunction, as for example in patients with arterial occlusion and patients with mitochondrial diabetes.[1] Understanding the diverse roles of bioenergetics and the microvasculature in the pathogenesis of such diseases may help to better understand the factors responsible for their onset and progression. Phosphorus (^{31}P) magnetic resonance (MR) can noninvasively assess skeletal muscle bioenergetics, whereas microvascular function in muscle can be measured using post-contractile changes in blood oxygenation level dependent (BOLD) MRI signals.[2] However, given the limited tissue coverage of most ^{31}P-MR approaches, the two measurements are typically obtained from different regions of the muscle. Many studies have shown that muscle recruitment in an exercising limb is not uniform. Therefore, co-localization of the ^{31}P and BOLD measurements in the recruited muscles following exercise may lead to a more accurate depiction of the metabolic and microvascular functions of the recruited muscles in healthy subjects and patients.[3] In this study, we combined a ^{31}P-MRI method[4] with BOLD MRI to obtain co-localized post-contractile microvascular and bioenergetics information in muscles of the lower leg of healthy subjects following plantar flexion.

METHODS: We recruited 10 healthy male subjects (age: 34.4 ± 6.2 years of age, with BMI 25.2 ± 3.7, mean ± standard deviation) with no history of metabolic or cardiovascular diseases. We measured their physical activity using the 7-day physical activity recall questionnaire.[5] We performed MRI measurements on a 3 T MRI system (Siemens Medical Solutions, Erlangen, Germany) using a dual-tuned (^{31}P/^{1}H) quadrature transmit-receive knee coil (Rapid MRI, Ohio). We measured BOLD changes in the plantar flexion following maximal isometric contractions using a one-shot gradient-recalled echo-planar sequence (TR: 1 s, TE: 35 ms, 22 cm field-of-view, 1 cm slice thickness, and 78×78 acquisition matrix). Images were acquired for 4 min, during which time subjects performed a 1 s duration maximal voluntary plantar flexion every 30 s. PCr images were also acquired during and after 2 min exercise. The participants performed plantar flexions at 0.33 Hz to an acoustic cue, using an in-house built magnetic resonance compatible ergometer. During exercise, subjects moved the footplate of the ergometer through a 30° range of motion. The resistance was applied by rubber tubing and was set to approximately 40% of the subjects' maximum voluntary contraction (MVC). The acquisition was done using a spectrally selective turbo spin echo PCr imaging sequence (voxel size: 4.2 mL, temporal resolution: 12 s).[4] We fit the acquired PCr data to a single exponential recovery function using a least squares minimization algorithm in order to estimate the PCr resynthesis rate constant, k_{PCr}. PCr concentration maps were acquired during rest.[6] We calculated oxidative capacity (Q_{max}) as the product of k_{PCr} and resting PCr concentration. Measured data were compared by cross-correlation analysis with a linear model.

RESULTS: Figure 1 shows a representative axial echo-planar image from a volunteer (a), and the corresponding PCr concentration map acquired with ^{31}P-MRI (b). The white marks in both images define the region-of-interest (ROI) drawn for analysis of the time course of BOLD and PCr signal changes. Figure 1.c shows the time course of BOLD signal changes[1] in the lateral gastrocnemius for the same subject. The spikes in the BOLD signal during contraction are followed by delayed transient signal increases. In the inset, definition of the TTP and ΔS_{max} are shown. In the same ROI, post-exercise PCr signal recovery is shown (Fig.1d) together with the data fit to an exponential growth function. The results of both experiments are summarized in Table 1. The correlation between k_{PCr} and activity was significant (r = -0.65 , p < 0.05), as was the correlation between ΔS_{max} and physical activity (r = 0.62, p < 0.05), which is consistent with previous reports in the literature.[7]

Table 1: Results (mean ± SD)

Subjects	10 male
Age (years)	34.4 ± 6.2
BMI (kg m^{-2})	25.3 ± 3.7
Activity (Kcal kg^{-1} d^{-1})	31.4 ± 13.0
[PCr] rest (mM)	33.0 ± 2.6
PCr depletion (%)	29.9 ± 15.9
k_{PCr} (s)	53.2 ± 25.0
Q_{max} (mmol l^{-1} s^{-1})	0.80 ± 0.49
ΔS_{max} (%)	2.15 ± 1.78
TTP (s)	5.89 ± 2.27

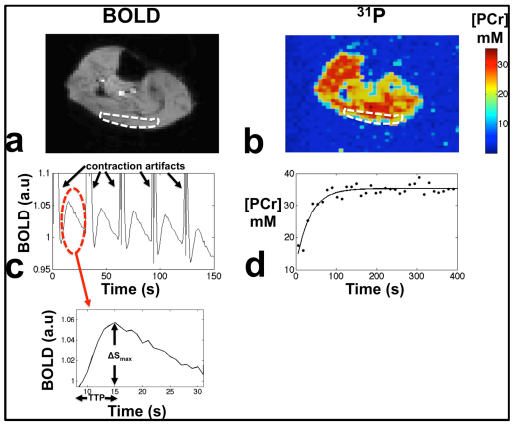

Fig.1: Co-localized Microvascular and Bioenergetics Assessment of Skeletal Muscle. a) Echo-planar axial image of the lower leg muscles from a healthy subject. b) Co-localized PCr concentration map of the same subject acquired with ^{31}P-MRI. c) BOLD signal time course in the gastrocnemius lateralis. The microvascular post-contractile response is characterized by the Peak BOLD change (ΔS_{max}) and the Time-to-Peak (TTP) shown in the magnified inset (bottom). d) PCr recovery following 40% MVC characterized in the same ROI.

DISCUSSION: Combined measurements of perfusion and bioenergetics are important for understanding muscle function in health and disease. Due to non-uniform muscle recruitment in an exercising limb, co-localization of BOLD and ^{31}P-MRI signals may bring new insights into the etiology of muscle diseases and help us understand whether they are a result of direct impairment in the mitochondria, or a consequence of impaired blood supply and tissue oxygenation.

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