Evaluation of Muscle Oxygenation Metabolism by Quantitative BOLD (qBOLD) Approach

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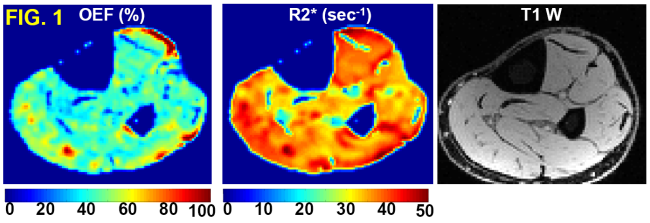
Introduction: Information on muscle hemodynamics and oxygen metabolism during baseline and after intense exercise is crucial in the management of various musculoskeletal (MSK) diseases such as mitochondrial myopathy (1), chronic exertional compartment syndrome (2) and chronic muscle fatigue syndrome (3). Conventional muscle functional MRI (mfMRI) can only provide semi-quantitative evaluation of muscle oxygen metabolism (4,5). During intense exercise, blood oxygenation within microvasculature, blood flow and blood volume are expected to increase and affect blood-oxygenation level-dependent (BOLD) MR contrast. Furthermore, intracellular muscle water content and acidity may also change and affect the R2 and R2* of muscle. To date, the mechanism of BOLD contrast in skeletal muscle, and the relative contributions of intra- and extra-vascular water remains controversial (6).

Previously, MR-based quantitative BOLD (qBOLD) approach established an analytical connection between brain BOLD signal decay profile and brain hemodynamic parameters, such as deoxygenated cerebral blood volume (dCBV) and oxygen extraction fraction (OEF) (7,8). In this study, we employed a similar approach, for the first time, to quantitatively describe the effect of muscle venous blood oxygenation (thus oxygen extraction fraction, OEF) on the muscle BOLD signal.

Methods: Just as in the brain MR qBOLD model, the T2* decay profile of muscle MR signal is influenced by intravascular blood and extravascular tissue water (7). Here we assume that the muscle venules and small veins can be modeled as randomly oriented infinitely long (relative to their diameter) cylinders. All experiments were performed on a 3T Siemens Trio scanner using standard 8 channel knee coil. Three healthy volunteer subjects were scanned in multiple sessions to study calf muscle oxygenation. In three sessions, subjects were asked to perform dorsiflexion of a foot for at least three minutes. The legs were positioned straight (parallel to B0 field) in all studies, except during one session when the subject was instructed to tilt the leg approximately 25 degrees with respect to the B0 field. MR parameters for multi-slice 2D GESSE (gradient echo sampling of spin echo) were: fat saturation; TR of 1.2 sec, echo train length of 41 with echo spacing of 2.9 ms, spin echo at 66 ms (9^{th} gradient echo); voxel size of 1x1x6 mm^3. The acquisition time was 2.6 minutes. A double echo 3D GRE sequence (TE1/TE2 of 4.92/12.30 ms) was used to acquire a high resolution field map (voxel size of 1x1x2 mm^3).



Results & Discussions: Fig. 1 shows typical baseline muscle OEF and R2* maps from a subject. OEF contrast was often visible among different muscle groups possibly due to differences in muscle tone. Within the same muscle group, voxels with abnormal OEF value that were attributed to blood vessel and fatty tissues or partial volume effect were detected. The estimated mean muscle OEF value for this subject was 44.5±11.2%, which is in good agreement with the reported values (mean value of 50%) from direct blood sampling (9), and blood magnetic susceptibility in femoral vein (36+/-8%) (10). The mean baseline muscle OEF across the subjects in six sessions was 41.4±2.8%.

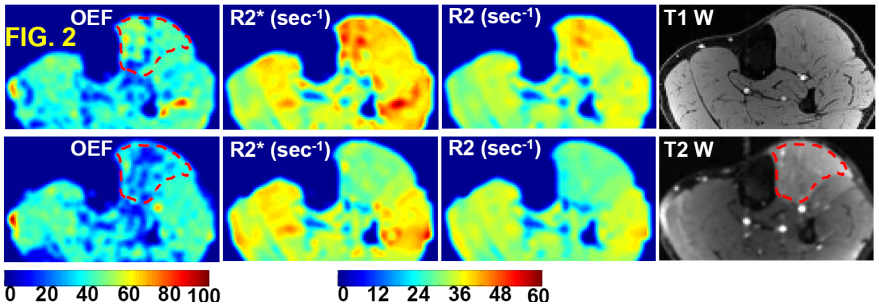
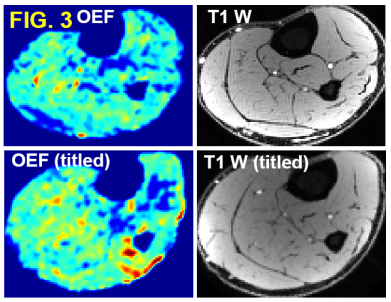


Fig. 2 presents the typical muscle venous blood oxygenation, R2* and R2 during baseline (top row) and within 3 mins after intensive dosiflex exercise (second row). Venous blood oxygenation increased considerably after exercise (i.e., OEF decreases from 40.6±13.7% at baseline to 28.3±10.8% at 3 mins and 29.4±11.5 at 6 mins after exercise).



A recent study (6) suggested that muscle BOLD fMRI effect originated mainly from intravascular relaxation effect, while extravascular BOLD contribution to muscle R2* is too small to be important. Our study demonstrated otherwise. Although capillary blood does contribute significantly to extravascular muscle R2 decay, its contribution to muscle R2' decay can be ignored due to rapid water diffusion around small capillaries (8). The decrease on muscle R2' after exercise, as illustrated in Fig. 2, cannot be attributed to longitudinally orientated capillaries.

The proposed muscle qBOLD model assumes random orientation for venules and small veins, as evident from existing vascular-casting experiments. For further validation, the leg was titled to be approximately 25 degrees with respect to B0 field. Although slight changes of muscle R2 and R2* changed slightly (not shown), no overall changes in the estimated venous blood oxygenation level based on the proposed muscle qBOLD model was detected (39.7±9.8% vs. 42.8±13.0%) (Fig 3). This demonstrated that there is no preferable orientation for qBOLD sensitive blood vasculature. **In conclusion,** we have demonstrated that qBOLD technique is able to measure in-vivo regional oxygen metabolism of human skeletal muscle.

References: **(1)** Jesen, et al., Neurology 2002; 58:1533. **(2)** Andreisek, et al., AJR Am J Roentgenol 2009; 193:W327. **(3)** Fulle, et al., JMuscleResCellMotil 2007;28:355. **(4)** Damon, et al, JApplPhysiol 2005; 98:264. **(5)** Damon, et al, JApplPhysiol 2003;95:1287. **(6)** SnaChez, et al, MRM 2010;64:527. **(7)** He & Yablonskiy, MRM 2007;57:115. **(8)** Yablonskiy & Haacke, MRM 1994;32:749. **(9)** Barcroft, et al, JPhysiol 1963:168:848. **(10)** Langham, et al, JAmCollCardiol 2010; 55:598.