MSK hemodynamics at quadriceps using blood-oxygen level dependent (BOLD) MRI at 3T; Volitional exercise VS Neuromuscular Electrical Stimulation (NMES)

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[Target Audience] Researchers who are interested in understanding of muscle hemodynamics during the exercise

[Purpose] The hemodynamic response of the muscle using BOLD MRI has been demonstrated in many parts of the body and this response has been shown to highly correlate with the changes of the deoxy-/oxyhemoglobin ratio (1). Although BOLD MRI indirectly measures neural activity in the tissue, this technique has been used to assess the muscle bioenergetics. The BOLD signal increase can be interpreted as a resultant of deoxyhemoglobin concentration decrease (1). Muscle atrophy in the rheumatoid arthritis (RA) patient is commonly seen that treating this muscle atrophy is important to improve the physical function. NMES has been shown to improve the muscle function as it stimulates all motor units within the field of current regardless of fiber type (2). Up to date, patient needs to undergo muscle biopsy to evaluate the muscle healthiness. In this study, we compared the BOLD signal change during the volitional exercise (VE) and NMES at 3T. In addition, we measured total hemoglobin (tHb), oxy- (HbO_2) and deoxy- (HbO) hemoglobin using near-infrared spectroscopy (NIRS) during VE. Our aim was to validate and interpret the mechanism of the muscle response at these two different settings.

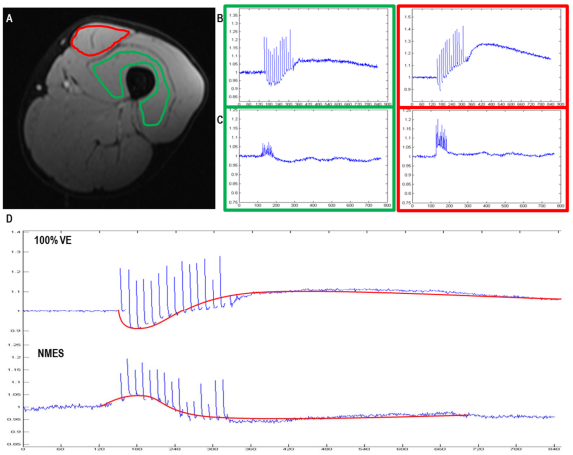

Figure 1 MR imaging of thigh muscle showing RF (red box) and VI (green box). ROIs of RF (red) and VI (green) muscles are manually drawn (A) to plot the time series BOLD SI change during VE (B) and NMES (C). Comparison of VE and NMES, opposite BOLD pattern (red solid lines) measured in subject 1 (D).

[Methods] ***Volition Exercise VS NMES;***

All scans were performed using a 3T whole body scanner (Siemens Medical Imaging, Erlangen, Germany). N = 4 healthy male volunteers (30 – 33 yrs) were recruited for this IRB approved study. The subject was positioned supine and matrix body coil was used for MR imaging. BOLD MRI was acquired during VE on right or left quadriceps and other thigh was used for NMES study. GRE-EPI sequence was used MRI acquisition. During each VE, subjects were asked to produce maximal contraction for 4 sec and rested for 8sec. For the NMES study, the stimulator was turned on for 4 sec and off for 8 sec. Sequence parameters are: TR/TE=1000/36 msec, FA=50°, in-plane resolution=1.95*1.95mm^2, slice thickness=5mm, total scan time= 14 min. Total of 840 data points were acquired (120 points for pre-exercise resting, 180 points for exercise (4 sec contraction 8 sec resting x 15 repetitions) and 540 points for post-exercise resting). Note that the data points acquired during the contraction were discarded due to the motion artifact. Acquired data was then post-process using MATLAB (Mathworks, MA). Rectus Femoris (RF) and Vastus Intermedius (VI) muscle was used for analysis since these two compartments are known to be the primary recruited during the exercise (3). Region of interest (ROI) was manually drawn and normalized time series signal change was plotted. ***NIRS;*** 2 receivers and 4 transmitters were used and sampled at 1.25 Hz to measure the total hemoglobin (tHb), oxy- (HbO_2) and deoxy- (HbO) hemoglobin in the thigh muscle. The experiment paradigm was identical to the MR imaging. Measured parameters were used to predict the BOLD signal and compared with the BOLD MRI. Detail of the BODL calculation can be found in reference 3 and 4.

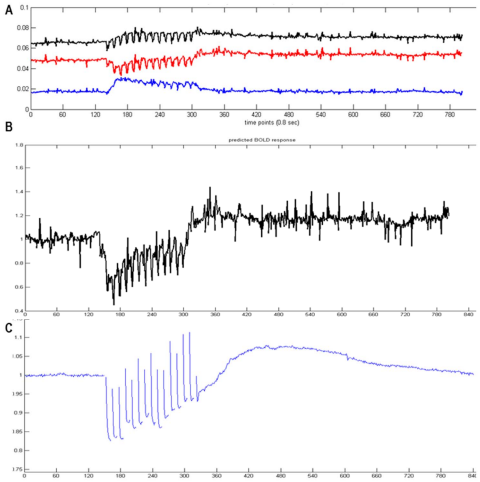

Figure 2 tHb (black), HbO_2 (red) and HbO (blue) concentration measured using NIRS (A). Predicted (B) and measured (C) BOLD SI showing good agreement.

[Results] ***Volition Exercise VS NMES;*** time series BOLD response during the VE and NMES in Rectus Femoris (RF) and Vastus Intermedius (VI) are shown in figure 1. During VE, the signal undershoot (from the baseline) was measured instantly after the first contraction and continued for ~30 sec (~2-3 contractions). After the signal intensity (SI) undershoot, increase of the SI was measured during entire exercise period and peak-SI was measured between ~7-8min at the post-exercise resting. The SI undershoot was 90% in RF and VI whereas the peak-SI measured in the RF was ~130% and VI was ~110% relatively to the baseline. Contrary to the VE, rapid SI increase was measured with absent of undershoot in two muscles. In addition, the peak-SI (~105 and ~110% in VI and RF) was measured during the exercise period and SI decrease started during the exercise and reached the baseline or under the baseline during the post-exercise resting. ***Predicted BOLD signal from NIRS;*** Figure 2 show measured total hemoglobin (tHb), oxy- (HbO_2) and deoxy- (HbO) hemoglobin in time series and calculated BOLD SI during the VE at RF. In the early exercise period, tHb and HbO increased and HbO_2 decreased. At the later stage of the exercise, HbO_2 increased and tHb and HbO decreased.

	Metabolic response dominant (MBV and MBF constant)	MBV response dominant (Metabolism constant)	Volitional Exercise
HbO_2 (oxy-hemoglobin) concentration	decrease	Increase	Decreased and started to increase after ~2-3 contractions
HbO (deoxy-hemoglobin) concentration	increase	decrease	Increased and started to decrease after ~2-3 contractions
So_2 (Oxygen saturation) concentration	decrease	increase	Rapidly decrease during ~2-3 contractions and started to increase

Table 1 Hemoglobin concentration change at metabolic VS MBV driven response.

[Discussion and conclusion] The measurements from the NRIS show that in the early period of contraction (where the SI undershoot is observable), the BOLD SI change is caused by the metabolic response (table1). Afterward, the BOLD SI can be interpreted as a combination of metabolic and muscle blood volume (MBV) increase response (table 1). In NMES study, it is possible that electrical stimulation can affect the MBV increase earlier than the metabolic response (table 1). In conclusion, as a feasibility study of using BOLD MRI to interpret the mechanism of the muscle response at different exercise (VE *VS* NMES), we were able to demonstrate that metabolic response is dominant during the VE at early exercise period and becomes combination of metabolic and MBV response while MBV response is the main source of the BOLD SI during the NMES. Since the BOLD SI can be altered by the habitual activity and pathology, further cross-validation in large population is necessary to accurately interpret the BOLD response which may replace the muscle biopsy for muscle assessment.

[References] (1) Theodore F. Towse et al. J Appl Physiol. 111: 27-39, 2011 (2) Gregory CM et al. Phys Ther. 2005; 85:358-64. (3) Alyaa H. Elzibak et al. Proc. Intl. Mag. Reson. Med. 20 (2012) #3250 (4) valentine et al. Jpurnal of Biomedical Optics 9(2), 413-420, 2004. (5) Buxton et al. NeuroImage 23,220-233.