Cerebral Autoregulation Is Associated With Skeletal Muscle pH in Patients Suffering from Chronic Fatigue Syndrome Both at Rest and During Dynamic Stimulation

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Introduction: Patients suffering from Chronic Fatigue Syndrome (CFS) have a compromised skeletal muscle response to exercise, and a proportion have impairment of maximal mitochondrial function compared to healthy controls18. Almost 90% of CFS patients describe orthostatic symptoms and autonomic nervous system dysfunction is a frequent finding. The severity of autonomic dysfunction has been shown to be correlated with impairment of skeletal muscle pH handling7. We have already confirmed that those with the skeletal muscle abnormality were significantly more likely to have concurrent impaired cardiac energetics9 and we therefore set out to determine whether this skeletal and cardiac muscle phenotype of CFS is associated with central nervous system abnormality, in particular cerebral vascular regulation. It has been shown that CFS patients have reduced cerebral blood flow (CBF) and orthostatic intolerance is associated with prolonged cerebral vascular constriction after autonomic challenge13. We therefore hypothesised that if CFS has a central mediating factor then there would be a correlation between the pH handling in skeletal muscle and cerebral vascular regulation in CFS patients. We performed arterial spin labelling (ASL) MRI to measure CBF in the brain and 13P MRS to probe skeletal muscle pH at rest.

The Valsalva manoeuvre (VM) is a physiological stressor which the subject exhales forcefully into a closed space12 resulting in a phased response in CBF and blood pressure, BP (Figure 1b), which can be used to test autonomic function. In skeletal muscle, plantar flexion exercise has been shown to expose pH handling abnormality in CFS patients2. We conducted functional MRI (fMRI), during which the patient performed the VM, as well as performed 13P MRS to measure recovered pH after plantar flexion exercise.

Methods: Seventeen consecutive CFS patients were recruited from the local CFS Clinical Service based at the Newcastle upon Tyne Hospitals NHS Foundation Trust. All participants fulfilled the Fukuda diagnostic criteria for CFS. The study was performed on a 3T whole body MR scanner (Achieva, Philips Medical Systems, the Netherlands). This study was approved by the Newcastle and North Tyneside Local Ethics Committee. All the brain scans were performed in a single session for each patient, using a body coil for transmission and an 8 channel head coil as a receiver.

Resting CBF: Resting CBF was measured using an ASL based sequence,11,12 with spiral readout module, TE of 11.13 ms, TR of 4 s, 4 × 4 mm2 in-plane resolution, FOV of 256 × 256 mm2, 30 averages and inflow time of 1500 ms. The image volume covered 14 contiguous slices of 6 mm thickness, which was positioned parallel to the anterior commissure (AC) – posterior commissure (PC) line and centred at the corpus callosum. Images were processed in SPM8 to correct for patient movement16. A grey matter mask, generated from anatomical images, was applied to the perfusion weighted images, and subsequently the grey matter CBF was quantified16.

Functional MRI: To investigate the effect of the VM on the cerebral circulation, subjects underwent a fMRI study with a stimulus paradigm shown in Figure 1a. Functional MRI was used a short TE GE EPI sequence. An imaging volume was selected parallel to the AC-PC line and centred at the anterior part of the corpus callosum (20 slices, 4 mm thickness, 2.1 × 2.1 mm2 in-plane resolution, 112 × 112 matrix size, TR of 2 s, TE of 14 ms). The signal based on short echo time is mainly sensitive to the tissue water density and hence transient changes in this signal during stimulation can reflect the vascular dilation7. Instructions to begin and end each VM were visually presented to the subject in the scanner via a projection system. During the VM, subjects were instructed to maintain an exhaled air pressure of 40 mmHg and were presented with graphical real-time pressure feedback. Functional MRI were processed using an fMRI time course analysis pipeline. The processing routine involved grey matter time courses for each individual subject15. The time and magnitude of the characteristic peak were measured (Figure 1b).

Muscle MRS: Phosphorus MRS data acquisition was performed on a different day to brain imaging, to avoid potential physiological interference between VM and skeletal muscle exercise. MRS data acquisition and quantification4-16 were performed in the same manner as our previous work17. The exercise protocol is shown in Figure 2a, with a fixed load of 35% of the maximum voluntary contraction12. From the pre-exercise baseline spectra (marked as “static” in Figure 2a), the resting pH was measured. To avoid muscular adaptation effects15,16, the recovered pH was obtained from the rest period after two plantar flexion cycle (marked as “dynamic” in Figure 2a).

Results: The time course showing the mean fMRI signals averaged across the subjects is shown in Figure 1c and shows the multiple phases seen in BP response (Figure 1b)20. Under resting conditions, CBF in this CFS group was significantly correlated with skeletal muscle resting pH (r = -0.67, p = 0.0096 corrected for multiple comparisons). Further, under stimulated conditions there was also significant correlation (r = 0.68, p = 0.0075 corrected for multiple comparisons) between the duration of vasomotor constriction after VM (Figure 1c) and the recovered pH (Figure 2a).

Discussion: This study explored the relationship between peripheral and central function in a series of patients with CFS and found that cerebral vascular regulation and skeletal muscle pH management are closely related, both at rest and when responding to dynamic stimulation in CFS patients. The negative correlation between CBF and skeletal muscle pH at rest indicates that higher skeletal muscle acidity is associated with higher CBF at rest. The positive correlation between recovered pH in skeletal muscle and the duration of vasomotor constriction after VM indicates that higher skeletal muscle acidity after recovery period is associated with a shorter vascular constriction after VM. It is clear from this work that cerebral vascular regulation and skeletal muscle pH management are closely related, both at rest and dynamic stimulation in CFS patients, and the underlying CFS mechanism may be systemic.

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Reference