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

Jiabao He[1], Kieren G Hollingsworth[1], Julia L Newton[2], and Andrew M Blamire[1]

[1]*Newcastle Magnetic Resonance Centre, Newcastle University, Newcastle upon Tyne, Tyne and Wear, United Kingdom,* [2]*Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, Tyne and Wear, United Kingdom*

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 controls[1,2]. Almost 90% of CFS patients describe orthostatic symptoms[3] and autonomic nervous system dysfunction is a frequent finding[1]. The severity of autonomic dysfunction has been shown to be correlated with impairment of skeletal muscle pH handling[2]. We have already confirmed that those with the skeletal muscle abnormality were significantly more likely to have concurrent impaired cardiac energetics[4] 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)[5] and orthostatic intolerance is associated with prolonged cerebral vascular constriction after autonomic challenge[6]. 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 ^{31}P MRS to probe skeletal muscle pH at rest.
The Valsalva manoeuvre (VM) is a physiological stressor which the subject exhales forcefully into a closed space[7,8] 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 patients[2]. We conducted functional MRI (fMRI), during which the patient performed the VM, as well as performed ^{31}P MRS to measure recovered pH after plantar flexion exercise.

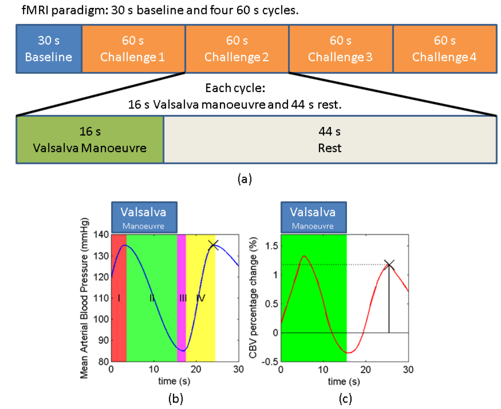

Figure 1 shows (a) fMRI paradigm, (b) schematic MABP response and (c) mean fMRI time course.

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 mm^2 in-plane resolution, FOV of 256 × 256 mm^2, 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 movement[10]. A grey matter mask, generated from anatomical images, was applied to the perfusion weighted images, and subsequently the grey matter CBF was quantified[13].
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 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 mm^2 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 dilation[9]. 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 MR images were processed to obtain the average fMRI signal time courses in global grey matter for each individual subject[10]. The time and magnitude of the characteristic peak were measured (Figure 1b).

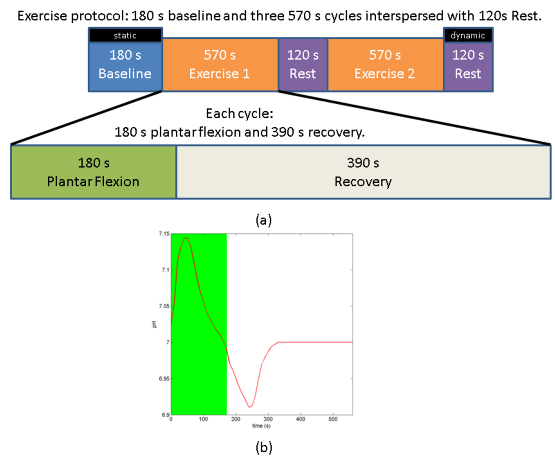

Figure 2 shows (a) plantar flexion protocol and (b) schematic pH time course.

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 quantification[14-16] were performed in the same manner as our previous work[17]. The exercise protocol is shown in Figure 2a, with a fixed load of 35% of the maximum voluntary contraction[17]. From the pre-exercise baseline spectra (marked as "static" in Figure 2a), the resting pH was measured. To avoid muscular adaptation effects[18,19], 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 comparison) between the duration of vascular 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 vascular 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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