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Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation

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ABSTRACT

Cerebral blood flow (CBF) is maintained despite changing systemic blood pressure through cerebral vascular control, with such tight regulation believed to be under local tissue control. Chronic fatigue syndrome (CFS) associates with a wide range of symptoms, including orthostatic intolerance, skeletal muscle pH abnormalities and cognitive impairment. CFS patients are known to have reduced CBF and orthostatic intolerance associates with abnormal vascular regulation, while skeletal muscle pH abnormalities associate with autonomic dysfunction. These findings point to autonomic dysfunction as the central feature of CFS, and cerebral vascular control being influenced by factors outside of the brain, a macroscopic force affecting the stability of regional regulation. We therefore explored whether there was a physiological link between cerebral vascular control and skeletal muscle pH management in CFS.

Seventeen consecutive CFS patients fulfilling the Fukuda criteria were recruited from our local CFS clinical service. To probe the static scenario, CBF and skeletal muscle pH were measured at rest using MRI and ^{31}P magnetic resonance spectroscopy (^{31}P-MRS).

To examine dynamic control, brain functional MRI was performed concurrently with Valsalva manoeuvre (VM), a standard autonomic function challenge, while ^{31}P-MRS was performed during plantar flexion exercise.

Significant inverse correlation was seen between CBF and skeletal muscle pH at rest ($r = -0.67$, $p < 0.01$). Prolonged cerebral vascular constriction during the sympathetic phase of VM was associated with higher pH in skeletal muscle after plantar flexion exercise ($r = 0.69$, $p < 0.008$).

In conclusion, cerebral vascular control is closely related to skeletal muscle pH both at rest and after dynamic stimulation in CFS.

1. Introduction

Cerebral blood flow (CBF) is maintained at a constant level across a range of blood pressure (BP) (Lassen, 1964). Although the cerebral vascular control mechanism is local in healthy subjects, it is affected by conditions such as hypertension (Immink et al., 2004) and chronic fatigue syndrome (CFS) (Sutcliffe et al., 2010).

Although CFS (Evengard et al., 1999; Sanders and Korf, 2008) is classified as a nervous system disease, its cause is unknown, and a number of factors have been shown to be related to the disease progression (Afari and Buchwald, 2003). Almost 90% of CFS patients describe orthostatic symptoms (Newton et al., 2007) and autonomic dysfunction is a frequent finding (Hollingsworth et al., 2010a). CFS patients have reduced CBF (Biswal et al., 2011) and orthostatic intolerance is associated with prolonged cerebral vascular constriction after autonomic challenge (Lin et al., 2011). In our own studies, we have shown effects in peripheral tissue including compromised skeletal muscle response to exercise, with CFS patients generating higher levels of acid within their muscle compared to matched sedentary controls (Hollingsworth et al., 2010a; Jones et al., 2010). We have also already confirmed that those CFS patients with the skeletal muscle abnormality were significantly more likely to have concurrent impaired cardiac energetics (Hollingsworth et al., 2012) and that the impairment of skeletal muscle pH handling correlates with the autonomic dysfunction (Jones et al., 2010). In combination, this data suggests that autonomic dysfunction is a central feature of CFS, indictable by pH handling measurement in skeletal muscle.

Given its local nature, we hypothesise that cerebral vascular control in CFS is affected by autonomic dysfunction, and this relationship

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would manifest itself in a correlation between the pH handling in skeletal muscle and cerebral vascular control.

To test our hypothesis in a resting state we performed arterial spin labelling (ASL) magnetic resonance imaging (MRI) to measure CBF in the brain and used ^{31}P magnetic resonance spectroscopy (MRS) to probe skeletal muscle pH.

The Valsalva manoeuvre (VM) has been widely used to identify deficits in autonomic and cardiac function (Remmen et al., 2006; Woo et al., 2007) as it induces phased changes in BP (Dawson et al., 1999) (Fig. 1b). In particular, sympathetic function is characterised by a rapid increase in BP at the end of the VM (marked "x" in Fig. 1b). The vascular dilation associated with sympathetic function can be detected by functional MRI (fMRI), tailored to reflect transient changes in blood volume (Glover et al., 1996). Plantar flexion exercise demonstrated a skeletal muscle pH handling abnormality in CFS patients (Jones et al., 2010). The recovery of pH in skeletal muscle after exercise is assisted by modulated blood flow through changing vascular calibre, a factor influenced by the autonomic function.

To examine the relationship between cerebral vascular control and skeletal muscle pH handling in response to dynamic stimulation, we explored the relationship between cerebral vascular parameters during the VM through fMRI and skeletal muscle pH during plantar flexion exercise through ^{31}P MRS.

2. 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 CDC 1994 (Fukuda) diagnostic criteria for CFS (Fukuda et al., 1994). The study was reviewed and approved by the Newcastle and North Tyneside Local Ethics Committee. The sponsor was Newcastle upon Tyne Hospitals NHS Foundation Trust and all participants provided written informed consent prior to the experiment. The study was performed on a 3 T whole body MR scanner (Achieva, Philips Medical Systems, The Netherlands). Two separate appointments were made for each patient to look at the brain and skeletal muscle, with a median time gap of 18 days.

2.1. Brain imaging

All the brain scans were performed in a single session for each patient using an 8 channel SENSE coil. Scans included 3D T_1 weighted anatomical images, resting CBF maps and dynamic imaging of the VM in a functional MRI study.

2.1.1. Anatomical images

Anatomical images in sagittal orientation were acquired using a standard T_1 weighted clinical protocol with a resolution of $1\times1\times1.2$ mm^3, field of view (FOV) of $240\times240\times216$ mm^3, repetition time (TR) of 8.1 ms and echo time (TE) of 4.6 ms. Segmentation in SPM8 (Frackowiak, 2004) was performed on the anatomical images to generate patient specific grey matter masks.

2.1.2. Resting CBF mapping

Resting CBF was measured using an arterial spin labelling (ASL) based sequence (Kim, 1995; He and Blamire, 2010), 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 (Frackowiak,

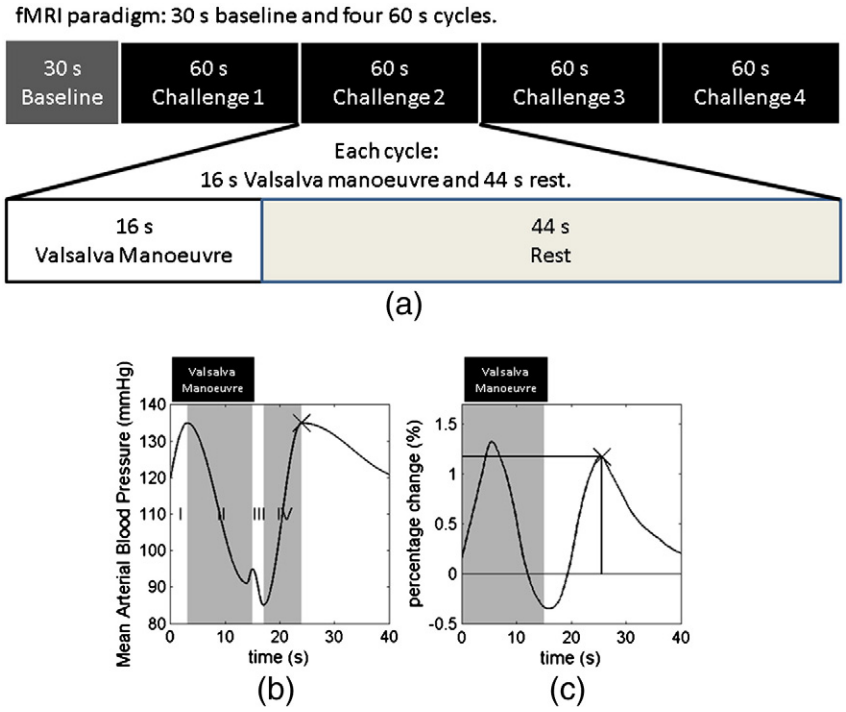

Fig. 1. Shows (a) the schematic paradigm of the fMRI experiment, (b) the schematic diagram illustrating the mean arterial blood pressure (MABP) time course during the four phases of Valsalva manoeuvre, and (c) the group mean of cycle averaged time course measured in fMRI experiment. The fMRI paradigm was composed of 30 s baseline and four 1 min cycles. Each cycle was composed of 16 s Valsalva manoeuvre and 44 s rest. The BP response is divided into four phases, each labelled in different shades and marked as "I", "II", "III" and "IV". The characteristic peak associated with sympathetic function is marked by "x". The fMRI protocol monitors a signal related to cerebral vascular dilation. Individual time courses were normalised to their respective baseline signal level to derive the percentage change time course. The onset of the Valsalva manoeuvre is aligned to 0 s, while its duration is marked by the grey window. For each time course, the peak associated with sympathetic function, marked by "x", was identified, with its time (dotted line) and magnitude (solid line) measured.