

Prefrontal cortex oxygenation during incremental exercise in chronic fatigue syndrome

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Summary

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This study examined the effects of maximal incremental exercise on cerebral oxygenation in chronic fatigue syndrome (CFS) subjects. Furthermore, we tested the hypothesis that CFS subjects have a reduced oxygen delivery to the brain during exercise. Six female CFS and eight control (CON) subjects (similar in height, weight, body mass index and physical activity level) performed an incremental cycle ergometer test to exhaustion, while changes in cerebral oxy-haemoglobin (HbO₂), deoxy-haemoglobin (HHb), total blood volume (tHb = HbO₂ + HHb) and O₂ saturation [tissue oxygenation index (TOI), %] was monitored in the left prefrontal lobe using a near-infrared spectrophotometer. Heart rate (HR) and rating of perceived exertion (RPE) were recorded at each workload throughout the test. Predicted VO_{2peak} in CFS (1331 ± 377 ml) subjects was significantly ($P \leq 0.05$) lower than the CON group (1990 ± 332 ml), and CFS subjects achieved volitional exhaustion significantly faster (CFS: 351 ± 224 s; CON: 715 ± 176 s) at a lower power output (CFS: 100 ± 39 W; CON: 163 ± 34 W). CFS subjects also exhibited a significantly lower maximum HR (CFS: 154 ± 13 bpm; CON: 186 ± 11 bpm) and consistently reported a higher RPE at the same absolute workload when compared with CON subjects. Prefrontal cortex HbO₂, HHb and tHb were significantly lower at maximal exercise in CFS versus CON, as was TOI during exercise and recovery. The CFS subjects exhibited significant exercise intolerance and reduced prefrontal oxygenation and tHb response when compared with CON subjects. These data suggest that the altered cerebral oxygenation and blood volume may contribute to the reduced exercise load in CFS, and supports the contention that CFS, in part, is mediated centrally.

Introduction

The underlying pathophysiology of chronic fatigue syndrome (CFS) has long baffled clinicians and medical practitioners. Typical symptoms include persistent fatigue, with sleep disturbances, neurocognitive difficulties, joint and muscle soreness and numerous other symptoms (Fukuda et al., 1994). Although CFS affects both men and women of various ethnic backgrounds and from childhood to adulthood, the syndrome is more commonly diagnosed in females (Fukuda et al., 1994; Yamamoto et al., 2003).

Although CFS has now been accepted as a medical condition, subjective symptoms are the primary focus of the currently used diagnostic criteria. As a result, the pathophysiology, aetiology and pathogenesis of the disease are still not clearly understood (Chaudhuri & Behan, 2004; Siemionow et al., 2004b), as

comorbidity (i.e. fibromyalgia) can influence the patients response to physical and cognitive assessment (Cook et al., 2005, 2006). In past research, it has been noted that CFS subjects may exhibit immune (Nijs et al., 2004b), metabolic (McCully & Natelson, 1999), endocrine and an autonomic dysfunction possibly originating in the central nervous system (Pagani & Lucini, 1999; Tanaka et al., 2002). Recently, Wallman et al. (2004a) suggested that the reduced exercise tolerance in CFS is the result of the impairment in the mechanisms that constitute effort sense and/or to avoidance behaviours that result in a reluctance by these subjects to exercise to full capacity. More recently, Wallman et al. (2005) examined the relationship between physiological, psychological and cognitive variables and determined that their data supported a central, as opposed to a peripheral, basis to the sensation of fatigue in CFS. Others have also suggested that central factors contribute to the reduced

exercise capacity in CFS (Kent-Braun et al., 1993; Georgiades et al., 2003).

Recently, it has been shown that near infrared spectroscopy (NIRS), a non-invasive optical technique, can be used to measure tissue oxygenation and blood volume changes during exercise and during standardized motor and cognitive tasks, and recent reviews on its application to exercise science have been reported for both muscle and brain tissue (Ferrari et al., 2004; Neary, 2004). Spatially resolved (or multi-distance) spectroscopy (SRS) is based on the attenuation (intensity) of light as it passes into the tissue and is measured at several different source-detector distances (Wolf et al., 2003, 2007). Thus, SRS-NIRS can be used to monitor quantitative changes in tissue HbO₂ saturation (independent of blood volume changes). With the recent collection of research data to suggest apparent oxygen impairment in skeletal muscles of CFS subjects (McCully & Natelson, 1999; McCully et al., 2004), NIRS presents both clinicians and researchers the opportunity to effectively observe and analyse changes in cortical tissue HbO₂ saturation. However, limited research is available that has examined regional cerebral blood flow and oxygenation changes in CFS (Schwartz et al., 1994; Tanaka et al., 2002), and no research to our knowledge is available on cortical tissue HbO₂ saturation in CFS subjects during maximal incremental exercise. Thus, NIRS represents a novel technique that can be used during maximal exercise and can be applied to examine central O₂-dependent mechanisms possibly implicated in CFS (Tanaka et al., 2002).

Therefore, the purpose of this study was to examine the effects of maximal incremental exercise to the limits of tolerance on quantitative changes in cerebral oxygenation and blood volume in CFS subjects. Based on previous findings in the literature that cerebral blood flow and oxygenation are altered in CFS during orthostatic testing (Tanaka et al., 2002; Yoshiuchi et al., 2006), we hypothesized that cerebral oxygenation measured from the prefrontal cortex would also be reduced in CFS subjects in comparison with controls under conditions of maximal incremental exercise.

Methods

Subjects

After ethical approval by a university ethics review committee, physician-referred female subjects were recruited for the CFS ($N = 6$) group. A summary of symptoms displayed by the CFS group is found in Table 1. The inclusion criteria for the CFS group were in accordance with the Center for Disease Control (Fukuda et al., 1994). Control (CON; $N = 8$) subjects were then recruited and matched for physical characteristics between the CFS and CON, making the groups similar for height, weight, body mass index (BMI), and current physical activity level (Table 2). The physical activity and history form was completed by all subjects and a numerical value was calculated [Canadian Physical Activity, Fitness and Lifestyle Approach, page 8–59 (CSEP 2004)]. All subjects signed written

Table 1 Summary of symptoms exhibited by chronic fatigue syndrome group.

Symptom	<i>N</i>	%
Impaired short-term memory or concentration	6	100
Sore throat	5	83.3
Tender cervical or axillary lymph nodes	5	83.3
Muscle pain	6	100
Multi-joint pain without arthritis	5	83.3
Headaches of a new type, pattern or severity	4	66.7
Unrefreshing sleep	6	100
Postexertional malaise lasting more than 24 h	6	100

Table 2 Summary of descriptive and resting physiological data for chronic fatigue syndrome (CFS) and control (CON) subjects.

Variable	CFS	CON
Age (years)	39 ± 13	27 ± 7
Height (m)	1.57 ± 0.3	1.62 ± 0.1
Weight (kg)	67 ± 20	66 ± 8
BMI	26 ± 4	25 ± 3
HR _{rest} (bpm)	94 ± 10	79 ± 10*
BP _{sys} (mmHg)	119 ± 14	112 ± 5
BP _{dia} (mmHg)	80 ± 9	76 ± 5
FSS	59 ± 5	27 ± 15*
Diagn _{months}	104 ± 44	0*
Physical activity level (sessions per week)	<1	<1

BMI, body mass index; HR_{rest}, resting heart rate; HR_{max}, heart rate maximum; FSS, fatigue severity scale; Diagn_{months}, how many months the subject has been diagnosed; physical activity level = sessions per week of 1.5 metabolic equivalent or greater.

*Significant group difference ($P \leq 0.05$).

informed consent forms after a complete description of the study, and were assured anonymity. All subjects were confirmed CFS by the referring rheumatologist in accordance with guidelines established by the Centre for Disease Control (Fukuda et al., 1994). Thus, we controlled for other comorbidity illnesses (i.e. fibromyalgia) as this has demonstrated an altered cognitive performance in comparison with CFS-only subjects following exercise (Cook et al., 2005).

Exercise modality and protocol

Cycle ergometry was chosen primarily for safety reasons for this group of subjects using a calibrated Monark cycle ergometer (Model 818E, Monark, Kroonsvag, Sweden). Testing took place in a comfortable exercise laboratory centre (20°C, relative humidity 30%) during a single 1-h testing session, with the participants instructed to continue exercising (and encouraged with verbal support) as long as possible during the graded cycle ergometer maximal test. NIRS was used to monitor prefrontal cortex tissue oxygenation and blood volume changes. The participants were asked to cycle at 60 rev min⁻¹ at an initial power output of 30 W for 3 min to warm up. Thereafter, all subjects cycled at 60 W for a period of 2 min, followed by a

workrate increase of 25 W every 2 min until exhaustion. This workrate was selected to obtain total exercise duration between approximately 8 and 14 min to avoid local muscle fatigue owing to deconditioning (Nijs et al., 2004b). All subjects were given strong verbal encouragement by the researchers to continue exercise as long as possible. At the end of every workload stage, the Rating of Perceived Exertion [RPE; (Borg, 1982)] was assessed along with heart rate (Polar HR Monitor, Finland). Finger prick samples for capillary-venous blood lactate (BLa, mM) was measured at rest and immediately postexercise using a Lactate Pro Analyser (H&P/Cosmos Sports & Medical GMBH, Nussdorf-Traunstein, Germany), which has been validated previously (Pyne et al., 2001). At the conclusion of the cycling exercise protocol, all subjects were asked to conform to a standardized resting, upright position with the hands on the handlebars and the feet remaining stationary on the pedals for 4 min. This passive recovery period was followed by allowing all subjects to cycling at 30 W for a period of 4 min for a cool down.

A predicted VO_{2peak} was calculated using American College of Sports Medicine (ACSM) Guidelines for Exercise Testing and Prescription for the control subjects (ACSM 2000), and the regression equation ($VO_{2peak} = 10.47 \times WR_{peak} + 284.1$; where VO_2 is given in $ml\ min^{-1}$ and WR in Watts) established by Nijs and De Meirleir (Nijs & De Meirleir, 2004a) was used to calculate VO_{2peak} for the CFS group. We also compared peak values by applying the same predictive equations (i.e. ACSM versus Nijs and De Meirleir) for each group data set to ensure that we were making an accurate comparison between groups. There was no significant difference for the within group comparison (regardless of formulae used), but the same statistically significant difference was found between the two groups (Table 3). This further supports research by Nijs et al. (2007) that used submaximal exercise to predict peak exercise performance in CFS.

Near-infrared spectroscopy and probe placement

The detection and emission probes of an SRS near-infrared spectrophotometer (NIRO-300; Hamamatsu Photonics, Japan) were separated by 5 cm allowing for approximately 2.5-cm

penetration depth with the near-infrared light (Bhambhani et al., 2007). The probe was fixed in place by using a dense rubber vinyl holder that also eliminated any incidental room light. It was placed over the left frontal lobe (1 cm above the eyebrow and 1 cm to the left of the skull centre) (Bhambhani et al., 2007), and held in place using double adhesive tape and a tensor bandage. The prefrontal lobe was chosen as it has been previously studied during exercise (Bhambhani et al., 2007), and has shown a linear relationship between frontal lobe oxygenation and exercise intensity in healthy subjects (Ide & Secher, 2000). In addition, single-positron-emission computed tomography imaging has shown that regional cerebral blood flow is altered in the frontal lobe of CFS subjects under resting conditions (Ichise et al., 1992).

The NIRO-300 uses laser light at four wavelengths (775, 810, 850, 905 nm) to calculate relative concentration changes in oxy-haemoglobin (HbO_2), deoxy-haemoglobin (HHb) and total blood volume (tHb = $HbO_2 + HHb$) using the modified Beer-Lambert Law (Ferrari et al., 2004). Tissue oxygenation index (TOI), a measure of oxygen saturation and independent of blood volume changes, can also be monitored (TOI, % = HbO_2/tHb) using the NIRO-300. A differential pathlength factor (DPF) was not used in this study, and thus values for HbO_2 , HHb and tHb are reported as relative quantitative changes in concentration from the baseline ($\mu M\ cm$). NIRS data during the recovery phase was only collected for 60 s and then removed for convenience of the subjects.

Statistical analyses

In this comparative study, data were presented in terms of central tendency and variability (as means and SD). Comparison of data between CFS and CON was performed by using a one-way analysis of variance (ANOVA) using a repeated measures design (HbO_2 , HHb, tHb and TOI). One-way ANOVA was used to determine other physiological (VO_{2peak} , HR_{max} , BLa) differences between groups. A Levene's test for equality of variances was used to present the data with 'equal variances assumed' and 'equal variances not assumed'. All statistical analyses were done using SPSS v11.5, and the alpha level for significance was set at $P \leq 0.05$.

Results

Subjects and cardiovascular responses

All subjects in this study were female and were asked to indicate their symptoms (Table 1) as outlined by the 1994 Centre for Disease Control diagnostic criteria for CFS (Fukuda et al., 1994). Six of the 14 subjects who participated in the study had been physician-diagnosed with CFS (Fukuda et al., 1994). CON and CFS subjects were deemed sedentary upon completing a physical activity inventory (CSEP 2004). A summary of the descriptive (Table 2) and maximal physiological data (Table 3) for all subjects are presented. When the group VO_{2peak} values were

Table 3 Summary of exercise capacity and physiological strain for the chronic fatigue syndrome (CFS) and control (CON) during the incremental exercise test at maximal exercise.

Variable	CFS	CON
TTE (s)	351 ± 223	716 ± 175*
HR_{max} (beats min^{-1})	154 ± 13	186 ± 11*
Predicted VO_{2peak} ($ml\ min^{-1}$)	1331 ± 377	1990 ± 332*
Predicted VO_{2peak} ($ml\ kg^{-1}\ min^{-1}$)	23.8 ± 10	33.0 ± 3*
PO_{max} (Watts)	100 ± 39	163 ± 34*

TTE, time to exhaustion (s); HR_{max} , maximal heart rate (beats min^{-1}); PO_{max} , maximal power output (Watts).

*Significant group difference ($P \leq 0.05$).

compared using the same prediction equation, no significant differences were found. For the CFS group, VO_{2peak} coefficient of variation (CV) was 14.7%, and percentage (%) change between the two equations (ACSM 2000) versus (Nijs & De Meirleir, 2004a) was 6.9% with a Pearson $r^2 = 0.96$. For the CON group, these values were 17.8%, 8.9% and 0.99%, respectively.

Prefrontal cerebral oxygenation

Figures 1–4 demonstrate the trend in the group means (\pm SD) for the NIRS variables measured for the CFS and CON subjects. During incremental exercise, there was a gradual increase ($P \leq 0.05$) in HbO_2 and tHb from rest until approximately 90% of time to exhaustion (TTE), and then a plateau or levelling off to maximal

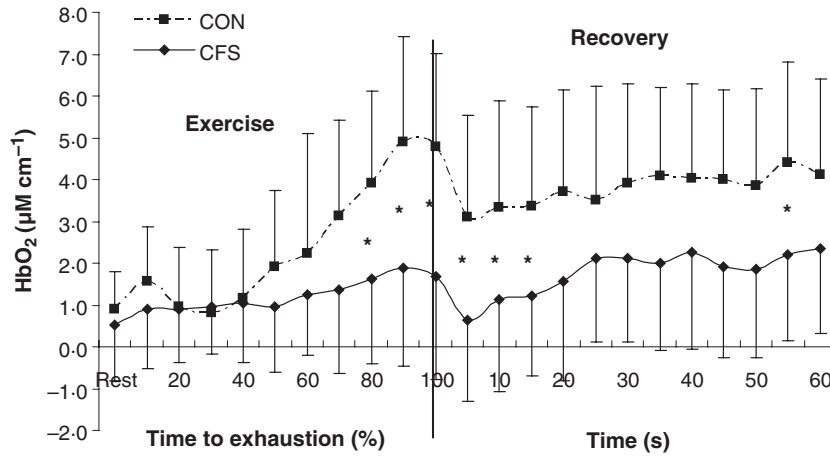


Figure 1 Left prefrontal cortex oxy-haemoglobin changes (HbO_2 ; $\mu M cm$) in the chronic fatigue syndrome (CFS) and control (CON) subjects during continuous incremental maximal exercise and resting recovery. *Significant differences ($P \leq 0.05$) between the CFS and CON during exercise and recovery.

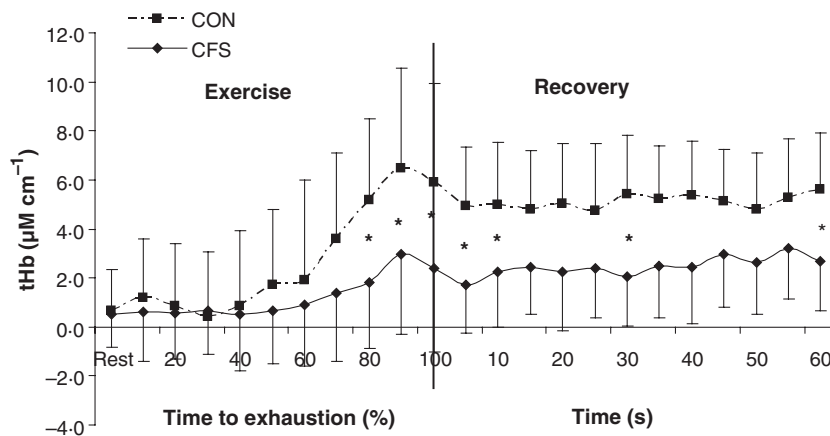


Figure 2 Left prefrontal cortex total blood volume changes (tHb; $\mu M cm$) in the chronic fatigue syndrome (CFS) and control (CON) subjects during continuous incremental maximal exercise and resting recovery. *Significant differences ($P \leq 0.05$) between the CFS and CON during exercise and recovery.

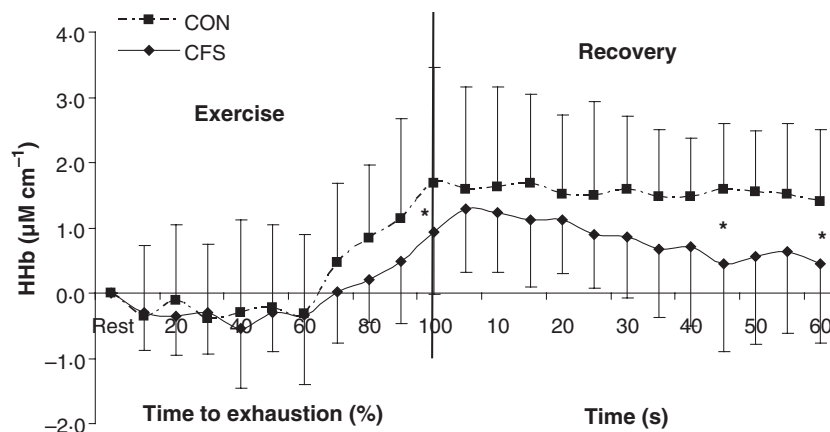


Figure 3 Left prefrontal cortex deoxy-haemoglobin changes (HHb; $\mu M cm$) in the chronic fatigue syndrome (CFS) and control (CON) subjects during continuous incremental maximal exercise and resting recovery. *Significant differences ($P \leq 0.05$) between the CFS and CON during exercise and recovery.

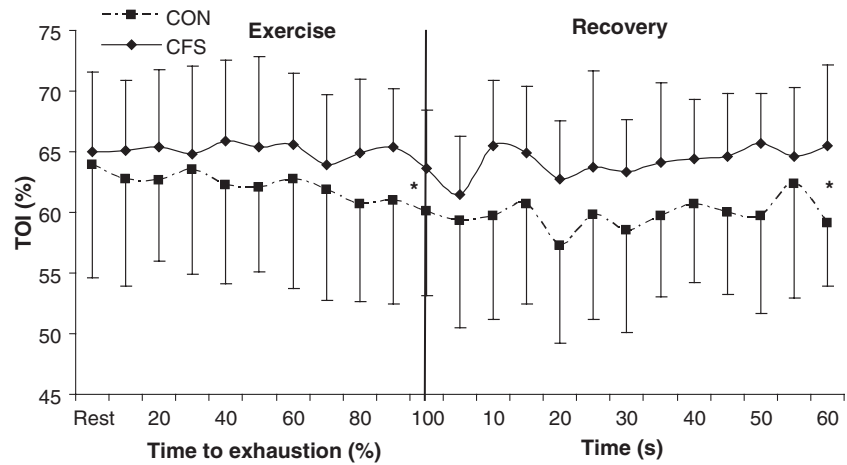


Figure 4 Left prefrontal cortex tissue oxygenation index (TOI %) in the chronic fatigue syndrome (CFS) and control (CON) subjects during continuous incremental maximal exercise and resting recovery. *Significant differences ($P \leq 0.05$) between the CFS and CON during exercise and recovery.

exercise was noted for both groups. However, the deoxy-Hb (HHb) continued to increase significantly from resting values in both groups until exercise was stopped. For the variable TOI (%), a reflection of the dynamic balance between O_2 supply and O_2 consumption, there was a gradual decrease with incremental exercise to volitional fatigue in both groups. During maximal exercise HbO_2 , HHb, tHb and TOI% were all significantly different ($P \leq 0.05$) between the CFS and CON group, with the CFS subjects having less relative quantitative change overall (HbO_2 : CFS = 0.51 ± 1.33 to $1.68 \pm 2.47 \mu M cm$, CON = 0.91 ± 0.89 to $4.91 \pm 2.24 \mu M cm$; HHb: CFS = 0 ± 0.59 to $0.94 \pm 0.96 \mu M cm$, CON = 0 ± 1.09 to $1.69 \pm 1.76 \mu M cm$; tHb: CFS = 0.51 ± 1.32 to $2.99 \pm 3.31 \mu M cm$, CON = 0.64 ± 1.72 to $6.49 \pm 4.04 \mu M cm$; TOI: CFS = 65.0 ± 6.6 to $63.7 \pm 4.8\%$, CON = 63.9 ± 9.3 to $60.1 \pm 7.0\%$). During recovery, there was an initial decline for the first 10–15 s and then a plateau or slight increase until recovery to 60 s. All variables demonstrated a significant difference between the CFS and CON groups during the recovery period.

Perception of effort

As a way to compare the actual and perceived exertion of the subjects during the incremental exercise test, the heart rate to rating of perceived exertion ratio (HR:RPE) was used (Fig. 5). Significant differences were observed during submaximal exercise at the first three workloads. These workloads were compared because all subjects, CFS and CON, were able to complete this quantity of physical work. However, HR was not different between groups at these three (30, 60, 85 W) workloads.

Discussion

Using NIRS, the results of this study are the first to our knowledge to demonstrate the novel findings that cerebral oxygenation and blood volume changes in female CFS subjects

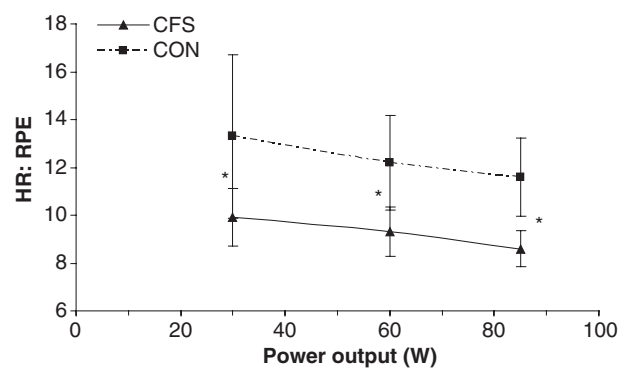


Figure 5 Group comparison of heart rate:rating of perceived exertion (HR:RPE) ratio at the same absolute power output. *Significant differences ($P \leq 0.05$) between the chronic fatigue syndrome and control.

were significantly different from control subjects during incremental maximal exercise. These data support previous research that cerebral oxygenation is reduced in CFS under other experimental conditions (i.e. orthostatic intolerance test) (Tanaka et al., 2002), and support our hypothesis that cerebral differences exist between CFS and sedentary control subjects. Collectively, these data suggest that there is a link between impaired cerebral oxygenation and chronic fatigue during a maximal exercise challenge.

Cerebral oxygenation and haemodynamics

The interpretation of our NIRS data is as follows: first, during incremental exercise, there was an activation of the brain as reflected by the increased HbO_2 , tHb, HHb and decreased TOI% (reflecting increased O_2 extraction) in both groups (Figs 1–4). Previous research has shown that changes in cerebral oxygenation is a reflection of neuronal activation (Ferrari et al., 2004; Bhambhani et al., 2007). Second, there was a significant difference (i.e. less change) in cerebral HbO_2 , tHb and HHb in the CFS versus the CON subjects. In addition, TOI decreased to a greater extent in the CON group than the CFS group (by 64.5%). Taken together, these results indicate that blood flow

was likely compromised during incremental exercise in the CFS subjects, as reflected by less change in tHb (NIRS-generated tHb has been used as an indirect measure of blood flow (Nioka et al., 2006), and less oxygen transport and utilization (extraction) by the brain (as reflected by the lesser change in HbO₂ and HHb in the CFS group).

It is well accepted that oxygen uptake is increased in the brain during exercise (Ide & Secher, 2000; Ferrari et al., 2004; Bhambhani et al., 2007; Wolf et al., 2007) when monitored using NIRS. Of the NIRS variables calculated, TOI is one of the most reliable parameters as it reflects the dynamic balance between O₂ consumption and utilization, and is independent of the pathlength of near-infrared photons in cerebral tissue (Ferrari et al., 2004). In this study, there was a 3.8% decrease in TOI in the CON group, in comparison with only 1.3% decrease in the CFS group during the exercise period (Fig. 4). This equates to a 64.5% difference in the amount of O₂ extraction between the two groups. In support of our observations, and under conditions of orthostatic intolerance, Tanaka et al. (2002) also used non-invasive NIRS to show that the majority of the CFS subjects in their study had decreased oxy-Hb concentration ([oxy-Hb]) in the brain during upright posture. They hypothesized that a reduced perfusion pressure and cerebral vasoconstriction may partly explain the reduction in [oxy-Hb]. This would support recent research by Rasmussen et al. (2007), which showed that a reduced cerebral oxygen delivery had a direct effect on motor performance. Thus, it is likely that the impaired motor performance demonstrated in that study (Rasmussen et al., 2007) as a result of the inadequate oxygen delivery to the brain resulted in the observed early onset of central fatigue that we observed in our CFS subjects in the current study, as demonstrated by the reduction in HbO₂, tHb and HHb in comparison with the CON subjects.

Research has shown that cerebral blood flow is reduced in subjects with CFS when using transcranial Doppler sonography (Ichise et al., 1992; Yoshiuchi et al., 2006). In particular, Ichise et al. (1992) showed a significant blood-flow reduction in multiple regions of the brain of CFS subjects, including the prefrontal cortex. Some have suggested that this reduction in blood flow is related to an autonomic (cerebral autoregulation) dysregulation also noted in subjects exhibiting neurally mediated syncope under a number of different experimental conditions (Stewart et al., 1998; Yamamoto et al., 2003). Because cerebral autoregulation, metabolic regulation of O₂ and CO₂-mediated vasodilation are the most important mechanisms to ensure cerebral blood flow (Nybo & Rasmussen, 2007), our results would support the premise that the central nervous system of CFS subjects is somehow altered, and support previous research that suggests a CNS mechanism(s) is implicated in the pathogenesis of CFS (Georgiades et al., 2003; Chaudhuri & Behan, 2004; Siemionow et al., 2004b).

Third, it is noteworthy to mention here that cerebral HbO₂ and tHb plateau at approximately 90% TTE (Figs 1 and 2). This supports previous research by others using healthy and active

individuals (Bhambhani et al., 2007). This plateau in HbO₂ and tHb before the termination of exercise is the result of a decline in end-tidal CO₂ (PETCO₂) and arterial CO₂ content (P_aCO₂) that occurs above the respiratory compensation threshold (RCT). When exercise intensity exceeds the RCT, the decreased P_aCO₂ results in a reduction in the local cerebral blood flow (Bhambhani et al., 2007; Nybo & Rasmussen, 2007). Thus, we have demonstrated for the first time that this also occurred in the CFS subjects in our study but at a lower threshold level than CON subjects. Therefore, although our CFS subjects demonstrated a similar response above the RCT as did the CON subjects, i.e. a decline in cerebral oxygenation and total blood volume at maximal exercise, this would suggest that their cerebrovascular reactivity to the changing P_aCO₂ levels must still be functional. However, the significant differences in cerebral metabolism (i.e. HbO₂ and tHb) between groups during submaximal and maximal levels of effort still suggests that cerebral blood flow regulation must be compromised in CFS sufferers. Unfortunately, we do not have blood pressure or direct blood flow measurements to confirm whether cerebral autoregulation was compromised.

Cardiovascular and performance variables

Although our groups were matched for sex, body size and general activity level, significant differences were found in their aerobic ability. This supports previous research that CFS subjects have a lower aerobic capacity than normal healthy untrained subjects of the same age and sex, whether measured using a submaximal predictive exercise test (Fulcher & White, 2000; Nijs et al., 2007) or a direct VO_{2max} test (Inbar et al., 2001; Nijs & De Meirleir, 2004a). We used the predictive equation reported by Nijs and De Meirleir (Nijs & De Meirleir, 2004a), which has been shown to reliably predict VO_{2peak} in CFS subjects. The CON subject' VO_{2peak} was predicted using the ACSM formulae (ACSM 2000) from the last steady-state (2-min) stage the subject was able to achieve. We acknowledge that we may have possibly overestimated VO_{2peak} by using this predictive equation (ACSM). However, we did control for this by using the same predictive equations (ACSM 2000; Nijs & De Meirleir, 2004a) on each data set and found no significant differences between compared equations. Thus, we believe that we have provided a fair comparison between groups and this did not affect the cerebral oxygenation results as presented here. Therefore, we are confident that our calculated aerobic capacity for the subjects in this study is both valid and reliable. The reason for the reduced aerobic capacity in CFS subjects is speculative, but it has been suggested that both central (Pagani & Lucini, 1999) and peripheral (McCully & Natelson, 1999) factors contribute. Therefore, it is possible that both deconditioning and physiological factors associated with the reduction in cerebral oxygenation and blood flow limit exercise in CFS subjects. Further research is needed to confirm whether peripheral factors, such as muscle oxygenation and blood volume

changes are altered in CFS during maximal incremental exercise, and postexercise recovery.

Heart rate was also significantly lower in our CFS (154 ± 13 beats min^{-1}) versus CON (186 ± 11 beats min^{-1}) subjects at maximal power output. The performance data showed that the peak PO and TTE were significantly lower in the CFS, reflecting their inability to perform incremental exercise for an extended period of time. The mean peak PO was 100 ± 39 W and 163 ± 34 W for the CFS and CON groups, respectively. These data are similar to other maximal values reported in the literature (Inbar et al., 2001; Nijs et al., 2004b; Wallman et al., 2004a).

We also used the HR:RPE ratio as a method to compare the actual and perceived exertion of the subjects during the incremental exercise test, and thus a way to control for self-reported fatigue (Cook et al., 2003b). The lower HR:RPE ratio for the CFS subjects indicates that at the same HR (or absolute workload), RPE was significantly higher, and this was a consistent finding for each of the three common submaximal workloads that were monitored (Fig. 5). Furthermore, HR was not different between groups for these workloads (35, 60, 85 W). This suggests that CFS individuals perceive their level of effort as being more difficult, and these results are in agreement with most previous research (Fulcher & White, 2000; Cook et al., 2003b; Georgiades et al., 2003; Wallman et al., 2004b), but in disagreement with others (Cook et al., 2003a). Whether these differences confirm that CFS individuals have an altered central dysregulation of perception of effort cannot be fully answered by our data. However, our documented changes in cerebral HbO₂ and tHb provide evidence that physiological differences do exist between CFS and CON subjects. It is possible that the reduced oxygenation (and blood volume) delivery to and utilization by the brain alter neural function and perception of effort. Reduced neural activation to the working muscles was demonstrated in CFS subjects by Kent-Braun et al. (1993) using twitch interpolation methods during maximal voluntary contractions. Furthermore, Wallman et al. (2004a) have suggested that an increase in the effort sensation may also occur as a result of a reduced neural drive to the working muscles in CFS sufferers owing to psychological factors, such as fear of pain and fear of relapse (Inbar et al., 2001). This can result in a lack of motivation (Inbar et al., 2001), which may consequently give rise to the habitual inhibition or reduced facilitation of motor unit recruitment as demonstrated by Kent-Braun et al. (1993). Siemionow et al. (2004b) also showed that brain (EEG) signals were altered and significantly different in CFS versus CON when performing motor tasks, and furthermore, their results indicated that stronger voluntary efforts were needed to perform the same motor tasks as CON subjects. Collectively, these results clearly showed that CFS involves altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue. Thus, the dysregulation of RPE may be related to the reduced cerebral oxygenation and blood volume changes that we observed, but requires further experimentation.

Potential limitations of the study

Ideally, it would be better to have a larger sample size of CFS subjects, especially as CFS is an unknown disorder with many reported complications. This potentially could have increased the variance of our NIRS data (owing to potential heterogeneity of the disorder). However, when we examined the standard deviation of both the CFS and CON groups, this was not significantly different. Therefore, our small sample size did not contribute to the significant differences between the groups. In future studies, it is recommended that a large sample size be tested to confirm our results. Furthermore, we believe that our cerebral oxygenation data clearly differentiates CFS from CON subjects, even though the data was recorded from the left frontal lobe only. Future research should include 'imaging' the brain with NIRS probes on more regions of the brain to provide a global reflection of brain oxygenation, as it has been shown that blood flow is altered in different regions of the brain in CFS subjects (Ichise et al., 1992). A direct measurement of blood velocity (flow) using transcranial Doppler, simultaneous with NIRS and blood pressure, would also assist to verify changes in cerebral blood flow and a direct measure of cerebral autoregulation under conditions of rest, exercise and recovery. Finally, although we matched our groups for physical activity level [and did confirm that the current physical activity level of our groups was similar; Canadian Society for Exercise Physiology (CSEP), 2004)], it is possible that the CFS subjects were more de-conditioned because of their inability to carry out additional activities of normal living. However, all subjects stated that they exercised to their maximal ability when performing the maximal incremental exercise protocol.

Summary and conclusion

We have clearly demonstrated that the CFS subjects in this study have an altered cortical oxygenation response (in comparison with control subjects) to incremental exercise when performed to the limit of tolerance. The reduced cerebral oxygenation and blood volume changes are most likely related to reductions in regional cerebral blood flow, which ultimately affects neural drive and possibly other central nervous system functions. Our results support a central basis of fatigue in CFS subjects (Siemionow et al., 2004a), but does not discount that peripheral changes, being neurally mediated, may also be occurring in this medical condition. Further research monitoring the cardiovascular (blood pressure) and metabolic changes simultaneous with cerebral oxygenation and blood flow with more subjects is warranted to confirm our novel findings.

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References

- ACSM. ACSM's Guidelines for Exercise Testing and Prescription (2000). Lippincott Williams & Wilkins, Philadelphia.
- Bhambhani Y, Malik R, Mookerjee S. Cerebral oxygenation declines at exercise intensities above the respiratory compensation threshold. *Respir Physiol Neurobiol* (2007); **156**: 196–202.
- Borg GA. Psychophysiological bases of perceived exertion. *Med Sci Sports Exerc* (1982); **14**: 377.
- Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet* (2004); **363**: 978–988.
- Cook DB, Nagelkirk PR, Peckerman A, Poluri A, Lamanca JJ, Natelson BH. Perceived exertion in fatiguing illness: civilians with chronic fatigue syndrome. *Med Sci Sports Exerc* (2003a); **35**: 563–568.
- Cook DB, Nagelkirk PR, Peckerman A, Poluri A, Lamanca JJ, Natelson BH. Perceived exertion in fatiguing illness: Gulf War veterans with chronic fatigue syndrome. *Med Sci Sports Exerc* (2003b); **35**: 569–574.
- Cook DB, Nagelkirk PR, Peckerman A, Poluri A, Mores J, Natelson BH. Exercise and cognitive performance in chronic fatigue syndrome. *Med Sci Sports Exerc* (2005); **37**: 1460–1467.
- Cook D, Nagelkirk P, Poluri A, Mores J, Natelson B. The influence of aerobic fitness and fibromyalgia on cardiorespiratory and perceptual responses to exercise in patients with chronic fatigue syndrome. *Arthritis Rheum* (2006); **54**: 3351–3362.
- CSEP. *The Canadian Physical Activity, Fitness & Lifestyle Approach* (2004). Canadian Society for Exercise Physiology, Ottawa.
- Ferrari M, Mottola L, Quaresima V. Principles, techniques, and limitations of near infrared spectroscopy. *Can J Appl Physiol* (2004); **29**: 463–487.
- Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* (1994); **121**: 953–959.
- Fulcher KY, White PD. Strength and physiological response to exercise in patients with chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry* (2000); **69**: 302–307.
- Georgiades E, Behan WM, Kilduff LP, Hadjicharalambous M, Mackie EE, Wilson J, Ward SA, Pitsiladis YP. Chronic fatigue syndrome: new evidence for a central fatigue disorder. *Clin Sci (Lond)* (2003); **105**: 213–218.
- Ichise M, Salit IE, Abbey SE, Chung DG, Gray B, Kirsh JC, Freedman M. Assessment of regional cerebral perfusion by 99Tcm-HMPAO SPECT in chronic fatigue syndrome. *Nucl Med Commun* (1992); **13**: 767–772.
- Ide K, Secher NH. Cerebral blood flow and metabolism during exercise. *Prog Neurobiol* (2000); **61**: 397–414.
- Inbar O, Dlin R, Rotstein A, Whipp BJ. Physiological responses to incremental exercise in patients with chronic fatigue syndrome. *Med Sci Sports Exerc* (2001); **33**: 1463–1470.
- Kent-Braun JA, Sharma KR, Weiner MW, Massie B, Miller RG. Central basis of muscle fatigue in chronic fatigue syndrome. *Neurology* (1993); **43**: 125–131.
- McCully KK, Natelson BH. Impaired oxygen delivery to muscle in chronic fatigue syndrome. *Clin Sci (Lond)* (1999); **97**: 603–608.
- McCully KK, Smith S, Rajaei S, Leigh JS Jr, Natelson BH. Muscle metabolism with blood flow restriction in chronic fatigue syndrome. *J Appl Physiol* (2004); **96**: 871–878.
- Neary JP. Application of near infrared spectroscopy to exercise sports science. *Can J Appl Physiol* (2004); **29**: 488–503.
- Nijs J, De Meirleir K. Prediction of peak oxygen uptake in patients fulfilling the 1994 CDC criteria for chronic fatigue syndrome. *Clin Rehabil* (2004a); **18**: 785–792.
- Nijs J, De Meirleir K, Meeus M, McGregor NR, Englebienne P. Chronic fatigue syndrome: intracellular immune deregulations as a possible etiology for abnormal exercise response. *Med Hypotheses* (2004b); **62**: 759–765.
- Nijs J, Demol S, Wallman K. Can submaximal exercise variables predict peak exercise performance in women with chronic fatigue syndrome? *Arch Med Res* (2007); **38**: 350–353.
- Nioka S, Kime R, Sunar U, Im J, Izzetoglu M, Zhang J, Alacam B, Chance B. A novel method to measure regional muscle blood flow continuously using NIRS kinetics information. *Dyn Med* (2006); **5**: 5.
- Nybo H, Rasmussen P. Inadequate cerebral oxygen delivery and central fatigue during strenuous exercise. *Exerc Sport Sci Rev* (2007); **35**: 110–118.
- Pagani M, Lucini D. Chronic fatigue syndrome: a hypothesis focusing on the autonomic nervous system. *Clin Sci (Lond)* (1999); **96**: 117–125.
- Pyne DB, Lee H, Swanwick KM. Monitoring the lactate threshold in world-ranked swimmers. *Med Sci Sports Exerc* (2001); **33**: 291–297.
- Rasmussen P, Dawson EA, Nybo L, van Lieshout JJ, Secher NH, Gjedde A. Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. *J Cereb Blood Flow Metab* (2007); **27**: 1082–1093.
- Schwartz RB, Garada BM, Komaroff AL, Tice HM, Gleit M, Jolesz FA, Holman BL. Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT. *AJR Am J Roentgenol* (1994); **162**: 935–941.
- Siemionow V, Fang Y, Calabrese L, Sahgal V, Yue G. Altered central nervous system signal during motor performance in chronic fatigue syndrome. *Clin Neurophysiol* (2004a); **115**: 2372–2381.
- Siemionow V, Fang Y, Calabrese L, Sahgal V, Yue GH. Altered central nervous system signal during motor performance in chronic fatigue syndrome. *Clin Neurophysiol* (2004b); **115**: 2372–2381.
- Stewart J, Weldon A, Arlievsky N, Li K, Munoz J. Neurally mediated hypotension and autonomic dysfunction measured by rate variability during head-up tilt testing in children with chronic fatigue syndrome. *Clin Auton Res* (1998); **8**: 221–230.
- Tanaka H, Matsushima R, Tamai H, Kajimoto Y. Impaired postural cerebral hemodynamics in young patients with chronic fatigue with and without orthostatic intolerance. *J Pediatr* (2002); **140**: 412–417.
- Wallman KE, Morton AR, Goodman C, Grove R. Physiological responses during a submaximal cycle test in chronic fatigue syndrome. *Med Sci Sports Exerc* (2004a); **36**: 1682–1688.
- Wallman KE, Morton AR, Goodman C, Grove R, Guilfoyle AM. Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Med J Aust* (2004b); **180**: 444–448.
- Wallman KE, Morton AR, Goodman C, Grove R. Reliability of physiological, psychological, and cognitive variables in chronic fatigue syndrome. *Res Sports Med* (2005); **13**: 231–241.
- Wolf U, Wolf M, Choi JH, Paunescu LA, Safonova LP, Michalos A, Gratton E. Mapping of hemodynamics on the human calf with near infrared spectroscopy and the influence of the adipose tissue thickness. *Adv Exp Med Biol* (2003); **510**: 225–230.
- Wolf U, Ferrari M, Quaresima V. Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. *J Biomed Optics* (2007); **12**: 062104.062101–062114.

Yamamoto Y, LaManca JJ, Natelson BH. A measure of heart rate variability is sensitive to orthostatic in women with chronic fatigue syndrome. *Exp Biol Med* (Maywood) (2003); **228**: 167–174.

Yoshiuchi K, Farkas J, Natelson BH. Patients with chronic fatigue syndrome have reduced absolute cortical blood flow. *Clin Physiol Funct Imaging* (2006); **26**: 83–86.