

Impaired oxygen delivery to muscle in chronic fatigue syndrome

Kevin K. McCULLY* and Benjamin H. NATELSON†

*Department of Medicine, Medical College of Pennsylvania and Hahnemann University, Philadelphia, PA 19129, U.S.A., and

†CFS Center and Department of Neurosciences, New Jersey Medical School, Newark, NJ 07103, U.S.A.

A B S T R A C T

The purpose of this study was to determine if chronic fatigue syndrome (CFS) is associated with reduced oxygen delivery to muscles. Patients with CFS according to CDC (Center for Disease Control) criteria ($n = 20$) were compared with normal sedentary subjects ($n = 12$). Muscle oxygen delivery was measured as the rate of post-exercise and post-ischæmia oxygen-haem resaturation. Oxygen-haem resaturation was measured in the medial gastrocnemius muscle using continuous-wavelength near-IR spectroscopy. Phosphocreatine resynthesis was measured simultaneously using ^{31}P magnetic resonance spectroscopy. The time constant of oxygen delivery was significantly reduced in CFS patients after exercise (46.5 ± 16 s; mean \pm S.D.) compared with that in controls (29.4 ± 6.9 s). The time constant of oxygen delivery was also reduced (20.0 ± 12 s) compared with controls (12.0 ± 2.8 s) after cuff ischaemia. Oxidative metabolism was also reduced by 20% in CFS patients, and a significant correlation was found between oxidative metabolism and recovery of oxygen delivery. In conclusion, oxygen delivery was reduced in CFS patients compared with that in sedentary controls. This result is consistent with previous studies showing abnormal autonomic control of blood flow. Reduced oxidative delivery in CFS patients could be specifically related to CFS, or could be a non-specific effect of reduced activity levels in these patients. While these results suggest that reduced oxygen delivery could result in reduced oxidative metabolism and muscle fatigue, further studies will be needed to address this issue.

INTRODUCTION

Chronic fatigue syndrome (CFS) is an illness characterized by medically unexplained fatigue lasting at least 6 months, accompanied by infectious, rheumatological and/or neuropsychiatric symptoms [1]. Complaints of muscle weakness and pain are common, and abnormal muscle metabolism has been reported to occur in CFS [2,3]. While some studies have not been able to confirm metabolic abnormalities [4], we found that CFS patients had a moderate reduction in oxidative capacity, as measured by the rate of recovery of phosphocreatine after submaximal exercise [5]. These measurements of oxidative metabolism are a function of mitochondrial

capacity and the ability to deliver oxygen to the muscle [6].

Recent work suggests that CFS is associated with autonomic dysregulation. Both sympathetic and parasympathetic autonomic tone have been reported to be abnormal [7–10]. Fibromyalgia, which is a syndrome that overlaps with CFS, has also been shown to be associated with altered sympathetic nervous system activity [11]. This autonomic dysregulation could affect blood flow to active muscles [12], could explain the alterations in muscle metabolism we have found, and could partially explain the post-exertional fatigue that is a characteristic of the illness.

The aim of the present study was to test the hypothesis

Key words: autonomic nervous system, magnetic resonance spectroscopy, muscle metabolism, near-IR spectroscopy.

Abbreviations: CFS, chronic fatigue syndrome; MRS, magnetic resonance spectroscopy; NIRS, near-IR spectroscopy; $\text{O}_2\text{Cuff}_{\text{TC}}$, time constant for O_2 recovery after cuff ischaemia; $\text{O}_2\text{Ex}_{\text{TC}}$, time constant for O_2 recovery after exercise; PCr, phosphocreatine; PCr_{TC} , time constant of recovery of PCr.

Correspondence: Dr Kevin McCully, Department of Exercise Science, Ramsey Center, University of Georgia, Athens, GA 30602-6554, U.S.A. (e-mail kmccully@coe.uga.edu).

that patients with CFS have reduced oxygen delivery to skeletal muscle compared with sedentary controls. To test our hypothesis we used near-IR spectroscopy (NIRS), which is a non-invasive method of determining relative oxygen saturation in capillaries and venules in muscle [13]. We measured the rate of recovery of oxygen saturation following either exercise or cuff ischaemia as our index of oxygen delivery. Simultaneous measurements of high-energy phosphates were made using magnetic resonance spectroscopy (MRS) to control for potential metabolic differences.

METHODS

Patient selection

This study was approved by the University Committee on Studies Involving Human Beings at the New Jersey Medical School, and the Medical College of Pennsylvania Hahnemann University, and all subjects gave informed consent before initiating the study. Patients were carefully evaluated to fulfil the case definition of CFS [1]; none had evidence of psychiatric illness in the 5 years prior to the onset of CFS, as determined by a diagnostic psychiatric interview. A total of 20 CFS patients were tested in this study [age 37 ± 9 years (mean \pm S.D.); 14 females and six males]. Healthy control subjects were chosen to be similar in age and to have a sedentary lifestyle by self report (regular exercise less than once a week for at least 6 months prior to testing). Twelve sedentary control subjects were tested (age 31 ± 6 years; eight females and four males). While the CFS patients tended to be heavier, there were no significant differences between groups in height (1.67 ± 0.09 m for CFS and 1.67 ± 0.11 m for controls; $P = 0.96$), weight (73 ± 17 kg for CFS and 64 ± 14 kg for controls; $P = 0.12$) or body mass index (25.7 ± 5.2 kg/m² for CFS and 22.6 ± 2.2 kg/m² for controls; $P = 0.06$).

NIRS measurements

The NIRS measurements used a continuous-light-source, dual-wavelength spectrophotometer (Runman®) modified to be used in the magnet [13]. The light source and detectors were connected to the leg with 3 m-long quartz light guides. The separation distance between the light sources and detectors was 3 cm. Light photons migrate through the tissue and are collected by the detectors with optical filters set at 760 and 850 nm. O₂-haem groups have a greater absorbance at 850 nm than at 760 nm, with deoxy-haem groups absorbing more at 760 nm than at 850 nm. The difference signal between 760 and 850 nm was used to indicate changes in oxygen saturation. Voltage signals were digitized into a computer by a commercial AD device (National Instruments A/D board). Values for the difference signal were converted

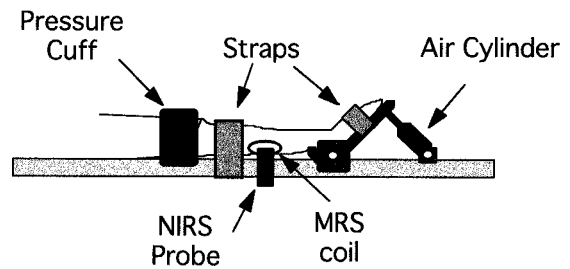


Figure 1 Experimental arrangement of the leg of subjects during MRS experiments

The MRS coil is placed adjacent to the medial gastrocnemius. Work levels are controlled by changing the pressure in the air cylinder. Cuff ischaemia was produced by setting with a Hokkansen rapid cuff inflator. The NIRS probe is placed on the medial gastrocnemius inside the MRS coil.

into a relative scale of 0–100%. Oxygen delivery capacity was measured as the time constant determined from an exponential curve fit of the difference signal during recovery from either exercise or cuff ischaemia [13].

MRS measurements

Phosphorus metabolites were measured using a 78 cm clear bore, 2.1 T magnet with a home-built spectrometer system [5]. The gastrocnemius muscle was examined using a 6 cm \times 8 cm surface coil tuned to both ³¹P and ¹H frequencies (34.86 and 86.12 MHz respectively). Phosphorus spectra (3000 Hz sweep width; 1024 points) were collected using pulses to produce a maximal signal intensity per pulse. The pulse repetition time was 4 s. Nuclear Overhauser enhancement was used to enhance the ³¹P signal. Spectra were Fourier-transformed with 5 Hz line broadening and integrated in the frequency domain. Areas of the P_i, phosphocreatine (PCr) and β -ATP peaks were computer-integrated, and corrections were made for differences in saturation and nuclear Overhauser enhancement between the peaks. Muscle pH was calculated from the frequency difference between P_i and PCr. The MRS coil was placed in the same location as the NIRS light guides, and both measurements were collected simultaneously [13].

In this study, PCr values during recovery were fitted to a single-exponential equation to determine a time constant (PCr_{Tc}) and rate constant (PCr_r = 1/PCr_{Tc}) of recovery. To correct for potential effects of the decreased pH on PCr_{Tc}, the maximal rate of ATP synthesis was calculated as $V_{\max} = PCr_r [1 + K_m / ADP_{ee}]$ [14]. In these calculations K_m is assumed to be 30 μ M and ADP_{ee} is the end-exercise ADP level, calculated by assuming [ATP] = 8.2 mM and [total creatine] = 42.5 mM.

In-magnet exercise

Subjects performed repeated plantar flexion in the prone position with their knees fully extended using a foot pedal attached to an air pressure ergometer (Figure 1).

Exercise intensity was modulated by changing the air pressure in the ergometer. Velcro straps were used to secure the subject to the foot pedal and the platform. Exercise consisted of repeated plantar flexions. Two protocols were used. In the first protocol the subject pushed the pedal once every 4 s for 5 min. Exercise intensity was increased gradually, such that PCr levels (monitored continuously) had decreased to ~60% of the resting value at the end of 5 min of exercise. In the second protocol, the subject pressed the pedal rapidly for 10–16 s at a pressure equal to two-thirds of the final pressure reached in the ramp protocol.

Recovery from cuff ischaemia

The rate of recovery of oxygen saturation was measured after 4 min of cuff ischaemia. A standard blood pressure cuff was placed just above the knee on the leg being tested. Ischaemia was produced by rapidly inflating the cuff (1–2 s) with a rapid cuff inflator (DE Hokkansen, Inc) to suprasystolic pressures (200 mm Hg). A duration of 4 min was chosen, as previous studies have shown that cuff ischaemia of less than 5 min duration results in decreased oxygen saturation without a significant depletion of high-energy phosphates [15]. Recovery after this duration of ischaemia thus represents the 'wash-in' of oxygenated blood without significant post-occlusion oxygen consumption.

Data analysis

Data are presented as means \pm S.D. The time constant and V_{\max} values for the three tests were averaged to produce a single value for each subject. This was possible as there were no significant differences between the tests in this study or in previous studies [14].

Statistical analysis consisted of two-tailed *t*-tests for comparison of baseline data between CFS subjects and controls. Significant differences were assumed at $P < 0.05$. 'Quantile-quantile' plots were used to allow visual assessment of differences between CFS patients and normal subjects [16]. In this graphical method, the results of the two subject groups are rank-ordered and plotted in pairs from the lowest to the highest value with appropriate interpolation for uneven sample sizes. If the samples of the two groups are similar, the data should lie along the line of identity, $y = x$.

An exploratory correlational analysis was performed between physiological data and several variables that assess or influence functional status in CFS; these included the existence of major psychopathology (e.g. most commonly, major depression), days in the last month spent in bed, days in the last month with reduced activity level, and a CFS severity score based on self-rated symptom severity.

RESULTS

Data were obtained for 20 CFS and 12 control subjects. Two additional CFS patients were tested, but they could not tolerate the ischaemic period; one patient had a previous history of venous problems in the lower leg, and the other reported greater than normal sensitivity to pain. Data from the two additional CFS subjects were not included in the data analysis.

Oxygen delivery

Figure 2 shows several examples of the changes in oxygen saturation with exercise and cuff ischaemia. As expected, the rate of recovery of oxygen saturation after exercise was significantly lower than the rate of recovery of oxygen saturation after cuff ischaemia. No change in PCr levels was seen during cuff ischaemia, indicating little or no accumulation of an oxygen debt. Oxygen delivery

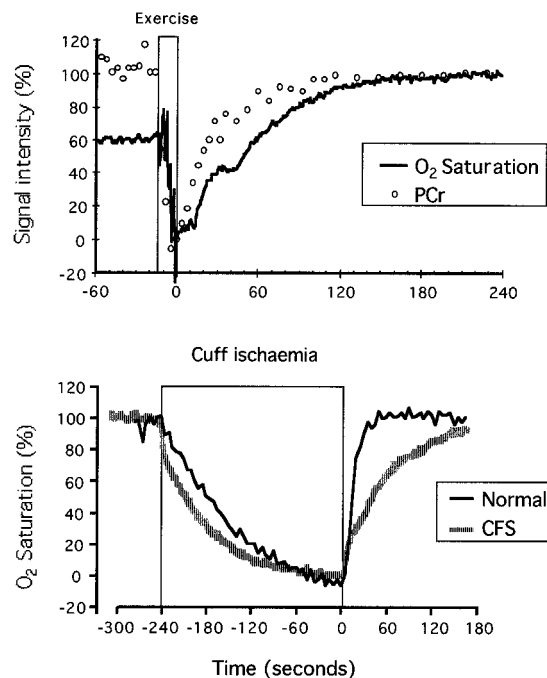


Figure 2 Examples of changes in oxygen saturation with exercise and cuff ischaemia

Upper panel: O_2 saturation measured by NIRS and PCr levels measured by MRS in a CFS patient during a short bout of rapid plantar flexion. Note the O_2 saturation levels recovered more slowly than did the PCr levels. Lower panel: examples of NIRS difference signal (oxygen saturation) during the 4 min cuff ischaemia experiment. The normal curve is for a control subject with a recovery rate similar to the mean value for normals. The CFS curve is for one CFS patient with a very low recovery rate (lower than mean value for the CFS group). Note that both curves have been normalized to the same y -axis scale. The actual y -axis signal magnitudes could be very different between subjects.

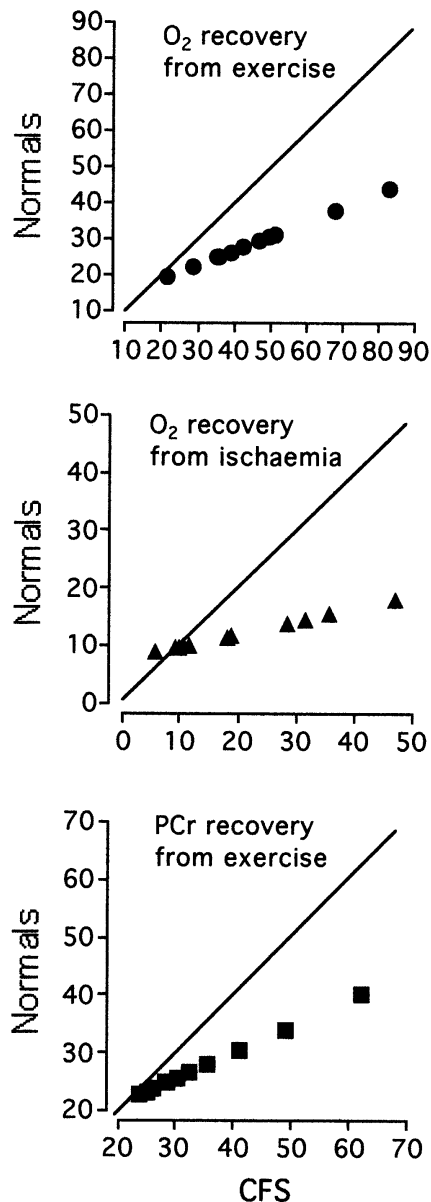


Figure 3 Data from CFS patients and normal subjects plotted using a 'quantile-quantile' plot

As the CFS group had a larger sample size, CFS data were interpolated to provide the data points for comparison with the normal subjects. Top: O₂ saturation recovery time constants after exercise. Middle: O₂ saturation recovery time constants after cuff ischaemia. Bottom: PCr recovery time constants after exercise. The solid line in each graph indicates the line of identity. Note that the slope in all three graphs was less than 1, indicating that CFS subjects had a greater range of recovery values than normal subjects.

after exercise was significantly slower in CFS patients (46.5 ± 16.4 s) compared with controls (29.5 ± 6.9 s; $P = 0.0019$). Oxygen delivery after cuff ischaemia was also significantly slower in CFS patients (20.0 ± 12.0 s) compared with controls (12.0 ± 2.8 s; $P = 0.03$). Figure 3 shows the data in quantile-quantile plots. Subjects with shorter recovery times were similar in the two groups,

while subjects with longer recovery times were slower in the CFS group. There was a significant correlation between oxygen delivery after exercise and oxygen delivery after cuff ischaemia ($r = 0.527$; $P = 0.0019$).

Oxidative metabolism

The submaximal exercise tests resulted in similar levels of metabolites at the end of exercise in CFS patients and controls. Final pH levels were 6.99 ± 0.06 in CFS patients and 6.99 ± 0.09 in controls. PCr levels were $53 \pm 9\%$ of resting values in CFS subjects, compared with $49 \pm 10\%$ in controls. Indices of oxidative metabolism measured during recovery from exercise were reduced in CFS patients compared with controls. PCr_{Tc} was 35.0 ± 10.3 s in CFS patients and 27.2 ± 5.3 s in controls ($P = 0.022$). V_{\max} was 72.8 ± 22.2 mmol·min⁻¹·litre⁻¹ in CFS patients, compared with 91.3 ± 13.1 mmol·min⁻¹·litre⁻¹ in controls ($P = 0.015$). When CFS and normal subjects were combined, significant correlations were found between PCr_{Tc} and the time constant for O₂ recovery after exercise (O₂Ex_{Tc}) ($r = -0.459$; $P = 0.0087$) and between V_{\max} and O₂Ex_{Tc} ($r = -0.614$; $P = 0.0002$). No correlation was found between PCr_{Tc} or V_{\max} and the time constant for O₂ recovery after cuff ischaemia (O₂Cuff_{Tc}) ($r = 0.116$; $P = 0.538$ and $r = -0.260$; $P = 0.160$ respectively).

Correlations with symptom severity

Examination of Pearson correlation coefficients indicated that 'days in bed' was correlated significantly with PCr_{Tc} ($r = 0.469$; $P = 0.032$), O₂Ex_{Tc} ($r = 0.546$; $P = 0.01$) and V_{\max} ($r = -0.506$; $P = 0.019$). There were no significant correlations between psychiatric status or any of the functional status variables and PCr_{Tc}, O₂Ex_{Tc}, O₂Cuff_{Tc} or V_{\max} .

DISCUSSION

This study has found that oxygen delivery was reduced in patients with CFS compared with that in control subjects. Normal subjects had recovery rates for oxygen saturation that were similar to those for PCr, consistent with our previous results [13]. However, CFS patients had recovery rates for oxygen saturation that were 34% lower than those for PCr recovery and 60% lower than those for recovery of oxygen saturation in normal subjects. The present study also measured the rate of recovery of oxygen saturation after cuff ischaemia, where no metabolic changes were detected. Thus cuff ischaemia allows us to separate metabolic effects related to oxidative metabolism from physiological effects related to the delivery of oxygen to muscle. Under these conditions CFS patients again had recovery rates that were signifi-

cantly lower (i.e. by 60%) than those of controls. These results suggest that impaired oxygen delivery could be a component of CFS. Oxygen delivery represents the ability to get oxygen into the small vessels of the muscle. This reflects both oxygen-carrying capacity and muscle blood flow. There is little to indicate that CFS is associated with abnormal oxygen-carrying capacity, although there are case reports of abnormal red blood cell shape in patients with chronic fatigue [17]. A growing number of reports have suggested that CFS may be associated with abnormal control of blood flow [7–10].

The impaired oxygen delivery seen in the CFS subjects in the present study could result in reduced oxidative metabolism and thus reduced exercise capacity. This is because oxygen delivery is a major determinant of muscle exercise capacity [6]. However, the ability of modest decreases in oxygen delivery to influence oxidative metabolism is controversial. Several studies have shown that oxidative metabolism is reduced when oxygen delivery to exercising muscles is reduced [18,19]. However, it is possible that oxygen delivery during submaximal exercise (like that in the present study) is in excess of what is needed for oxidative metabolism, so that reduced oxidative metabolism need not result from the changes in oxygen delivery that we found. The lack of a strong correlation between oxidative metabolism (V_{\max}) and oxygen delivery ($O_2\text{Cuff}_{Tc}$) in our study supports this. Further research is needed to determine the potential impact of decreases in $O_2\text{Cuff}_{Tc}$ on muscle function.

We found that the oxidative V_{\max} was 20% lower in the CFS population compared with the controls, which was similar to the 25% reduction reported in our previous study [5]. In a recent study, Lane et al. [20] found that CFS subjects could be classified into subjects with a high (and normal) oxidative capacity or a low (and abnormal) oxidative capacity. The marked variability in the results from CFS subjects compared with those from the normal group in the Lane study was similar to that found in the present study.

By definition, a syndrome is a heterogeneous process, and probably has multiple causes that can lead to the same clinical picture. Data exist indicating that some CFS patients have a problem in cardiovascular control that is manifested in some by delayed orthostatic intolerance [10] and subtle autonomic abnormalities [7,8]. Patients with complaints of syncope and abnormal responses to orthostatic challenge (not necessarily CFS patients) have been found to have increased forearm vascular resistance [21], an indicator of abnormal muscle blood flow. In the case of patients with CFS, while mean differences do occur, many CFS subjects have data in the normal range. This shows up as increased variation in the CFS results. The quantile–quantile plots display this variability graphically; the lower values of patients and controls lie near the line of identity, while higher values diverge from that line.

If muscle metabolism and oxygen delivery were responsible in part for CFS, we would have expected to find significant correlations between the physiological variables and CFS severity. Such consistent correlations were not found, but we did find a significant relationship between days spent in bed in the last month and the physiological variables. This does suggest a relationship between the disability produced by CFS and reduced oxidative metabolism and oxygen delivery. For this suggestion to have credence will require replication of our results. An interim conclusion is that these physiological abnormalities may be a marker of the underlying disorder.

Deconditioning as a result of inactivity is an alternative explanation for the decreases in oxygen delivery and oxidative capacity seen in the CFS patients in the present study [22]. While the CFS patients used in the present study were community-living and ambulatory (often with full-time jobs), they did have reduced activity levels compared with healthy control subjects. Using 24 h activity monitors, Sisto et al. [23] found CFS patients to have a 15% reduction in activity compared with sedentary healthy controls. Inactivity in healthy subjects has been shown to reduce muscle blood flow and vasodilatory capacity [24]. In addition, exercise training in healthy subjects has been shown to improve blood flow [25]. However, the studies of inactivity and exercise training in healthy subjects used much larger changes in activity level to induce their effects than the difference in activity levels we have found between CFS patients and sedentary healthy controls. Because of the relatively small decreases in activity level in CFS patients, it is difficult to find appropriate control groups with similar activity levels. Otherwise healthy subjects who are in forced bed-rest for non-muscle-related problems show too great a decrease in activity level, and while some chronic diseases might produce similar decreases [26], they come with their own potential complications. While we feel that there is a potential for the difference in activity level to influence oxygen delivery and oxidative capacity, at this point we feel that another cause inherent to CFS is more likely.

In summary, the present study has demonstrated direct impairments in oxygen delivery in CFS patients compared with normal subjects. These impairments were more clearly seen after exercise rather than after ischaemia, and did not occur in all CFS patients. The magnitude of the alterations in oxygen delivery may be sufficient to impair exercise capacity in some patients, but no consistent relationship between impaired oxygen delivery and CFS symptom severity was found. Further studies testing this relationship are needed. The reduced oxygen delivery seen in the present study could be due to impairments related to the cause of CFS, or to inactivity as a result of CFS. Further studies are needed to discriminate between these two possibilities.

ACKNOWLEDGMENTS

We are grateful to Jennifer Nelson and Quanwu Zhang for help with statistical analysis. This work was supported in part by NIH grants AI-32247 and RR02305.

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Received 2 November 1998/21 June 1999; accepted 20 July 1999