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Research Article

Muscle Haemodynamics and Oxygen Saturation during Exercise and Recovery in Chronic Fatigue Syndrome Patients

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Abstract

Introduction: Controversy exists in the literature whether or not muscle metabolism is altered in chronic fatigue syndrome (CFS) patients.

Purpose: To examine the effects of incremental exercise to volitional exhaustion and recovery on muscle haemodynamics and oxygen saturation in CFS patients.We hypothesized that fatiguing exercise would demonstrate differences in comparison to healthy control (CON) subjects. Methods: Six CFS patients and eight physically similar CON subjects performed an incremental cycle ergometer test. The warm-up workload began at 30W for 3 min, followed by an increase to 60W for 2 min, and then 25W increments every 2 min thereafter. Total hemoglobin (tHb; μM), deoxyhemoglobin (HHb; μM), and tissue oxygenation index (TOI; %) were monitored during exercise and passive recovery (2 min) from the right vastus lateralis muscle using spatially resolved near-infrared spectroscopy (NIRS).

Results: ANCOVA from the NIRS data revealed that the CFS group had a significantly lower TOI% (58.9 ± 1.8% vs. 64.0 ± 1.2%) throughout exercise, and longer recovery time ($t^1/_2$; Tau) after exercise (τ = 29.5s vs. 17.7s; $P<0.05$). Kinetics for tHb (τ = 18.5s vs. 39.7s), and HHb (τ = 18.7s vs. 31.7s), was significantly reduced after passive recovery in the CFS patients vs. CON, respectively.

Conclusion: The reduced muscle TOI% during and after exercise in the CFS patients suggests that peripheral muscle metabolism was altered and different from CON subjects. Furthermore, the longer recovery kinetics (τ), in tHb and HHb during recovery suggests altered metabolic and hemodynamic changes in CFS, and may indicate a peripheral autonomic imbalance.

ABBREVIATIONS

NIRS: Near Infrared Spectroscopy; TOI: Tissue Oxygenation Index; HbO_2: Oxyhaemoglobin; HHb: Deoxyhaemoglobin; tHb: Total Haemoglobin; CFS: Chronic Fatigue Syndrome

INTRODUCTION

Chronic fatigue syndrome (CFS), is characterized by a set of symptoms, such as cognitive difficulties and muscle soreness, of unknown etiology causing severe disabling fatigue which can lead to cognitive impairment [1,2]. In 2010, it was reported that 1.4% of the Canadian household population aged 12 years and over were diagnosed with CFS, and females aged 40 years and older with low income were associated with prevalent CFS [3]. Others have stated that females between the ages of 20 and 40 seem to be the most prevalent population [4].

The pathophysiology and pathogenesis of CFS are not clearly understood. Previous research has shown that peripheral muscle metabolism may be altered in CFS patients [5], but not all reports support this contention [6]. However, more recently, it has been suggested that bioenergetic muscle dysfunction is evident in CFS, along with impaired acid clearance after exercise [7]. Some literature suggests that people affected by CFS experience impaired oxygen delivery to working muscles [8,9], meaning that the transport capacity of oxygen may be limited in CFS patients [10]. Also, recovery rates for oxygen saturation, using both near infrared spectroscopy (NIRS) and nuclear magnetic resonance (NMR), have shown to be substantially blunted in CFS patients following an exercise period [5]. Other reports suggest that re-saturation after arterial occlusion may serve to indicate changes in muscle metabolism in CFS patients [11].

NIRS represents a simple, non-invasive technique that can be used to monitor muscle metabolism [12,13]. In human tissue (muscle and brain) light is transparent in the NIR region of the electromagnetic spectrum (approx. 650-1000nm) [14], and can allow for measurement of haemodynamic chromophores, being deoxyhaemoglobin, [HHb] and oxyhaemoglobin (HbO_2) [15], and can also allow calculation of total haemoglobin (tHb = HbO_2+HHb), which may correlate to cerebral blood volume [16]. Therefore, the ability to discern metabolic changes related to pathophysiology in CFS using a simple cycle ergometry test and post-exercise measurement would be helpful from a clinical and research perspective.

Previous studies have also shown decreases in cerebral HbO_2 and HHb changes, suggesting reduced cerebral oxygenation and blood volume with exercise [16,17]. Furthermore, postural change from seated to standing in CFS patients has also shown impaired cerebral haemodynamics [18]. Haemoglobin kinetics can be measured using a time constant of an exponential function used to create regression models, and this time constant (tau, τ) can be thought of as the effect of blood flow kinetics, thereby representing the speed with which a particular system can respond to change [19-22]. Therefore, this measure can provide great insight as to the changes occurring with the haemoglobin kinetics in CFS.

Other physiological parameters have also been assessed in CFS. Changes in regional cerebral blood flow (CBF) and functional brain abnormalities in CFS patients has been shown [23,24], and hyperthermia techniques have shown increased CBF in CFS patients, suggesting that cardiac therapies can aid in CFS recovery. This further implies the importance of NIRS as an imaging technique for monitoring CFS, both in the brain and in the peripheral muscle.

Because there are very limited strategies for diagnosing and treating patients suffering from CFS [25], it follows that more research into the possible underlying mechanism is required. Therefore, this study attempts to provide a better understanding as to the abnormal muscle oxygenation characteristics in CFS patients. We examined the effects of incremental exercise completed to exhaustion and passive recovery on muscle haemodynamics and oxygen saturation in CFS patients. It was hypothesized that there would be metabolic differences between CFS patients compared to healthy controls during exercise and passive recovery.

MATERIALS AND METHODS

Subjects

Six physician-referred female CFS patients and eight control (CON) subjects of similar body composition provided written informed consent after ethical review by a University committee was approved.The inclusion criteria for the CFS group were in accordance with the Center for Disease Control and confirmed CFS by the referring rheumatologist, thus, allowing for control of other comorbidity illnesses (i.e., fibromyalgia) as this has demonstrated an altered cognitive performance and physiological response in comparison with CFS-only subjects following exercise (26,27). The height (CFS: 1.53 ± 0.3m; CON: 1.62 ± 0.1m), body mass (CFS: 67 ± 20kg; CON: 66 ± 8kg), body mass index (BMI) (CFS: 26 ± 4; CON: 25 ± 3), and current physical characteristics (Age(years) (CFS: 39 ± 13; CON: 27 ± 7); Resting heart rate (beats per minute) (CFS: 94 ± 10; CON: 79 ± 10; $p<0.05$); Systolic pressure (mmHg) (CFS: 119 ± 14; CON: 112 ± 5); Diastolic Pressure (mmHg) (CFS: 80 ± 9; CON: 76 ± 5); Fatigue Severity Scale (CFS: 59 ± 5; CON: 27 ± 15; $p<0.05$); Length since Diagnosis (months) (CFS: 104 ± 44; CON: 0; $p<0.05$); Physical activity level (sessions per week > 1.5 metabolic equivalent) (CFS: <1; CON: <10)) were matched for control of possible influences. From these characteristics, fatigue severity scale, resting heart rate and length since diagnosis were significantly different. 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)). The exercise modality and protocol used has been outlined previously [16].

As a quick review, the exercise protocol consisted of tissue oxygenation and haemodynamics monitoring on the right vastus lateralis (VL) muscle using NIRS (NIRO-300, Hamamatsu, Japan) during and following incremental exercise. The warm-up workload began at 30W for 3 min, followed by an increase to 60W for 2 min, and then 25W increments every 2 min thereafter. Passive (2 min) recovery followed exercise. During the recovery period the participants remained seated on the Monark 818E cycle ergometer (Monark, Sweden), with their legs remaining stationary at 90 degrees and their feet on the pedals. All CON subjects and CFS patients successfully completed the entire protocol.

Data analysis and processing

Data was exported, and parameters of interest consisted of deoxyhaemoglobin (HHb), total haemoglobin (tHb = HbO_2+HHb), and tissue oxygenation index (TOI; % = HbO_2/tHb), a measure of oxygen saturation. Analysis of covariance (ANCOVA) was used to compare muscle oxygen and haemodynamic changes during exercise and recovery (SPSS v11.5, IBM, Chicago, IL). Alpha was set at $p \leq 0.05$.

Data were modeled by using a nonlinear, least squares regression fitting procedure with a monoexponential function of the form:

$$y = y_0 + a*(1 - e^{-bx})$$

for tHb and %TOI where y_0=[x=0], a is the amplitude, $b=1/\tau$, and x is the time;

$$y = y_0 + a*e^{-bx}$$

for HHb where y_0=(x=0), a is the amplitude, $b=1/\tau$, and x is the time.

RESULTS AND DISCUSSION

Results

During the incremental exercise test the CFS subjects reached volitional exhaustion at a lower power output (CFS: 100 ± 39 W; CON: 163 ± 34 W), and in a significantly shorter time (CFS: 351 ± 224 s; CON: 715 ± 176 s). Maximal exercise heart rate was also significantly lower (154 ± 13 bpm vs. 186 ± 11 bpm) in the CFS group in comparison to the CON group.

The CFS group had lower oxygen saturation throughout the exercise test (TOI; 58.9 ± 1.8 % vs. 64.0 ± 1.2%; Figure 1). tHb changes were significantly ($p<0.05$), different during exercise in the CFS patients (-4.45 ± 0.66μM) vs. the CON group (-5.7 ± 1.07μM0. During recovery, τ (sec) was significantly faster in the CON vs. the CFS group for TOI% (τ = 17.7s vs. 29.4s), for tHb (τ = 18.5s vs. 39.7s), and for HHb (τ= 18.7s vs. 31.7s) (Figure 2).

Discussion

This study was novel as it showed that skeletal muscle metabolism during exercise and resaturation kinetics during recovery was significantly lower in patients with CFS in comparison to normal healthy control participants. Using the time constant Tau (τ; sec), we examined the kinetics of tHb and HHb, and resaturation of TOI%, and found that these muscle oxygenation variables were significantly blunted in the CFS patients when assessed using non-invasive NIRS. Furthermore, our research demonstrates that skeletal muscle oxygen kinetics using a simple method, i.e., recovery from exercise, can differentiate healthy from pathological states of function. The incremental exercise metabolic response was also reduced in the CFS patients, supporting previous research that showed both muscle [11] and pre-frontal cortex oxygenation was altered during exercise in CFS [16].

This research supports previous studies that CFS patients may have an abnormal muscle metabolism. McCully et al. [11], used a high repetition, low load protocol in combination with blood flow restriction at the knee and NIRS measured in the medial gastrocnemius to showthat CFS patients had reduced peripheral muscle oxygen delivery and oxygenation during recovery.Our data supports this contention, as recovery saturation (TOI%) was reduced, and tHb and HHb kinetics (τ; sec) was slower in CFS patients in comparison to CON (Figure 2).

TOI% reflects an absolute change in oxygenated hemoglobin in the muscle tissue, a measure of oxygen saturation independent of blood volume changes [16]. Thus, TOI% reflects the dynamic balance between O_2 supply and O_2 consumption. TOI% was lower both at the start of exercise and the termination of exercise, and the start and termination of recovery in the CFS patients in comparison to CON subjects (Figure 1). When we plotted the post-exercise recovery saturation, τ (sec), we showed that CFS patients (τ = 29.4s) took significantly longer than CON participants (τ = 17.7s) (Figure 2). These data indicate a delayed response in restoring this balance in O_2 supply and consumption in CFS relative to controls. There are a number of possible reasons for this delay, including a reduced metabolic function in the muscle due a potential mitochondrial dysfunction. Tomas et al. [28], and others have suggested that CFS patients have an abnormal metabolic bioenergetic function, and some have suggested a 'hypometabolic syndrome'[29-31]. Tomas et al. [28], showed that CFS patients had lower mitochondrial respiration rate and ATP production which would support our data during exercise as well as during recovery.

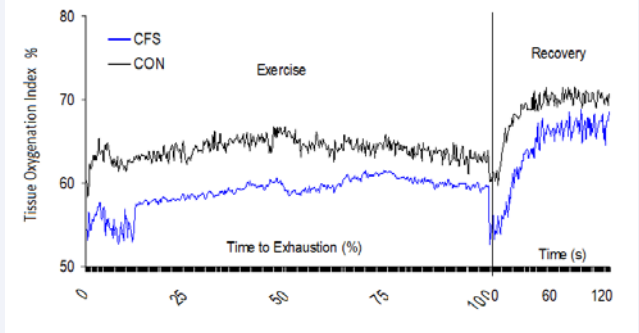

Figure 1 Tissue oxygenation index (%) during incremental exercise and post-exercise recovery in the CFS and CON groups.

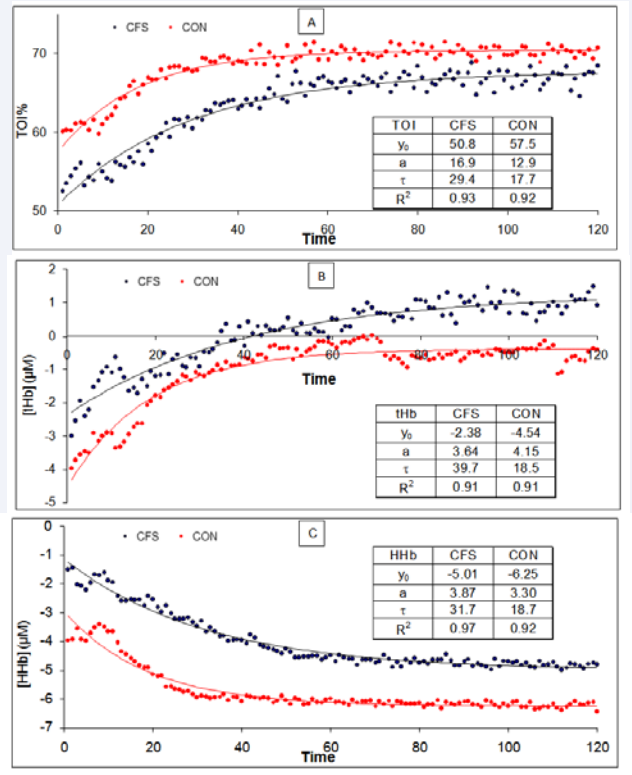

Figure 2 (A)-Resaturation trend of tissue oxygenation index (TOI%) during passive recovery following incremental exercise in the CFS and CON groups (B) Resaturation trend of total haemoglobin (tHb) during passive recovery following incremental exercise in the CFS and CON groups. (C) Resaturation trend of deoxyhaemoglobin (HHb) during passive recovery following incremental exercise in the CFS and CON groups.

The decrease in recovery %TOI kinetics noted in our study has been shown in similar diseases such as fibromyalgia [32]. However, other studies have found differences between fibromyalgia and CFS [26,27], and thus our haemodynamic kinetic changes reflect a new finding which may be of potential use for prognosis.

Similarly, there was a lower relative change in tHb in the CFS patients (-2.38μM) in comparison to the normal healthy CON subjects (-4.54μM) at the end of exercise (beginning of recovery). tHb has been used as an indirect measure for blood flow [33], indicating that blood flow to the muscle was compromised to a greater extent in CFS. Our kinetic τ (sec) data would suggest that there was a greater vasoconstriction in the muscle of CFS

vs. CON subjects (Figure 2). Others have shown that CFS patients might have an altered control of blood flow [11]. Furthermore, decreases in blood volume in CFS has been noted before [16,34], and this hypovolaemic state can therefore influence blood volume at the muscle during exercise. Increases in stroke volume occur to supply the greater metabolic demand with exercise [35], and blood pressure indices have been shown to be decreased in CFS [36], meaning that a possible reduction in stroke volume [37], may contribute to the decreased tHb in CFS. Also, CFS patients have shown exaggerated stroke index, low pressure, and elevated exertion and pain [26]. Vasoconstriction is a possibility in CFS [38], and this factor can provide a basis as to why there is a change in haemoglobin kinetics during recovery.

It is also important to note that changes in resting state can be altered in CFS [39], such as alterations in oxidative metabolism, and thus the changes that occur post-exercise in tHb can serve as a possible protective mechanism. It is possible that exercise induces an uncomfortable physiological state (as suggested by symptoms [40]), and therefore, the difficulty of an individual to adjust to this change can be counteracted by a quick return of blood volume as shown by the τ value.

HHb has been used to reflected O_2 extraction in muscle tissue [41,42]. Similar to the TOI% and tHb variables, our results showed that HHb kinetics was significantly slower in CFS patients (τ= 31.7s) in comparison to CON (τ = 18.7s) (Figure 2). Large decreases in HHb for CFS patients relative to control cases has been shown [17], but to our knowledge, HHb changes during recovery has not. The kinetics here suggests O_2 extraction impairment in an attempt for HHb to reach a steady-state level. This would support mitochondrial dysfunction and abnormal metabolic function in the muscle of CFS patients [28,29,31]. Taken together, the absolute changes in TOI%, and relative changes and recovery resaturation in tHb and HHb indicate significantly impaired hemodynamic and metabolic response in the muscle tissue of CFS patients during incremental exercise to volitional fatigue and during passive recovery.

Although potential peripheral mechanisms have been suggested for the differences in the muscle between CFS and CON, i.e., mitochondrial dysfunction [7,43], other research studies have shown that central nervous system dysfunction may also be contributing to this peripheral muscle fatigue in CFS patients [16,23,44]. For example, in our previous research we documented that prefrontal cortex HbO_2, 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 $HbO_2$and tHb may contribute to the reduced exercise load in CFS, and supports the contention that CFS, in part, is mediated centrally [16]. Boissoneault et al., 2016 [45], using fMRI showed altered functional connectivity in certain brain regions associated with memory and higher cognitive function in CFS. They also demonstrated using a clinical fatigue rating scale that connectivity to memory was correlated to fatigue symptoms, and supported evidence to suggest that brain network abnormalities exist. In a follow-up study, Boissoneault et al., 2018 [44], showed that cerebral blood flow variability (CBFV) and heart rate variability (HRV) was reduced in individuals with CFS compared to healthy controls, and that increased CBFV and HRV was associated with lower levels of fatigue in affected individuals. This would further suggest altered autonomic nervous system function.

CONCLUSION

Despite previous conflicting studies in the literature, our study provides support that muscle metabolism is impaired, specifically following exercise during recovery. Specifically, we provide further evidence of impaired oxygenation kinetics when returning to baseline. Questions regarding the exact mechanisms still remain, but taken together, alterations appear to exist in the brain and likely contribute to the peripheral dysfunction in muscle both during exercise and recovery that we noted in our study. We also showed that haemoglobin kinetics measures using NIRS can provide a simple, non-invasive technique to understand how the body is re-adapting to changes which occur following stressful events such as exercise.

LIMITATIONS

Further research is needed to investigate the effects of other perturbations on CFS patients [27], such as chronic exercise training, tilt-table experiments [18], and possibly pharmacological intervention to examine possible alterations in autonomic control (i.e., ANS dysregulation). More studies measuring muscle metabolism and oxygenation using NIRS with a larger cohort of participants is also required.

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