Title: Physiological cost of walking in those with Chronic Fatigue Syndrome (CFS): a case control study

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ABSTRACT

Purpose: To examine the physiological cost when walking in subjects with CFS and a matched control group, walking at their preferred and at matched walking speeds.

Methods: Seventeen people with CFS and 17 matched controls participated in this observational study of physiological cost during over-ground gait. Each subject walked for five minutes at their preferred walking speed (PWS). Controls then walked for five minutes at the same pace of their matched CFS subject. Gait speed and oxygen uptake, gross and net, were measured and oxygen uptake was expressed per unit distance ambulated. CFS subjects completed the CFS- Activities and Participation Questionnaire (CFS-APQ).

Results: At PWS the CFS group walked at a slower velocity of 0.84 ±0.21ms^{-1} compared to controls with a velocity of 1.19 ±0.13m·s^{-1} ($P<0.001$). At PWS both gross and net oxygen uptake of CFS subjects was significantly less than controls ($P=0.023$ and $P=0.025$ respectively). At matched velocity both gross and net physiological cost of gait was greater for CFS subjects than controls ($P=0.048$ and $P=0.001$ respectively).

Conclusion: The physiological cost of walking was significantly greater for people with CFS compared to healthy subjects. The reasons for these higher energy demands for walking in those with CFS have yet to be fully elucidated

INTRODUCTION

Chronic fatigue syndrome (CFS) is a debilitating condition of unknown aetiology and disputed pathophysiology, though there is mounting evidence that factors, such as lipid peroxidation and immune dysregulation can be involved in the development or maintenance of the illness. There are a number of published criteria used to diagnose people with CFS however the most commonly used and accepted are the criteria developed by the Centres for Disease Control (CDC) [1]. Diagnosis is based on signs and symptoms and exclusion of other conditions with similar features e.g. Hypothyroidism. The exact prevalence of CFS is difficult to determine but it is thought to be at least 0.2% - 0.4% [2]. Various groups have studied the gene expression in peripheral blood of patients with CFS, and from those studies the most predominant functional theme is that of immunity and defence. Work is ongoing to develop a "gene signature" for the illness [3] which might lead to a more objective diagnostic test being available in the future [4].

With such an array of clinical features, as defined by the CDC [1], it is not surprising that CFS appears to result in significant and lasting functional impairment. Few studies have objectively examined these functional limitations, in particular the walking ability of this group of patients. Boda et al. [5] analysed subjects' gait at three different speeds on a treadmill and reported that, at slower speeds, those with CFS took smaller and slower steps compared to healthy controls. In our initial study we measured the temporal and spatial gait parameters of those with CFS and controls using an instrumented walkway [6]. Similar to the study by Boda et al. we reported a number of statistically significant differences in the gait parameters between the two groups and concluded that those with CFS took smaller and slower steps. It was also noted that these differences were still present after a 15 minute period of sub-anaerobic exercise. In a subsequent study [7] we confirmed the previous

findings but also observed a number of differences between CFS and control subjects in terms of kinematic gait parameters when subjects walked at their preferred walking speed. However it might have been that the differences we observed were due to the slower walking speed of those with CFS and not a manifestation of the condition itself.

Overall there is objective and repeatable evidence to support the presence of locomotor impairment in those with CFS walking at their PWS. It is known that the physiological cost of walking is increased in many other pathological conditions with associated locomotor impairment, such as stroke [8,9], multiple sclerosis [10] and following lower limb amputation [11]. However, it is generally recognised that these higher energy costs may be due to the condition itself or simply a reflection of the relatively slow preferred walking speed of most patient groups. We were unable to find any previous studies investigating the physiological cost of walking in CFS. If indeed the physiological cost of walking is relatively higher in those with CFS this may go some way to explain the reduction in the functional abilities of the sufferer [12].

Therefore the aims of the study were to firstly examine the physiological cost of overground walking of subjects with CFS and a group of matched control subjects whilst walking at their PWS. Secondly to compare the physiological cost of walking between the two groups when the gait speed was matched i.e. when controls walked at the PWS of the CFS person to whom they were matched.

METHODS

Subjects

Seventeen people (12 females, 5 males) with CFS were recruited from local support groups. All subjects had a confirmed medical diagnosis of CFS and at the time of assessment current symptoms were examined to ensure the subjects complied with the CDC diagnostic criteria for CFS [1]. Our inclusion criteria stipulated that participants had to be aged between 18-65 years, have no co-morbidity that would restrict gait e.g. musculoskeletal, respiratory problems, and be able to walk continuously for a period of 5 minutes with or without a walking aid, although no subject chose to use a walking aid. The control group (12 females, 5 males) were a convenience sample and were matched to the patient group in terms of age and gender. The level of activity for the control participants was recorded using the short self-administered version of the International Physical Activity Questionnaire (IPAQ) [13]. The IPAQ categorises the participants' level of physical activity into one of three categories; low, moderate or high. For this study those with high levels of activity were excluded from taking part. The control group ultimately consisted of 6 subjects categorised as having low and 11 subjects as having moderate levels of activity.

Ethics

All subjects were given written information on the study and written, informed consent was obtained. All procedures were approved by Glasgow Caledonian University's Ethics Committee.

Procedure

A COSMED K4b^2 (Cosmed, Rome, Italy) gas analysis system was used to measure oxygen uptake during free walking. Gait speed and distance were measured using a standard stop-watch and a lap-counter. The gas analysis system was fitted to the participants were then were asked to sit at rest for a period of 2mins. At the end of this period the gait test commenced.

Subjects walked around an elliptical course on a level floor outlined by two cones 9.5m apart. This gave a shuttle length of 10m encouraging them to walk at a more consistent pace. For each test the participants walked for five minutes and the total distance walked and the time taken was recorded.

All subjects were asked to walk around the cones at their PWS. The control group were then given a minimum recovery period of five minutes, during which the COSMED system remained in place, and were then requested to walk at the PWS of the CFS patient to which they were matched. The matched pace was achieved by providing a tone at the start of each repetition, generated using PowerPoint slide transition advance slide facility (Microsoft Corporation), of the walking circuit and expecting the control to have completed the circuit by the successive bleep.

Activity and Participation Questionnaires

CFS subjects completed the Chronic Fatigue Syndrome Activity and Participation Questionnaire (CFS-APQ); this is a disease specific questionnaire that measures the activity limitations and participation restrictions over the last seven days [14]. Two scores are obtained from the questionnaire; the total score (CFS-APQ1), and satisfaction score (CFS-APQ2). The scores for CFS-APQ1 range from 1 indicating no activity limitations to 16

representing very severe activity limitations. The score for CFS-APQ2 ranges from 1 to 4, higher scores indicating more severe activity participation limitations [15].

Data Analysis

Descriptive statistics are presented as means and standard deviations. Age, weight, height and Body Mass Index (BMI) of the two groups, patient and control were compared using a paired t-test using Minitab version 15 (Minitab Inc.). Distance and duration of the walk were recorded. Gross and net oxygen uptake per kg body weight (VO2 kg^{-1} ($mL \cdot min^{-1} \cdot kg^{-1}$)) and VO2 kg^{-1} per unit distance walked (physiological cost) ($VO2 \cdot kg^{-1} \cdot m^{-1}$ ($mL \cdot min^{-1} \cdot kg^{-1} \cdot m^{-1}$) was used to analyse metabolic cost of gait. Gross measures are the actual values recorded during gait whereas the net measures are the measures taken during gait with the resting levels subtracted. The net measures are representative of the individuals' metabolic requirement to undertake gait. The average of these parameters was calculated between minutes 3 and 4 of the 5 minute walking period using Excel (Microsoft Corporation). Minutes 3-4 were selected as literature suggests that steady state is achieved at this time [16,17]. Test data was analysed using a one-way ANOVA using Minitab version 15 (Minitab Inc.) and the confidence level set at 95%.

RESULTS

There was no difference in anthropometric data between the CFS and the control group. Additionally there was no difference in resting VO_2 between the groups (Table 1). The CFS-APQ1 measured a median value of 10.6 (range 6.7 – 12.6) and, the CFS-APQ2 a median value of 3.0 (range 2.1 – 3.5). Both scores were on the mid to higher end of the scale indicating obvious activity and participation limitations [18]. All CFS subjects were unable to work or to undertake further education. Fifteen of the CFS subjects reported that their condition was stable and the remaining two reported that their condition was 'getting worse'.

Table 1 near here

At PWS the CFS group walked with a velocity of 0.84m·s^{-1} (±0.21ms^{-1}) and controls with a velocity of 1.19m·s^{-1} (±0.13m·s^{-1}) (P<0.001). When the control group were asked to walk at a pace equivalent to their matched patient's velocity the control population walked at a velocity of 0.84m·s^{-1} (±0.21m·s^{-1}) (P=0.236).

Figure 1 (a-b) shows the gross and net oxygen uptake, (c-d) and gross and net physiological cost for both CFS subjects and controls at their PWS and for the controls at the PWS of the CFS subjects. At PWS the gross oxygen uptake of CFS subjects was significantly less than controls (10.18 ±1.81mL·kg^{-1}, and 11.69 ±1.87mL·kg^{-1} respectively, P=0.023). When the controls walked at the PWS of the CFS subjects the value for controls was significantly lower than CFS subjects (8.61 ±1.37mL·kg^{-1}, P = 0.008). For net oxygen uptake at PWS the results for CFS subjects were significantly less than controls (6.97 ±1.73mL·kg^{-1}, and 8.58

±1.87mL·kg^{-1} respectively, P=0.025). At the matched speed, explained above, the values for controls were significantly lower than CFS subjects (5.5 ±1.34mL·kg^{-1}, P = 0.002)

Figure 1a - d near here

When the distance subjects walked was considered in relation to gross oxygen uptake, at PWS the physiological cost for CFS subjects was significantly greater than the controls (0.21 ±0.05mL·kg^{-1}·m^{-1} and 0.16 ±0.02mL·kg^{-1}·m^{-1} respectively, P=0.001). At matched speed the values for controls walking at the PWS of the CFS subjects was significantly less than CFS subjects at their PWS (0.18 ±0.04mL·kg^{-1}·m^{-1}, P=0.048). For net physiological cost at PWS the results for CFS subjects were significantly greater than controls (0.14 ±0.03mL·kg^{-1}m^{-1}, and 0.12 ±0.03mL·kg^{-1}m^{-1}) respectively, P=0.012) and again at matched velocity the values for controls at the PWS of the CFS subjects was significantly less than CFS subjects at their PWS (0.11 ±0.02mL·kg^{-1}m^{-1}, P = 0.001)

Thus it appears that, at PWS, both groups have a different metabolic oxygen requirement both for gross and net measures. The CFS subjects demonstrate a significantly greater physiological cost to walk a much shorter distance and thus walk with a much less energy efficient gait pattern. At PWS there was a 28% gross and a 17% net increase in metabolic cost per unit distance for CFS subjects in comparison to controls. Even when the controls were asked to walk at the speed matched to that of the subjects, the physiological cost for the CFS subjects remained significantly higher than that of the controls; a 17% gross and a 26% net increase in physiological cost for CFS subjects at matched speeds.

DISCUSSION

Results of the study demonstrated that the average preferred walking speed PWS of subjects with CFS was significantly lower than that of the control subjects. The PWS of the CFS subjects was around 25% less than the reported normal range of walking speed of approximately 1.2m·s^{-1}-1.4m·s^{-1} [19] whereas control subjects were within the reported range. The walking speed of the CFS subjects reported here is lower than that previously reported by our group (1.05 & 0.99m·s^{-1}) [6,7]. However in our previous study subjects walked for relatively short time and distance. In contrast the present study required subjects to walk continuously for five minutes. The PWS of our CFS subjects was higher than that recorded by Clapp et al [20] (0.71m·s^{-1}) however these subjects were walking on a motorised treadmill rendering direct comparisons questionable.

In summary those with CFS had a slower walking speed and lower oxygen uptake when walking at PWS. Although the relative oxygen uptake requirement for walking was lower in those with CFS, when the speed of walking was taken into consideration, the metabolic cost of walking in those with CFS was higher than that of controls. The fact that there remained a difference between the two groups when the speeds were matched suggests that the relatively high energy demands which occur when walking for those with CFS are in some way related to the condition itself, or deconditioning associated with the condition, and not just to the relatively slow PWS observed.

These results demonstrate that CFS subjects, for whatever reason, adopt a PWS that reduces their oxygen uptake but increases the energy cost of walking as measured by oxygen uptake per unit distance. This maybe explained by a desire to conserve energy (reduce oxygen uptake) and prevent fatigue but has the opposite effect (increase oxygen uptake per unit

distance). One possible explanation for this may be kinesiophobia, an excessive and debilitating fear of movement which may be a common feature of CFS [21]. Although no significant correlation between kinesophobia and maximal exercise capacity has been found [18] the presence of kinesiophobia would explain the slow walking speed observed in this study. In addition it may be that fear of movement in those with CFS leads, like fear of falling in other patient groups, to an increase in muscle activation which in turn increases the oxygen demand per unit distance ambulated.

Higher energy cost of walking may be due to biomechanical or metabolic factors [9]. A number of biomechanical factors have been proposed to explain the reason for relatively low PWS seen in other patient groups; these factors include poor balance, fear of falling, spasticity, joint stiffness [9,22]. There is some evidence that those with CFS may suffer from dizziness which is related to orthostatic intolerance [23]. This may lead to impaired balance although the consequential effect on gait has not been reported. Indeed our group have previously reported no difference between CFS subjects and healthy controls in terms of standing balance [6].

There is debate within the literature as to the presence and extent of metabolic impairments in those with CFS. Some studies have proposed that metabolic differences between CFS and control subjects may be due to mitochondrial abnormality. McCully et al [24] reported reduced muscle oxidative capacity in those with CFS and suggested this might be due to mitochondrial abnormality or deconditioning. Barnes et al [25] argued against mitochondrial abnormality but again suggested that observed metabolic differences between CFS and control subjects could be explained by deconditioning. It is possible that the present results may be partly explained by the presence of deconditioning in those with CFS. Even though the IPAQ was used to exclude control subjects with high levels of physical activity and thus

to match CFS and control subjects more closely in terms of physical activity profiles it may be that overall CFS subjects had lower activity levels than control subjects and, as such an increased likelihood of deconditoning.

A high energy cost of walking can limit the type and duration of everyday activity [26] as reflected in the results obtained from the CFS-APQ. These scores suggest that this group of CFS subjects experienced limitations in at least some aspects of their daily life and this may be due to the increased energy requirements discussed.

Graded exercise and cognitive behavioural therapy are management strategies which may be useful for some people with CFS to try to reduce the adverse physiological effects of inactivity and possible deconditioning. However exercise in itself can exacerbate the symptoms of CFS as exercise performed at too high an intensity can trigger immune dysfunction [27]. In order to increase physical activity, reduce deconditioning and reduce the physiological cost of walking, whilst avoiding exacerbations, any exercise programme for people with CFS should be undertaken under direction of an appropriately qualified practitioner.

Previous research has investigated oxygen uptake per unit distance, or the related energy expenditure, in other pathophysiological conditions. Even allowing for the methodological differences between the studies the situation appears to be that the physiological cost of walking for those with CFS is not very dissimilar to that of other patient groups such as those with Multiple Sclerosis [10], Post-poliomyelitis Syndrome [28], patients with orthopaedic conditions such as post hip fracture [22] or patients four years following a stroke [9].

LIMITATIONS

One of the main criticisms of previous research in CFS is that the control subjects are not matched to the patient group in terms of their level of activity. In the present study control subjects were excluded if they had high levels of activity as determined by the IPAQ. Even allowing for that control subjects who were included may have been more physically active compared to the CFS subjects.

As with all studies of this nature one of the limitations of this work is sample size. Whilst statistical differences have been shown it would have been advantageous to have larger numbers. To achieve a statistical power of 80% based on these data a sample size of approximately 35 would be required. As a result of the small sample size and of differences in activity levels between the populations the generalisability of these data should be viewed cautiously.

CONCLUSION

The results of this study suggest that the metabolic cost of walking is higher for those with CFS compared to their healthy peers and furthermore that the higher energy requirement is due in part to the condition itself, or the associated deconditioning, and not solely a reflection of the relatively slow preferred walking speed of those with CFS. Whilst the reasons for the relatively high energy costs of walking in those with CFS have yet to be fully elucidated, ultimately the functional effects appear to be a reduction in activity and participation in activities of daily living for those who suffer from this condition.

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	CFS			Control			
Variable	Mean	SD	Range	Mean	SD	Range	P
Age (Years)	49.2	8.4	35 - 64	48	8.4	32 - 64	0.13
Body Mass (kg)	72.6	11.3	55 - 100	77.3	14.1	55 - 105	0.08
Height (m)	1.67	0.07	1.59 – 1.77	1.68	0.07	1.53 – 1.76	0.46
BMI (kgm^{-2})	26.2	3.5	20.2 – 33.8	27.5	4.5	20 - 40	0.17
Duration of Symptom (Years)	12.8	6.4	2-24	NA	NA	NA	NA
Resting VO_2 ($mLkg^{-1}$)	3.2	0.18	2 – 4.4	3.1	0.15	1.8 – 4.2	0.67

Table 1 – Description of subjects, both CFS and control