DOI: 10.1111/j.1365-2362.2010.02310.x

ORIGINAL ARTICLE

Impaired cardiovascular response to standing in Chronic Fatigue Syndrome

Kieren G. Hollingsworth[*,†], David E. J. Jones[*], Roy Taylor[*,†], Andrew M. Blamire[*,†] and Julia L. Newton[*,‡]

[*]Institute of Cellular Medicine, [†]Newcastle Magnetic Resonance Centre and [‡]Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

ABSTRACT

Background Impaired skeletal muscle metabolism is recognized in chronic fatigue syndrome (CFS). This study examined the relationship between skeletal and cardiac muscle function and symptoms on standing in CFS using magnetic resonance spectroscopy (MRS) and impedance cardiography.

Materials and methods Phosphocreatine (PCr)/adenosine triphosphate (ATP) ratio by cardiac MRS, PCr/ADP and proton efflux by muscle MRS were performed in 12 CFS (Fukuda) and 8 controls. Head up tilt (HUT) and cardiac contractility (left ventricular work index, LVWI) (n = 64 CFS and matched controls) were found. Fatigue impact was accessed by Fatigue Impact Scale and orthostatic symptoms by Orthostatic Grading Scale (OGS).

Results Cardiac PCr/ATP correlated with measures of muscle bioenergetic function (half-time PCr recovery [$\kappa = -0{\cdot}71$, $P = 0{\cdot}005$] and half-time ADP recovery [$\kappa = -0{\cdot}60$, $P = 0{\cdot}02$]) suggesting that the muscle and cardiac bioenergetic function correlate in CFS. Four of 12 (33·3%) CFS patients had PCr/ATP values consistent with significant cardiac impairment. Those with impaired cardiac energy metabolism had significantly reduced maximal and initial proton efflux rates ($P < 0{\cdot}05$). Cardiac PCr/ATP ratio correlated with myocardial contractility (LVWI) in response to standing ($P = 0{\cdot}03$). On HUT, LVWI on standing was significantly higher in CFS ($P = 0{\cdot}05$) with symptoms on standing (OGS) occurring in 61/64 (95%) (vs. 25/64 [39%] controls; $P < 0{\cdot}0001$). OGS scores were significantly higher in those with abnormal LVWI responses to standing ($P = 0{\cdot}04$), with the LVWI on standing correlating with OGS scores ($r^2 = 0{\cdot}1$; $P = 0{\cdot}03$). HUT was positive in 19 (32%).

Conclusions Skeletal muscle and cardiac bioenergetic abnormalities associate in CFS. Cardiac bioenergetic metabolism associates with increase in cardiac contractility on standing. Haemodynamic assessment in CFS is well tolerated and safe with a high diagnostic yield comparable with unexplained syncope.

Keywords Cardiac function, diagnosis, fatigue.

Eur J Clin Invest 2010

Introduction

We have recently shown using magnetic resonance spectroscopy (MRS) that a proportion of patients with chronic fatigue syndrome (CFS) have impaired skeletal muscle bioenergetic function [1]. Significant exacerbations of symptoms with the physiological stressor of orthostasis are frequently described by those with CFS [2]. In addition, studies assessing noninvasive cardiac function have confirmed that those with severe CFS have reduced cardiac output in response to standing compared with controls [3–6]. In light of these combined findings, we hypothesized that the impaired muscle function seen in our recent magnetic resonance studies is not isolated to skeletal muscle but arises due to a systemic abnormality in those with CFS that also affects cardiac muscle. If our hypothesis is correct, this mechanism could explain the impaired cardiovascular function, particularly in response to physiological stressors such as standing, and the symptoms that arise in almost 90% of those with CFS [2], as well as providing an important new avenue for treatment intervention. Head up tilt (HUT) is a diagnostic tool used routinely in cardiovascular laboratories to explore the physiological responses to standing. Currently, the potential of this assessment modality alone or in combination with other diagnostic tools, such as MRI and noninvasive cardiac function, in those with CFS is not well studied.

In this study, we first examined the relationship between impaired skeletal muscle metabolism and cardiac muscle function using MRS. Using noninvasive impedance cardiography

(ICG), we then examined the relationship between cardiac bioenergetics and cardiac function in response to standing and, finally, we evaluated the diagnostic potential of the assessment of haemodynamic and cardiac functions in response to standing in a large cohort of patients with CFS.

Methods

Subjects

Subjects with CFS (Fukuda Criteria [7]) were identified via the patient support group 'ME North East'. Subjects had been diagnosed with CFS in a specialist CFS service within 2 years of assessment in the autonomic laboratory and all fulfilled the Fukuda diagnostic criteria. Each CFS patient was matched for age and sex to a sedentary control, recruited via notices placed within the hospital. Both patients and controls were excluded if taking any medication that could influence the assessment of haemodynamics (e.g. beta blockers, calcium antagonists, antidepressants), whether diabetic or with renal or hepatic disease. Subjects were excluded if not in sinus rhythm, unable to stand or unable to attend the autonomic laboratory for assessment. Details are shown in Table 1.

Symptom assessment tools

Subjects and controls completed two questionnaires assessing symptoms on the day of ICG. Fatigue impact was assessed by the Fatigue Impact Scale [8,9]. All subjects also completed the Orthostatic Grading Scale (OGS), a fully validated self-report assessment tool for the symptoms of orthostatic intolerance [10,11].

Muscle and cardiac magnetic resonance spectroscopy

In light of our recent findings of muscle bioenergetic function in CFS, we performed muscle ^{31}P MRS in 12 CFS patients and 8 controls using our previously published method [1]: maximum voluntary contractions were assessed on the basis of the best of five attempts using an MR-compatible force-metre, calibrated to a dyanometer (Cybex, Medway, MA, USA), and the muscle volume of the entire gastrocnemius and soleus was assessed by the region-of-interest definition on standard T_1-weighted images. Muscle pH was calculated from the phosphorus spectra of the muscle as previously outlined [1]. Assessment of cardiac metabolic function was also performed by cardiac high-energy phosphate metabolism measured using ^{31}P MRS [12]. Quantification of phosphocreatine (PCr), the γ resonance of adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (DPG) was performed using the AMARES time domain fit routine in the jMRUI processing software (Alter Systems, Lyon, France). After fitting, the ATP peak area was corrected for blood contamination by one-sixth of the amplitude of the combined 2,3-DPG peak [13], and the PCr/ATP ratios were calculated and corrected for saturation, with T_1 values of cardiac PCr and ATP taken from the literature [14]. Flip angle correction was made using a gadolinium-doped 20-mM phenyl phosphonic acid phantom at the centre of the coil [15,16]. A value of 1·6 was considered indicative of significant cardiac impairment [17]. MR imaging of the heart ruled out gross structural abnormalities (hypertrophy) in the subjects at the time of spectroscopy, although a detailed multiple-phase analysis was not performed.

Table 1 Subject characteristics for those patients who attended for the magnetic resonance spectroscopy studies

	CFS/ME impaired cardiac energetics	CFS/ME normal cardiac energetics	Controls
n	6	6	8
Age, mean ± SD	51 ± 11	49 ± 14	56 ± 12
FIS	105 ± 19*	97 ± 29*	2 ± 4
OGS	4·3 ± 2·0**	7·7 ± 3·0**	0·5 ± 0·8
HAD A	10 ± 4**	11 ± 5**	3 ± 2
HAD D	11 ± 6**	9 ± 5**	2 ± 1
Weight (kg)	66·5 ± 10·9	61·0 ± 9·9	66·5 ± 15·4
Maximum voluntary contraction (kg)	12·5 ± 2·7***	15·3 ± 4·0	18·4 ± 4·9
Muscle volume (cm^3)	460 ± 108	563 ± 144	541 ± 71
Phosphocreatine at rest (mM)	33·8 ± 3·5	34·4 ± 1·6	33·6 ± 2·7
Inorganic phosphate at rest (mM)	3·5 ± 0·6	3·3 ± 0·4	3·1 ± 0·8
Adenosine diphosphate at rest (mM)	9·65 ± 0·31**	9·38 ± 0·43	9·30 ± 0·30
pH at rest (–)	7·034 ± 0·015	7·020 ± 0·021	7·025 ± 0·011

FIS, Fatigue Impact Scale; OGS, Orthostatic Grading Scale; HAD, Hospital Anxiety and Depression Scale.
*$P < 0.0005$ wrt controls.
**$P < 0.05$ wrt controls.
***$P < 0.02$ wrt controls.

Assessment of haemodynamic responses to standing

A second cohort of CFS patients ($n = 64$) and matched controls also underwent formal autonomic assessment in the cardiovascular laboratory using continuous heart rate, beat-to-beat blood pressure measurement and ICG (Taskforce; CNSystems, Graz, Austria). Details of this cohort are shown in Table 2.

Immediate haemodynamic responses to standing. Responses to standing over 2 min were assessed. Positional orthostatic

Table 2 Subject characteristics and diagnoses reached on haemodynamic testing

	CFS/ME	Controls	*P*
n	64	64	
Age mean ± SD	46 ± 12	48 ± 15	0·5
Males (%)	23 (36)	23 (36)	NS
FIS	97 ± 28	12 ± 20	**< 0·0001**
Hx of loss of consciousness (%)	27 (40)	15 (23)	**0·04**
HUT positive (in those able to tolerate the test)	19	7	**0·004**
Systolic OH	24	26	0·6
Delayed OH	2	0	0·5
POTS	20	4	**0·0005**

HUT, head up tilt; Hx, history; OH, orthostatic hypotension; POTS, positional orthostatic tachycardia syndrome; FIS, Fatigue Impact Scale. Statistically different values are in bold.

tachycardia syndrome (POTS) and orthostatic hypotension were diagnosed using recognized diagnostic criteria [18,19].

Haemodynamic response to prolonged standing assessed during head up tilt. Passive HUT was performed according to established protocols [20]. Vasovagal syncope was diagnosed using recognized diagnostic criteria [20,21]. During HUT, cardiac function was assessed noninvasively by ICG using previously described methods [22,23] to derive:

1 Indicators of cardiac function:
- cardiac index (CI) – output from the heart per minute;
- left ventricular work index (LVWI) – amount of work the left ventricle must perform to pump blood each minute – considered the best impedance measure of myocardiac contractility.

2 Indicators of afterload, i.e. the pressure against which the heart must pump:
- systemic vascular resistance index.

3 Parameters of pre-load, i.e. the pressure with which the heart fills:
- thoracic fluid content;
- end-diastolic index.

Statistical analysis

Analysis was performed blinded to the status of patients and controls. Parametric variables are presented as mean and standard deviation, and comparisons drawn between groups using the student's *t*-test and proportions by Fishers exact test. Nonparametric data are presented as median and range, and comparisons drawn using Mann–Whitney tests. Correlation analyses were obtained using 'Prism-Graphpad' (http://www.graphpad.com/prism/Prism.htm). $P < 0{\cdot}05$ was considered a statistically significant result.

Ethical permission

Ethical permission was received from the Newcastle and North Tyneside Local Research Ethics Committee. All patients and controls provided written informed consent.

Results

The relationship between cardiac and skeletal muscle metabolism measured by ^{31}P MRS

We found a strong correlation between cardiac PCr/ATP ratio in the CFS group with measures of muscle bioenergetic function including both the half-time for PCr recovery ($\kappa = -0{\cdot}71$, $P = 0{\cdot}005$) and the half-time for ADP recovery ($\kappa = -0{\cdot}60$, $P = 0{\cdot}02$), suggesting that peripheral muscle bioenergetic function of the type found to be abnormal in CFS correlates with cardiac muscle bioenergetic abnormality, a finding supportive of linked underpinning mechanisms.

Mean PCr/ATP ratio in the CFS group was lower than that seen in the control group (Fig. 1), although this did not reach the statistical significance ($P = 0{\cdot}07$). Although values in the control group were tightly banded, those in the CFS group were widely scattered with 4 of the 12 (33·3%) having values consistent with significant cardiac impairment. The CFS group was dichotomized according to the median cardiac PCr/ATP ratio, forming a low PCr/ATP ratio group (PCr/ATP ratio = 1·57 ± 0·22) and a group with normal PCr/ATP ratio (1·90 ± 0·09) when compared with age-matched controls (who had a PCr/ATP ratio of 1·90 ± 0·10). There were no significant differences in fatigue severity, length of history or other symptoms

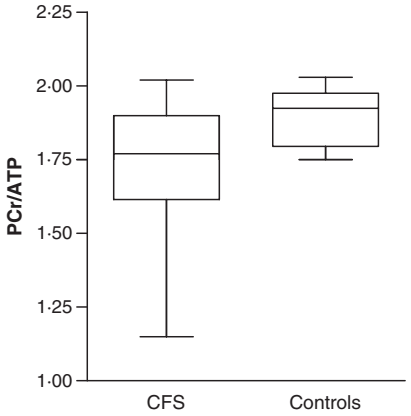

Figure 1 Cardiac bioenergetics assessed as mean ± SD PCr/ATP ratio measured using magnetic resonance spectroscopy.

between the two CFS groups (Table 1). This allowed us to study muscle metabolic function and acid handling in a CFS group with impaired cardiac energetics compared with a CFS group with normal cardiac energetics.

Baseline concentrations of PCr, inorganic phosphate and muscle pH were normal between the three groups (Table 1), although resting ADP was significantly higher in the impaired cardiac CFS energetics group. Muscle volumes were not significantly different between the three groups (Table 1). The maximum voluntary contraction achieved by the impaired cardiac energetics group was significantly lower than for the control subjects (12·5 ± 2·7 vs. 18·4 ± 4·9 kg; $P = 0·02$). However, the ratio of MVC in the two CFS groups was exactly the same as the ratio of muscle mass in the two groups (table 1), indicating that the two CFS groups performed equivalent work. Despite this, there was no significant difference in the percentage PCr depletion achieved during the second exercise (impaired cardiac energetics group: 19·8 ± 15·3%; normal cardiac energetics group: 25·5 ± 12·8%; and controls: 25·0 ± 8·3%, ns between groups), indicating that the three groups performed comparable work during exercise.

Chronic fatigue syndrome patients with impaired cardiac energetics also have impaired oxidative function compared with controls (Fig. 2a and b). Where there is cardiac energetic impairment in CFS patients, there also appears a oxidative metabolism impairment in muscle. Those CFS patients with impaired cardiac energy metabolism also had significantly reduced both maximal and initial proton efflux rates (Fig. 3a and b).

Cardiovascular function and cardiac muscle metabolism measured by ^{31}P MRS

We found strong and significant correlations between the impaired cardiac bioenergetics assessed by PCr/ATP ratio and the ICG markers of cardiac contractility in response to standing, particularly CI and LVWI (considered to be the best impedance indicator of myocardial contractility [LVWI]) (Fig. 4a and b), confirming that low PCr/ATP ratio (impaired cardiac energetics) corresponds with impairment in cardiac contractility parameters in response to prolonged standing. There were no relationships seen with preload parameters; however, there was a significant inverse relationship between cardiac bioener-

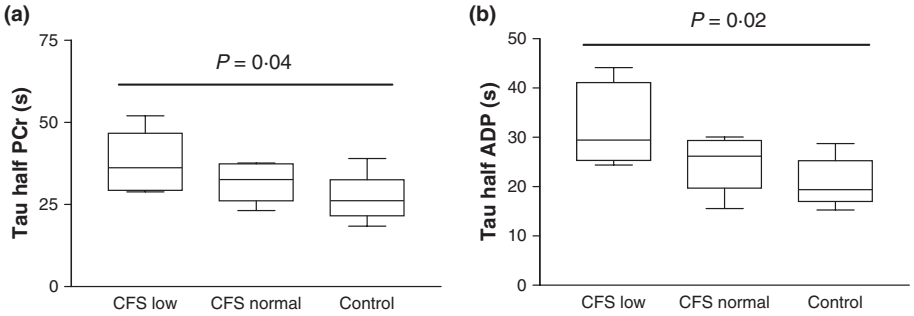

Figure 2 Comparison of the CFS groups and controls for (a) half-time for PCr recovery from end-exercise to baseline concentrations and (b) half-time for ADP recovery from end-exercise to baseline concentrations.

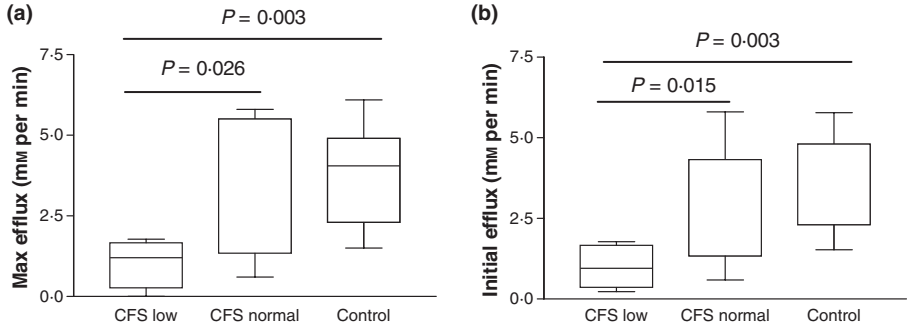

Figure 3 Comparison of the CFS groups and controls for (a) maximum proton efflux and (b) initial proton efflux.

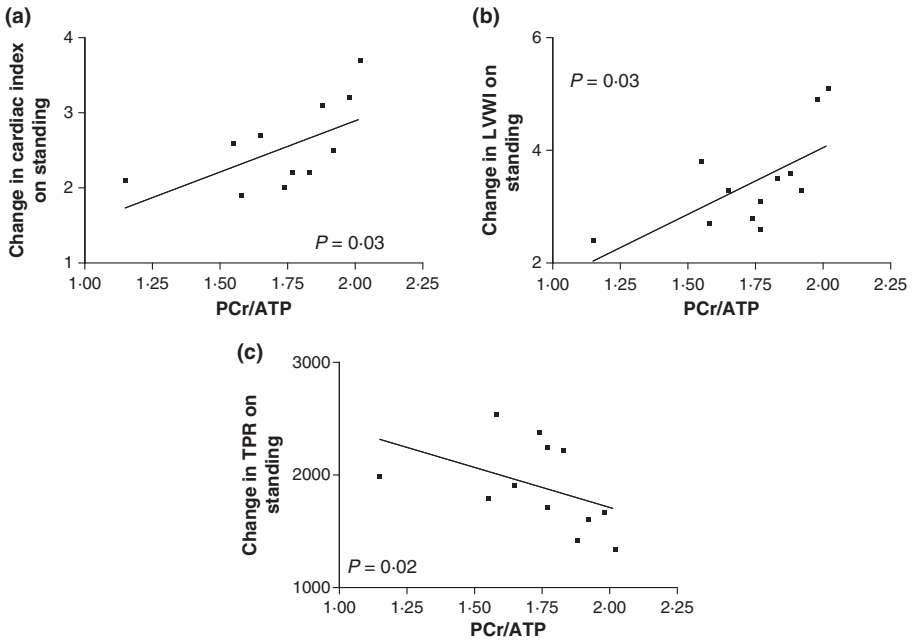

Figure 4 Correlations between the CFS cardiac PCr/ATP ratio and the change on HUT of: (a) cardiac index (CI), (b) left ventricular work index (LVWI) and (c) total peripheral resistance (TPR).

getics and afterload with increased total peripheral resistance being associated with impaired cardiac bioenergetic function (Fig. 4c), relationships were not present in the normal group.

Haemodynamic characteristics of CFS/ME patients

We went on to examine haemodynamic responses to immediate and prolonged standing in a second large and independent cohort of 64 CFS/ME patients compared with age- and sex-matched controls. LVWI on standing was significantly higher in the CFS group than in controls (Fig. 5a), confirming that the hearts of the CFS group appear to be working harder in response to the stress of standing compared with controls. Further clinical evaluation of the CFS/ME group confirmed that symptoms on standing assessed using the OGS occurred in 61/64 (95%) of cases compared with 25/64 (39%) of controls ($P < 0{\cdot}0001$) and that OGS scores were significantly higher in those with abnormal LVWI responses to standing (mean + 2 SD of the normal group) compared to those with normal LVWI (Fig. 5b), with the LVWI on standing correlating weakly but significantly with OGS scores ($r^2 = 0{\cdot}1$; $P = 0{\cdot}03$).

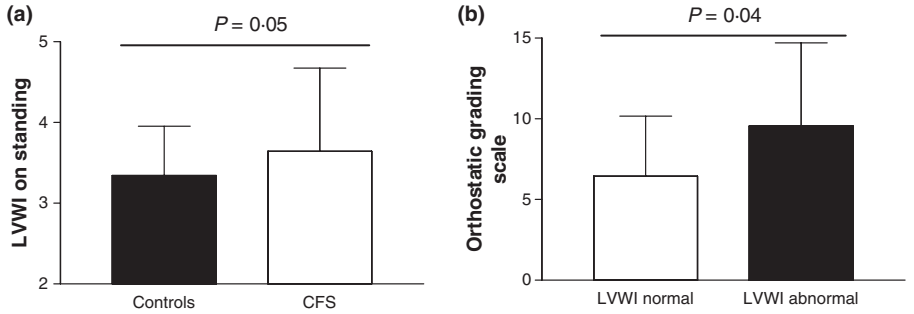

Figure 5 (a) Left ventricular work index in the CFS group attending for head up tilt with impedance cardiography ($n = 64$) compared with matched controls. (b) Orthostatic grading scale is significantly higher in those with LVWI outside the normal range (determined as mean + 2SD of the normal population).

Significantly more of the CFS group described a history of loss of consciousness (LOC) compared with the control group (Table 2). The assessment process was well tolerated, with only six of the CFS group unable to tolerate the HUT (9%) due to weakness compared with none of the control group ($P = 0{\cdot}03$). More of the CFS group had symptoms during the tilt test compared with the controls (32 [49%] vs. 17 [26%]; $P = 0{\cdot}01$).

More of the CFS group were found to have a diagnosis of POTS [24] (Table 2). Of those able to tolerate the HUT, 32% (19/66) of those with CFS were positive compared with 11% of controls, $P = 0{\cdot}02$. Of the 27 of the CFS patients who described a history of LOC, the HUT was positive in 15 (56%), which is comparable with previous studies of the predictive value of HUT in those with unexplained syncope.

Discussion

We have demonstrated that the skeletal muscle bioenergetic abnormality recently described in patients with CFS [1] associates with a similar cardiac bioenergetic abnormality. This impairment is associated with an increase in cardiac contractility on standing (i.e. the heart has to work harder for the same degree of physiological stress), the severity of which associates with symptoms on standing in those with CFS.

Our study provides a significant way to defining a bioenergetic phenotype in those with CFS, which appears to be systemic and associates with the symptoms on standing frequently described by those with CFS. The finding of varying degrees of muscle abnormality may account for the contradictory results in the previous CFS muscle literature [25–29] and underlines the need for a whole organ systematic approach to studies in CFS. Clearly, from this data, the cardiac status of the CFS population recruited for a given study will matter. If our CFS patients are considered as a single group, then oxidative muscle metabolism is not significantly impaired compared with controls, as we had previously reported [1], and this would not change by recruiting greater numbers: division by cardiac status, however, suggests the presence of subgroups within the population, one of which has impaired oxidative muscle metabolism. Within the observation that the maximal oxidative function is impaired, it is not possible to determine from these MRS experiments whether this is due to primary mitochondrial defects or alterations in muscle blood flow. Given the relationship between autonomic parameters and cardiac metabolism, the latter may well be true: further large studies are required to confirm the true prevalence of this bioenergetic phenotype in CFS with subsequent interventional studies to explore this relationship.

We had previously reported abnormalities in proton efflux in the CFS group as a whole [1] while end-exercise and minimum pH were not significantly different. Stratification by cardiac energetics helps us to explore this further and suggest that the impaired cardiac energetic group are weaker and less able to access anaerobic pathways, therefore producing less acid during exercise and having smaller proton effluxes post-exercise.

Considering the high prevalence of orthostatic symptoms in CFS [2], it was no surprise to find strong correlations between cardiac bioenergetics and cardiovascular responses to standing. The relationship between cardiac contractility on standing and symptoms was an important finding as it suggests that symptoms in those with CFS are potentially modifiable by treatment of the underlying cardiac abnormality. These abnormalities were CFS-specific, as there were no such correlations in the control population.

At this stage, we have not proven causation, and it is difficult to determine whether the impaired cardiac bioenergetics in CFS/ME represent 'cause' or 'effect'. Two mechanisms are possible. First, those with CFS have an intrinsic cardiac abnormality [30] that leads to impaired functional cardiac impairment, subsequent hypotension and reduced organ perfusion, all of which manifests as the characteristic symptoms of CFS. Alternatively, afterload abnormalities involving impaired vascular response to orthostatic pooling may lead to a secondary cardiac dysfunction. Our findings of a relationship between total peripheral resistance and cardiac bioenergetics would support this alternative hypothesis, but further work is needed to elucidate each of these mechanisms completely.

When we considered cardiac energy metabolism in the whole CFS patient group, this appeared to be mixed, with many individuals falling in the normal range with some individuals showing impairment. This suggests that within the symptom complex of CFS, there is a group of patients in whom an actual cardiac abnormality is present (defined by the presence of PCr/ATP ratio < 1·6 [17]). The heterogeneity of patients included in CFS studies is well recognized, however, despite the usage of specific diagnostic criteria for inclusion, and we could not symptomatically differentiate between the normal and impaired cardiac energetic group. This underlines how important it is to correctly characterize patients with CFS and to study the underlying physiological parameter rather than the symptom complex. We would therefore suggest that there are a group of patients with CFS who have an underlying cardiac abnormality and it is only on performing appropriate examination that these high-risk patients will be identified, and understanding of the physiological mechanisms that lead to the abnormality explored. It is unclear what the long-term impact of the cardiac abnormalities will have for those with CFS. However, our findings of reduced survival in those with the fatigue-associated chronic disease and primary biliary cirrhosis [31] and studies confirming a comparable fatigue phenotype between primary biliary cirrhosis and CFS [32] would point to an (as yet) unidentified

risk for those with CFS, and our findings of cardiac dysfunction in a proportion of patients may suggest the group at increased risk.

This study has examined the tolerability and diagnostic potential of assessment protocols that examine haemodynamic responses to immediate and prolonged standing in CFS and, for the first time, examines the relationship between measures of cardiovascular function, cardiac energetics at rest and muscle energetics under exercise in CFS patients. HUT is one of the assessment modalities of choice in the evaluation of those with unexplained syncope, and is recommended in national and international guidelines [33–35]. In contrast, the UK NICE CFS guidelines [36] actively discourage the assessment by HUT. This is surprising considering the apparent pathophysiological overlap between neurally mediated hypotension and CFS [37,38,39]. Our study confirms a comparatively high diagnostic rate in CFS particularly in those with a history of syncope. We would recommend therefore that referral for cardiovascular testing, including HUT testing, is encouraged in those where symptoms on standing are predominant, and particularly where there is a history of syncope or presyncope. Importantly, our positivity rate in our control group was similar to previous controls [40].

This study has some limitations. The study group could clearly be considered to be self-selected, and as a result biased, as they were recruited via the local patient support group. However, all participants had been seen within a local CFS service within 2 years and been diagnosed with the formal Fukuda criteria. A further limitation is that this study cannot establish a direction of causality for the associations seen in cardiac metabolism, skeletal muscle metabolism and autonomic function. The findings are, however, consistent with a model in which a cardiovascular impairment might lead to impaired oxidative function, perhaps through impaired venous run-off post-exercise. Our future work will involve assessing groups of newly diagnosed CFS patients to determine their cardiac and muscle phenotypes and following them through time. In addition, large-scale bioenergetic phenotyping of cohorts of patients with CFS are required with a view to understanding those biomarkers that are unique to CFS, which will subsequently allow the development of investigative treatment algorithms specific to this disease.

Sources of funding

Funding was provided by the Medical Research Council, ME Research UK, Irish ME Trust, John Richardson Research Group and CFS/ME Northern Clinical Network.

Author contributions

None of the funders contributed to the design, performance or interpretation of the results of this study.

Conflict of interest

None of the authors have any conflict of interest.

Address

Institute of Cellular Medicine (K. G. Hollingsworth, D. EJ Jones, R. Taylor, A. M. Blamire, J. L. Newton); Newcastle Magnetic Resonance Centre (K. G. Hollingsworth, R. Taylor, A. M. Blamire); Institute for Ageing and Health, Newcastle University, UK (J. L. Newton).

Correspondence to: Professor Julia L. Newton, Institute for Ageing and Health, Medical School, Framlington Place, Newcastle-upon-Tyne NE2 4HH, UK. Tel.: 0191 2824128; fax: +44 191 2825370; e-mail: julia.newton@nuth.nhs.uk

Received 13 January 2010; accepted 9 April 2010

References

1 Jones DEJ, Hollingsworth KG, Taylor R, Blamire AM, Newton JL. Abnormalities in Ph handling by peripheral muscle and potential regulation by the autonomic nervous system in chronic fatigue syndrome. *J Int Med* 2009;**267**:394–401.
2 Newton JL, Okonkwo O, Sutcliffe K, Seth A, Shin J, Jones DEJ. Symptoms of autonomic dysfunction in chronic fatigue syndrome. *QJM* 2007;**100**:519–26.
3 Peckerman A, La Manca JJ, Dahl KA, Chemitiganti R, Qureishi B, Natelson BH. Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome. *Am J Med Sci* 2003;**326**:55–60.
4 LaManca JJ, Peckerman A, Walker J, Kesil W, Cook S, Taylor A *et al*. Cardiovascular response during head-up tilt in chronic fatigue syndrome. *Clin Physiol* 1999;**19**:111–20.
5 Karas B, Grubb BP, Boehm K *et al*. The postural orthostatic tachycardia syndrome: a potentially treatable cause of chronic fatigue, exercise intolerance, and cognitive impairment in adolescents. *PACE* 2000;**23**:344–51.
6 Yoshiuchi K, Quigley KS, Ohashi K, Yamamoto Y, Natelson BH. Use of time-frequency analysis to investigate temporal patterns of cardiac autonomic response during head-up tilt in chronic fatigue syndrome. *Autonom Neurosci* 2004;**113**:55–62.
7 Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A *et al*. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Int Med* 1994;**121**:953–9.
8 Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis* 1994;**18**(Suppl. 1):S79–83.
9 Kos D, Nagels G, D'Hooghe MB, Duportail M, Kerckhofs E. A rapid screening tool for fatigue impact in multiple sclerosis. *BMC Neurol* 2006;**6**:27.
10 Schrezenmaier C, Gehrking JA, Hines SM, Low PA, Benrud-Larson LM, Sandroni P. Evaluation of orthostatic hypotension: relationship of a new self-report instrument to laboratory-based measures. *Mayo Clin Proc* 2005;**80**:330–4.
11 Newton JL, Jones DEJ. The population prevalence of autonomic dysfunction and daytime somnolence in primary biliary cirrhosis. *Hepatology* 2007;**47**:1496–505.

12 Schar M, Kozerke S, Harvey PR, Boesiger P. Local linear shimming for cardiac SSFP imaging at 3T. *Proc ISMRM* 2002;**10**:1735.
13 Conway MA, Bottomley PA, Ouwerkerk R, Radda GK, Rajagopalan B. Mitral regurgitation. Impaired systolic function, eccentric hypertrophy, and increased severity are linked to lower phosphocreatine/ATP ratios in humans. *Circulation* 1998;**97**:1716–23.
14 Tyler DJ, Hudsmith LE, Neubauer S, Clarke K, Robson MD. Measurement of the longitudinal relaxation time (T_1) of cardiac phosphorus metabolites at 3T. *Proc ISMRM* 2006;**14**:3099.
15 Buchli R, Boesiger P. Comparison of methods for the determination of absolute metabolite concentrations in human muscles by ^{31}P MRS. *MRM* 1993;**30**:552–8.
16 Haase A, Hanicke W, Frahm J. The influence of experimental parameters in surface-coil NMR. *JMR* 1984;**56**:401–12.
17 Neubacher S, Horn M, Cramer M, Newell JB, Peters W *et al*. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. *Circulation* 1997;**96**:2190–6.
18 Grubb BP, Kanjwal Y, Kosinski DJ. The postural orthostatic tachycardia syndrome: a concise guide to diagnosis and management. *J Cardiovasc Electro* 2006;**17**:108–12.
19 Anon. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *J Neurol Sci* 1996;**144**:218–9.
20 Parry SW, Reeve P, Lawson J, Shaw FE, Davison J, Norton M *et al*. The Newcastle Protocols 2008: an update on head-up tilt table testing and the management of vasovagal syncope and related disorders. *Heart* 2009;**95**:416–20.
21 Brignole M, Alboni P, Benditt DG, Bergfeldt L, Blanc JJ, Bloch-Thomsen PE *et al*. Guidelines on management (diagnosis and treatment) of syncope – update 2004. *Europace* 2004;**6**:467–537.
22 Parry SW, Norton M, Pairman J, Baptist M, Wilton K, Reeve P *et al*. Impedance cardiography: a role in vasovagal syncope diagnosis?. *Age Ageing Adv Access*; 2009;**38**:718–23.
23 Fortin J, Habenbacher W, Heller A, Hacker A, Grullenberger R, Innerhofer J *et al*. Non-invasive beat-to-beat cardiac output monitoring by an improved method of transthoracic bioimpedance measurement. *Comput Biol Med* 2006;**36**:1185–203.
24 Hoad A, Spickett G, Elliott J, Newton JL. Postural orthostatic tachycardia syndrome is an under-recognised condition in chronic fatigue syndrome. *QJM* 2008;**101**:961–5.
25 Lane RJM, Barrett MC, Taylor DJ, Kemp GJ, Lodi R. Heterogeneity in chronic fatigue syndrome: evidence from magnetic resonance spectroscopy of muscle. *Neuro Disorders* 1998;**8**:204–9.
26 Wong R, Lopaschuk G, Zhu G, Walker D, Catellier D, Burton D *et al*. Skeletal muscle metabolism in the chronic fatigue syndrome. *Chest* 1992;**102**:1716–22.
27 McCully KK, Smith S, Rajaei S, Leigh Jnr JS, Natelson BH. Blood flow and muscle metabolism in the chronic fatigue syndrome. *Clin Sci (Lond)* 2003;**104**:641–7.
28 Barnes PRJ, Taylor DJ, Kemp GJ, Radda GK. Skeletal muscle bioenergetics in the chronic fatigue syndrome. *JNNP* 1993;**56**:679–83.
29 Paul L, Wood L, Behan WMH, Maclaren WM. Demonstration of delayed recovery from fatiguing exercise in chronic fatigue syndrome. *Eur J Neurol* 1999;**6**:63–9.
30 Myhill S, Booth N, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. *Int J Clin Exp Med* 2009;**2**:1–16.
31 Jones DEJ, Bhala N, Burt JA, Goldblatt J, Newton JL. Four year follow up of fatigue in a geographically defined primary biliary cirrhosis patient cohort. *Gut* 2006;**55**:536–41.
32 Jones DEJ, Gray JC, Newton JL. Perceived fatigue is comparable between difference disease groups. *QJM* 2009;**102**:617–24.
33 Parry SW, Frearson R, Steen N, Newton JL, Tryambake P, Kenny RA. Evidence-based algorithms and the management of falls and syncope presenting to acute medical services. *Clin Med* 2008;**8**:157–62.
34 Parry SW, Kenny RA. Diagnosis and differential diagnosis of syncope using the head-up tilt table test. *QJM* 1999;**92**:623–9.
35 Strickberger SA, Benson DW, Biaggioni I, Callans DJ, Cohen MI, Ellenbogen KA *et al*. AHA/ACCF scientific statement on the evaluation of syncope. *Circulation* 2006;**113**:316–27.
36 Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (encephalopathy); diagnosis and management. Available at: http://www.nice.gov.org. Accessed on 24 April 2010.
37 Rowe PC, Calkins H. Neurally mediated hypotension and chronic fatigue syndrome. *Am J Med* 1998;**105**:15S–21S.
38 Schondorf R, Freeman R. The importance of orthostatic intolerance in the chronic fatigue syndrome. *Am J Med Sci* 1999;**317**:117–23.
39 Schondorf R, Benoit J, Wein T, Phaneuf D. Orthostatic intolerance in the chronic fatigue syndrome. *J Auton Nerv Syst* 1999;**75**:192–201.
40 Parry SW, Gray JC, Baptist M, O'Shea D, Newton JL, Kenny RA. ''Front-loaded'' glyceryl trinitrate-head-up tilt table testing: validation of a rapid first line tilt protocol for the diagnosis of vasovagal syncope. *Age Ageing* 2008;**37**:411–5.

