

Muscle fibre characteristics and lactate responses to exercise in chronic fatigue syndrome

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Abstract

Objectives—To examine the proportions of type 1 and type 2 muscle fibres and the degree of muscle fibre atrophy and hypertrophy in patients with chronic fatigue syndrome in relation to lactate responses to exercise, and to determine to what extent any abnormalities found might be due to inactivity.

Methods—Quadriceps needle muscle biopsies were obtained from 105 patients with chronic fatigue syndrome and the proportions of type 1 and 2 fibres and fibre atrophy and hypertrophy factors were determined from histochemical preparations, using a semiautomated image analysis system. Forty one randomly selected biopsies were also examined by electron microscopy. Lactate responses to exercise were measured in the subanaerobic threshold exercise test (SATET).

Results—Inactivity would be expected to result in a shift to type 2 fibre predominance and fibre atrophy, but type 1 predominance (23%) was more common than type 2 predominance (3%), and fibre atrophy was found in only 10.4% of cases. Patients with increased lactate responses to exercise did have significantly fewer type 1 muscle fibres ($p < 0.043$ males, $p < 0.0003$ females), but there was no evidence that this group was less active than the patients with normal lactate responses. No significant ultrastructural abnormalities were found.

Conclusion—Muscle histometry in patients with chronic fatigue syndrome generally did not show the changes expected as a result of inactivity. However, patients with abnormal lactate responses to exercise had a significantly lower proportion of mitochondria rich type 1 muscle fibres.

pathogenesis, and many theories concerning its origins have been proposed.² One area of contention is the possibility that neuromuscular dysfunction may contribute to the fatigue in some cases. In general, muscles in patients with chronic fatigue syndrome do not exhibit characteristics of physiological fatigue or reduced static muscle strength.^{3,4} However, neuromuscular abnormalities, including disordered muscle energy metabolism on phosphorus magnetic resonance spectroscopy,⁵⁻⁷ abnormalities on single fibre electromyography,⁸⁻¹⁰ and various non-specific histological, histometric, and ultrastructural abnormalities on muscle biopsy, have been reported in some patients with chronic fatigue syndrome (table 1).¹⁰⁻¹⁸ Previous studies of incremental exercise indicated a "left shift" in anaerobic threshold in some patients with chronic fatigue syndrome, with a premature increase in plasma lactate concentrations at low work rates.¹⁹ We reported subsequently that 31 of 96 (32%) consecutive patients with chronic fatigue syndrome had abnormal lactate responses to a short period of exercise at work rates below the predicted anaerobic threshold.²⁰ Whereas this may have been due to the effects of inactivity, patients with abnormal lactate responses showed no more evidence of cardiovascular deconditioning than those with normal responses, and were less likely to have psychiatric disorders. Eighty four of these patients underwent muscle biopsy. In this paper, we report the histometric analysis of the biopsies in relation to the lactate responses to exercise, together with findings in an additional 21 cases ascertained subsequently. The findings are discussed in relation to previous observations on muscle biopsy changes in chronic fatigue syndrome, and we consider the issue of whether the changes reflect the effects of inactivity alone or some additional pathological process.

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Chronic fatigue syndrome comprises disabling fatigue, present for more than six months, together with symptoms that feature prominently impairments in concentration and short term memory, sleep disturbances, musculo-skeletal pain, and exertional intolerance, in the absence of definable medical or psychiatric disorders.¹ It is likely that a condition with such wide ranging and non-specific symptoms will prove to be heterogenous in aetiology and

Patients and methods

ASCERTAINMENT OF PATIENTS

The 96 patients in the original cohort fulfilled operative criteria for the diagnosis of chronic fatigue syndrome (Oxford criteria²¹). Eighty four patients underwent needle biopsy from the left quadriceps under local anaesthetic; the remainder either refused biopsy or the attending physicians requested that this procedure should not be performed. Subsequently, an additional 21 patients with chronic fatigue syndrome were ascertained and studied in a similar way, giving a total of 105 cases.

Table 1 Histological and histometric findings in patients with chronic fatigue syndrome

Authors	No of patients biopsied/studied	Histology	Histometry	Other findings and comments
Behan <i>et al</i> (1985) ¹¹	20/50	15/20 scattered necrotic fibres	Moderate type 2 fibre predominance and hypertrophy in all	Conspicuous increase in peripheral mitochondria and occasional tubular inclusions. 30/40 abnormal jitter on SFEMG, 6/6 abnormal magnetic resonance spectroscopy of muscle
Byrne <i>et al</i> (1985) ¹²	2/2	Normal	Type 2 atrophy in both consistent with disuse	Mild reduction in state 3 respiration on polarography of isolated mitochondria
Byrne and Trounce (1987) ¹³	11/11	Minicore change in one case	10/11 normal or mild 2b fibre atrophy	Glycolytic and mitochondrial enzymes normal in vitro
Karpati <i>et al</i> (1990) ¹⁴	?	Slight excess of central myonuclei, scattered small fibres in most. No inflammation		Striking MHC class I expression in 2 cases
Behan <i>et al</i> (1991) ¹⁵	50/50	3 cases occasional necrotic fibres. 2 cases tiny inflammatory foci. 4 cases regenerative changes. 25 cases prominent mitochondria on Gomori stain	39/50 mild and focal (6 cases) to severe and diffuse (33 cases) type 2 atrophy. 4 cases type 1 atrophy	40/50 (80%) cases showed structural mitochondrial abnormalities
Grau <i>et al</i> (1992) ¹⁶	20/20	9/20 non-specific abnormalities, including scattered small or necrotic fibres, abnormal oxidative enzyme staining, focal myofibrillar loss	3/20 type 2 hypertrophy	0/20 MHC class I expression
Preedy <i>et al</i> (1993) ¹⁷	23/23	2 cases had occasional split fibres, 2 others centronuclear chains	3/20 type 2 atrophy, 5 others hypertrophy of one or both fibre types	Significant reduction in muscle RNA/DNA composition (15%) but not muscle protein/DNA ratio
Edwards <i>et al</i> (1993) ¹⁸	74/74	Non-specific abnormalities in 81% of cases	27% low prevalence, 12% high prevalence of type 1 fibres, 5/74 fibre atrophy or hypertrophy	Similar abnormalities in 1/3 of normal control biopsies, TA studied in most cases
Connolly <i>et al</i> (1993) ¹⁰	26/35	Non-specific abnormalities in 9/10 cases with prominent myalgia cf. 3/16 other CFS cases		Abnormal biopsy findings in CFS cases with prominent myalgia associated with increased fibre density on SFEMG, EDC biopsied in all cases

SFEMG=Single fibre electromyography, TA=tibialis anterior, EDC=extensor digitorum communis.

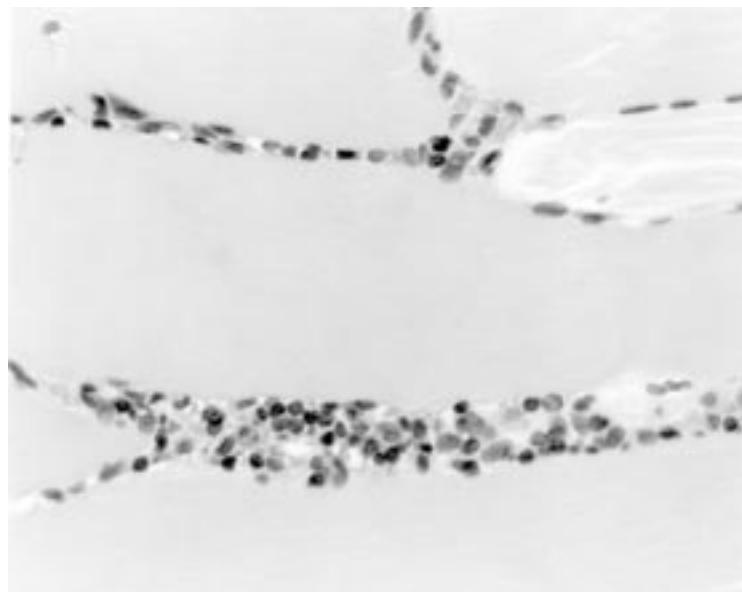
LACTATE RESPONSES TO EXERCISE

All patients undertook a subanaerobic threshold exercise test (SATET) as described previously.^{22, 23} Briefly, the anaerobic threshold was determined for each subject based on their age, weight, and sex, and patients exercised at 90% of this predicted work rate for 15 minutes. Venous lactate concentrations were determined before and immediately after

exercise, and 30 minutes after exercise. An abnormal SATET was defined as one in which lactate responses exceeded the upper 99% confidence limits at two or more time points (SATET+ve).

MUSCLE BIOPSY STUDIES

Biopsy samples were snap frozen in isopentane cooled in liquid nitrogen and prepared for histological and histochemical analysis using standard procedures.²⁴ Portions were also prepared for ultrastructural examination. Histometric analyses were performed on histochemical preparations using ATPase pH 9.4, the observer (MB) being blinded as to the patients' diagnoses. Slides were viewed with a $\times 16$ or $\times 25$ objective on a Leitz Dialux microscope fitted with a drawing tube attachment. This arrangement permitted simultaneous viewing of sections and the surface of an x-y coordinate digitising tablet (WACOM Ultra-pad). Diameters of type 1 and type 2 muscle fibres were measured using the NIH-Image v1.6 software package (NIH-Image is in the public domain and is available from the URL <http://www.rsb.info.nih.gov/nih-image> or FTP: zippy.nimh.nih.gov/pub/nih-image) on a Power Macintosh 7100/66 computer. Measurements were made of fibres in contiguous groups so that the fibre type proportions were automatically obtained. The system was calibrated using a ruled slide (Graticules Ltd) and the calibration checked across the viewing field in all planes. Type 1 fibre predominance was deemed to be present if the percentage of type 1 fibres exceeded 55%, and type 2 predominance if type 2 fibres exceeded 80%.²⁴



Longitudinal section from needle muscle biopsy, showing focal inflammation comprising T lymphocytes and macrophages. This 44 year old man was investigated three years after developing chronic fatigue syndrome, characterised by prominent myalgia after a flu-like illness. There were no abnormal signs on examination. His serum creatine kinase was mildly increased at 304 (normal <150) IU/l and SATET was abnormal. (haematoxylin and eosin originally $\times 400$).

Table 2 Histometric analysis of needle muscle biopsies from the vastus lateralis in 105 patients with chronic fatigue syndrome, (n (%)) of cases to nearest whole number

Type 1 Predominance	Type 1 Atrophy	Type 1 Hypertrophy	Type 2 Predominance	Type 2 Atrophy	Type 2 Hypertrophy
24 (23)	4 (4)*	34 (32)†	3 (3)	7 (7)*	25 (24)†

* Two cases both type 1 and type 2 atrophy.

† 13 cases both type 1 and type 2 hypertrophy.

Atrophy and hypertrophy factors were calculated for type 1 and type 2 fibres by the method of Brooke and Engel, as summarised by Dubowitz.²⁴ Fibre atrophy and hypertrophy were considered to be present if these limits were exceeded.

STATISTICAL ANALYSIS

Data for percentages of type 1 and type 2 fibres were normally distributed and between sample differences in distribution were analysed with Welch's *t* test (two tailed), which does not assume equal sample variances. Data for atrophy and hypertrophy factors were compared using the Mann-Whitney *U* test (two tailed). *p* Values <0.05 were considered significant.

Results

The 105 patients comprised 48 men and 57 women, of mean age 35.7 (SD 10.9) years. Thirty nine of 105 (37%) patients had abnormal lactate responses to exercise (SATET+ve). Histological and histochemical abnormalities were rare. One patient had an inflammatory infiltrate (figure), and non-specific abnormalities, such as occasional necrotic fibres and scattered atrophic fibres were seen in a few cases, as noted previously by others (table 1), but there were no consistent changes. Table 2 shows the histometric analysis for the entire patient group. Only 11 of 105 (10.4%) cases had muscle fibre atrophy, affecting type 1 fibres in four cases, type 2 fibres in

two, and both in two cases. Muscle fibre hypertrophy was more common, being found in 59 cases (56.2%). Type 1 and type 2 fibres were affected with similar frequency, with both fibre types showing hypertrophy in 13 of 59 cases (22%). Type 1 predominance was found in 23% cases overall, compared with only 3% showing type 2 predominance. Table 3 compares the histometric data in patients with abnormal SATET with findings in patients with normal lactate responses to exercise. The average atrophy and hypertrophy factors for type 1 and type 2 fibres did not differ significantly in these two groups, but patients, particularly women, with abnormal lactate responses to exercise (SATET+ve) had significantly fewer mitochondria rich type 1 muscle fibres (men 40.1 (SD 13.5)% *v* 48.0 (SD 12.3%), *p*=0.043; women 37.3 (SD 10.1) *v* 50.4 (SD 13.9)%, *p*<0.0003). In addition, SATET+ve women had a significantly higher mean type 2 fibre hypertrophy factor (333.4 (SD 343.9) *v* 134.5 (SD 241.3), *p*=0.013). It should be noted, however, that there was only a relative deficiency of type 1 fibres in the SATET+ve patients; absolute type 1 fibre deficiency (<20% type 1 fibres) was seen in only three SATET+ve patients (7.7%), and in none of the SATET-ve patients. This relative deficiency of type 1 fibres was more pronounced in those SATET+ve patients with the most pronounced abnormal lactate responses to exercise (raised baseline lactate and/or postexercise lactate>6 mM, table 4) (men 32.0 (SD 10.4)% *v* 48.0 (SD 12.3)%, *p*=0.011; women 35.3 (SD 9.9)% *v* 50.4 (SD 13.9)%, *p*<0.0017). In this subgroup analysis, SATET+ve women again showed the trend to type 2 hypertrophy found in the overall chronic fatigue syndrome patient group (table 3) (411.6 (SD 434.2) *v* 134.5 (SD 241.3), *p*<0.06). Examination of electron microscopic

Table 3 Comparison of histometric data in relation to lactate responses to exercise, (mean (SD) for type 1 and type 2 fibre composition, atrophy, and hypertrophy factors)

	% Type 1	% Type 2	Type 1 atrophy factor	Type 1 hypertrophy factor	Type 2 atrophy factor	Type 2 hypertrophy factor
Upper normal limit	55	80	M=150, F=100	M=150, F=400	M=150, F=200	M=400, F=150
SATET +ve:						
Men (n=22)	40.1 (13.5)	59.9 (13.5)	49.8 (74.2)	233.6 (323.5)	45.8 (52.6)	250 (333.9)
Women (n=17)	37.3 (10.1)	62.7 (10.1)	7.2 (8.8)	436.1 (360.3)	41 (81.9)	333.4 (343.9)
SATET -ve:						
Men (n=26)	48.0 (12.3)	52.0 (12.3)	55.0 (104.2)	168.9 (176.7)	72.0 (132.2)	271.9 (403.6)
Women (n=40)	50.4 (13.9)	49.6 (13.9)	12.8 (26.3)	353.7 (488)	56.2 (80.6)	134.5 (241.3)
SATET +ve <i>v</i> SATET -ve (p value):						
Men	0.043	0.043	0.63	0.49	0.793	0.64
Women	0.0003	0.0003	0.90	0.17	0.18	0.013

Table 4 Histometric comparison of patients with increased lactates at rest or > 6 mM after exercise, with patients with normal lactate responses to exercise (SATET-ve, table 3)

	% Type 1	% Type 2	Type 1 atrophy factor	Type 1 hypertrophy factor	Type 2 atrophy factor	Type 2 hypertrophy factor
Upper normal limit	55	80	M=150, F=100	M=150, F=400	M=150, F=200	M=400, F=150
SATET +ve (mean (SD)):						
Men (n=6)	32 (10.4)	68 (10.4)	45.2 (59.7)	447.7 (531.3)	36.5 (53.9)	442.2 (574.2)
Women (n=9)	35.3 (9.9)	64.7 (9.9)	10.0 (9.94)	437.8 (318.8)	24.4 (24.4)	411.6 (434.2)
SATET +ve <i>v</i> SATET -ve (p value):						
Men	0.011	0.011	0.86	0.17	0.42	0.31
Women	0.0017	0.0017	0.48	0.22	0.35	0.06

preparations from 41 randomly selected cases (11 men and nine women from the SATET+ve group and 12 men and nine women from the SATET-ve group) disclosed no significant abnormalities, and in particular, mitochondria appeared structurally normal in all cases.

Discussion

Histological examination in our study disclosed no consistent abnormalities, although non-specific changes were seen occasionally, as noted by others (table 1). Edwards *et al*¹⁸ found abnormalities such as fibre necrosis, regenerating fibres, nemaline rods, targetoid fibres, and histochemical changes such as single fibre glycogen depletion in 81% of biopsies (mainly from the tibialis anterior) in patients with chronic fatigue syndrome, although these were also present in about a third of normal control samples. A high prevalence of such changes was also noted by Connolly *et al*¹⁰ in a subgroup of patients with chronic fatigue syndrome in whom myalgia and muscle tenderness were prominent. Notably, these abnormalities were found in the extensor digitorum communis, a muscle which would not normally be affected by inactivity to the same extent as a leg muscle. One of our patients had an inflammatory infiltrate, and it would seem that inflammation and class I MHC expression may occur occasionally in biopsies from patients with chronic fatigue syndrome.¹⁴⁻¹⁸ This is of some interest, as we have argued previously that some forms of chronic fatigue syndrome may follow a previous virally mediated inflammatory myopathy,²⁵ suggesting a continuum with polymyositis which could also encompass benign postinfection polymyositis.²⁶ Muscular function might be expected to deteriorate in patients with chronic fatigue syndrome, who are by definition relatively inactive. The magnitude and nature of the consequences of physical inactivity deserve emphasis, as some of the symptoms experienced by patients with chronic fatigue syndrome are reminiscent of those resulting from bed rest or immobilisation.² Complete immobilisation of the quadriceps results in reduced muscle protein turnover,²⁷ detectable within six hours,²⁸ and healthy young males lost 20% of static strength within one week of immobilisation in one study,²⁹ whereas in another, cardiorespiratory capacity was impaired by 25% after three weeks of bed rest.³⁰ Lack of physical activity in normal subjects increases the sense of mental and physical effort on subsequent exertion, reduces the desire for exercise,³¹ and impairs neuropsychological function, despite normal environmental stimulation.³² Autonomic changes, including postural hypotension and defective thermoregulation may also occur.³³ Changes in muscle fibre size and fibre type proportions with inactivity are variable, and differ in humans and experimental animals, and under different clinical and experimental situations. For example, immobilisation after surgery or injury to a limb results in sequential changes in muscle architecture, with an initial shift of fibres with type 1 characteristics to type 2, fol-

lowed by muscle fibre atrophy, which can affect either fibre type, or both, causing loss of muscle bulk and strength.³⁴⁻³⁶ Conversely, prolonged bed rest^{37,38} or unilateral lower limb unloading in young healthy subjects^{39,40} produced no consistent changes in fibre type distribution, but was associated with fibre atrophy and reduction in cross sectional area of muscles, whereas muscle unweighting experiments in rats produced a shift from slow twitch (mitochondria rich) to fast twitch fibres.⁴¹ The results of the histometric analysis of biopsies from our patients with chronic fatigue syndrome, however, did not reflect the effects of inactivity. There was no evidence of a shift from type 1 to type 2 fibres; indeed, type 1 fibre predominance was more common than type 2 predominance, and fibre atrophy was uncommon, with fibre hypertrophy being present in more than half the cases. Others have noted fibre hypertrophy in qualitative^{11,16} and quantitative^{17,18} studies of biopsies from patients with chronic fatigue syndrome, although some authors have reported significant muscle fibre atrophy.^{12,13,15} These discrepancies might reflect various factors, including the case mix of patients with chronic fatigue syndrome studied, and use of qualitative rather than quantitative analysis in some series. The aetiology and relevance of fibre hypertrophy found in the present study, and in some earlier reports, is presently unclear. By contrast with the whole group of patients with chronic fatigue syndrome studied, the patients with abnormal lactate responses to exercise did have significantly fewer type 1 fibres (and correspondingly more type 2 fibres) than patients with normal SATET (table 3), whereas there was no difference in mean atrophy factors. This difference was still more pronounced in the group of patients with the most abnormal lactate responses to exercise (table 4). Could this type 1 fibre deficiency in the SATET+ve patients have been the result of a greater degree of inactivity in this subgroup? This is possible, but there is no evidence to support the contention. As discussed above, whereas a shift from type 1 to type 2 fibres can be found with immobilisation, Ferretti *et al*²⁸ recently reported that six weeks of total bed rest in healthy young males did not result in significant changes in fibre type proportions, and only a non-significant trend to fibre atrophy; others have reported similar findings.³⁷ None of the patients in this study were bedbound or severely immobile at the time of investigation, and we reported previously that the SATET+ve patients did not differ from the SATET-ve patients in demographic characteristics such as employment status, and were no more deconditioned in terms of heart rate responses to exercise.²⁰ Other studies have also failed to show that patients with chronic fatigue syndrome are significantly less fit in terms of cardiac responses and oxygen consumption during exercise than normal sedentary subjects.^{42,43} This relative deficiency of mitochondria rich type 1 fibres may account for the left shift in anaerobic threshold in the subgroup of patients with increased lactate responses to exercise.¹⁹

However, there were frequent examples of patients with abnormal SATET who had a normal proportion of type 1 fibres, so this finding cannot be used to predict the situation in individual cases. There is some evidence that type 2 fibre predominance, and thus a relative deficiency of type 1 fibres, might have biological relevance. Type 2 fibres are stronger for their cross sectional area than type 1 fibres⁴⁴ and a preponderance of type 2 fibres might preserve static strength in patients with chronic fatigue syndrome while reducing endurance. Those with type 2 predominance tend to have poorer exercise endurance, which probably results from the relative inefficiency of ATP production in type 2 fibres compared with the mitochondria rich type 1 fibres.⁴⁵ Inherited fibre type characteristics may determine athletic aptitude and performance,⁴⁶ but inherited or acquired changes in fibre types may also predispose to disease. Type 2 fibre predominance has been reported previously in patients with "idiopathic exertional myalgia and fatigue"^{34,47} and in a recent study from Taiwan,⁴⁸ military recruits who had had heatstroke complicated by rhabdomyolysis had significantly higher proportions of type 2 fibres than those with heatstroke who did not develop this complication. In addition, as in the present study, there was a correlation between the proportion of type 2 fibres and blood lactate responses to exercise. It is interesting to note in this context that abnormal lactate responses to exercise were documented some 50 years ago in servicemen said to have "neurocirculatory asthenia".⁴⁹ Our findings suggest that abnormal lactate responses to exercise in some patients with chronic fatigue syndrome are unlikely to be due solely to inactivity. Although we found no abnormalities of mitochondrial structure, the relative deficiency of type 1 muscle fibres is in keeping with other reports concerning reduced oxidative metabolism and mitochondrial enzyme activity in muscle in some patients with chronic fatigue syndrome.^{5-7, 50} Whether this deficiency is due to changes in muscle activity patterns or more fundamental disorders of mitochondrial function remains to be determined.

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