Hyperventilation and chronic fatigue syndrome

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Summary
We studied the link between chronic fatigue syndrome (CFS) and hyperventilation in 31 consecutive attenders at a chronic fatigue clinic (19 females, 12 males) who fulfilled criteria for CFS based on both Oxford and Joint CDC/NIH criteria. All experienced profound fatigue and fatigability associated with minimal exertion, in 66% developing after an infective episode. Alternative causes of fatigue were excluded. Hyperventilation was studied during a 43-min protocol in which end-tidal PCO$_2$ (P$_{ETCO_2}$) was measured non-invasively by capnograph or mass spectrometer via a fine catheter taped in a nostril at rest, during and after exercise (10–50 W) and for 10 min during recovery from voluntary overbreathing to approximately 2.7 kPa (20 mmHg). P$_{ETCO_2} < 4$ kPa (30 mmHg) at rest, during or after exercise, or at 5 min after the end of voluntary overbreathing, suggested either hyperventilation or a tendency to hyperventilate. Most patients were able voluntarily to overbreathe, but not all were able to exercise. Twenty-two patients (71%) had no evidence of hyperventilation during any aspect of the test. Only four patients had unequivocal hyperventilation, in one associated with asthma and in three with panic. Only one patient with severe functional disability and agoraphobia had hyperventilation with no other obvious cause. A further five patients had borderline hyperventilation, in which P$_{ETCO_2}$ was < 4 kPa (30 mmHg) for no more than 2 min, when we would have expected it to be normal. There was no association between level of functional impairment and degree of hyperventilation. There is only a weak association between hyperventilation and chronic fatigue syndrome. When present, hyperventilation is usually related to known causes of respiratory stimulation such as asthma or panic.

Introduction
Chronic fatigue syndrome (CFS), sometimes known as post-viral fatigue syndrome or myalgic encephalomyelitis (ME), continues to attract attention and controversy. Despite competing claims for virology, immunology and psychiatry, its aetiology remains unclear. It has recently been claimed that hyperventilation plays an important role in the pathogenesis of CFS, with ‘every case’ amongst 100 consecutive referrals suffering from ‘chronic habitual hyperventilation’. Considerable publicity has surrounded these claims; however, doubts have been expressed about the methods used to determine hyperventilation, including excessive reliance on non-specific symptoms, and the reliability of provocation tests such as the ‘think test’. Establishing the clinical relevance of hyperventilation to CFS is therefore important, not least because of the treatment implications.

The definition and diagnosis of hyperventilation syndromes is controversial. Acute hyperventilation has been poorly described, but may result from a combination of undiagnosed organic disease, misattribution to serious disease and anxiety and panic. Using a non-invasive measure of P$_{ETCO_2}$ during a range of provocations, we have previously described patients who are either chronically hypocapnic at rest, or who are precipitated into prolonged hyperventilation by either exercise or voluntary overbreathing. On the basis of these results, we have since developed a screening test for hyperventilation based on a three-part provocation procedure which we...
have found useful as an adjunct to lung function testing. We applied a modified version of these procedures to patients with CFS.

Methods

Patients

We studied 31 consecutive attenders (19 females, 12 males) referred to a clinic specializing in chronic fatigue syndrome run by SW. Most had been referred from either hospital specialists or local general practitioners. None had been referred by mental health specialists. Nearly all had been extensively investigated for alternative causes of fatigue before referral. As is typical of such samples, there was an over-representation of women (20, 62%), and of upper socio-economic groups.

Twenty-eight (88%) fulfilled both the Oxford and the Joint CDC/NIH criteria for CFS. The remaining four had previously fulfilled criteria, but no longer satisfied the functional impairment criteria at the time of testing. Thirteen patients who did not fulfill these criteria were excluded. All subjects therefore experienced profound fatigue and fatigability associated with minimal exertion. In 66%, fatigue had developed after an infective episode. Post-exertional myalgia was reported by 72%. Twenty-seven (87%) belonged to a self-help organization. The mean duration of illness was 6 years prior to assessment (95% CI 3.6–8.3 years). In summary, we feel the sample is representative of the population of patients seen in specialist referral centres with a label of CFS/ME/PVFS. Standardized psychiatric diagnoses were made according to the DSM-III-R criteria (APA, 1987) after the initial interview which included the relevant sections of the Schedule for Affective Disorders and Schizophrenia. The pattern of diagnoses is listed in Table 1. Functional capacity was assessed using a four-question visual analogue scale for work, social and private leisure activities. The results were arbitrarily divided into mild, moderate and severe, ranging from some impairment in leisure activities with impairment in numbers of hours worked or work efficiency (mild), to being confined to bed or wheelchair (severe).

<table>
<thead>
<tr>
<th>Table 1 DSM-III-R psychiatric diagnoses in CFS patients (n = 31)</th>
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<td>Diagnosis</td>
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<td>Major depressive episode</td>
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<td>Dysthymia</td>
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<td>Panic disorder with or without agoraphobia</td>
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<td>Somatization disorder</td>
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<td>Generalized anxiety disorder</td>
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<td>Other psychiatric disorders</td>
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<td>Any psychiatric disorder</td>
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Respiratory measurements

End tidal PCO₂ (P_{ETCO2}) was measured by either a respiratory mass spectrometer (Centronic 200 MGA) or a rapid response infrared CO₂ analyser (Gould Capnograph IV), sampling via a fine-bore catheter taped a few mm inside one nostril to give a continuous measure of alternatively inspired and expired PCO₂. This gave an non-invasive recording of P_{ETCO2}, minimizing the possibility of higher centre modification of breathing inherent in more uncomfortable techniques using the mouthpiece. In patients with normal lungs, P_{ETCO2} is very close to arterial PCO₂.

Recording and analysis of the analogue CO₂ output used the Codas II data acquisition system running on a Viglen 486 computer. The PCO₂ signal was digitized at 100 Hz, and stored on disc for subsequent off-line breath-by-breath measurement of P_{ETCO2} using an electronic cursor calibrated to read in kilopascals (kPa). The signal was also displayed in real time on the computer screen during the experiment. A two-point calibration signal was added to the recording at the start and end of the run, using atmospheric gas for the low point and a certified respiratory instrument calibration standard gas containing 5% CO₂ (Corning) for the high value. P_{ETCO2} was measured under several conditions over 43 min. Rest in a comfortable chair for 10 min was followed by exercise on an electric cycle ergometer at a work rate sufficient to stress the subject, but one that could be maintained without exhaustion for a 10-min period. The work load was chosen by the subject roughly to simulate the level of activity outside the laboratory and ranged from 0 to 50 W, with a mean of 16.2 W. Two patients were unable to exercise, and three were unable to continue for the full 10 min, stopping after 5, 6 and 7 min, respectively. A further 10 min rest in a chair was followed by 3 min of voluntary overbreathing (VHV) to a P_{ETCO2} of about 2.7 kPa (20 mmHg) to simulate in the laboratory everyday activities such as talking and laughing which might precipitate hyperventilation. This also allowed patients to recognize the symptoms of hypocapnia if not present at rest. Recovery of P_{ETCO2} was recorded over the subsequent 10 min. P_{ETCO2} was averaged over successive 2-min periods throughout the protocol.

Our criteria for hypocapnia were more stringent than is usual. P_{ETCO2} > 4.0 kPa (30 mmHg) at rest, at all times during and after exercise, and at 5 min.
after the end of VHV was considered normal or at least indicative that hyperventilation was unlikely to be contributing significantly to symptomatology. 

\[ P_{\text{ETC}O_2} < 4.0 \text{ kPa (30 mmHg)} \] at rest indicated severe hyperventilation. A value > 4.0 kPa (30 mmHg) at rest combined with a low value either during or after exercise, or beyond 5 min after the end of VHV, suggested that hyperventilation could be easily induced by provocations even if absent at rest.

Results

Of 31 patients with CFS, 22 (71%) had a normal hyperventilation screen, 4 (13%) had unequivocal evidence of hyperventilation or a tendency to hyperventilate, and a further 5 (16%) had a borderline normal result. In the normal group there were 8 males (67% of males) and 14 females (74% of females). The abnormal group comprised one male (8% of males) and 3 females (16% of females) and the borderline group 3 males (25% of males) and 2 females (11% of females).

For the group of 22 patients without evidence of hyperventilation, mean resting \( P_{\text{ETC}O_2} \) was 4.90 ± 0.03 kPa (36.7 ± 0.20 mm Hg). During exercise, this increased to a mean of 5.30 ± 0.03 kPa (39.6 ± 0.23 mmHg), falling to a mean of 4.87 ± 0.02 kPa (36.5 ± 0.18 mm Hg) after exercise. During VHV, \( P_{\text{ETC}O_2} \) fell to a mean of 2.77 ± 0.21 kPa (20.8 ± 1.58 mm), recovering to over 4.0 kPa (30 mm Hg) within 2 min for males and by a mean time after the end of hyperventilation of 3.3 ± 0.5 min for females. Seventeen (77%) of these patients had no other apparent medical conditions and reported no symptoms other than chronic fatigue. Two patients admitted to frequent attacks of anxiety and two had asthma and hay fever. One patient complained of symptoms compatible with acute hyperventilation when younger and had been treated with pindolol.

Four patients, one male and three female, had unequivocal evidence of hyperventilation (Table 2, top four rows: ML, CF, AW, SW). Two were hypoxic throughout, one (CF) was precipitated into hypocapnia by exercise, and the fourth (SW) showed a slow recovery of \( P_{\text{ETC}O_2} \) following VHV and had general instability of resting \( P_{\text{ETC}O_2} \) throughout the run. Only one of these (AW) had severe functional impairment, two had moderate and one mild impairment, but three suffered from panic and the fourth agoraphobia. One (CF) suffered from asthma. Five more patients (IR, AH, BS, LC and YE in Table 2), three males and two females, had borderline evidence of hyperventilation with \( P_{\text{ETC}O_2} \) either at or near 4.0 kPa (30 mmHg), or below 4.0 kPa for not more than 2 min during any of the protocols. These patients were all moderately or severely incapacitated and, like the more unequivocally hyperventilating group, two had panic or anxiety which may have contributed to the hyperventilation.

Discussion

That hyperventilation can give rise to substantial fatigue is undisputed, although this is not associated with any decrement of muscle function on objective testing. Hypokalaemia and reduction in cerebral blood flow may be contributory factors. Similarly, profound fatigue is associated with panic disorder, a condition that is also associated with CFS and hyperventilation although the relationship between panic disorder and hypocapnia is far from simple. Thus the combination of hyperventilation and anxiety disorders can reproduce many, if not most, of the symptoms of CFS. If this is combined with a diagnosis of 'ME' or 'postviral fatigue', which in turn leads to continued rest and avoidance of activity, there is little difficulty in accepting the argument that hyperventilation and CFS are directly linked. The question is, how strong is this association? The current study addresses that question and, unlike previous studies, used rigorous criteria for the diagnosis of hyperventilation combined with accepted international operational criteria for the diagnosis of both CFS and psychiatric disorders.

Our results suggest that the link between hyperventilation and chronic fatigue syndrome is weak. The majority of our patients had no evidence of hyperventilation either at rest or in response to the physiological provocations of exercise and voluntary overbreathing. Indeed, it is remarkable that only two patients out of the entire group were unable to voluntarily overbreathe to < 20 mmHg, a physically demanding task even for normal subjects. When hyperventilation was demonstrated, there were often known respiratory stimuli such as asthma and panic to explain the hypocapnia. Only in one patient (AW, Table 2) was unequivocal hyperventilation associated with fatigue without a history of panic, but she suffered from agoraphobia, known to be associated with chronic hyperventilation. It could be argued that hyperventilation may occur when CFS becomes extreme, but there appeared to be no relation between the severity of hyperventilation and the degree of functional impairment, many of our borderline hyperventilation patients being severely impaired. Our patient sample appears clinically similar to that described by Rosen and colleagues (and indeed of other CFS patients seen in tertiary care, as most to date have been) but our results are closer to those of Riley et al., who found no difference in the mean end-tidal PCO₂ between 13 patients with CFS and 13 controls, both before and after exercise.
### Table 2 Abnormal and borderline patient details

| Initials | Age (years) | Sex | Illness duration (years) | Symptoms/conditions | Psychiatric diagnoses | Viral trigger | Functional impairment | Symptoms reproduced by VHV? | Mean rest $P_{E\text{CO}_2}$ (kPa) | Mean exercise $P_{E\text{CO}_2}$ (kPa) | Mean rest $P_{E\text{CO}_2}$ (kPa) | VHV Recovery $P_{E\text{CO}_2}$ (kPa) at 5, 10 min | Recovery $P_{E\text{CO}_2}$ (kPa) at 5, 10 min |
|----------|-------------|-----|--------------------------|---------------------|----------------------|--------------|---------------------|-------------------------------|-------------------------------|-----------------------------------|-----------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| ML       | 20          | M   | 1                        | Dyspnoea            | Panic disorder       | Y            | Mild                | N                            | 3.6 [3.5–3.7]                | 3.9 [3.7–4.0]                     | 4.0 [3.7–4.1]                      | 2.8 [3.1–3.5]                     | 3.1, 3.5                             |
| CF       | 42          | F   | 3                        | Asthma, Headaches   | Panic disorder       | Y            | Moderate            | N                            | 4.3 [4.1–4.4]                | 4.9 [4.7–5.3]                     | 3.2 [2.8–4.0]                      | 2.0 [3.7, 3.7]                    | 3'                                  |
| SW       | 28          | F   | 1.5                      | Dizziness           | Panic disorder       | Y            | Moderate            | Some                         | 4.4 [3.7–4.8]                | 4.8 [4.5–5.3]                     | 4.8 [4.7–5.1]                      | 3.3 [3.3, 3.6]                    | 3'                                  |
| BS       | 56          | M   | 33                       | Hypertension        | Somatization disorder| N            | Moderate            | N/A                          | 4.7 [4.3–5.1]                | 4.7 [4.0–4.5]                     | 4.7 [3.7–5.1]                      | 1.6 [4.0, 3.2]                    | 3'                                  |
| LC       | 39          | F   | 0.5                      | Memory loss         | Depression           | N            | Moderate            | N/A                          | 4.0 [3.7–4.3]                | 4.4 [4.3–4.4]                     | 4.0 [3.9–4.1]                      | 2.3 [3.9, 4.0]                    | 3'                                  |
| YE       | 40          | F   | 3                        | Dyspnoea at rest & exercise | Somatization disorder| Y            | Severe              | Most                         | 5.3 [4.9–5.5]                | Unable to push pedal at 0 load    | 2.5 [3.5, 3.5]                     | 3'                                  |

*Other than fatigue and myalgia*
These results cannot simply be generalized to CFS in the community or primary care. However, it is probable that many of the factors associated with hyperventilation, such as anxiety disorders, somatic symptoms and functional impairment, will have a strong influence on help-seeking behaviour. The prevalence of hyperventilation in cases of CFS in the community is unlikely to be greater than that reported here. We are unable to think of a selection bias that reduce the prevalence of hyperventilation in our sample below the ‘true’ prevalence in the community.

Our results do not support a role for hyperventilation in the aetiology of CFS as previously suggested. Indeed, we doubt that any single universal aetiological factor could underlie a disorder as heterogenous as CFS. Hyperventilation is a pathophysiological finding which implies excessive respiratory drive, and the cause or causes of this must always be sought.4

Acknowledgements
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