Breathing pattern awake and asleep in patients with myotonic dystrophy

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ABSTRACT: Patients with myotonic dystrophy often have an irregular pattern of breathing at rest, implying abnormality of breathing control. No central medullary defect has been found in such patients. We postulated that irregular breathing in myotonic dystrophy due to abnormal central respiratory output would persist during slow-wave sleep.

We examined the patterns of breathing whilst awake and asleep in seven patients with myotonic dystrophy, seven similarly weak nonmyotonic subjects and seven normal controls. Polysomnography was performed, and the coefficients of variation (CoV) of the breath intervals were analysed during different stages of sleep.

The myotonic group showed significantly greater variation in breath intervals than the other two groups whilst awake (median CoV 37 vs 18% for nonmyotonics) and during light sleep (31 vs 13%). This difference was not evident during slow-wave sleep (median CoV 12 vs 9% in nonmyotonic).

We conclude that irregular breathing in patients with myotonic dystrophy whilst awake and during light sleep, does not persist during slow-wave sleep. These results suggest that "behavioural" influences play a role in the abnormal breathing pattern found in myotonic dystrophy. The source of the irregular breathing is unlikely to be found in the medulla, but may originate from forebrain influences.


Abnormalities of ventilatory control have been suspected in patients with myotonic dystrophy (MD) because of undue sensitivity to sedative drugs [1], and the frequent finding of hypercapnia [2, 3]. Several studies [1–4] have shown a reduced ventilatory response to CO2 in MD. Although initially attributed to impairment of central respiratory drive, Saugier et al. [3] showed that the reduced response to CO2 was related to the degree of respiratory muscle weakness and, therefore, cannot be used as a valid index of central respiratory output in such patients.

A further characteristic of respiratory function in MD is a grossly disordered pattern of resting awake ventilation [1–3]. During wakefulness, breathing is governed by both the "metabolic" and "behavioural" systems of respiratory control, whilst during non-rapid-eye movement (non-REM) sleep, particularly slow-wave sleep (SWS), breathing is regulated predominantly by the metabolic control system [5]. Consequently, in normal subjects, breathing during SWS is characteristically very regular [6, 7]. As shown by ourselves and others, subjects with MD are prone to sleep apnoea syndrome (SAS), which may be either obstructive or apparently central [8–11]. We postulated that, if irregular breathing in MD is due to disordered central respiratory output, it should persist during slow-wave sleep. We have now extended our earlier study [10] by analysing the regularity of breathing awake and in nonapnoeic sleep in patients with MD; the findings are compared with those in patients with nonmyotonic muscle diseases, where defective central control has not been implicated.

Patients and methods

Subjects

Seven patients with MD were compared with seven patients with nonmyotonic generalized muscle disease and seven normal subjects [10] (table 1). The three groups were of similar age and sex distribution, and the two patient groups had similar severity of respiratory muscle weakness as assessed by vital capacity and maximum respiratory pressures. The study was approved by the Ethics Committee of Newcastle Health Authority. No patient was taking any medication likely to affect the pattern of respiration or quality of sleep.

Sleep studies

Each subject was admitted to hospital for two consecutive nights, the first night being an acclimatization night during which no detailed measurements were made. On the second night, polysomnography was performed with recording of electroencephalogram (EEG), electrooculogram (EOG), oral and nasal airflow using thermocouples, arterial oxygen saturation (Sao2) using an ear oximeter, and chest and abdominal motion using linearized magnetometers [12]. All the signals were recorded on FM tape and on paper using a heated pen recorder (Lectromed M19). Sleep staging was performed, after the method of Rechtschaffen and Kales [13], from the paper record by one experienced observer.
Analysis of breath intervals

The regularity of breathing was assessed by analysing the range of intervals between successive breaths from each subject whilst awake, and during light (Stage 1–2), deep (Stage 3–4) and REM sleep. Representative sections with at least 50 breaths without the presence of artefacts were chosen at random for analysis of breath intervals. Any periods with apnoeas >10 s duration were excluded from analysis. The intervals between successive breaths were examined by marking the apex of each breath waveform with a digitizer pen on a graphics tablet attached to an Apple IIe computer. For each subject, the mean and SD of 50–100 breath intervals were calculated and the results expressed as coefficient of variation (CoV%).

Statistical differences between the three groups of subjects were analysed using the nonparametric Kruskall-Wallis analysis of variance (ANOVA), using the Mann-Whitney U-test to assess the significance of differences between pairs of groups where ANOVA showed statistically significant differences.

Results

Sleep apnoea

All the subjects slept well on the study night as reported previously [10]. Sleep architecture was similar in the three groups, although there were considerable variations between subjects. One of the myotonic patients had no REM sleep during the study night. The myotonic subjects had more apnoeas and hypopnoeas than the normal and nonmyotonic subjects, particularly during non-REM sleep (table 1).

Breathing pattern

Figure 1 shows an example of tidal breathing in one patient with MD whilst awake and during Stage 4 sleep. The "chaotic" breathing awake was no longer present in SWS. The CoV% for each individual during wakefulness and the different levels of sleep are shown in figure 2. There was significantly greater variability of breath interval in the myotonic subjects than in the other two groups in the awake state (median CoV 37 vs 18% for

| Table 1. – Demographic data, respiratory function and apnoea/hypopnoea indices |
|------------------------------------------|-----------------|-----------------|
| Normal subjects                        | Myotonic dystrophy | Nonmyotonic weakness* |
| Sex F/M                                 | 3/4             | 4/3             | 4/3          |
| Age yrs                                 | 42              | 45              | 45           |
| VC % pred                               | (25–48)         | (39–52)         | (27–53)      |
|                                        | (109–134)       | (50–93)         | (28–93)      |
| Pmax cmH₂O                              | 94.4            | 48.1*           | 45.0*        |
|                                        | (48–120)        | (32–70)         | (10–86)      |
| Pmax cmH₂O                              | 103             | 37.0*           | 43.9*        |
|                                        | (100–170)       | (20–70)         | (15–75)      |
| A1 events·h⁻¹                           | 0.7             | 12.1            | 1.1          |
|                                        | (0–3)           | (0.4–39)        | (0–2.3)      |
| AHI events·h⁻¹                          | 4.1             | 29.4*           | 2.7          |
|                                        | (0.2–13)        | (3.7–84)        | (0.5–46)     |

Data are presented as mean, and range in parenthesis. F: female; M: male; VC: vital capacity; % pred: percentage of predicted; Pmax: maximum inspiratory pressures; Pmax: maximum expiratory pressure; A1: apnoea index; AHI: apnoea + hypopnoea index. *: diagnoses: facio-scapulo-humoral dystrophy (2), limb girdle dystrophy (1), spinal muscular atrophy (2), mitochondrial myopathy (1), polymyositis (1); †: significantly different from normal group, p<0.01; ‡: significantly different from nonmyotonic group, p<0.01.

Figure 1. – Magnetometer recording of ribcage and abdominal anteroposterior dimensions during tidal breathing in a patient with myotonic dystrophy: a) awake; and b) in Stage 4 sleep, supine. The upper tracing shows ribcage movement and the lower trace shows abdominal movement.

Figure 2. – Coefficient of variation (CoV%) of breath intervals in normal subjects (•), nonmyotonic muscle weakness (○) and myotonic dystrophy (□), whilst awake and during light (Stage 1–2) and deep (Stage 3–4) and REM sleep. *: CoV significantly different between myotonic group and other groups, whilst awake and during Stage 1–2 sleep (p<0.05).
Discussion

MD is a predominantly inherited disease characterized by myotonia, muscle weakness and various non-neuromuscular features. Involvement of the respiratory system is a major factor contributing to mortality. Several studies have shown disordered respiratory function in MD; the abnormalities include the predicted consequences of respiratory muscle weakness, i.e. reduction in vital capacity, increase in residual volume, and decrease in maximum static respiratory pressures [1–4].

In earlier studies, the frequent finding of elevation of arterial carbon dioxide tension (P_{a,CO2}) in patients with MD raised the question of a possible central respiratory defect in this disorder [1, 2]. In many of these studies, however, the importance of respiratory muscle weakness was underestimated [1, 2, 4]. Furthermore, the common finding of a reduced ventilatory response to CO2 is also attributable to the degree of muscle weakness [3]. A brain stem abnormality has also been suggested because of the frequent symptoms of hypersomnia and undue sensitivity to anaesthetic agents and sedatives. There is, however, no anatomical evidence of abnormalities in the brainstem in MD [14].

An irregular pattern of resting breathing in MD has been noted previously [1–3], but has not hitherto, been formally analysed. We, like others [8–11], have shown that sleep apnoea frequently occurs in MD. In our earlier study, we showed that patients with MD had a significantly greater number of apnoeas and hypopnoeas than a comparable group of patients with nonmyotonic weakness [10]. Apnoeas are conventionally defined as discrete episodes of cessation of breathing associated with arterial oxygen desaturation. In the present analysis, we have specifically excluded periods where such apnoeas or hypopnoeas are present, and we have shown that the disordered respiratory rhythm is seen predominantly in the awake state and during light sleep, and is no longer present in SWS. Because of uncertainty over prolonged calibration of the magnetometers, we have reported results of respiratory timing only. The recordings clearly show, however, that both the rate and depth of inspiration are abnormally variable in MD.

Analysis of changes in tidal volume with sleep stage would have needed a highly sophisticated method of continuous recalibration, which was impractical. We feel that by looking for small differences in breathing pattern (fraction of inspiration to duration of total breathing cycle (t/tot)) without a definite reference point for volume, no greater information can be gained over and above the analysis we performed.

Central sites which influence the breathing pattern include the forebrain and precise neuronal patterns within the brainstem respiratory complex and their functional interconnections [15]. The neural connections between the forebrain, brainstem and the respiratory muscles provide the potential for tonic or phasic influences on breathing when awake. Such influences may be voluntarily induced, or may be involuntary or subconscious [16].

Stage 4 sleep is characterized by a direct inactivation of the cerebral cortex through the reticular activation system via reduced excitability and increased inhibition of neurons of many thalamic nuclei which relay information to and from the cortex. There is indirect evidence that there is disappearance of forebrain drive to breathing at the onset of sleep, as there is an immediate reduction in ventilation and increase in Pa_{a,CO2} [5].

Our results suggest that the irregularity in breathing in MD does not arise primarily in the medullary output. It is possible that there are abnormal forebrain influences, which result in irregular breathing whilst awake and which are no longer active in SWS. It may be relevant in this context that impaired intellectual function with early dementia is a recognized feature in MD [17].

Other relevant factors influencing the pattern of breathing include afferents impinging on the respiratory centres from airways, lungs and chest wall. The breathing patterns of patients with MD differ markedly from normal subjects in resting conditions. They have low tidal volumes and higher respiratory frequencies, but normal central respiratory drive [18]. The irregular breathing pattern cannot be attributed simply to muscle weakness, as nonmyotonic patients with comparable severity of weakness showed no such irregularity. Nor is it likely that myotonia per se is a factor, as patients with another myotonic condition, myotonia congenita, show no significant respiratory abnormality. It could be possible, however, that there is abnormal information deriving from muscle spindles, as abnormalities of the spindles have been shown in MD [19, 20], but of course these inputs from the spindles should still be operative during sleep.

We have previously shown a reduction in CO2 response in myotonic patients whilst awake [10]. In normal subjects, ventilatory responses to CO2 decreases in non-REM sleep [21]. We did not see any difference in ventilatory responses between myotonic and nonmyotonic patients whilst awake when the breathing patterns were different. CO2 response is unlikely to change sufficiently to be so different between the groups as to explain the change whilst asleep. We would hypothesize that afferent input becomes less relevant in slow-wave sleep, when the control of breathing is dominated by the metabolic pathway or plant gain and other influences are minimal. Thus, there may be a change in overall gain and in the control of breathing during slow-wave sleep.

In conclusion, we have confirmed an abnormality of respiratory rhythm in patients with MD whilst awake and during light sleep. Since this is no longer present in SWS, it seems unlikely that it arises from the medulla. Possible alternative sources include aberrant influences from the forebrain, and these influences become less important as the level of non-REM sleep deepens.
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References