

# Respiratory effort perception at rest and during carbon dioxide rebreathing in patients with dystrophia myotonica

John E Clague, Julie Carter, John Coakley, Richard H T Edwards, Peter M A Calverley

## Abstract

**Background** – Breathlessness appears to be closely related to the perception of the outgoing motor command to breathe and should be increased in the presence of muscle weakness. However, breathlessness is not a common symptom in patients with chronic muscle disease who have weak respiratory muscles. The factors that determine the perception of respiratory effort in such patients have not been examined.

**Methods** – The inspiratory effort sensation during resting breathing and progressive hypercapnia was investigated in 12 patients with dystrophia myotonica with weak respiratory muscles (nine men and three women of mean (SD) age 41.1 (10.5) years; maximum inspiratory pressure 43.1 (17.2) cm H<sub>2</sub>O) and an age and sex matched control group of normal subjects of mean age 39.6 (10.6) years and a maximum inspiratory pressure of 123 (15.2) cm H<sub>2</sub>O.

**Results** – During resting breathing with a mouthpiece no differences were seen in inspiratory effort sensation, mouth occlusion pressure, or tidal volume, but inspiratory time and cycle duration were significantly shorter in the patients with dystrophia. Minute ventilation ( $\dot{V}_E$ ) was significantly higher in the patients (15.8 (4.0) l/min v 12.5 (2.6) l/min), while resting breathing was no more variable in the patients than in controls. The ventilatory response to carbon dioxide ( $\dot{V}_E/P_{CO_2}$ ) was not significantly lower in the patients (14.9 (6.9) l/min/kPa) than in the controls (17.4 (4.3) l/min/kPa). Effort sensation responses to carbon dioxide driven breathing were similar in the control subjects and the patients. With regression analysis of pooled data neither maximum inspiratory pressure nor disease state contributed to perceived inspiratory effort during hypercapnia.

**Conclusions** – Moderately severe global respiratory muscle weakness does not appear to influence the ventilatory response to rising carbon dioxide tension or the perception of inspiratory effort in patients with dystrophia myotonica.

many situations and its character varies with the clinical setting.<sup>1</sup> The mechanism underlying this sensation remains disputed<sup>2</sup> but has been equated with an increased sense of effort.<sup>3,4</sup> The sense of effort is believed to be the conscious awareness of the outgoing motor command to breathe and it has been proposed as a possible unitary explanation of breathlessness. The sense of inspiratory effort should increase when ventilation or the velocity of inspiratory muscle contraction increases, when the respiratory system impedance is high, or in the presence of muscle weakness. Inspiratory effort sensation increases when a large percentage of the static maximum pleural pressure is developed by normal subjects.<sup>5</sup> In studies with acute inspiratory loading, the maximum inspiratory pressure is an important determinant of the severity of breathlessness.<sup>6</sup> However, breathlessness is not a prominent complaint of patients with chronic muscle disease with generalised respiratory muscle weakness. One explanation may be that these patients cannot exercise enough to increase their ventilation to a point where breathlessness occurs. Alternatively there may be a defect in sensory perception, or temporal adaptation of respiratory sensation might occur in these chronically weak patients.

Respiratory sensation has not been systematically examined in patients with respiratory muscle disease. In this study we have examined respiratory sensation in a group of patients with dystrophia myotonica. This is an autosomal dominant disorder producing significant sternomastoid and facial weakness together with less marked but slowly progressive limb weakness.<sup>7</sup> Variable respiratory muscle weakness occurs and respiratory complications such as hypersensitivity to anaesthetic agents and respiratory failure due to alveolar hypoventilation have been reported.<sup>8-11</sup>

In this study we wished to determine whether the perception of respiratory effort was normal in patients with dystrophia myotonica, and whether this was related to the degree of respiratory muscle weakness. As exercise is not always feasible in patients with muscle weakness, carbon dioxide rebreathing was used as a standard stimulus to increase inspiratory effort in a carefully characterised group of patients with dystrophia myotonica and a group of age and sex matched normal controls. In addition to measuring the ventilatory response to carbon dioxide we measured the mouth occlusion pressure response to car-

Aintree Chest Centre,  
Fazakerley Hospital,  
Liverpool  
J E Clague  
J Carter  
P M A Calverley

University  
Department of  
Medicine, Royal  
Liverpool University  
Hospital, Liverpool  
J Coakley  
R H T Edwards  
P M A Calverley

Reprint requests to:  
Dr PMA Calverley, Aintree  
Chest Centre, Fazakerley  
Hospital, Lower Lane,  
Liverpool L9 7AL.

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The sensation of breathlessness occurs in

bon dioxide as a more direct measure of respiratory centre output which is uninfluenced by the changes in pulmonary mechanics that occur with chronic respiratory muscle weakness. Effort sensation during resting breathing and resting breathing pattern were also assessed, as resting breathing pattern has been reported to be abnormal in patients with dystrophia myotonica.<sup>10-12</sup>

## Methods

### SUBJECTS

Twelve patients with clinical, electromyographic, and histologically diagnosed dystrophia myotonica who were attending a muscle clinic were studied. All were mobile without aid, two were working, and none complained of excessive daytime sleepiness or orofacial muscle weakness sufficient to impair respiratory measurements. All were able to sit without support and no patient had scoliosis. With the use of a disability grade<sup>12</sup> three subjects were only mildly disabled (grade 1) and nine were moderately disabled (grade 2). No patients were severely disabled (grade 3) or bedbound (grade 4). No patient had radiographic evidence of diaphragmatic paralysis. A sex and age matched control group of normal subjects was also studied. Group mean (SD) data are given in table 1. The study protocol was approved by our hospital ethical committee and all subjects gave their informed consent.

### STUDY DESIGN

Subjects attended on two occasions and all measurements were made while seated. Spirometric measurements (FEV<sub>1</sub> and FVC) were recorded with a dry bellows spirometer (Vitalograph Ltd), and static maximum mouth pressures were measured with a pressure transducer (Validyne MP45) using the technique of Black and Hyatt.<sup>13</sup> The mean result of the three best recordings from five made after adequate training was used. Particular care was taken to avoid mouth leaks by supporting the cheeks of the patients. Arterial blood gas tensions were measured in the patients at rest breathing air and were analysed by an automatic blood gas analyser (Instrumentation Laboratories IL 213).

Resting breathing measurements were made with the subject seated wearing a noseclip and breathing through a mouthpiece from a low resistance two way valve (Hans Rudolph

2600). Airflow was measured with the use of a heated pneumotachograph (Fleisch No. 2) in the main circuit, and the integrated volume signal was recorded onto a strip chart recorder (Gould 2000 series). Tidal volume (V<sub>T</sub>) and respiratory frequency were measured, and minute ventilation (V̇E), inspiratory time (T<sub>I</sub>), total breathing cycle duration (T<sub>TOT</sub>), mean inspiratory flow (V<sub>T</sub>/T<sub>I</sub>), and duty cycle (T<sub>I</sub>/T<sub>TOT</sub>) were calculated. Mouth pressure was measured at the mouthpiece with a separate pressure transducer (Gould P23XL). From this signal mouth occlusion pressure was measured after airway occlusion by a manually operated helium balloon valve (Hans Rudolph 9300) occluded in expiration and recorded onto the chart recorder 100 ms after airway occlusion was determined from the trace. One to two breaths before each airway occlusion the subject was asked "How difficult is it to breathe?" and the response was recorded on the modified Borg scale.<sup>14</sup> Occlusion pressure measurements and effort sensation scores were recorded at 30 second intervals during resting breathing. End tidal carbon dioxide tension (PETCO<sub>2</sub>) was measured continuously with a fast response infrared carbon dioxide analyser (Gambro Engstrom).

Ventilatory responses to carbon dioxide were measured by a rebreathing technique with initial gas concentrations of 6% carbon dioxide and 94% oxygen. The circuit consisted of a reservoir bag (six litres) in a sealed box with inspiratory and expiratory connections to the two way valve used during resting breathing. Minute ventilation (V̇E) was measured by air displacement from the box through a turbine spirometer and carbon dioxide tension by a fast response infrared carbon dioxide analyser (P K Morgan Ltd). Mouth occlusion pressure and inspiratory effort sensation were measured at 30 second intervals (the same as during resting breathing) throughout each rebreathing run, which lasted 3-5 minutes.

Resting breathing data were recorded on each occasion for three minutes. Recordings were taken after allowing five minutes for breathing pattern and PETCO<sub>2</sub> to stabilise. Control subjects and patients also attempted resting breathing with an inspiratory resistive load of 10 cm H<sub>2</sub>O in the breathing circuit. Resting breathing and hypercapnic responses were performed in duplicate on separate days. At least one training run was performed before data were collected to reduce initial overscoring.<sup>15</sup> Subjects wore headphones playing music to mask external sounds.

### DATA ANALYSIS

Mean values for inspiratory effort sensation, mouth occlusion pressure, T<sub>I</sub>, T<sub>TOT</sub>, V<sub>T</sub>, and PETCO<sub>2</sub> during resting breathing were determined for each subject. Mean values of V<sub>T</sub>/T<sub>I</sub>, V̇E, and respiratory frequency were calculated. The variability of T<sub>TOT</sub> was determined by measuring the coefficient of variation of T<sub>TOT</sub> for all breaths in the three minute recording. Comparisons of the mean resting breathing

Table 1 Mean (SD) group data for controls and patients with dystrophia myotonica

	Controls	Patients with dystrophia myotonica	p
Sex (M:F)	9:3	9:3	
Age (years)	39.6 (10.6)	41.1 (10.5)	NS
Height (m)	1.76 (0.07)	1.73 (0.08)	NS
Weight (kg)	71.2 (9.7)	70 (15.4)	NS
FVC (l)	4.91 (1.1)	3.14 (1.21)	<0.01
FVC (% predicted)	104 (14.5)	70.2 (19.3)	<0.01
MIP (cm H <sub>2</sub> O)	123 (15.2)	43.1 (17.2)	<0.01
MIP (% predicted)	108 (17.3)	41.3 (17.3)	<0.01
Paco <sub>2</sub> (kPa)	—	5.6 (0.7)	
Resting SaO <sub>2</sub> (%)	98 (1)	97 (1)	NS

FVC=forced vital capacity; MIP=maximum inspiratory pressure; Paco<sub>2</sub>=arterial carbon dioxide tension; SaO<sub>2</sub>=arterial oxygen saturation; NS=not statistically significant.

Table 2 Mean (SD) group resting breathing pattern data

	Controls	Patients with dystrophia myotonica	p
IES (units)	0.35 (0.58)	0.74 (0.9)	NS
P <sub>0.1</sub> (cm H <sub>2</sub> O)	1.67 (0.7)	1.55 (0.72)	NS
T <sub>I</sub> (s)	1.75 (0.5)	1.43 (0.37)	<0.05
T <sub>TOT</sub> (s)	4.73 (1.3)	3.44 (0.79)	<0.01
T <sub>I</sub> /T <sub>TOT</sub>	0.37 (0.05)	0.42 (0.07)	<0.05
V <sub>T</sub> (l)	0.96 (0.2)	0.88 (0.18)	NS
V <sub>T</sub> /T <sub>I</sub> (l/s)	0.58 (0.14)	0.65 (0.14)	NS
f (bpm)	13.6 (3.9)	18.3 (4.7)	<0.01
VE (l/min)	12.5 (2.6)	15.8 (4.0)	<0.05
P <sub>ETCO<sub>2</sub></sub> (kPa)	5.3 (0.5)	5.1 (0.7)	NS

IES=inspiratory effort sensation; P<sub>0.1</sub>=mouth occlusion pressure; T<sub>I</sub>=inspiratory time; T<sub>TOT</sub>=respiratory cycle time; T<sub>I</sub>/T<sub>TOT</sub>=duty cycle; V<sub>T</sub>=tidal volume; V<sub>T</sub>/T<sub>I</sub>=mean inspiratory flow; f=frequency; VE=minute ventilation; P<sub>ETCO<sub>2</sub></sub>=end tidal carbon dioxide tension; NS=not statistically significant.

data were made between patients and control subjects with the Wilcoxon signed rank test.<sup>15</sup>

The relations between minute VE and carbon dioxide tension, inspiratory effort sensation and carbon dioxide tension, VE and mouth occlusion pressure, and mouth occlusion pressure and carbon dioxide tension during rebreathing were calculated by linear regression with the least squares method using data points at 30 second intervals. Statistical analyses of the mean calculated slopes were performed with the Wilcoxon signed rank test.<sup>16</sup> All data are expressed as mean (SD) unless otherwise stated.

To maximise the data available for analysis, multiple linear regression analysis<sup>16</sup> was applied to the pooled data from normal subjects and patients with dystrophia myotonica (DM). We considered the effects of disease, respiratory muscle weakness and respiratory impedance

(measured as P<sub>0.1</sub>/VE derived by dividing mouth occlusion pressure (P<sub>0.1</sub>) by VE at each time point) on the relation between the stimulus (PCO<sub>2</sub>) and inspiratory effort sensation (IES) using the following equations:

$$IES = a + b(PCO_2) + c(\text{normal or DM}) \quad (1)$$

$$IES = a + b(PCO_2) + d(MIP) + c(\text{normal or DM}) \quad (2)$$

$$IES = a + e(\dot{V}E) + d(MIP) + f(P_{0.1}/\dot{V}E) \quad (3)$$

where c is a categorical variable assigned as 0=normal, 1=DM, and MIP=maximum inspiratory pressure. Total sums of squares and partial F values were calculated.

## Results

### BREATHING AT REST

Summary data describing spirometric parameters and maximum inspiratory pressures are shown in table 1. Only one patient had a PaCO<sub>2</sub> greater than 6 kPa. Respiratory muscle weakness as assessed by measurements of maximum inspiratory pressure was variable, but was not well reflected by a reduced vital capacity in the patients with dystrophia.

Mean resting breathing pattern data are presented in table 2. Under isocapnic unloaded conditions there were no differences in inspiratory effort sensation, mouth occlusion pressure, P<sub>ETCO<sub>2</sub></sub> or V<sub>T</sub> between patients and controls. Both T<sub>I</sub> and T<sub>TOT</sub> were reduced in the patients and the latter accounted for the higher respiratory frequency and the higher VE than in the normal subjects. Breath to breath variability in T<sub>TOT</sub>, a measure of ventilatory control, was similar in both groups (figure).

All the normal subjects tolerated the resistive load during resting breathing, but no patient was able to do so. Some patients were unable to breathe at all with the resistor in place, while others gave up before a stable breathing pattern could be established. No data are therefore presented on loaded breathing.

### CO<sub>2</sub> REBREATHING

Individual linear regression analyses between VE, carbon dioxide tension, mouth occlusion pressure, and inspiratory effort sensation were highly intercorrelated in all the normal subjects and patients (all r values >0.9). Group mean results are given in table 3. Ventilatory responses (VE/PCO<sub>2</sub>) and occlusion pressure (P<sub>0.1</sub>/PCO<sub>2</sub>) responses were lower in the patient group, although not significantly so. Similarly, there were no differences between the occlusion pressure/litre of ventilation (P<sub>0.1</sub>/VE) slopes, a measure of respiratory impedance, between the two groups, nor was there any significant difference in the rate of increase of effort sensation with increasing PCO<sub>2</sub>. This was true whether inspiratory effort sensation was related to PCO<sub>2</sub>, VE, or occlusion pressure, and was not explained by differences in the initial or final levels of PCO<sub>2</sub> or VE during the rebreathing (table 3).

Individual variability of T<sub>TOT</sub> during resting breathing. N=normal, DM=dystrophia myotonica.

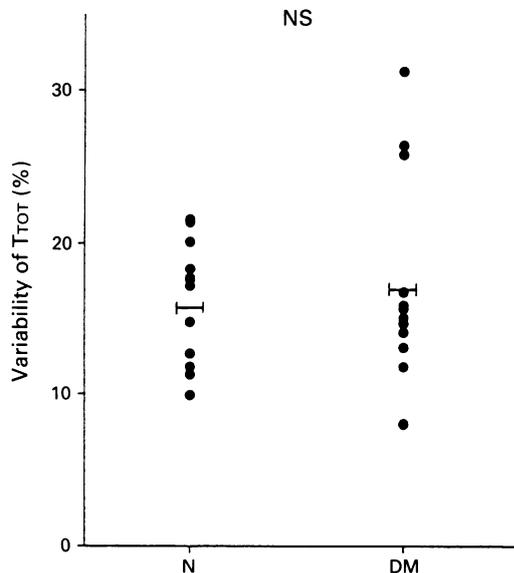


Table 3 Mean (SD) group results following carbon dioxide rebreathing

	Controls	Patients with dystrophia myotonica	p
VE/PCO <sub>2</sub> (l/min/kPa)	17.4 (4.3)	14.9 (6.9)	NS
P <sub>0.1</sub> /PCO <sub>2</sub> (cm H <sub>2</sub> O/kPa)	2.96 (1.1)	2.24 (1.0)	NS
IES/PCO <sub>2</sub> (units/kPa)	1.85 (0.6)	2.4 (1.9)	NS
IES/P <sub>0.1</sub> (units/cm H <sub>2</sub> O)	0.63 (0.24)	0.96 (0.35)	NS
IES/VE (units/l/min)	0.13 (0.06)	0.16 (0.06)	NS
P <sub>0.1</sub> /VE (cm H <sub>2</sub> O/l/min)	0.19 (0.09)	0.16 (0.06)	NS
Initial PCO <sub>2</sub> (kPa)	6.32 (0.46)	6.34 (0.36)	NS
Final PCO <sub>2</sub> (kPa)	8.48 (0.47)	8.41 (0.67)	NS
Initial VE (l/min)	15.9 (4.9)	17.6 (4.6)	NS
Final VE (l/min)	55 (15.9)	48.3 (16.3)	NS

VE=minute ventilation; PCO<sub>2</sub>=carbon dioxide tension; P<sub>0.1</sub>=mouth occlusion pressure; IES=inspiratory effort sensation; NS=not statistically significant.

No correlation was found between resting arterial carbon dioxide tension and the ventilatory or occlusion pressure responses to carbon dioxide in patients with dystrophia myotonica. No relation was found between age and effort sensation responses to carbon dioxide, nor between age and ventilatory and occlusion pressure responses to carbon dioxide.

#### FACTORS INFLUENCING INSPIRATORY EFFORT SENSATION

In equations 1 and 2 effort sensation (IES) was related only to the stimulus ( $P_{CO_2}$ ) and was not influenced by either disease state or maximum inspiratory pressure (MIP). When the stimulus to inspiratory effort sensation was considered in mechanical terms (equation 3) it was principally determined by  $\dot{V}E$  ( $F=59.2$ ,  $p<0.0001$ ), impedance ( $P_{0.1}/\dot{V}E$ ,  $F=22.1$ ,  $p<0.0001$ ) with MIP making a smaller independent contribution ( $F=11.5$ ,  $p<0.001$ ).

#### Discussion

Dystrophia myotonica is a well characterised cause of muscle weakness without major abnormality in respiratory mechanics. Our results suggest that this weakness does not reduce the ventilatory response to carbon dioxide and is not an important determinant of respiratory sensation when respiratory impedance is normal.

We assessed resting ventilation using a mouthpiece and noseclip. This method yields higher values during uninstrumented recordings, mainly because of an increase in inspiratory flow.<sup>17</sup> Such problems were common to both our study groups, but the minute ventilation of our control subjects was close to that seen in other studies,<sup>18</sup> and higher than those reported by Serisier *et al.*<sup>10</sup> As reported by other studies,<sup>10,19</sup> our patients with dystrophia myotonica had a rapid breathing pattern but they did not generate a higher mouth occlusion pressure or experience greater resting inspiratory effort sensation to produce this. The relatively regular breathing pattern seen in both groups may reflect the stimulant effect of an added dead space.

Previous studies have suggested that the ventilatory response to carbon dioxide is depressed in patients with dystrophia myotonica<sup>10</sup> which might predispose to carbon dioxide retention, or reflect inspiratory muscle weakness, or both.<sup>12</sup> We found no differences in the ventilatory, occlusion pressure, or effort sensation responses of our groups, nor were the  $P_{0.1}/P_{CO_2}$  slopes disproportionately elevated in the patients as has been suggested previously.<sup>19</sup>

Respiratory sensation during carbon dioxide stimulated breathing has not been reported previously in patients with isolated respiratory muscle weakness. In our patients without respiratory symptoms we saw no evidence of increased sensory scoring at rest or during carbon dioxide stimulated increases in ventilation. Multiple regression analyses of the pooled data confirmed that neither disease

category nor maximum inspiratory pressure influenced inspiratory effort sensation, and only when considered in mechanical terms did muscle weakness, as represented by lower maximum inspiratory pressure, make a small contribution to effort sensation.

There are several possible explanations for these findings. Patients with dystrophia myotonica may systematically mis-score their sensory responses, but this seems unlikely. Sensory adaptation might occur in the patients, but no correlation was found between age – and hence disease duration – and effort sensation responses. There may be a defect in the muscle spindles or a failure of central nervous system processing in patients with dystrophia myotonica which reduces their perception of muscle weakness and leads to an inappropriately low effort sensation for a given level of muscle activation. The inability of our patients to tolerate a small inspiratory resistive load makes this explanation and sensory adaptation unlikely.

Alternatively, effort perception may rise only when the additional impedance requires a greater degree of muscle activation to produce the same volume change. This would explain the results of equation 3 where inspiratory effort sensation increased when  $P_{0.1}/\dot{V}E$  was increased. This was the only circumstance where maximum inspiratory pressure explained some of the variance of inspiratory effort sensation, presumably because weak muscles require a greater degree of activation to produce the same pressure. Even here changes in  $P_{0.1}/\dot{V}E$  or maximum inspiratory pressure would have to be large, as the principal determinant of inspiratory effort sensation was  $\dot{V}E$ .

The limited role for maximum inspiratory pressure as a predictor of respiratory sensation is in keeping with data from thyrotoxic patients whose respiratory muscle function improved after treatment, but whose breathlessness scoring remained unaltered.<sup>20</sup> The quality of the sensation perceived differs with the stimulus, at least in normal subjects,<sup>21</sup> and these differences may reflect changes in the relative importance of impedance, maximum inspiratory pressure, and ventilatory components of respiratory sensation.

These results emphasise that significant respiratory muscle weakness can be present in the absence of clinical symptoms and without the patient perceiving changes in unloaded ventilation as being abnormal. In our patients breathing pattern rather than ventilatory control was the most consistent abnormality, and respiratory effort perception was unrelated to the degree of respiratory muscle weakness. When respiratory impedance is increased, however, the scope for load compensation may be more restricted, and carbon dioxide retention and symptoms may rapidly develop when there is a background of respiratory muscle weakness. Assessment of static maximum mouth pressure may be of predictive value in these circumstances.

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