Central and peripheral respiratory electrophysiological studies in myotonic dystrophy

Udo A. Zifko,1 Angelika F. Hahn,1 Hussein Remtulla,1 Charles F. P. George,2 Whit Wihlidal1 and Charles F. Bolton1

Departments of 1Clinical Neurological Sciences and 2Medicine, University of Western Ontario, Victoria Hospital, London, Canada

Correspondence to: Dr C. F. Bolton, Department of Clinical Neurological Sciences, University of Western Ontario, Victoria Hospital, 375 South Street, London, Ontario, Canada N4A 6G5

Summary
Acute and chronic respiratory failure is a common and potentially life-threatening feature in patients with myotonic dystrophy (MD). The causes may be varied, and can involve both the central and peripheral nervous system. To evaluate the incidence of respiratory muscle involvement and the function of the central motor inspiratory pathway to phrenic motor neurons we performed magnetic stimulation of the cortex and cervical spinal cord, phrenic nerve conduction studies and needle EMG of diaphragm and intercostal muscles in 25 patients with MD. The results were compared with those from 35 healthy subjects. In addition, pulmonary function tests, blood gas analyses and static mouth pressures were evaluated. Abnormalities in response to magnetic stimulation, including a reduced compound muscle action potential (CMAP) from the diaphragm and increased excitability threshold, indicated impaired central inspiratory drive in 20% of cases. Phrenic nerve conduction showed a reduced diaphragmatic CMAP amplitude in 20%, and a delayed negative peak onset latency in 4% of cases. Abnormalities in diaphragm and intercostal muscle needle EMG were found in 76% of cases, these were mainly myotonic discharges (68%) and a decrease in the number of active motor units (36%). Patients with abnormal respiratory electrophysiological parameters had a significantly lower functional vital capacity (FVC; P = 0.005). The duration of the disease correlated negatively with diaphragmatic CMAP amplitude to phrenic nerve, but not magnetic, stimulation. Our results demonstrate that the involvement of the central inspiratory pathway is common in MD patients. Central and peripheral electrophysiological studies of the diaphragm should be considered in the diagnosis and management of patients with MD and dyspnoea.

Keywords: myotonic dystrophy; respiratory insufficiency; magnetic stimulation; phrenic nerve conduction; diaphragmatic needle EMG

Abbreviations: CMAP = compound muscle action potential; FRC = functional residual capacity; FEV = forced expiratory volume; FVC = functional vital capacity; MD = myotonic dystrophy; MEP = maximal expiratory mouth pressure; MIP = maximal inspiratory mouth pressure; TLC = total lung capacity

Introduction
Myotonic dystrophy is a dominantly inherited disease, with a prevalence of five per 10 000 in Europe and North America (Klein, 1958) and an exceptionally high prevalence in Quebec, Canada (Mathieu et al., 1990). The defect has been localized to chromosome 19q13.3, where there is an expanded cytosine–thymine–guanine repeat in the 3' untranslated region of the gene involved in encoding the putative serine-threonine protein kinase (Tsilfidis et al., 1992; Fischbeck, 1994; Hudson et al., 1995). Occasionally, patients with characteristic features of MD may present without repeat expansion in the myotonin-protein kinase gene (Shaw et al., 1993; Thornton et al., 1994).

Chronic respiratory failure in MD is a frequent complication that can lead to premature death, but the incidence is uncertain. In 1935 Londres found microscopic alterations in the diaphragm at autopsy, similar to those found in limb muscles. Benaim and Worster-Drought (1954) initially reported a case of MD affecting the diaphragm bilaterally and causing pulmonary hypoventilation with hypoxaemia and secondary polycythaemia. These authors were able to record
myotonia of the intercostal muscles electromyographically, but were unable to record electromyograms from the diaphragm. Caughey and Gray (1954) observed unilateral elevation of the diaphragm in three out of 25 MD patients. Causes of chronic ventilatory insufficiency include a wide variety of abnormalities. Respiratory muscle weakness is evenly distributed between inspiratory and expiratory muscles with a significantly impaired static mouth pressures (Jammes et al., 1985). However, performing ventilatory pressure measurements requires intact facial muscles to sustain the pressure while breathing through a mouthpiece. Hence, these tests are of limited value in MD. Morphological studies of the diaphragm demonstrated variation in the size of the muscle fibres, an increase of connective and fatty tissue, and formation of central chains of nuclei (Caughey and Pachomov, 1959). The influence of altered central control of breathing in MD is controversial. Whereas some authors suggest that ventilatory failure may be caused by an abnormality of respiratory centre function rather than respiratory muscle weakness (Kilburn et al., 1959; Carrol et al., 1977); others found that the central drive to breathe is normal (Begin et al., 1980). These studies tested the chemical control of respiration by measuring the sensitivity of peripheral and central chemoreceptors utilizing recordings of breathing pattern, pulmonary function and strength of respiratory muscles (Begin et al., 1982; Jammes et al., 1985). Hypersomnia, a common feature in MD, may be partly caused by alveolar hypoventilation due to diaphragmatic weakness (Coccagna et al., 1975), but it is mainly of central origin. Polysomnographic studies have shown evidence of central apnoea throughout all the stages of sleep. This was found in six out of eight mild to moderately affected MD patients (Cirignotta et al., 1987) but was not found to be related to results of pulmonary function tests (Gilmartin et al., 1991; Finnimore et al., 1994) and does not cause day time sleepiness (Van der Meche et al., 1994). Nocturnal hypoaxemia is a risk factor for sudden death (Harper 1989; Shepard et al., 1985). The differential diagnosis of chronic ventilatory insufficiency is further compounded by cardiac involvement which occurs in 90% of MD patients (Church, 1967). Significant arrhythmias due to selective involvement of the conducting system (Griggs et al., 1975), hypotension (O’Brien and Harper, 1983) and cardiomyopathy (Orndahl et al., 1964) may contribute to nocturnal hypoaxemia.

Acute respiratory failure caused by respiratory muscle weakness is a particular concern in the management of MD patients. It may become apparent as an unexpected complication during recovery from general anaesthesia (Simpson 1975; Aldrige 1985; Maestre et al., 1994). Extreme diaphragmatic hypoplasia and severe respiratory distress is common in the congenital form of MD and results in persistent pulmonary hypertension, unresponsive to ventilatory and pharmacological support, and in death (Rais-Bahrami et al., 1994; Sandler et al., 1994).

Although there have been a number of studies on respiratory insufficiency in MD (Hansotia and Frens, 1981; Jammes et al., 1985; Gilmartin et al., 1991; Sandler et al., 1994), none of them tested the volitional control of breathing or included detailed electrophysiological measurements of phrenic nerve and respiratory muscles. We have further developed the technique of recording phrenic nerve conduction and needle EMG of the diaphragm (Bolton et al., 1992; Collins et al., 1994; Chen et al., 1995a), and have found them valuable in the diagnosis and management of neuromuscular respiratory failure (Zifko et al., 1995a, b, 1996a). Testing the corticospinal tract to phrenic motor neurons using magnetic stimulation of the cortex is a reliable method for diagnosing and monitoring patients with impaired central respiratory drive (Zifko et al., 1995c) and it was used to clarify upper motor neuron function in MD patients.

Hence, the present study is designed to assess the central and peripheral respiratory pathway using cortical and cervical magnetic stimulation, phrenic nerve conduction, and needle EMG of diaphragm and intercostal muscles. In addition, we performed conventional pulmonary function tests, inspiratory and expiratory static mouth pressure and blood gas analysis, and correlated the results with the electrophysiological findings and the duration of MD.

Material and methods

Subjects

Twenty-five patients from 17 families (13 male and 12 female), aged from 21 to 68 years (mean 43.0 years), were recruited from 108 patients with MD attending the Neuromuscular Clinic, Department of Clinical Neurological Sciences, Victoria Hospital. The patients were not selected because of respiratory symptoms, sleep disturbance or somnolence but were recruited from those who were willing to cooperate. The MD diagnosis was made using clinical, electrophysiological and biochemical criteria. The mean disease duration was 16.3 years (range 1.5–40 years). Forty eight per cent of the patients had some complaints of shortness of breath. None of the patients suffered from epileptic seizures and none were on antispastic, anxiolytic or hypnotic medication. All electrophysiological measurements were compared with those from 35 healthy volunteers (18 male, 17 female) aged 20–76 years (mean 41.0 years). All patients and volunteers gave informed consent and the study was approved by the university ethics committee.

Nerve conduction

In all subjects phrenic nerve conduction studies were performed bilaterally with percutaneous stimulation in the suprACLAVICULAR fossa. The diaphragmatic CMAPs were recorded with self-adhesive surface electrodes (2.5×2.5 cm²; 3M, St Paul, Minn., USA). These electrodes were applied 5 cm superior to the tip of the xiphoid process (the G1 electrode) and to both costal margins 16 cm from the G1 electrode (the G2 electrodes). The position of each G2 electrode usually

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corresponds to the seventh intercostal space. Recordings were rejected if electrocardiogram artifacts were encountered and the stimuli were repeated. The latency to the onset of the negative peak and the diaphragmatic CMAP amplitude from the baseline to the negative peak were analysed. Phrenic nerve conduction studies were found to have excellent repeatability (Chen et al., 1995b), and to be as reliable as median nerve conduction studies (Bolton, 1993). To exclude a neuropathy affecting the limbs, standard nerve conduction tests were performed on the motor and sensory ulnar nerves (Kimura 1989).

**Needle EMG**

Needle EMG of the diaphragm was performed with a monopolar needle electrode inserted between the anterior axillary line and the medial clavicular lines, just above the costal margin (Bolton et al., 1992). On the monitor, the sweep speeds were 10 ms per division, and the amplitudes 100 and 500 μV per division. The presence or absence of abnormal spontaneous activity, myotonic discharges, fibrillation potentials and positive sharp waves, were observed during the inspiratory bursts of motor unit potentials. During inspiratory bursts, the number of motor unit potentials, their amplitude, duration and complexity (number of phases and high frequency components) were estimated by visual and auditory means. Experience in recording from the diaphragm in 25 normal subjects assisted us in these interpretations (Collins et al., 1994). Difficulties in distinguishing normal motor unit potentials from those due to myopathy are described in the discussion. Needle EMG recordings of the intercostal muscles were made as the needle traversed the chest wall before entering the diaphragm. Spontaneous activity; and the number, amplitude, duration and complexity of motor unit potentials were analysed. Nerve conduction studies and needle EMG were performed with an Advantage EMG machine (Clark Davis Medical Systems, London, Ontario, Canada).

**Transcortical and cervical magnetic stimulation**

A Magstim 200 magnetic stimulator (Magstim Co. Ltd, Whitland, Dyfed, UK) was used for all subjects. Cortical and cervical stimulation was performed with a circular stimulating coil (part number 9784-00) with a mean diameter of 90 mm and 2.0 Tesla maximum magnetic flux density at the coil surface was centred exactly at the vertex, flat against the skull (Zifko et al., 1996c). Anticlockwise coil current (side A of the coil facing upward) was used to stimulate the left hemisphere and clockwise coil current (side B of the coil facing upward) was used to stimulate the right hemisphere. Transcortical stimulation was performed at 95% of the maximal magnetic output. Cervical stimuli were applied with the coil centred on the posterior spinous processes in a parasagittal position between C2 and T2 at 65% of maximal magnetic output. Higher stimulation at the neck often resulted in large stimulation artifacts. Cortical and cervical stimulation was applied during the onset of a regular breath and during diaphragmatic facilitation (at the end of a forced deep inspiration), determined by visual observation of abdominal movement. Each stimulation was repeated at least twice. All stimuli were delivered with the subject at rest, either lying down (for cortical stimulation) or seated (for cervical stimulation). A time interval of 45–60 s between each stimulation was chosen to avoid measurement errors of the excitability threshold (Reuten et al., 1993). Recordings were performed with the same surface electrodes used for phrenic nerve conduction. Filters were set at 1–2 kHz. The sweep speeds were 10 ms per division, and the amplitudes between 200 and 500 μV per division.

Six measurements of the magnetically evoked diaphragmatic CMAPs were made. (i) The onset latency was determined from the onset of the negative peak. (ii) The amplitude was measured from the baseline to the negative peak. (iii) The threshold was defined as the lowest intensity level that evoked three or more clearly discernable diaphragmatic CMAPs in a consecutive sequence of six stimuli after decreasing the magnetic field output in 10% steps, starting from 95% of the maximum strength. (iv) The amplitude ratios were calculated by dividing the electrically evoked CMAP amplitudes (after stimulating phrenic nerves peripherally) by the magnetically evoked CMAP amplitudes (after cortical and cervical stimuli). (v) The central motor conduction time (CMCT) was calculated by subtracting the cervical onset latency from the cortical onset latency. (vi) The influence of facilitation on latency and amplitude was described by the percentage increase of the mean value defined as \[\frac{(V_2-V_1)}{(V_2+V_1)}\].

**Classification of findings**

Regarding electrophysiological findings of the diaphragm, we classified five categories of diaphragmatic muscle involvement. A myopathic pattern: reduced diaphragmatic CMAP amplitude after direct phrenic nerve stimulation, normal phrenic nerve latency, a normal or reduced number of motor units on the diaphragmatic needle EMG and a normal response to magnetic stimulation (or a reduced absolute value of CMAP amplitude with a normal amplitude ratio). A central pattern: abnormal responses to magnetic stimulation, normal phrenic nerve conduction, a normal or reduced number of motor units on the diaphragmatic needle EMG. A combined myopathic and central pattern: abnormal diaphragmatic CMAP amplitude after direct phrenic nerve and cortical magnetic stimulation and a reduced number of motor units on the diaphragmatic needle EMG. A non-specific pattern: a reduced number of motor units on the diaphragmatic needle EMG, normal phrenic nerve conduction, normal responses to magnetic stimulation. A normal pattern: normal electrophysiological findings, except for myotonic discharges.
Pulmonary function tests
Pulmonary function tests were performed in the seated position using a PK Morgan Autolink system (P. K. Morgan, Chatham, Kent, UK). The spirometry, measured with a dry rolling seal spirometer, used the best of the three consecutive trials (Knudson et al., 1983). Static lung volumes were measured by the gas dilution technique using helium (Crapo et al., 1982). The diffusing capacity was measured using the single breath method and corrected for haemoglobin and lung volume (Cotes, 1979). Maximal inspiratory (MIP) and maximal expiratory (MEP) mouth pressure were measured from the functional residual capacity (FRC) and total lung capacity (TLC) respectively (Black and Hyatt, 1969). Reference values for spirometry, lung volumes, diffusing capacity, and MIPs and MEPs were those of Knudson et al. (1983), Crapo et al. (1982), Cotes (1979) and Black and Hyatt (1969), respectively. Blood gases were analysed using an ABL 520 BG analyser (Radiometer, Copenhagen, Denmark).

Data analysis
Simple regression analysis was used to analyse the relationship between results of respiratory electrophysiological measurements and pulmonary function tests, static mouth pressures and blood gas analyses, and the relationships between disease duration, respiratory electrophysiological measurements and pulmonary function tests. The results of pulmonary function tests in the electrophysiologically normal group were compared with those in electrophysiologically abnormal group using the unpaired t test (two-tailed). Differences were considered statistically significant if P < 0.01.

Results
Nerve conduction
Mean phrenic nerve conduction parameters in healthy subjects and in MD patients are summarized in Table 1 (normal range is ±2SD). A significant right–left difference on phrenic nerve conduction was not observed in healthy subjects or in patients, so the results are presented as mean values of pooled data from both sides. Phrenic nerve conduction in MD patients were abnormal in six patients (24%). The mean latency was 6.6±0.7 ms, and it was delayed in only one patient (4%), the only one suffering from diabetes mellitus. The mean amplitude was 487±202 μV, and it was reduced in five (20%) patients (Figs 1A and 2A). Ulnar motor nerve conduction was normal in all patients. The mean ulnar sensory nerve conduction velocity was 52±6 m s⁻¹, and it was reduced in two (8%) patients. The mean sensory ulnar nerve action potential amplitude was 41±16 μV, and it was normal in all patients.

Needle EMG studies
There were abnormalities in respiratory muscles in 19 patients (76%), of these 16 (64%) involved the diaphragm. Fourteen patients (56%) had myotonic discharges observed at the end of inspiration as a sustained run of either positive sharp waves or negative spikes with a small initial positivity in the diaphragm. One patient had denervation potentials, fibrillation potentials and positive sharp waves in addition to myotonic discharges. Eight (32%) had a decreased number of motor units firing during inspiration (Fig. 1C); 7 (28%) had motor unit potentials of short duration. In studies of the intercostal muscles 16 (64%) were abnormal. All patients had myotonic discharges (Fig. 2C), four (16%) had a decreased number of motor units firing and three (12%) had motor unit potentials of short duration.

Transcortical and cervical magnetic stimulation
Transcortical and cervical magnetic stimulation was performed in all except one patient, who had a cardiac pacemaker. There were no unpleasant side effects during, or after, magnetic stimulation. Table 1 shows the mean values of latencies, amplitudes, amplitude-ratios, excitability thresholds and CMCTs obtained in 35 healthy subjects and 24 MD patients. There were abnormal transcortical evoked diaphragmatic CMAPs in seven patients (29%); this was the only electrophysiological abnormality in two of them (8%). All had normal cortical latencies (13.9±0.3 ms) and CMCTs (5.1±0.9 ms). Six (25%) had a reduced CMAP amplitude (165±98 μV) (Figs 1B and 2B); but two (8%) of the patients with reduced CMAP amplitudes had normal amplitude ratios (2.9±1.4). One (4%) had an abnormally high excitability threshold (57.7±10.9%). Facilitation (with magnetic stimulation at the end of a deep breath) was normal in all patients, increasing the mean diaphragmatic CMAP amplitude from 192 μV to 308 μV (62.3 %) and shortening the mean latency from 13.9 to 13.1 ms. All patients had normal cervical evoked diaphragmatic CMAPs.

Classification of electrophysiological findings
Myopathic and abnormal central diaphragmatic patterns were both present in four patients (16%), unclassified diaphragmatic patterns in three (12%), combined central and myopathic patterns in one (4%) and a normal pattern (except for myotonic discharges) in 13 (52%) (Figs 3 and 4).

Pulmonary function tests
The results of pulmonary function tests are summarized in Table 2. Sixty per cent demonstrated a restrictive pattern of pulmonary function with reductions in FVC, TLC and FRC. The diffusing capacity was normal in all but two patients indicating an extraparenchymal restriction in keeping with muscle weakness. Only one showed any signs of airflow obstruction (FEV/FVC ratio = 62%; see Table 2, where FEV = forced expiratory volume). All patients had abnormal MIPs and MEPs. In seven patients (28%) no reliable measurements of mouth pressures could be obtained due to...
insufficient cooperation. Thirteen (52%) had abnormal blood gas analysis, but only five had clinically significant abnormalities (pO\textsubscript{2} < 55 and pCO\textsubscript{2} > 50 while breathing room air). All patients had normal haemoglobin and pH.

**Electrophysiology—pulmonary function relationship**

None of the electrophysiological parameters correlated with pulmonary function tests, static mouth pressures or blood gas analyses. The only exception was patients with abnormal electrophysiological parameters who had significantly lower FVC values than patients with normal FVC values (P = 0.005). All other pulmonary function tests had no significantly different values in patients with normal versus abnormal respiratory electrophysiological parameters. The duration of the disease correlated inversely with the diaphragmatic CMAP amplitude (P = 0.001) (Fig. 5) and FVC (P = 0.001) (Fig. 6). None of the results of magnetic stimulation correlated with the disease duration. The symptom

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**Fig. 1** Electrophysiological study in a 49-year-old MD patient. (A) Normal phrenic nerve conduction: Latency: 7.0 ms; CMAP-amplitude: 625 μV. (B) Abnormal response to cortical magnetic stimulation, recording from the diaphragm. Latency: 13.6 ms; CMAP-amplitude: 40 μV. (C) Diaphragmatic needle EMG during inspiration shows no denervation potentials, but a markedly decreased number of firing motor units. The short arrow indicates an ECG artifact. The two long arrows show a low amplitude myotonic discharge, beginning at the end of inspiration and ending at the beginning of the next inspiration. Note the single motor unit firing during the whole inspiration in line 3, and that only one motor unit is firing during the first and last third of each inspiration. The firing rate is 10–15 Hz, which may be normal for the diaphragm. Also note the irregular breathing pattern, with a short duration expiration. The reduced cortically evoked diaphragm CMAP amplitude and the reduced number of motor units firing during inspiration indicate impaired central inspiratory drive. Calibration for A and B: 10 ms and 0.2 mV per division; for C: 200 ms and 0.1 mV per division.
Fig. 2 Electrophysiological study of the diaphragm in a 35-year-old MD patient. (A) Abnormal phrenic nerve conduction. Latency = 6.3 ms; CMAP-amplitude = 190 µV. (B) Normal response to cortical magnetic stimulation, recording from the diaphragm. Latency = 13.5 ms; CMAP-amplitude = 110 µV. (C) The insertion activity (line 1) is followed by myotonic discharges (lines 2–3), and positive sharp waves and fibrillation potentials (lines 4–5). These needle EMG abnormalities and the reduced diaphragm CMAP amplitude after direct phrenic nerve stimulation indicates myopathic diaphragm weakness. Calibration for A and B: 10 ms and 0.2 mV per division; for C: 10 ms and 0.1 mV per division.

Discussion

This is the first electrophysiological study of the central and peripheral respiratory nervous system in patients with MD. The major findings were (i) respiratory electrophysiological abnormalities were common in patients with MD (48%); (ii) central respiratory drive was impaired in 20%; (iii) myopathic, but not central abnormalities correlated with the duration of MD; (iv) patients with abnormal respiratory electrophysiological results had significantly lower FVC. Hence, electrophysiology of the central and peripheral respiratory system is of clinical value in detecting respiratory muscle dysfunction in MD. They should also be of value in other myotonic disorders such as proximal myotonic myopathy (Thornton–Griggs–Moxley disease) (Rowland, 1994; Thornton et al., 1994; Ricker et al., 1995). Differentiation of central and peripheral causes of respiratory insufficiency will assist in the planning and performance of respiratory muscle training. The relationship of respiratory function to the quality of life and functional ability underlines...
Myotonic dystrophy

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Phrenic CMAP
(n = 5)

Diaphragmatic
EMG (n = 8)

Magnetic Stimulation
(n = 7)

Fig. 3 The distribution of abnormal diaphragmatic electrophysiological findings.

Table 1 Summary of electrophysiological results, recording from the diaphragm in 25 patients with MD and 35 healthy subjects

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Healthy subjects (mean±SD)</th>
<th>MD patients (mean±SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phrenic nerve conduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>6.1±0.7</td>
<td>6.6±0.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td>669±159</td>
<td>487±202</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Responses to cervical magnetic stimulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>8.3±1.2</td>
<td>8.9±0.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td>281±128</td>
<td>192±85</td>
<td>0.005*</td>
</tr>
<tr>
<td>Amplitude-ratio</td>
<td>3.1±9.0</td>
<td>2.9±1.4</td>
<td>0.70</td>
</tr>
<tr>
<td>Threshold (%)</td>
<td>31.4±9.0</td>
<td>34.1±8.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Responses to cortical magnetic stimulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>13.5±1.4</td>
<td>13.9±0.3</td>
<td>0.10</td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td>263±144</td>
<td>165±98</td>
<td>0.003*</td>
</tr>
<tr>
<td>Amplitude-ratio</td>
<td>3.0±1.5</td>
<td>3.9±2.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Threshold (%)</td>
<td>49.1±7.5</td>
<td>57.4±10.9</td>
<td>0.0009*</td>
</tr>
<tr>
<td>Central motor conduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time (ms)</td>
<td>5.3±1.1</td>
<td>5.1±0.9</td>
<td>0.44</td>
</tr>
</tbody>
</table>

The amplitude-ratios were calculated by dividing the electrically evoked CMAP amplitudes (after stimulating phrenic nerves peripherally) by the magnetically evoked CMAP amplitudes (after cortical and cervical stimulation). *Statistically significant at P < 0.01.

Fig. 4 The distribution of normal and abnormal types of diaphragm in the patient group according to electrophysiological criteria.

the importance of careful diagnosis and management of chronic respiratory insufficiency in MD (Ahlström et al., 1994).

Peripheral respiratory dysfunction
The most common finding in the patients was an abnormalities in the respiratory needle EMG (seen in 76%). Myotonic
Table 2 Results of pulmonary function tests and blood gas analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Mean value (±SD)</th>
<th>% of predicted value (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>(l)</td>
<td>3.0±1.0</td>
<td>75±18</td>
</tr>
<tr>
<td>FEV/FVC</td>
<td>(%)</td>
<td>84.1±7.2</td>
<td>74±17</td>
</tr>
<tr>
<td>TLC</td>
<td>(l)</td>
<td>4.4±1.3</td>
<td>68±24</td>
</tr>
<tr>
<td>FRC</td>
<td>(l)</td>
<td>2.1±0.8</td>
<td>107±27</td>
</tr>
<tr>
<td>DL/AV</td>
<td>(ml/min/mmHg/l)</td>
<td>5.3±1.2</td>
<td>21±6</td>
</tr>
<tr>
<td>MEP</td>
<td>(cm H₂O)</td>
<td>35.0±12.2</td>
<td>71±27</td>
</tr>
<tr>
<td>pCO₂</td>
<td>(mmHg)</td>
<td>27.8±21.5</td>
<td>96±18</td>
</tr>
<tr>
<td>pO₂</td>
<td>(mmHg)</td>
<td>43.4±5.4</td>
<td>91±8</td>
</tr>
<tr>
<td>SAO₂</td>
<td>(%)</td>
<td>39.4±7.3</td>
<td>91±8</td>
</tr>
</tbody>
</table>

DL = diffusing capacity of the lung (ml min⁻¹ per mmHg); AV = alveolar volume (l); SAO₂ = O₂ saturation.

Discharges, representing recurring single fibre potentials from an injured area of the muscle membrane with increased excitability, were recorded in either the diaphragm or chest wall muscles. Electrical myotonia is typically unevenly distributed in MD with the highest incidence of involvement in distal muscles of the upper extremity or the orbiculari oculi muscle (90%) and the lowest incidence in the deltoid (38%) (Ricker and Meinck, 1972; Streib and Sun, 1983). In this study the incidence of myotonic discharges was similar for intercostal muscles and the diaphragm. Although muscles with myotonia have reduced tension during maximal voluntary contraction (Belanger and McComas, 1983), in the absence of clinical myotonia, it is uncertain whether there is true respiratory muscle weakness, where the diaphragmatic needle EMG examination is otherwise normal.

Needle EMG findings in myopathic limb muscles may or may not demonstrate spontaneous electrical activity. The motor unit potentials appear either normal or with decreased duration and amplitude, increased complexity and high frequency components. The motor units tend to recruit early with an increased firing rate. Estimating motor units in the human diaphragm by auditory and visual means is challenging. Motor unit potentials in the healthy diaphragm are of shorter duration and smaller amplitude, but more numerous than chest wall muscles, suggesting a relatively low innervation ratio (Bolton, 1993). Hence, this appearance is also suggestive of a myopathy, and was not included in the diagnosis of peripheral respiratory dysfunction. Phrenic nerve conduction was complimentary to the diaphragmatic EMG in detecting inspiratory muscle dysfunction. A reduced number of motor units firing during each inspiration in association with a reduced diaphragmatic CMAP amplitude (and normal phrenic nerve latency) indicated a reduction in the number of intact motor units, suggestive of diaphragmatic muscle weakness due to myopathy. Theoretically, this abnormality could also be attributed to proximal conduction block on phrenic nerve stimulation at the neck, but this possibility was excluded in our patients by a normal diaphragmatic response amplitude ratio (comparing responses to cervical magnetic and peripheral electrical stimulation). In three patients there was a decreased number of motor units on diaphragmatic EMG, but all other electrophysiological tests were normal; consequently a pathophysiological classification could not be determined.

Early detection of patients with MD and diaphragmatic muscle weakness is of potential value in considering inspiratory muscle training. Wanke et al. (1994) demonstrated in a randomly assigned prospective study that inspiratory muscle training in patients with muscular dystrophy improved pulmonary function parameters and the transdiaphragmatic pressure significantly. Patients without improvement had advanced muscle weakness, with vital capacity <25% of predicted values and PaCO₂ values >45 mmHg. In patients with MD and ventilatory insufficiency it may also be helpful to detect those patients with respiratory muscle dysfunction due to myopathy as early as possible in order to perform inspiratory muscle training on a regular basis.

The rare case of a mixed axonal-demyelinating polyneuropathy in MD (von Giesen et al., 1994; Spaans...
after cortical stimulation, the amplitude ratio was normal by Maskill et al. (1995c). Twenty-nine per cent of MD patients showed abnormalities of central motor conduction. In two of the six patients with reduced diaphragmatic CMAP amplitudes, the amplitude ratio was normal indicating abnormal phrenic nerve–diaphragm muscle function rather than impaired central respiratory drive. In contrast to the abnormal values obtained in demyelinating disorders (Hess et al., 1987), the central motor conduction time was normal in all our patients. Central motor conduction abnormalities in MD patients consisted of a reduced CMAP amplitude ratio and an abnormally high excitability threshold. This indicates that a reduced number of spinal motor neurons were recruited by the corticospinal tract volleys (Komori and Brown, 1993). Abnormal central motor conduction was associated with a moderate decrease in the number of motor units in the diaphragm firing on inspiration in three patients; and it was the only abnormality in two of them. One patient had abnormalities in both the upper and lower motor neurons supplying the diaphragm. Unilateral abnormalities were not detected. Due to the high incidence of brain MRI abnormalities in patients with MD (84%), such as white matter hyperintense lesions and cortical atrophy (Censori et al., 1994), and clinical evidence of neuropsychological deficits such as apathy, inertia, impaired short and long-term memory and speed of information processing (Broughton et al., 1990; Culebras, 1994), the relatively high incidence of impaired central integrity in our study is not surprising. The duration of the disease did not correlate with results of magnetic stimulation. This finding is probably explained by the fact that the central nervous system may be affected in some patients at an early stage of the disease, and may not be affected at any time in others. Magnetic stimulation studies are sensitive in monitoring the function of corticospinal tract fibres, but no information can be obtained about the function of brainstem respiratory centres. The literature is controversial on the influence of autonomic central control as a contributing factor to ventilatory insufficiency (Carrol et al., 1977; Begin et al., 1982). Our study did not test this part of central respiratory control, but our results imply that at least one component of the central respiratory weakness is due to impaired motor control, and this has not been described before.

Central respiratory weakness
Breathing is a sensorimotor act integrating metabolic and behavioural respiratory control by nervous influences that arise from nearly every level of the brain and upper spinal cord. The metabolic respiratory control, regulated by a number of respiratory centres within the reticulum of the lower brainstem between the mid pons and the cervical–medullary junction, has been extensively studied in MD. A primary brainstem disorder has been proposed on the basis of a tendency toward carbon dioxide retention that is inappropriate for the degree of respiratory muscle dysfunction (Gillam et al., 1964). Conversely, Begin et al. (1980, 1982) found the chemosensivity of respiratory centres in MD intact. Behavioral control of breathing takes its origins from prepontine structures lying mainly at forebrain level, with impulses descending via corticospinal tracts. These mechanisms have not been studied in MD so far. In this study we used electrophysiology for assessing volitional breathing control. Needle EMG studies of limb muscles in upper motor neuron disorders show absent spontaneous activity, decreased number of motor units of normal size and duration, which are firing slowly. Similar changes occur in the diaphragm, except that the assessment of the firing rate of diaphragm motor units is difficult. Percutaneous electrical stimulation of the motor cortex demonstrated rapidly conducting, oligosynaptic pathways to the diaphragm motor neurons. (Gandevia and Rothwell, 1987). Magnetic stimulation of the respiratory motor cortex, which causes less discomfort than the electrical method, was introduced by Maskill et al. (1991) and Lissens (1994). We found this technique feasible in diagnosing central respiratory disorders (Zifko et al., 1995c). Twenty-nine per cent of MD patients showed abnormalities of central motor conduction. In two of the six patients with reduced diaphragmatic CMAP amplitudes after cortical stimulation, the amplitude ratio was normal indicating abnormal phrenic nerve–diaphragm muscle function rather than impaired central respiratory drive. In contrast to the abnormal values obtained in demyelinating disorders (Hess et al., 1987), the central motor conduction time was normal in all our patients. Central motor conduction abnormalities in MD patients consisted of a reduced CMAP amplitude ratio and an abnormally high excitability threshold. This indicates that a reduced number of spinal motor neurons were recruited by the corticospinal tract volleys (Komori and Brown, 1993). Abnormal central motor conduction was associated with a moderate decrease in the number of motor units in the diaphragm firing on inspiration in three patients; and it was the only abnormality in two of them. One patient had abnormalities in both the upper and lower motor neurons supplying the diaphragm. Unilateral abnormalities were not detected. Due to the high incidence of brain MRI abnormalities in patients with MD (84%), such as white matter hyperintense lesions and cortical atrophy (Censori et al., 1994), and clinical evidence of neuropsychological deficits such as apathy, inertia, impaired short and long-term memory and speed of information processing (Broughton et al., 1990; Culebras, 1994), the relatively high incidence of impaired central integrity in our study is not surprising. The duration of the disease did not correlate with results of magnetic stimulation. This finding is probably explained by the fact that the central nervous system may be affected in some patients at an early stage of the disease, and may not be affected at any time in others. Magnetic stimulation studies are sensitive in monitoring the function of corticospinal tract fibres, but no information can be obtained about the function of brainstem respiratory centres. The literature is controversial on the influence of autonomic central control as a contributing factor to ventilatory insufficiency (Carrol et al., 1977; Begin et al., 1982). Our study did not test this part of central respiratory control, but our results imply that at least one component of the central respiratory weakness is due to impaired motor control, and this has not been described before.

Electrophysiology–pulmonary function relationship
Pulmonary function tests and blood gas analyses are of limited value in diagnosing neuromuscular respiratory weakness (Newsom-Davis, 1967, 1980). In particular, the diagnostic value of mouth pressures is limited in patients with facial weakness. All patients had abnormal MIPs and MEPs in this study, even though 40% of them had other measures of respiratory function which were normal. In addition, nearly one-third of MD patients could not cooperate sufficiently to obtain reliable results in this test. The clinical symptom of dyspnoea did not correlate with pulmonary function tests or electrophysiology. This may reflect variability in the patients’ subjective perception of dyspnoea. In particular, impaired cognitive functions in MD may complicate objective interpretation of symptoms. Patients with abnormal
electrophysiological results had significantly lower FVC values. Correlation of phrenic nerve conduction studies and findings of diaphragmatic needle EMG with FVC is also described in other neuromuscular diseases, such as Guillain–Barré syndrome (Gourie-Devi and Ganapathy, 1985; Zifko et al., 1996b). No other measurements of pulmonary function or blood gases correlated with diaphragmatic electrophysiology. Thus, electrophysiological measurements provide an easy and detailed assessment of the nervous system control of respiration in MD patients.

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