Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis

R. A. Lyall,1 N. Donaldson,2 M. I. Polkey,1 P. N. Leigh3 and J. Moxham1

1Respiratory Muscle Laboratory, 2Department of Palliative Care and Policy, Guys, Kings and St Thomas’ School of Medicine, Kings College Hospital, London UK, and 3Department of Neurology and the Kings’ MND Care and Research Centre, Guys, Kings and St Thomas’ School of Medicine and The Institute of Psychiatry, Kings College, London UK

Correspondence to: Dr R. A. Lyall, Department of Respiratory Medicine and Allergy, Guys, Kings and St Thomas’ School of Medicine, Denmark Hill Campus, Bessemer Road, London SE5 9PJ, UK
E-mail: lyallrebecca@hotmail.com

Summary
Although ventilatory failure is the most common cause of death in amyotrophic lateral sclerosis (ALS) and measurement of respiratory muscle strength (RMS) has been shown to have prognostic value, no single test of strength can predict the presence of hypercapnia reliably. RMS was measured in 81 ALS patients to evaluate the relationship between tests of RMS and the presence of ventilatory failure, defined as a carbon dioxide tension \(>6\) kPa. We studied the predictive value of vital capacity (VC), static inspiratory and expiratory mouth pressures (MIP, MEP), maximal sniff oesophageal (sniff Poes), transdiaphragmatic (sniff Pdi) and nasal (SNP) pressure, cough gastric (cough Pgas) pressure and trans-diaphragmatic pressure after bilateral cervical magnetic phrenic nerve stimulation (CMS Pdi) to identify the risk of ventilatory failure in the whole group and in subgroups of patients with and without significant bulbar involvement. For patients without significant bulbar involvement, sniff Pdi had greatest predictive power (odds ratio 57) with specificity 87%, sensitivity 90%, and positive and negative predictive values (PPV, NPV) of 74 and 95%, respectively. Of the less invasive tests, per cent predicted SNP had greater overall predictive power (OR 25, specificity 85%, sensitivity 81%) than per cent predicted VC (9, 89%, 53%) and per cent predicted MIP (6, 83%, 55%). No test had significant predictive power for the presence of hypercapnia when used to measure RMS in a subgroup of patients with significant bulbar weakness. Thirty-five patients underwent polysomnography. CMS Pdi, sniff Pdi and per cent predicted SNP were significantly correlated with the apnoea/hypopnoea index (AHI) \((P = 0.035, 0.042 and 0.026, respectively)\). The correlations between AHI and per cent predicted MIP and VC were less strong (both non-significant). In ALS patients without significant bulbar involvement, novel tests of RMS have greater predictive power than conventional tests to predict hypercapnia. In particular, the non-invasive SNP is more sensitive than VC and MIP, suggesting that it could usefully be included in tests of respiratory muscle strength in ALS and will be helpful in assessing the risk of ventilatory failure. In patients with significant bulbar involvement, tests of respiratory muscle strength do not predict hypercapnia. Sleep-disordered breathing is correlated with RMS and the novel tests of RMS having the strongest relationship with the degree of sleep disturbance.

Keywords: ALS; ventilation; respiratory muscles; sleep

Abbreviations: AHI = apnoea/hypopnoea index; ALS = amyotrophic lateral sclerosis; CMS Pdi = transdiaphragmatic pressure after bilateral cervical magnetic phrenic nerve stimulation; cough Pgas = cough gastric pressure; ELBG = ear lobe blood gas; FEV1 = forced expiratory volume in 1 s; MIP, MEP = static inspiratory and expiratory mouth pressures; NIPPV = non-invasive positive-pressure ventilation; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value; REM = rapid eye movement; RMS = respiratory muscle strength; SDB = sleep-disordered breathing; SNP = maximal sniff nasal pressure; sniff Pdi = maximal sniff transdiaphragmatic pressure; sniff Poes = maximal sniff oesophageal pressure; VC = vital capacity

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Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by progressive weakness of all muscle groups, and in most cases death is due to ventilatory failure caused by respiratory muscle weakness (Kaplan and Hollander, 1994). The methods used most commonly to evaluate respiratory muscle strength (RMS) are the measurement of vital capacity (VC) and maximal inspiratory and expiratory mouth pressures (MIP and MEP). These techniques have the advantages that they are widely available, portable and non-invasive, and that age- and sex-related normal ranges are available from previous population study data (Black and Hyatt, 1969; Vincken et al., 1987; Working Party Standardization of Lung Function Tests, 1993). However, all are volitional tests and require maximal respiratory muscle activation to achieve optimal results. Values below those predicted for an individual may arise from submaximal effort rather than respiratory muscle weakness.

Suboptimal results may also occur when bulbar or facial weakness prevents the formation of a tight lip-seal around a mouthpiece. Recently, methods of RMS testing that do not require the use of a mouthpiece have been developed. The sniff is a natural manoeuvre that is performed easily by most patients, and the measurement of oesophageal or transdiaphragmatic pressure during a maximal sniff manoeuvre (sniff $P_{oes}$ and sniff $P_{di}$, respectively) is an established method of evaluating inspiratory muscle strength (Miller et al., 1985; Laroche et al., 1988). The maximal sniff nasal pressure (SNP) has been shown to correlate closely with sniff $P_{oes}$ and has been proposed as a simple, non-invasive method of assessing inspiratory muscle strength (Heritier et al., 1994; Uldry and Fitting, 1995). In a recent study of 16 ALS patients (Fitting et al., 1999), SNP was shown to be more sensitive than VC to small changes in muscle strength, to decline in a linear fashion as the disease progresses and, in contrast to MIP and MEP, to be performed without difficulty late in the course of the disease and in the presence of orofacial weakness.

VC, MIP, sniff $P_{oes}/P_{di}$ and SNP are all volitional tests of inspiratory muscle strength and, as previously stated, may underestimate strength because of submaximal patient effort. Non-volitional tests of muscle strength do not require patient effort. The strength of the major inspiratory muscle, the diaphragm, can be quantified non-volitionally by measurement of transdiaphragmatic pressure after bilateral cervical magnetic stimulation of the phrenic nerves (CMS $P_{di}$) (Similowski et al., 1989).

Expiratory muscle strength is conventionally evaluated by measurement of the MEP. An alternative volitional test is to measure the gastric pressure generated during a maximal cough (cough $P_{gas}$) (Kyroussis et al., 1996). As yet, no non-volitional test of expiratory muscle strength exists.

The accurate measurement of RMS is clearly of interest to the clinician. Patients with ALS die from ventilatory failure and frequently experience symptoms of hypoventilation, including sleep-disordered breathing (SDB), before entering respiratory failure. Survival is prolonged by the use of invasive and, more recently, non-invasive ventilation (Pinto et al., 1995; Aboussouan et al., 1997; Kleopa et al., 1999). Mild hypoventilation may not initially produce hypoxia (Stone and Keltz, 1963; Kreitzer et al., 1978) and oxygen saturation may be normal at this stage. Recognition of the presence of hypoventilation is clearly important for the individual ALS patient, so that there can be timely discussion regarding ventilation. However, as yet it is not known at what level of respiratory muscle weakness this complication occurs. Measures of respiratory muscle strength that predict the presence of hypoventilation reliably may alert the clinician and prompt appropriate management. However, such measures are also relevant to investigators conducting trials of novel pharmacological agents since the use of an accurate measurement as a trial end-point should permit the use of a smaller sample. The presence of dyspnoea, sleep disturbance and a poor prognosis is associated with diaphragm and respiratory muscle weakness in ALS patients (Ringel et al., 1993; Haverkamp et al., 1995; Vitacca et al., 1997; Stambler et al., 1998; Arnulf et al., 2000; Similowski et al., 2000). However, the relationship between the degree of respiratory muscle weakness and the onset of respiratory failure has not been investigated in this patient group. We performed both novel and established tests of RMS on 81 ALS patients to determine the relationship between RMS and the presence of ventilatory failure and to define the tests that are most useful to predict ventilatory failure.

Methods

Eighty-one patients (16 female) took part in the study. All had been referred to the Kings’ Motor Neurone Disease Care and Research Centre, where the diagnosis of ALS was confirmed and classified as El Escorial Definite, Probable or Possible ALS (World Federation of Neurology Research Group on Neuromuscular Diseases, 1994). The study was approved by the Ethics Committee of Kings College Hospital and all patients gave informed consent. Entry into the study was not dependent on the presence or absence of respiratory symptoms. All data from an individual patient were collected during one visit. At the time of the assessment, no patient had received ventilatory support, although several were subsequently treated with non-invasive positive-pressure ventilation (NIPPV). In addition, no patient had been treated for, or had evidence of, pneumonia in the month preceding the assessment. The patients were subdivided into bulbar and limb groups depending on the site of onset of ALS. Patients in the bulbar group had presented with either dysarthria or dysphagia and patients in the limb group with weakness and wasting in muscles of the upper or lower limbs. The level of disability present in these areas was quantified using a
modified Norris bulbar and limb scale (Norris et al., 1974; Lacomblez et al., 1996). To calculate a modified Norris score, the patient is asked to rate how he or she can perform certain functions. The possible ratings are ‘normal’ (indicating that the function is performed without impairment, score 3), ‘impaired’, ‘slight’ and ‘none’. The lowest score (0) indicates that the function cannot be carried out. The limb score consists of ratings for 21 functions requiring the use of limb musculature, such as holding a fork or standing, with a maximum possible score of 63. Similarly, the bulbar score describes 13 functions requiring bulbar musculature, such as blowing, whistling and swallowing, the maximum possible score being 39.

**Measurement of MIP and MEP**

Both manoeuvres were performed in the sitting position using a flanged mouthpiece attached to a metal tube incorporating a 2 mm leak to prevent glottic closure and recruitment of the orofacial musculature. Mouth pressure was recorded with a Validyne MP-45 transducer and amplifier (Validyne, Northridge, Calif., USA) with signals passed via a 12-bit NB-MIO-16 analogue–digital converter (National Instruments, Austin, Tex., USA) to a Macintosh Quadra computer (Apple Computer, Cupertino, Calif., USA) running Labview software (National Instruments) sampling at 100 Hz. To record the MIP, subjects breathed out to residual volume, the three-way tap at the end of the metal tube was turned to obstruct flow and the subject then performed a maximum inspiratory effort for at least 1 s. MEP measurement was performed in the same way, from total lung capacity. Subjects were seated opposite the monitor to provide visual feedback, in order to maximize activation (Laporta and Grassino, 1985). At least three manoeuvres were performed. If the MIP or MEP continued to increase the patient made further attempts until a plateau was reached. The highest value sustained for 1 s was used in the analysis and was compared with the predicted value (Vincken et al., 1987). Unfortunately, it was not possible to use an anaesthetic mask to make these measurements, and in the presence of a poor lip-seal any leak was reduced by either the patient or operator holding the lips closed.

**Measurement of sniff P_di, sniff P_oes, SNP and cough P_gas**

The measurement of sniff P_di, sniff P_oes and cough P_gas required the placement of oesophageal and gastric balloon catheters. These consisted of a latex balloon, 10 cm long and 2 cm in circumference, mounted on polyethylene catheter tubing, 110 cm long, with internal and external diameters of 1.02 and 1.98 mm, respectively (P. K. Morgan), attached to the amplifier and transducer set-up described above. P_di was calculated continuously (P_di = P_gas – P_oes) and displayed online, and pressure tracings were visible to both subject and investigator in real time. SNP (Miller et al., 1985; Laroche et al., 1988; Heritier et al., 1994; Fitting et al., 1999) was measured using a nasal plug made of hand-moulded dental putty (Protosil; Vannini Dental Industry, Grassina, Italy) and fashioned around polyethylene catheter tubing of the same dimensions as those given above, connected to a pressure transducer. The nasal plug was placed in one nostril and, after a demonstration of the sniff manoeuvre, the patient was encouraged to perform short, sharp maximal sniffs, seated, from functional residual capacity through the unoccluded nostril. Patients continued to make maximal sniff efforts until a plateau was reached. After a period of rest, the plug was placed in the opposite nostril and the process repeated. Sniff P_di, P_oes and SNP were measured simultaneously, and the sniff giving the maximal oesophageal pressure was chosen for analysis. Predicted SNP values were calculated (Uldry and Fitting, 1995).

To measure cough P_gas, patients performed maximal cough efforts from functional residual capacity until a plateau was reached.

**Measurement of CMS P_di**

Bilateral cervical magnetic stimulation of the phrenic nerves was performed as described previously (Similowski et al., 1989; Wragg et al., 1994a). Stimulation was performed with the patient seated at functional residual capacity, using a Magstim 200 DEM stimulator (Magstim, Whitland, UK). A 90 mm circular coil was placed over the cervical spine at the level of C5 with the neck flexed; the patient was stimulated with the mouth closed and wearing a nose-clip. Having located the coil position that produced the maximum twitch P_di response, five twitches at maximal stimulator output were recorded and the mean value was calculated. CMS P_di was measured before the volitional manoeuvres and after 20 min of quiet breathing to avoid twitch potentiation (Wragg et al., 1994b).

**Measurement of blood gas tensions**

Blood gas tensions were obtained from arterialized earlobe samples (Spiro and Dowdeswell, 1976; Sauty et al., 1996).
Capillary blood flow was maximized by the application of a rubefacient (Algipan; Wyeth Laboratories, Maidenhead, UK) and a small cut was made in the earlobe. A capillary sample of blood was analysed in a standard blood gas analysis machine (Radiometer ABL 30; Radiometer, Copenhagen, Denmark). For the purposes of statistical analysis, ventilatory failure was defined as an earlobe blood gas (ELBG) carbon dioxide tension of >6 kPa.

**Polysomnography**

Thirty-five of the 81 patients who had full RMS testing underwent polysomnography during the course of their clinical management. Polysomnography was performed to identify the presence of SDB; all patients had symptoms suggestive of this complication, such as restless sleep, daytime sleepiness, morning headache and reduced appetite. Polysomnography was performed in a sleep laboratory using the Alice 3 diagnostic system (Respironics Inc., Pittsburgh, Pa., USA). Polysomnograms were scored manually according to standard criteria (American Sleep Disorders Association, 1992; American Academy of Sleep Medicine, 1999). Obstructive hypopnoea/apnoea was defined as a reduction (hypopnoea) or complete cessation (apnoea) of airflow despite ongoing inspiratory effort. Central hypopnoea/apnoea was characterized by reduced or absent airflow and the absence of respiratory effort. The presence of more than five events per hour of sleep was considered abnormal (American Academy of Sleep Medicine, 1999). In some patients, ELBG was taken immediately on waking after polysomnography and in others nocturnal transcutaneous carbon dioxide was measured (performed in 17 patients). The time between RMS testing and polysomnography varied. In all cases polysomnography was performed within 8 weeks of RMS testing (in 90% of cases within 3 weeks).

**Data handling and statistical analysis**

Sniff \( P_{\text{di}} \), sniff \( P_{\text{oes}} \), SNP, cough \( P_{\text{gas}} \) and CMS \( P_{\text{di}} \) were defined as the differences between the pressures at resting end-expiration and the subsequent peak pressures. For simplicity, sniff \( P_{\text{oes}} \) and SNP were given positive values.

Differences between the bulbar and limb subgroups were assessed using the Mann–Whitney test (GraphPad Prism version 3.00 for Windows; GraphPad Software, San Diego, Calif., USA). The results obtained from the group as a whole and the bulbar and limb subgroups were analysed by logistic regression (SPSS 9; SPSS, Chicago, Ill., USA). For the logistic regression analysis, the main outcome measure was a dichotomous indicator (presence or absence) of ventilatory failure, defined as \( pCO_2 \) >6 kPa. We derived logistic regression models for all the potential predictors of the presence of ventilatory failure, namely the various tests of RMS. We used simple logistic regression models to assess the predictive value of each individual test. The predictive accuracy of this discrimination is given in terms of its sensitivity, specificity, NPV and PPV. Receiver operating characteristic curves were constructed in order to determine cut-off levels for each test that maximized the sensitivity and specificity of the prediction of hypercapnia. These cut-off levels were also assessed using the logistic discriminant given by the logistic regression model.

**Results**

The demographic details, ELBG results and modified Norris scores are given in Table 1. Only 20% of the sample were women. This was not the result of any deliberate recruitment bias, since the overall clinic population had a male : female ratio of approximately 1.5 : 1, as expected. The Norris bulbar score was reduced in both the limb and bulbar groups, but was significantly lower in the bulbar group (\( P < 0.0001 \)). Similarly, limb function was reduced in both groups, although to a greater degree in the limb group.

**Results of RMS testing**

Table 2 shows the results of RMS testing for the group as a whole and for the bulbar and limb subgroup. Only 71 patients performed the SNP test (56 in the limb group, 15 in the bulbar group). All patients performed all other RMS tests but MEP data were lost for two subjects (one from each subgroup) and MIP data were lost for one subject (limb group). FEV\(_1\) values were obtained for 72 subjects (57 in the limb group, 15 in the bulbar group). The relationship between RMS and \( pCO_2 \) is shown in Figs 1 and 2, in which each symbol represents the result of an individual test. The mean values of all volitional tests were below normal in both the group as a whole and the subgroups. The bulbar subgroup patients appeared to have lower values than the limb subgroup, but statistical analysis revealed a significant difference only for MIP, MEP and per cent predicted MEP (Table 2). For the non-volitional CMS \( P_{\text{di}} \), the mean value was just below normal in all groups, but the range was wide and a number of patients had values of CMS \( P_{\text{di}} \) that are associated with normal diaphragm function (Hamnegard et al., 1996) (Fig. 2A).

**Predictive value of tests of RMS for detection of hypercapnia**

When analysed individually with simple regression analysis, with each test as a continuous variable, for the group overall, each test of RMS achieved statistical significance (defined as \( P < 0.05 \)). Thus, all tests shared some predictive power for the detection of hypercapnia. For all of the tests, the odds ratio (OR) was <1, indicating that low values achieved on RMS testing signal led to the presence of hypercapnia. Most tests showed a considerable predictive power when the results were analysed as a continuous variable. However, when a threshold or cut-off level was introduced (dichotomization), all tests...
became more discriminatory and some displayed superior predictive power. Threshold values were calculated using receiver operating characteristic curves to maximize the predictive power of a dichotomized form of the test. Table 3 shows the results of logistic regression analysis of all tests in the limb group (performed on the continuous and dichotomized versions of the tests) as well as the sensitivity, specificity, NPV and PPV. In the context of this study, sensitivity was the proportion of hypercapnic patients (according to the ELBG data) whose RMS test result was below the threshold or cutoff value. Specificity was defined as the proportion of patients with normal ELBG pCO₂ whose RMS tests were above the cut-off level. The PPV was the proportion of hypercapnic patients found among those who were predicted to be hypercapnic from the RMS result. Similarly, the NPV was the proportion of normal ELBG patients among those who were predicted to have a normal pCO₂. Using a cut-off level of 30 cmH₂O, the sniff Pdi test was a highly discriminatory test, with a sensitivity, specificity, PPV and NPV of 90, 87, 74 and 95%, respectively. The odds of having ventilatory failure were 57 times more for patients who failed to achieve a sniff Pdi of 30 cmH₂O (P < 0.0001).

However, this significance was not preserved in the assessment of the bulbar group alone, suggesting that RMS was not strongly related to the presence or absence of hypercapnia for this subgroup of patients. In spite of initial analysis suggesting that none of the tests had discriminant power when performed on bulbar subjects, having observed the highly significant results of sniff Pdi in the limb group, we considered dichotomization of this test in order to increase its sensitivity in the bulbar group. This resulted in a threshold or cut-off value of 40 cmH₂O providing the best discrimination of sniff Pdi in the bulbar patients. Nevertheless, this cut-off point still gave poor sensitivity and specificity and did not reach statistical significance in the bulbar group (P = 0.69).

### Polysomnography results

Thirty-five patients underwent polysomnography. Because of computer problems, full polysomnographic data were

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**Table 1 Group and subgroup characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Bulbar group</th>
<th>Limb group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (females)</td>
<td>81 (16)</td>
<td>16 (6)</td>
<td>65 (10)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 ± 9 (35–85)</td>
<td>61 ± 8 (45–72)</td>
<td>61 ± 9 (35–85)</td>
</tr>
<tr>
<td>pO₂ (kPa; normal range 10–12)</td>
<td>10.41 ± 1.6 (6.12–14.1)</td>
<td>11.08 ± 1.5 (8.66–13.58)</td>
<td>10.25 ± 1.6 (6.12–14.1)</td>
</tr>
<tr>
<td>pCO₂ (kPa; normal range 4.8–6)</td>
<td>5.56 ± 1.1 (4.11–10.6)</td>
<td>5.29 ± 0.4 (4.82–6.08)</td>
<td>5.63 ± 1.2 (4.11–10.6)</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l; normal range 24–28)</td>
<td>27.6 ± 5.3 (20.5–58)</td>
<td>26.4 ± 2.2 (22.7–29.9)</td>
<td>27.9 ± 5.7 (20.5–58)</td>
</tr>
<tr>
<td>Norris bulbar score (maximum value 39)**</td>
<td>32.6 ± 7.8 (8–39)</td>
<td>21.7 ± 7.8 (19–33)</td>
<td>35.7 ± 4.2 (24–39)</td>
</tr>
<tr>
<td>Norris limb score (maximum value 63)*</td>
<td>40.8 ± 13.5 (8–63)</td>
<td>47.4 ± 14.3 (17–63)</td>
<td>38.9 ± 12.8 (8–58)</td>
</tr>
</tbody>
</table>

Results are mean ± standard deviation (range). Asterisks indicate significant differences between bulbar and limb groups: *P < 0.05; **P < 0.0001 (Mann–Whitney test). There was no significant difference between the subgroups in all other tests shown.

**Table 2 Results of respiratory strength testing**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Bulbar group</th>
<th>Limb group</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (litres)</td>
<td>2.7 ± 1.2 (0.3–6.4)</td>
<td>2.3 ± 0.9 (0.3–4.5)</td>
<td>2.8 ± 1.2 (0.7–6.4)</td>
</tr>
<tr>
<td>VC % predicted (N &gt; 80% predicted)</td>
<td>71 ± 28 (13–133)</td>
<td>65 ± 26 (13–104)</td>
<td>72 ± 28 (19–133)</td>
</tr>
<tr>
<td>MIP (cmH₂O)*</td>
<td>38 ± 27 (0–115)</td>
<td>25 ± 17 (0–60)</td>
<td>41 ± 28 (9–115)</td>
</tr>
<tr>
<td>MIP % predicted*</td>
<td>45 ± 31 (0–127)</td>
<td>34 ± 29 (0–114)</td>
<td>48 ± 32 (9–127)</td>
</tr>
<tr>
<td>MEP (cm H₂O)*</td>
<td>50 ± 30 (0–140)</td>
<td>32 ± 23 (0–80)</td>
<td>56 ± 30 (15–140)</td>
</tr>
<tr>
<td>MEP % predicted*</td>
<td>42 ± 22 (0–105)</td>
<td>29 ± 19 (0–62)</td>
<td>45 ± 22 (15–105)</td>
</tr>
<tr>
<td>Sniff P₈ (N &gt; 80 cmH₂O)</td>
<td>60 ± 46 (0–194)</td>
<td>48 ± 33 (0–116)</td>
<td>63 ± 49 (8–194)</td>
</tr>
<tr>
<td>Sniff P₉ (N &gt; 60 cmH₂O)</td>
<td>55 ± 33 (0–138)</td>
<td>47 ± 25 (0–81)</td>
<td>58 ± 35 (10–138)</td>
</tr>
<tr>
<td>SNP (cmH₂O)</td>
<td>51 ± 32 (0–130)</td>
<td>39 ± 23 (0–65)</td>
<td>54 ± 33 (8–130)</td>
</tr>
<tr>
<td>SNP % predicted</td>
<td>52 ± 31 (0–126)</td>
<td>42 ± 25 (0–81)</td>
<td>55 ± 32 (10–126)</td>
</tr>
<tr>
<td>Cough P₉ (N &gt; 120 cmH₂O)</td>
<td>92 ± 60 (13–303)</td>
<td>76 ± 39 (21–147)</td>
<td>96 ± 64 (13–303)</td>
</tr>
<tr>
<td>FEV₁ (litres)</td>
<td>2.1 ± 0.9 (0.2–5)</td>
<td>1.8 ± 1.0 (0.2–3.9)</td>
<td>2.2 ± 0.9 (0.6–5)</td>
</tr>
<tr>
<td>FEV₁ % predicted (N &gt; 80% predicted)</td>
<td>70 ± 26 (10–125)</td>
<td>62 ± 30 (10–105)</td>
<td>72 ± 25 (21–125)</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Limb group</th>
</tr>
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<tbody>
<tr>
<td>CMS P₈ (N &gt; 18 cmH₂O)</td>
<td>16 ± 12.7 (1–55)</td>
<td>17 ± 11 (2–35)</td>
<td>15 ± 13 (1–55)</td>
</tr>
</tbody>
</table>

Results are mean ± standard deviation (range). N = normal value. *Significant difference between bulbar and limb groups for these tests, P < 0.05, Mann–Whitney test. There was no significant difference between the subgroups in all other tests shown.
available on only 28 patients at the time of preparation of the manuscript. The RMS values of the patients whose polysomnographic data were lost (mean ± SD CMS Pdi 8.8 ± 8.8 cmH2O) were similar to those of the patients whose data were available (8.7 ± 6.6 cmH2O). All of the lost polysomnograms had been viewed the morning after the sleep study by one of the authors; no subject had significant obstructive apnoea and the findings were broadly similar to those of the studies available for full analysis.

The majority of patients who underwent polysomnography had significantly reduced RMS. The mean ± SD CMS Pdi was 8.4 ± SD 6.4 cmH2O (range 1.9–29.0). Only four of the 35 patients undergoing polysomnography had a CMS Pdi above the lower limit of normal (18 cmH2O; Hamnegard et al., 1996), with a mean CMS Pdi of 22 ± 5.1 cmH2O.

Twenty-three of the 28 patients for whom full data were available had significant SDB with an apnoea/hypopnoea index (AHI) >5/h. For the group as a whole the mean AHI was 30 ± 30/h (range 0.8–132). In the majority of patients with significant SDB, arousal was predominantly due to central apnoea or hypopnoea. The incidence of mixed and obstructive apnoea was low in both rapid eye movement (REM) sleep and non-REM sleep, with mean indices of 0.05/0.46/h and 0.13/0.48/h, respectively.

The mean AHI for the four patients with normal diaphragm strength was 10 ± 9/h. One patient had predominantly obstructive apnoea. He had significant bulbar abnormality and had an abnormal flow volume loop that suggested upper airway obstruction. A second patient had central apnoea in REM sleep. The other two patients had an AHI <5.

Polysomnographic data are presented in Table 4, in which the 28 patients are divided into three groups according to the ELBG result obtained on the day of RMS testing. The patients with normal ELBG had the least disturbed sleep, but the majority of patients within this group still had a clinically significant AHI. Several patients in this group had a raised nocturnal transcutaneous carbon dioxide despite normal daytime ELBG pCO2 and bicarbonate. Raised nocturnal transcutaneous carbon dioxide was seen invariably in the group with raised ELBG bicarbonate despite a normal daytime ELBG carbon dioxide. The majority of patients with nocturnal hypercapnia, despite having normal daytime blood gases, had severe SDB due to hypoventilation on polysomnography and were offered and accepted NIPPV, and thus no progression to daytime hypercapnia was seen. However, two patients with nocturnal hypercapnia, raised daytime bicarbonate but normal daytime ELBG pCO2 did not accept NIPPV. Both developed daytime hypercapnia within 3 months. In patients with significant SDB, REM sleep was the most affected and in the majority the percentage of REM sleep was reduced.

RMS, as measured by the novel volitional and non-volitional tests, correlated significantly with several indices of sleep disturbance (Table 5). The strongest correlation was between CMS Pdi and AHI in REM sleep, with a Pearson correlation coefficient of -0.63 (P = 0.0005). RMS, as measured by percent predicted VC and MIP, did not correlate significantly with
Fig. 2 Relationship between RMS and pCO$_2$ for tests of RMS. Each graph shows ELBG pCO$_2$ in kPa on the y-axis and RMS on the x-axis. Open symbols represent the bulbar patients and closed symbols the limb patients. The dotted lines represent the lower and upper limits of normal for ELBG pCO$_2$ (4.8–6.0 kPa).

Discussion

Respiratory muscle strength is an important prognostic factor in ALS. Decline in RMS, as assessed by VC, MIP and MEP, has been shown to correlate closely with death (Ringel et al., 1993). Haverkamp and colleagues (Haverkamp et al., 1995) used a scoring system based on bulbar function, respiratory function, muscle strength and upper and lower limb function to measure progression in ALS and found that the only significant covariates of survival were age, time from first symptom until first examination, rate of change of the total score and rate of change of the respiratory subscore, using the VC to assess RMS. Stambler and colleagues (Stambler et al., 1998) confirmed the association between shorter survival and lower VC and further reported the correlation of serum chloride (reflecting the degree of respiratory acidosis) with prognosis in ALS. Furthermore, several recent studies have indicated that the treatment of ventilatory failure with NIPPV can prolong survival in ALS (Pinto et al., 1995; Aboussouan et al., 1997; Kleopa et al., 1999), underlining the importance of timely diagnosis of this complication. However, the recent American Academy of Neurology report on the management of ALS (Miller et al., 1999) stated that...
no evidence exists as to which test best detects respiratory failure. No previous study has evaluated such a wide variety of RMS measurements in such a large cohort or addressed the relationship between RMS and ventilatory failure in such a large sample of ALS patients. However, in the interpretation of our results a number of factors need to be considered.

**Relationship of RMS to hypercapnia**

Figures 1 and 2 demonstrate the inverse relationship between all tests of RMS and pCO2, as previously noted in studies of patients with neuromuscular disease and specifically ALS (Kreitzer et al., 1978; Serisier et al., 1982). With mild weakness, pCO2 falls below normal as hyperventilation compensates for alveolar hypoxaemia. Hypercapnia only occurs as weakness becomes profound. This has been described previously in other neuromuscular diseases (Stone et al., 1963; Harrison et al., 1971) and ALS (Kreitzer et al., 1978). However, a number of factors other than RMS may affect the pCO2 measured.

Arterial blood samples are painful to obtain and were not measured at various times of the day depending on the time patients may be seen at any time of day. In addition, no bicarbonate determination that the pCO2 measured was an accurate reflection of arterial pCO2.

There is diurnal variation in arterial carbon dioxide concentration, the highest values being found at the time of waking. In patients with respiratory muscle weakness, hypercapnia first develops nocturnally. Sleep, particularly REM sleep, is accompanied by reduced activity of skeletal muscles, including the accessory muscles of respiration, which, in the presence of reduced diaphragm strength, can lead to significant hypoventilation (Bye et al., 1990). We have demonstrated (Table 4) that ALS patients can have normal daytime blood gases but nocturnal hypoxia and hypercapnia. Patients with normal daytime ELBG pCO2 and pO2 but raised ELBG bicarbonate invariably had significant nocturnal hypercapnia. In this study, blood gases were measured at various times of the day depending on the time that the patients could attend the department, and few measurements were taken within an hour of waking. Thus, patients with isolated nocturnal hypercapnia may have achieved a normal pCO2 at the time of RMS assessment, which may have reduced the precision of the prediction of hypercapnia from the level of respiratory muscle strength. Nevertheless, this reflects standard clinical practice, in which patients may be seen at any time of day. In addition,
Table 4 Polysomnography results

<table>
<thead>
<tr>
<th>pCO₂</th>
<th>pO₂</th>
<th>HCO₃</th>
<th>CMS P⊥</th>
<th>Sniff P⊥</th>
<th>% SNP</th>
<th>% MIP</th>
<th>% VC</th>
<th>Min. O₂</th>
<th>TCC</th>
<th>Hyp. REM</th>
<th>Hyp. nREM</th>
<th>AI</th>
<th>% REM sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ELBG normal</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>n</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>7</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Range</td>
<td>4.6–5.9</td>
<td>9.7–11.9</td>
<td>23.2–27.9</td>
<td>4–29</td>
<td>14–120</td>
<td>16–97</td>
<td>15–97</td>
<td>26–120</td>
<td>74–97</td>
<td>5.5–9.0</td>
<td>0–72</td>
<td>0.4–42</td>
<td>13–76</td>
</tr>
<tr>
<td>Mean</td>
<td>5.3 (0.4)</td>
<td>10.8 (0.7)</td>
<td>25.6 (1.6)</td>
<td>13 (8)</td>
<td>48 (29)</td>
<td>42 (20)</td>
<td>36 (24)</td>
<td>58 (27)</td>
<td>84 (7)</td>
<td>7.0 (1.3)</td>
<td>32 (27)</td>
<td>12 (14)</td>
<td>37 (21)</td>
</tr>
</tbody>
</table>

| **ELBG: raised bicarbonate, normal pCO₂** | | | | | | | | | | | | | | |
| n     | 7     | 7     | 7      | 7       | 7      | 7      | 7    | 7       | 6   | 7        | 7         | 7   | 7          |
| Range | 5.2–5.9 | 9.4–12.2 | 28.4–30.3 | 2–10 | 0–52 | 13–50 | 0–63 | 32–80.5 | 79–89 | 6–10.67 | 24–86      | 20–81 | 46–248  | 2–21 |
| Mean  | 5.7 (0.3) | 10.4 (1.3) | 29.2 (0.7) | 5 (3) | 27 (16) | 25 (14) | 24 (17) | 54 (13) | 85 (3) | 8.4 (1.4) | 60 (29)   | 40 (25) | 109 (75) | 7 (7) |

| **ELBG: raised bicarbonate and pCO₂** | | | | | | | | | | | | | | |
| n     | 8     | 8     | 8      | 8       | 8      | 8      | 8    | 7       | 4   | 8        | 8         | 8   | 8          |
| Mean  | 6.7 (0.7) | 9.7 (1.9) | 32.5 (3.3) | 5 (2) | 22 (10) | 31 (4) | 30 (13) | 56 (14) | 79 (15) | 9 (2)   | 66 (27)   | 36 (29) | 63 (42) | 12 (11) |

Data are mean (standard deviation). pCO₂, pO₂ = carbon dioxide and oxygen tensions of ELBG (kPa). HCO₃ = bicarbonate concentration of ELBG (mmol/l). ELBG results were obtained during daytime. TCC = maximum transcutaneous carbon dioxide obtained overnight (kPa). Min. O₂ = minimum oxygen saturation obtained overnight (%). Hyp. REM and Hyp. nREM = hypopnoea per hour in REM and non-REM sleep, respectively. AI = arousal index (number of arousals per hour of sleep). % REM = percentage of total sleep time in REM sleep. n = number of subjects for whom data were available.
Table 5 Correlation between RMS and sleep parameters

<table>
<thead>
<tr>
<th></th>
<th>Minimum O₂ saturation</th>
<th>Maximum TC CO₂</th>
<th>Hypopnoea/h REM sleep</th>
<th>Hypopnoea/h non-REM sleep</th>
<th>AHI</th>
<th>% REM sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS Pdi</td>
<td>0.01</td>
<td>-0.54</td>
<td>-0.63***</td>
<td>-0.53**</td>
<td>-0.39*</td>
<td>0.25</td>
</tr>
<tr>
<td>Sniff Pdi</td>
<td>0.17</td>
<td>-0.55*</td>
<td>-0.59**</td>
<td>-0.48*</td>
<td>-0.38*</td>
<td>0.04</td>
</tr>
<tr>
<td>% SNP</td>
<td>0.11</td>
<td>-0.41</td>
<td>-0.47*</td>
<td>-0.46*</td>
<td>-0.44*</td>
<td>-0.04</td>
</tr>
<tr>
<td>% MIP</td>
<td>0.08</td>
<td>-0.41</td>
<td>-0.25</td>
<td>-0.38</td>
<td>-0.37</td>
<td>-0.29</td>
</tr>
<tr>
<td>% VC</td>
<td>-0.07</td>
<td>-0.19</td>
<td>-0.37</td>
<td>-0.10</td>
<td>-0.09</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Data are Pearson correlation coefficients. Minimum O₂ saturation and Maximum TC CO₂ = minimum oxygen saturation and maximum transcutaneous carbon dioxide tension achieved overnight, respectively; AHI = apnoea/hypopnoea index; % REM sleep = percentage of night spent in REM sleep. *P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001; no asterisk = non-significant, P ≥ 0.05.

Fig. 3 Relationship between RMS and sleep disturbance for patients undergoing polysomnography. Each graph shows the apnoea/hypopnoea index on the y-axis. RMS, as measured by per cent predicted VC and per cent predicted SNP, is shown on the x-axis. r = Pearson correlation coefficient.

this approach does not invalidate comparisons between the RMS tests.

Neuromuscular patients may have episodes of obstructive sleep apnoea (Labanowski et al., 1996) leading to hypercapnia. We performed full polysomnography on 35 of the 81 subjects in the study (38%). Only one subject had evidence of significant obstructive events. This subject had severe bulbar disease and complained of stridor. He was not hypercapnic. Ten of the 21 hypercapnic subjects had polysomnography and all had disrupted sleep with hypoventilation leading to arousal, and minimal evidence of obstructive apnoea. Although it is possible that obstructive sleep apnoea may have been present in some of the other hypercapnic patients (thus confounding the relationship between pCO₂ and measurements of RMS), the published data on sleep in ALS suggests that, although obstructive events can occur, the predominant sleep abnormalities are ‘central’ hypopnoea and apnoea due to hypoventilation (Gay et al., 1991; Kimura et al., 1999), even in bulbar patients (Ferguson et al., 1996). Central apnoea and hypopnoea may arise from a number of causes, including brainstem disorders and neuromuscular weakness. In the case of ALS, neuromuscular weakness has been presumed to be the predominant cause, although it is difficult to differentiate between central and peripheral origins polysomnographically.

Acceptability of the novel tests

Several of the novel tests of RMS described are more invasive and time-consuming than established methods and are perhaps distressing for a relatively frail group of subjects such as ALS patients. We have found that acceptance of these tests by patients is good. Over the past 4 years, our group has studied >150 ALS patients, some with severe impairments (Polkey et al., 1998). More than 40 patients have consented to repeated assessments as part of an ongoing serial study of respiratory muscle strength. Balloon catheter insertion has been successful in >95% of patients and the only complications have been slight nasal and throat discomfort and trivial nasal bleeding in <5%.

SNP was measured in 71 of 81 (88%) subjects, as this test was not performed routinely in the department at the beginning of the study. This does not represent a bias towards those patients who were able to do the test, since all patients who attended the department after the introduction of the test were asked to perform it.
Clinical significance of the findings

Bulbar versus limb patients

Patients were subdivided into bulbar and limb groups on the basis of the site of onset of the ALS and the presence or absence of significant bulbar impairment. The bulbar group had a significantly reduced Norris bulbar score (mean 21.7, normal function 39), indicating significant bulbar involvement. However, the bulbar score of the limb group was also reduced (mean 32.6), indicating a minor degree of bulbar involvement, as expected. In the limb group, the reduced bulbar score generally resulted from the patient rating several functions, such as blowing or whistling, as mildly impaired, usually as a result of advanced disease. No limb patient had significantly impaired speech or swallowing.

Table 2 shows the results of all tests performed. RMS by all methods of measurement was reduced in the group as a whole, suggesting that respiratory muscle weakness is present in many ALS patients at the time of diagnosis, as reported previously (Nakano et al., 1976; Kreitzer et al., 1978; Fallat et al., 1979; Fitting et al., 1999). There was no difference between the subgroups in diaphragm strength as measured by the CMS P_{di}, a non-volitional test of diaphragm strength which should reflect the true strength of the patient. In all of the volitional tests of RMS, values were below the normal range. Volitional tests require full activation of the respiratory muscles for a maximal value to be obtained, and many subjects, for a variety of reasons (including submaximal effort), do not achieve this (Allen et al., 1995). Recent reports (Arnulf et al., 2000; Similowski et al., 2000) have suggested that some ALS patients may have abnormalities of central activation of the diaphragm, perhaps resulting from upper motor neurone lesions (UMN) of the phrenic nerve nuclei. In such cases, reduced values of volitional tests would arise not from weakness of the peripheral muscles but from impaired generation or transmission of central commands. The presence of UMN lesions in the corticospinal pathways serving the phrenic nerve may explain the lower predictive value for the estimation of hypercapnia of CMS P_{di} compared with sniff P_{di}. If UMN lesions are present in an individual, cervical magnetic stimulation of the phrenic nerves may overestimate the diaphragm strength available to the patient. The sniff P_{di} may represent more closely the degree of diaphragm weakness of central or peripheral origin. The bulbar group had lower mean values for the volitional tests of RMS than the limb group, the difference reaching statistical significance in the tests of MIP, MEP and per cent predicted MEP. Bulbar ALS is often associated with a greater degree of UMN involvement than limb-onset ALS, and the presence of central activation abnormalities may, in part, explain the difference seen. Alternatively, the lower mean values of these tests in patients with bulbar abnormality may reflect the poor use of a mouthpiece by these subjects.

Prior to our study, we hypothesized that patients with bulbar weakness may perform tests requiring a mouthpiece submaximally because of impaired lip-seal, and that tests that do not rely on a mouthpiece would have greater predictive power for the presence of hypercapnia. However, in patients with significant bulbar involvement, all tests had less power to predict hypercapnia, and when all such patients were excluded all tests had higher predictive power (Table 3). This finding may have been due largely to a small sample size; only two bulbar subjects were hypercapnic and this may have affected the results of logistic regression. A further explanation is that pathology other than respiratory muscle weakness contributed to hypercapnia in the bulbar patients, particularly as the non-volitional test of diaphragm strength, CMS P_{di}, did not appear to predict hypercapnia well in this subgroup. Previous studies have demonstrated upper airway abnormality in neuromuscular patients in general (Vincken et al., 1986) and bulbar ALS patients in particular (Garcia-Pachon et al., 1994). A study of coughing and choking episodes in ALS (Hadjikoutis et al., 2000) found that patients with bulbar abnormality, although they coughed more, had a less effective cough with a reduced cough peak flow. During the course of the study, Hadjikoutis and colleagues did not document an increased incidence of pneumonia, although they did not formally assess for aspiration. It is, however, possible that patients with upper airway abnormality may have episodes of aspiration particularly in the presence of swallowing difficulties, and the resulting atelectasis may alter the relationship between the level of respiratory muscle weakness and hypercapnia. It is also possible that upper airway instability, as previously reported in ALS (Garcia-Pachon et al., 1994), may occur whilst patients are performing tests of RMS leading to a reduction in flow transmission, resulting in submaximal pressures being recorded above the cords, e.g. at the nose. In our study, one patient developed audible stridor whilst performing repeated maximal sniffs. Although the patient made increased inspiratory effort, as demonstrated by increasingly negative oesophageal pressure swings, the nasal pressure was lost. On recovery, the nasal pressure matched oesophageal pressure again, without alteration to the nasal plug or catheter. We have described previously the vocal cord abnormality of this subject (Polkey et al., 1998), demonstrating abnormal vocal cord movement endoscopically and by the maximal flow volume loop. We suggest that uncoordinated closure of the vocal cords prevented transmission of the negative intrathoracic pressure to the nose. However, in the majority of bulbar patients there was good transmission of intrathoracic pressure to the nose, as reflected by the strong relationship between sniff P_{oes} and SNP (mean 47 and 39 cmH2O, respectively, r = 0.95, P < 0.001).

Relationship of RMS to sleep disturbance.

We have shown that respiratory muscle strength, as measured by novel volitional and non-volitional tests (sniff P_{di}, per cent predicted SNP and CMS P_{di}) correlates with the degree of SDB. The correlation between RMS as measured by per cent predicted MIP and VC, is less strong. However, our
data cannot be used to answer the interesting question of the level of respiratory muscle weakness at which SDB is likely to occur. Sleep studies were performed as part of the clinical management of individual patients, in response to the presence of suggestive symptoms. This is likely to explain the high prevalence of SDB found in our data. Very few patients with normal or nearly normal strength underwent polysomnography. Two out of the four patients with normal diaphragm strength had SDB. It is therefore possible that patients with moderate degrees of weakness may have SDB that may be asymptomatic. Further studies are necessary to establish whether measurement of RMS is predictive of the onset of SDB.

The predominant cause of SDB appeared to be hypoventilation secondary to respiratory muscle weakness. The incidence of obstructive apnoea was low. In previous studies of sleep in ALS, the predominant cause of symptomatic SDB and nocturnal desaturation appears to have been hypoventilation. However, obstructive apnoeas have been described, particularly in patients with relatively well-preserved respiratory muscle strength. Gay and colleagues (Gay et al., 1991) studied 18 ALS patients with SDB who had a mean VC of 82% of the predicted value. Nine patients had predominantly obstructive apnoea, the remainder having predominantly mixed or central apnoea. Kimura and colleagues (Kimura et al., 1999) studied 18 ALS patients. They found SDB in only three patients, two of whom had episodes of obstructive apnoea. The mean VC in their study was 83% of the predicted value. The mean VC of the patients undergoing polysomnography in our study was 56% of the predicted value. In weak patients, insufficient negative intrathoracic pressure may be generated to suck against the upper airway structures and generate upper airway obstruction. As we were studying weaker patients, this may explain the lower incidence of obstructive apnoea compared with that found in previous studies.

**Prediction of the presence of hypercapnia using tests of RMS**

In a previous study of patients with respiratory muscle weakness due to proximal myopathy (Braun et al., 1983) a VC <55% of the predicted value was associated with hypercapnia. This level has not been defined in patients with ALS, although examination of the figures presented by Serisier and colleagues (Serisier et al., 1982) shows hypercapnia over a wide range of percentage predicted VC (~40–73%) and MIP and MEP (approximately −11 to −44 and +31 to +60 cmH2O, respectively). Similarly, we recorded hypercapnia in patients with VC ranging between 19–78% of predicted, MIP between 11–47% of predicted and MEP between 15–74% of predicted values (see scatterplots in Fig. 2B–D). This is reflected in the results of logistic regression, which show that although these tests are relatively specific for the detection of hypercapnia, sensitivity is low.

Although it is known that ventilatory failure is the most frequent cause of death in ALS and it has been shown that measurement of respiratory muscle strength has prognostic value (Ringel et al., 1993; Haverkamp et al., 1995; Stambler et al., 1998), no single test has been able to predict the presence of respiratory failure reliably (Miller et al., 1999). Our results suggest that the newer tests of respiratory muscle assessment are better able to predict hypercapnia in ALS patients. Identification (or exclusion) of patients at risk of ventilatory failure supports good clinical practice. Patients in whom RMS testing suggests that hypercapnia is unlikely may be spared further investigation.

The tests of RMS with the greatest discriminatory power to predict hypercapnia are the measurement of CMS Pdi, sniff Pdi and sniff Poes, particularly in patients without significant bulbar involvement. The widespread use of these tests may be restricted because they are more technically demanding and time-consuming than conventional methods. Nevertheless, they could be considered for clinical trials, in which their greater discriminatory power could result in reduced sample sizes or more homogeneous stratification of patients. Additionally, patients who cannot achieve normal values in conventional volitional tests may be found to have normal strength when more invasive tests are used.

In the clinic setting, the non-invasive SNP has considerably more discriminatory power for the detection of hypercapnia than both actual and per cent of predicted VC, MIP and MEP. It can be measured with a hand-held meter (Watson, 1997). We suggest that the SNP be used as a screening test for the presence of ventilatory failure, since a cut-off level of 32% of the predicted value has a specificity of 85% and a sensitivity of 81% for the presence of hypercapnia. Any patient approaching this level should be assessed carefully for symptoms and signs of ventilatory failure. Further studies are required to assess the role of RMS testing in the management of ALS patients with severe bulbar abnormality.

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**References**


Amyotrophic lateral sclerosis and ventilatory failure


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