Respiratory muscle assessment in motor neurone disease

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Introduction

In this issue, Hadjikoutis and Wiles correctly identify that respiratory failure is the commonest cause of death in Motor Neurone Disease (MND) and discuss the use of venous bicarbonate and chloride to assess respiratory function. The study’s finding that this domiciliary investigation can provide prognostic information regarding the respiratory status of MND patients is interesting, and it is useful to consider its place amongst the many tests of respiratory muscle and ventilatory function that are available.

Respiratory muscle weakness is a common feature of MND and is often present at diagnosis. Although such weakness is usually asymptomatic at this stage, respiratory failure can be the presenting feature of MND. Respiratory muscle strength continues to deteriorate during the course of the disease, with symptoms developing insidiously, eventually leading to respiratory failure and, if untreated, death. Due to the impaired mobility of the patients, symptoms of hypoventilation are initially subtle and depend on the pattern of respiratory muscle weakness. If the diaphragm is predominantly involved, orthopnoea will be a major symptom, due to the weak diaphragm failing to counter the gravitational displacement of the abdominal contents into the thorax when the patient lays flat. More global respiratory muscle weakness will cause exertional dyspnoea; however, if disability due to limb weakness limits physical activity, a history of breathlessness during speech, dressing or eating must be sought. Hypoventilation (i.e. hypercapnia) occurs first during sleep. This is particularly the case in REM sleep, as a result of the reduction of intercostal and accessory muscle activity, leaving only a weakened diaphragm to support ventilation. In many patients, sleep-related hypoventilation occurs before resting dyspnoea, and abnormal daytime arterial blood gases develop. This may lead to a reduction in the time spent in REM or an increase in accessory muscle activity in REM sleep. As respiratory muscle weakness progresses, all stages of sleep are affected by hypoventilation, with repeated desaturations, which result in arousals and sleep fragmentation. Patients complain of unrefreshing sleep and develop symptoms of sleep-disordered breathing, including fatigue and increasing somnolence, which may initially result in frequent but deliberate naps during the day, which are then unrefreshing, and then progress to falling asleep inappropriately, e.g. during a conversation. This excessive daytime somnolence can be quantified by the Epworth Sleepiness Score, which if > 10/24, suggests significant somnolence. Other less obvious symptoms of sleep-disordered breathing include poor appetite, headache, and cognitive and intellectual impairment. However, it should be noted that upper airway abnormalities are also an occasional feature of MND and are associated with obstructive events causing sleep disruption, independent of peripheral respiratory muscle weakness. Discomfort, cough, and excessive saliva may also disturb sleep, although it is equally true that arousals as a result of hypoventilation may make patients more aware of these symptoms. It is important to establish the precise...
cause of disturbed sleep in MND for the correct treatment to be administered.

With increasing evidence that non-invasive ventilation (NIV) extends life \(^{15}\) and improves quality of life in MND \(^{16}\), it is important that impaired ventilatory capacity is diagnosed at an early stage. In this disabled group of patients, the decision to initiate NIV raises many issues that require discussion.

Lung function tests can be difficult to perform in patients with MND. The use of venous bicarbonate and chloride, measured in blood sampled at the patients' home and independent of patients ability to perform tests, has clear benefits. \(^2\) Venous bicarbonate is raised as a result of renal compensation of sustained or repeated respiratory acidosis. However, patients may already have considerable symptoms of sleep-disordered breathing and even breathlessness at this stage, and indeed earlier. Therefore tests that indicate reduced ventilatory capacity earlier than abnormalities of venous bicarbonate are clinically useful.

Ventilatory failure is largely due to weakness of inspiratory muscles. Expiratory muscle weakness is also impaired in MND \(^{17}\) with the important clinical consequence that cough is compromised. The impact of inspiratory muscle weakness can be mitigated by non-invasive ventilation, and that of expiratory muscle weakness can be compensated for by techniques that augment cough. \(^{18,19,20}\) To anticipate and appropriately apply such therapies, assessment of both inspiratory and expiratory muscle function is needed. Table 1 outlines the symptoms and physiological changes that occur as weakness progresses, and indicates useful tests to help in the management of these vulnerable patients. Tests that assess, directly or indirectly, respiratory muscle function and ventilatory capacity in MND may be non-invasive or invasive, volitional or non-volitional.

### Non-invasive volitional tests

**Vital capacity and routine lung function**

Respiratory muscle testing has traditionally focussed on vital capacity. This is a widely available test, however the accuracy of measurement is dependent on the subject's effort and co-operation, as well as the ability to create an adequate mouth seal. This is not always possible, particularly for bulbar patients. VC lacks discrimination, as a VC of 19–78% of predicted may be associated with hypercapnia. \(^21\) VC can be easily repeated to detect deterioration in patients being followed up serially, although mild weakness will not be

<table>
<thead>
<tr>
<th>Degree of weakness</th>
<th>Symptoms</th>
<th>Blood gases</th>
<th>Sleep studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Orthopnoea*</td>
<td>Mild hypoxa</td>
<td>Probably normal</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea on exertion</td>
<td>Hypcapnia</td>
<td>Sitting VC</td>
</tr>
<tr>
<td>Moderate</td>
<td>Dyspnoea on slight activity</td>
<td>Hypoxia</td>
<td>Total time in REM sleep, Desaturation in REM</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Normocapnia</td>
<td>Sitting VC, TwPdi</td>
</tr>
<tr>
<td>Substantial</td>
<td>Dyspnoea on eating, talking, dressing</td>
<td>Hypoxia, Hypercapnia</td>
<td>Sitting VC, Sniff Pdi &amp; Poes, (\Delta HCO_3)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Normocapnia</td>
<td>Total time in REM sleep, Desaturation in REM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morning headaches</td>
<td>May be unable to register recordable results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daytime HCO_3&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Twitch pressures may be zero</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epworth #</td>
<td>Hypoxia at rest</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morning HCO_3&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Difficulty staying awake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epworth Score</td>
<td>Severe repeated desaturations markedly limit sleep attained</td>
</tr>
</tbody>
</table>

*Substantial specific weakness of the diaphragm causes orthopnoea, regardless of the strength of other respiratory muscles.
identified.\textsuperscript{6} VC can be performed lying and standing to improve sensitivity as a screening test, with a $>25\%$ fall when in the supine posture suggesting diaphragm weakness.\textsuperscript{22}

Patients with inspiratory muscle weakness are unable to take an adequate breath, and transfer factor (TLCO) is reduced because not all alveoli are ventilated and available to take part in gas exchange. However, if TLCO is corrected for lung volume and the transfer coefficient (KCO) calculated, this is increased, due to blood flow to the ventilated alveoli being diverted from hypoventilated units.

### Static mouth pressures

These are a more direct measure of global respiratory muscle strength (RMS), and are measured using a pressure meter attached to a mouthpiece while the patient performs a maximal inspiratory effort (PI-max, normal value more negative than 80 cmH\textsubscript{2}O) from functional residual capacity (FRC) and a maximal expiratory effort (PE-max, normal value $>80$ cmH\textsubscript{2}O) from total lung capacity (TLC). There remains, however, the difficulty with securing an adequate mouth seal and the dependence on patient effort. The manoeuvres are unfamiliar to patients, and some find them unpleasant. Maximum mouth pressures have a poor correlation with respiratory failure in MND.\textsuperscript{21}

### Sniff nasal pressure (SNIP)

This is measured by placing a nasal bung in one nostril and asking the patient to sniff through the patent nostril from FRC (Figure 3).\textsuperscript{6} A value more negative than 60 cmH\textsubscript{2}O excludes significant inspiratory muscle weakness. Sniff is a natural manoeuvre, and patients find it easier to perform than static mouth pressures. It is superior to VC in assessing RMS in MND patients,\textsuperscript{21} particularly if used for serial measurements.\textsuperscript{6}

### Peak cough expiratory flow (PCEF)

The importance of cough flow is becoming clearer, with retrospective data suggesting that a cough peak flow of 160 l/min may be required to clear the lung adequately.\textsuperscript{24} The measurement has conventionally been made using a peak flow meter, although a pneumotachograph and electrospirometer may be more accurate. Alternatively patients can be asked to perform a series of flow volume loops with superimposed coughs.\textsuperscript{17} This test demonstrates whether the patient is able to achieve supramaximal flow (cough spikes) indicative of an adequate cough.

All these tests are widely available in lung function departments. Many are also portable and can be performed in the patient’s home. The SNIP test is particularly useful, and can be used serially to identify ventilatory impairment early and consider undertaking more invasive and comprehensive investigations.

### Non-invasive non-volitional tests

During a sniff manoeuvre, nasal and pharyngeal pressures closely reflect oesophageal pressure (Poes). Similarly, twitch mouth pressure (Tw Pmo) can be measured using a mouthpiece occluded at FRC following magnetic stimulation of the phrenic nerves, to provide an indication of twitch Pes.\textsuperscript{23} However, glottic closure and airways obstruction can make Tw Pmo less accurate by impairing transmission of intrathoracic pressure to the pharynx. Splinting the airways by the use of continuous positive airway pressure (CPAP) may avoid this difficulty, and is currently being evaluated in our unit. This could provide a much needed non-invasive non-volitional method of assessing respiratory muscle strength.

### Invasive volitional tests

These require the placement of pernasal balloon catheters into the oesophagus and stomach to allow the measurement of oesophageal (Poes), gastric (Pgas) and transdiaphragmatic pressures (Pdi).\textsuperscript{25} Pdi provides an accurate measure of diaphragm contractility. Although these are invasive tests, they are well tolerated by the vast majority of patients, including those with bulbar dysfunction.

### Sniff Poes and sniff Pdi

Poes and Pdi can be monitored during the sniff manoeuvre to give a more accurate assessment of RMS than nasal pressure alone (Figure 1).\textsuperscript{25} A sniff Poes of 80 cmH\textsubscript{2}O and a sniff Pdi of 100 cmH\textsubscript{2}O exclude significant inspiratory and diaphragm weakness. During the sniff test Pgas may be negative, reflecting upward movement of the weak diaphragm (Figure 2). Sniff Poes and sniff Pdi are probably the most accurate tests of respiratory muscle weakness that predict ventilatory failure in non-bulbar MND patients.\textsuperscript{21}
Cough Pgas

Measurement of Pgas during a maximal cough can be used to assess expiratory muscle strength. Measuring PCEF while also recording Pgas will avoid underestimating PCEF due to poor cough efforts, which will be reflected by submaximal Pgas.

Invasive non-volitional tests

Magnetic stimulation of the phrenic nerves

With oesophageal and gastric balloon catheters in situ, the phrenic nerves can be magnetically stimulated unilaterally or bilaterally, and Twitch Pdi measured. As this is a non-volitional test, it is does not rely on the patients’ ability to perform manoeuvres and requires no mouthpiece. The technique is particularly useful in assessing bulbar patients.

Magnetic stimulation of T10

The abdominal muscles can be stimulated magnetically via their nerve roots by positioning

Figure 1. Pressure generated during an inspiratory sniff manoeuvre in a subject with normal respiratory muscle strength, demonstrating a negative oesophageal pressure and a positive gastric pressure. Pgas, gastric pressure; Pdi, transdiaphragmatic pressure; Poes, oesophageal pressure; Pnasal, nasal pressure.

Figure 2. Pressure generated during an inspiratory sniff manoeuvre in a subject with weak respiratory muscles, demonstrating a negative oesophageal pressure trace and a negative gastric pressure deflection. This illustrates paradoxical diaphragm movement, which may be detected clinically (as discussed in the text). Pgas, gastric pressure; Pdi, transdiaphragmatic pressure; Poes, oesophageal pressure.

Figure 3. The sniff manoeuvre, using a nasal bung and an adapted pressure meter.
the stimulating coil at the level of T10. Twitch gastric pressure provides a measure of abdominal muscle strength.\textsuperscript{29}

**Earlobe blood gases (ELBG)**

Blood gas analysis is essential in the management of respiratory muscle weakness, and for the detection of respiratory failure secondary to hypoventilation. To minimize patient discomfort, earlobe blood gas samples are preferred. With mild weakness, there is usually hypoxia, but patients hyperventilate and the $\text{CO}_2$ may be normal or low. With increasing weakness the ventilatory capacity is compromised, especially at night. Daytime $\text{CO}_2$ levels rise to normal values, but there may be nocturnal hypercapnia, which then leads to an elevated bicarbonate. Eventually, with substantial weakness, there is hypoxia and hypercapnia. Venous bicarbonate is also elevated as a result of sustained respiratory acidosis, however, the sequential changes that occur in $\text{CO}_2$ and $\text{O}_2$, and the prognostic information that they provide, can only be determined by analysis of blood gases.

**Sleep studies**

In MND patients with respiratory muscle weakness the earliest abnormalities of ventilation are usually detected during sleep. Much can be learned non-invasively by overnight oximetry, which can be performed at the patient’s home. Hypoventilation is reflected by desaturations, and if there is arousal there is repeated tachycardia. Overnight oximetry does not provide any information on sleep staging or on the causes of desaturations. Full polysomnography, performed in hospital, more accurately determines the cause of desaturations. If they are hypoventilatory in nature, there is reduction in flow and thoracic movement. The abdomen may move paradoxically. Obstructive events can be distinguished by thoracic paradox, with inrawing of the thoracic cage as the diaphragm contracts against a closed airway, creating a negative intra-thoracic pressure, but no airflow. Obstructive events need to be distinguished from hypoventilatory desaturations because they may simply require CPAP therapy to maintain upper airway patency. Mixed obstructive and hypoventilatory states may require inspiratory support with NIV combined with a positive end expiratory pressure (PEEP). Full polysomnography also allows the staging of sleep. This can help determine the severity of weakness, because initially abnormalities of ventilation are confined to REM. Eventually there is desaturation throughout all stages of sleep and such patients are most likely to benefit from treatment with NIV.

**Conclusion**

In MND, respiratory muscle weakness leads to an insidious onset of symptoms. The treatment of ventilatory failure in MND, whilst often effective and beneficial, raises many important issues requiring discussion with the patient and carers. Therefore it is important to identify respiratory muscle weakness early to allow adequate time for any concerns to be addressed. As Hadjikoutis and Wiles point out, serum chloride and bicarbonate can provide an assessment of respiratory status and prognosis in MND patients, but a range of other tests are available which, if used appropriately, can achieve an accurate and comprehensive assessment.

**References**


