Cough in motor neuron disease: a review of mechanisms

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Introduction

For patients with neuromuscular diseases which affect breathing and swallowing, coughing and choking are frightening and distressing symptoms sometimes perceived (correctly) as life-threatening. Cough is an important function of the larynx and respiratory system which allows an individual to clear the airway of foreign material and secretions and prevent aspiration of food and fluid. Choking is the feeling of strangulation or suffocation which may result from the presence of foreign material in the airway, often accompanied by airway obstruction so that there is an inability to draw breath.

Motor neuron disease (MND) is a progressive degenerative disorder of the nervous system affecting the anterior horn cells of the spinal cord, the motor nuclei of the brain stem, and the corticospinal tracts. For MND patients, airway obstruction, aspiration and pneumonia are major causes of morbidity and mortality; episodes of coughing and choking are commonly reported by patients, and presumably represent episodes of decompensation of bulbar and respiratory mechanisms as progressive dysfunction develops. Such patients have, on the one hand, an increased need to cough but, on the other, a reduced capacity to do so effectively. To try to develop a clearer clinical approach to dealing with these symptoms, we review some aspects of cough and, subsequently, its pathophysiology in MND.

The cough reflex

The cough reflex is divided into three main elements: the sensory limb, the central control, and the efferent limb (Figure 1).

Sensory limb

The epithelium of the larynx, trachea, and larger bronchi contains sensory nerves that are responsible for triggering cough. There are two main categories of cough receptors: the rapidly-adapting pulmonary stretch receptors (RAR) with small-diameter myelinated fibres, and the pulmonary and bronchial C fibre receptors with non-myelinated afferent fibres. The pattern of cough depends on the stimulus and on the part of the respiratory tract stimulated. Receptors in the larynx and trachea are extremely sensitive to mechanical stimuli, but in the bronchi receptors become more chemosensitive. The cough response from the bronchi is different from that triggered by the presence of food and fluid in the larynx and trachea. The bronchial response is triggered by the presence of airway mucus which cough helps to clear. Mucus production in the bronchi is part of the airway defence mechanism and increases with inflammation and infection; the presence of inflammatory mediators such as bradykinin can sensitize airway receptors and cause hyper-reactivity. Cough is a side-effect of ACE inhibitors: these cause increased levels of bradykinin which...
may be the cause of the hyperreactivity of the cough reflex. By contrast, water triggers cough when it comes into contact with the larynx and trachea, perhaps due to an osmotic stimulus, as cough is not triggered by the watery mucus normally in contact with the larynx and trachea. However, aspiration of saliva triggers cough: possibly the osmolarity of saliva is different from airway secretions. Mechanical stimulation of the larynx causes immediate expiratory efforts, which are usually referred to as the ‘expiration reflex’, rather than cough. However, more classical cough, including deep inspiration before the forced expiration, can also be triggered from the laryngopharyngeal region.

Stimulation lower down in the respiratory tract makes the inspiratory phase of coughing more prominent; indeed, the deep inspiratory efforts or augmented breaths that can be produced from the bronchial tree may resemble a fragment of an entire cough, quite the opposite to the laryngeal expiration reflex. Teleologically, it would be desirable for a foreign body touching the vocal cords to induce an immediate expiratory effort since preliminary inspiration would draw the foreign body into the lungs. Conversely, debris in the bronchi might not be effectively cleared by cough unless a preliminary slow inspiration first drew air distal to the material cervical cord adjacent to the spinothalamic tracts. In anaesthetized and decerebrate cats, bilateral slow inspiration first drew air distal to the material cervical cord adjacent to the spinothalamic tracts. In anaesthetized and decerebrate cats, bilateral slow inspiration first drew air distal to the material cervical cord adjacent to the spinothalamic tracts. In anaesthetized and decerebrate cats, bilateral slow inspiration first drew air distal to the material cervical cord adjacent to the spinothalamic tracts.

If a contrast agent enters the bronchial tree from the pleural cavity during fluoroscopy in patients with bronchopleural fistula, the patient does not cough until it reaches segmental bronchi. However, alveolar diseases such as fibrosing and allergic alveolitis are characterized by cough, which is commonly the presenting symptom of these diseases: this clinical observation appears to conflict with experimental findings suggesting an absence of alveolar cough receptors. Points of airway branching, including the tracheal carina, seem especially sensitive to cough.

Afferent nerves mediating the cough reflex are mainly (e.g. cat) or exclusively (e.g. man and rabbit) in the vagus nerve. Afferent laryngeal innervation is by the recurrent laryngeal nerve (RLN), and the internal and external branches of the superior laryngeal nerve (SLN). The RLN supplies the subglottic portion of the larynx: the internal branch of the SLN is mainly composed of afferent fibres from the supraglottic region. Cough may also be stimulated through nerve endings located in the mucous membrane of the pharynx, oesophagus, and pleural surfaces as well as the external auditory canal.

Some findings have been contradictory concerning the larynx and the cough reflex. Experiments in healthy awake subjects whose cough was elicited by inhaled nebulized citric acid showed no difference in cough thresholds with and without block of the SLNs. Explanations are that both excitatory and inhibitory pathways might have been blocked, or that contamination of distal areas of the airway, innervated by other vagal afferents, may have occurred. Another observation which raises questions concerns cardiopulmonary transplanted patients who had poor or absent cough in response to a stimulus: these patients have a virtually denervated tracheobronchial tree, but a fully innervated larynx. Why have supposedly normal laryngeal afferents become unable to trigger the expected defence reflex? Pulmonary slowly-adapting stretch receptors (SARs) might have an important facilitatory role in the elicitation of cough: rabbits in which SARs are blocked become unable to cough.

Central control of the cough reflex

Various clinical observations and experimental studies identify the brain stem as the site of the cough motor generator. Whether the cough motor pattern is produced by the same brainstem neurons that generate the normal respiratory rhythm or by a separate ‘cough centre’ is unclear. Efferent respiratory activity from the ‘respiratory centre’ in man, mainly passes in crossed pathways in the ventrolateral cervical cord adjacent to the spinothalamic tracts. In anaesthetized and decerebrate cats, bilateral lesions largely restricted to the ventral part of the lateral columns abolished spontaneous breathing: pathways mediating spontaneous ‘metabolic’ drive to inspiratory and expiratory motor neurons appear dissociated, the latter lying more medially in the ventral columns. The descending projection serving the abdominal muscle component of the cough response was separate from that serving spontaneous inspiration, and lay just ventral to the ventral horn. Opioids such as morphine depress cough reflex before respiration, and some evidence suggests the involvement of endogenous opioids in the cough reflex. Beta-endorphin, a potent endogenous opioid peptide, is synthesized in the nucleus tractus solitarius (NTS) which, in addition to regulating respiration and swallowing, plays an important role in the regulation of the cough reflex. However, some studies have been unable to find any experimental evidence that opioids have a significant antitussive effect on cough associated with acute upper respiratory tract infections or on capsaicin-induced cough (see also below).

By contrast with spontaneous ‘metabolic’ or ‘reflex’ control of breathing, volitional manoeuvres are probably mediated through pyramidal (corticospinal) pathways (dorsolateral in the cord) and the upper and lower motor neuron contribution to various respiratory muscles can be assessed.
neurophysiologically using magnetic stimulation of the motor cortex and spinal roots.\textsuperscript{21–23} Neurological lesions in the ventral pons or the anterior high cervical cord can produce clinical situations where there may be differential involvement of volitional or metabolic (reflex) activation, respectively. Thus lesions of corticospinal pathways may result in inability to voluntarily breath hold, deep breathe, cough or perform a vital capacity manoeuvre, despite adequate spontaneous ventilation, tidal volume responsive to $\text{CO}_2$ and preservation of reflex cough. Lesions of the metabolic pathway may leave the former volitional activities intact, but result in respiratory failure to sleep. Lesions of the lower motor neuron ‘final common pathway’ would not be expected to have such a differential effect, although it is possible that disease processes may selectively influence the intensity of reflex/metabolic and volitional activation pathways.

Similarly there may be separate pathways for the voluntary and reflex cough. In awake patients, cough induced by inhalation of irritants can be suppressed voluntarily, suggesting the presence of inhibitory pathways from the higher centre to the brainstem where the existence of a cough centre is postulated.\textsuperscript{24} A patient with locked-in syndrome due to ventral pontine infarction was unable to cough or take and hold his breath to command, though emotional modulation occurred.\textsuperscript{25} However, it was possible to induce cough reflexely, and spontaneous respiratory rhythm was preserved. Furthermore, drugs may differentially affect pathways for voluntary and reflex cough. Codeine suppresses cough in animals models, and is also effective in controlling chronic cough and induced cough in man,\textsuperscript{26–29} but there is no evidence to support an antitussive action of codeine for cough associated with upper respiratory tract infection (URTI).\textsuperscript{30} Cough associated with URTI might be elicited by a voluntary (cortical) pathway, with the sensation of airway irritation acting as a trigger: such cough can be voluntarily suppressed.\textsuperscript{31} A possible explanation for the lack of efficacy of codeine in cough associated with URTI is that it is ineffective against voluntary cough whilst inhibiting reflex cough.\textsuperscript{32} A possible model to illustrate the voluntary and reflex pathways involved in the control of cough is shown in Figure 2.

### Efferent limb

Integrated activation of the efferent limb of the cough reflex leads to a classical response, split into four phases. Coughing starts with a brief inspiration of a variable volume of gas above functional residual capacity (FRC). In this inspiratory phase the major muscles used are the diaphragm and intercostals. During forced inspiration, accessory inspiratory muscles are recruited, such as sternocleidomastoid, scalenus anterior and medius, trapezius, levator scapulae, rhomboids, serratus anterior and pectoralis minor.\textsuperscript{33} Secondly, inspiration is followed by glottic closure for about 0.2 s, which allows pressure to build-up in the abdominal, pleural, and alveolar spaces to about 50–100 mmHg during the expiratory effort. The intrathoracic pressure developed when the glottis is closed is approximately 50 to 100% greater than that obtained during the forced expiratory manoeuvres in which the glottis is open.\textsuperscript{34} The main muscles involved are the lateral cricoarytenoids and the transverse arytenoid innervated by the recurrent laryngeal nerve.\textsuperscript{32}

Thirdly, the expiratory phase involves the major muscles of expiration (anterior and lateral abdominal wall): other accessory expiratory muscles include the serratus posterior inferior, latissimus dorsi, and quadratus lumborum.\textsuperscript{35} Strong expiratory muscles develop the high expiratory pressures for an effective cough. Active opening of the glottis is followed by accelerating expiratory flow at the mouth, reaching a peak within 30–50 ms of as much as 12 l/s and terminating half a second later, usually with glottic closure. These peak flows may be associated with the high linear gas velocities that are a function of the cross-sectional area of the airways (velocity = flow/cross-sectional area) and which are important for the removal of secretions. For a given flow, the linear velocity is high in airways that are dynamically compressed by high intrathoracic pressures. Secondly, they vibrate the lung and airway tissues, causing the characteristic coughing sound.\textsuperscript{34} The coughing sequence may be repeated rapidly several times.
times going down through the lung volumes to residual volume and progressively collapsing more and more of the intra-thoracic airways. Finally the relaxation phase occurs where expiratory muscles relax and normal ventilation ensues.

Motor impulses to the pharynx and larynx are mediated predominantly through the vagus nerve. The spinal cord cervical and thoracic segments control coordinated expulsive movements for tracheal and bronchial clearance, which are executed by the diaphragm, the intercostals and the abdominal muscles. The diaphragm plays an active role in coughing. After descent during the initial deep inspiration, the diaphragm remains low as long as the glottis is closed, because the elevations of both the intra-pulmonary and the intra-abdominal pressures (resulting from expiratory muscle contraction) are approximately equal. When the glottis opens during the expulsive phase, the intra-pulmonary pressure falls and the diaphragm sharply ascends. It is likely that the diaphragm rises passively during this phase of cough, but modulation of diaphragmatic contraction may regulate the expulsive force of the cough by controlling the upward push of the abdominal muscles.35

There is conflicting evidence on the importance of glottic closure and high flows in coughing for effective expulsion of debris. The advent of laryngoscopy led to more information about the pathophysiology of the larynx but, except in very gentle voluntary coughs when glottic closure can be observed, the movements of the vocal cords are obscured by the false cords and the epiglottis. Patients with tracheostomies or laryngectomies can cough effectively, and tracheostomy tubes must be well secured so that they are not coughed out. Measurements were made of sound, air flow and chest/abdominal volumes in early morning involuntary coughing in patients with obstructive airway disease and during various voluntary cough techniques in normal subjects.36 Glottic closure did not appear critical in determining the maximum pressure or the pressure profile, and overall cough could be productive without glottic closure and despite low air flow rates.

**Motor neuron disease**

In MND patients the requirement to cough is increased, whereas the effectiveness of coughing is reduced. Why do MND patients have an increased requirement to cough? A major problem is difficulty in swallowing, with an increase risk of aspiration which can be either symptomatic or asymptomatic. The oral phase of deglutition is compromised most often, and even in those with no clinical evidence of dysphagia, videofluoroscopic features have been found similar to those in the dysphagic group.37 Other studies also confirm the asymptomatic involvement of swallowing in MND patients.38 Thus the need to clear pharyngeal residues or aspirated material, combined with the susceptibility to increased airway and lung secretions consequent on peripheral atelectasis secondary to respiratory muscle weakness, may increase the requirement to cough. Possibly changes in oropharyngeal flora may increase the likelihood of infection following aspiration and hence increase the need to cough.39

How can MND affect each component of the cough reflex? (Table 1).

**Sensory limb**

The absence of sensory changes is a cardinal point in the clinical diagnosis of MND, and routine histological examination does not usually reveal obvious change in sensory ganglia, posterior spinal roots or posterior columns. However, systematic counting has shown some loss of both motor and sensory cells and axons in cases of classic MND. Thus the assumption that the sensory system is normal in MND may not be absolutely valid.40 Recurrent aspiration of food and fluids can lead to laryngeal/tracheal inflammation, and possibly hyperreactivity of cough reflex in the early phase of inflammation, due to the presence of inflammatory mediators such as bradykinin and prostaglandins. However, with time it may cause damage to the airway and desensitization (see below).

**Central control**

Although there is a tendency for experimentally-induced cough sensitivity to be lower with age (perhaps due to effect on receptors, bronchial small muscle tone or other unknown factors),41 patients with MND seem to have an enhanced cough reflex. Capsaicin, an agent which induces cough through sensory nerve stimulation, was used to test cough sensitivity in groups of patients with and without dysphagia, including patients with MND. Cough threshold tended to be lower in those with abnormal swallowing.42 Several possible reasons for this finding seem possible. Awareness that swallowing is abnormal may result in heightened sensitivity to objects in the mouth and pharynx, with an associated reduction in the threshold for initiating protective responses. Loss of corticobulbar pyramidal fibres may lead to brisker palatal and pharyngeal responses, due to a reduction in descending inhibition, by analogy with a brisk jaw jerk and brisk tendon reflexes. A comparison of palatal and pharyngeal motor responses between healthy adults and MND
Table 1  How MND can affect cough

<table>
<thead>
<tr>
<th>MND change</th>
<th>Physiological consequence on cough reflex</th>
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<tbody>
<tr>
<td><strong>Sensory limb</strong></td>
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<tr>
<td>Aspiration of food and fluids leading to laryngeal/tracheal inflammation</td>
<td>?Hyperreactivity initially and desensitization with time</td>
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<tr>
<td>Role of poor oral hygiene and of bacteriological flora in mouth and pharynx</td>
<td>?Aspiration of infective material</td>
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<tr>
<td><strong>Central control</strong></td>
<td></td>
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<tr>
<td>1. Conscious awareness of abnormal swallowing pattern &amp; risk of aspiration or choking</td>
<td>?Development of heightened sensitivity to objects in the mouth and pharynx; decreased threshold for initiating protective responses</td>
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<tr>
<td>2. Loss of corticobulbar pyramidal fibres</td>
<td>Reduced volitional control of tongue, pharynx and larynx</td>
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<tr>
<td>3. Increase of PaCO₂: metabolic consequence of respiratory failure type 2</td>
<td>Increased risk of laryngeal penetration and enhancement of cough development</td>
</tr>
<tr>
<td>4. Impaired control of respiratory pattern around deglutition apnoea</td>
<td>Increased rate of post-deglutition inspirations and risk of aspiration</td>
</tr>
<tr>
<td><strong>Efferent limb</strong></td>
<td></td>
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<tr>
<td>1. Decrease of inspiratory capacity.</td>
<td>Decrease inspiratory reserve volumes, minimizing the generation of high expiratory pressures/flows</td>
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<tr>
<td>2. Decreased glottis closure</td>
<td>Decrease of diaphragmatic regulation of expulsive force of the cough by controlling the upward push of the abdominal muscles</td>
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<tr>
<td>3. Decreased expiratory muscle strength</td>
<td>Peripheral atelectasis with increased work of breathing</td>
</tr>
<tr>
<td>4. Decrease in voluntary cough capacity (corticospinal impairment)</td>
<td>Reduction of high expiratory pressures, pressure dissipation, reduction of capacity to develop high pleural pressure</td>
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patients showed that pharyngeal motor responses were brisker in patients with MND than in matched normal subjects: a brisk pharyngeal response was associated with symptoms of a swallowing problem and reduced swallowing capacity.43

A swallow and the related deglutition apnoea is nearly always followed by expiration.44 This relationship is often changed in a range of neuromuscular diseases so that there is an increased risk of inspiration immediately after a swallow.45 Clearly this may promote laryngeal penetration or aspiration if there are pharyngeal residues. The reason for this change in pattern is currently unclear but respiratory rate or hypercapnia might be exacerbating factors, whereas the specific nature of the neurological lesion seems not to be.

Many patients with MND probably develop type II respiratory failure due to denervation of the respiratory muscles. Hypercapnia may enhance the development of coughing.46 The effect of increasing PaCO₂ on the co-ordination of respiration and reflex swallowing was investigated by continuous infusion of distilled water into the pharynx (2.5 ml/min) in normal subjects. The ventilatory response to CO₂ is not influenced by continuous reflex swallowing, but hypercapnia influences the timing and frequency of these swallows. Signs of aspiration were never observed during continuous infusion of water at eucapnia, but the majority of subjects showed laryngeal irritation during hypercapnia. Hypercapnia also decreased the frequency of swallowing. It seems possible that the automatic respiratory control system prevails over the swallowing reflexes when the maintenance of ventilation is particularly important in conditions of loaded breathing, since the time available for breathing could be significantly reduced during repeated swallowing.

**Efferent limb**

All the recognized muscles for inspiration, expiration and opening/closure of glottis needed for effective
cough can be affected by MND. Studies using electrical or magnetic stimulation (using cranial and motor root stimulation) suggest that both the final common pathway (lower motor neurons) and the volitional pathways (corticospinal) may be affected, and this presumably occurs to a variable extent and proportion in individual patients.45

**Inspiratory capacity**

One major advantage of a large inspiratory reserve volume is improved expiratory muscle function during cough with the length-tension relationships optimized and greater expiratory pressures and flows. Additionally, the number of closed lung units is minimized at high lung volumes, thereby allowing potential clearance of more distal airways.5,31 Thus, ineffective inspiratory muscle strength will detrimentally affect the generation of maximal expiratory flow rates.

**Glottis closure**

When glottic closure is impaired due to denervation, ineffective rise of the intrathoracic pressures (combined with expiratory weakness) will prevent efficient expiratory flows needed for coughing. Although glottic closure (vide supra) does not seem to be critical for the development of an effective cough it could still be an important contributory factor in MND patients with a weakened expiratory muscle activation.

**Expiratory muscle strength**

Denervation of the expiratory muscles in MND will weaken coughing significantly. Normally during cough the anteroposterior (AP) diameter of the upper rib cage decreases, the AP diameter of the lower rib cage clearly increases and the AP diameter of the abdomen decreases. In the absence of sufficient abdominal muscle contraction, patients use the accessory expiratory muscles (e.g. clavicular portion of pectoralis major which compresses the upper portion of the rib cage) to increase pleural pressure. However, increases in intrapleural pressure may be dissipated by reduced diaphragmatic stiffness and weak abdominal musculature during cough, resulting in an increase in abdominal AP diameter. Because the degree of dynamic airway narrowing (and hence expiratory flow) depends primarily on the magnitude of increase in pleural pressure, any factor reducing this will decrease cough effectiveness.48,49

In predominantly bulbar-type MND, airway encumbrance is usually caused by some combination of aspiration of food and upper airway secretions, whereas in predominantly non-bulbar-type MND, as in other neuromuscular disorders, it has been observed that it usually only occurs during intercurrent chest infections. MND patients with sufficient bulbar muscular function to permit assisted peak cough flows (PCF) of >160 l/min can benefit from intermittent long-term non-invasive ventilatory support. Once PCF decreases below this level however, flows are inadequate to clear airway debris, and it is a matter of time until airway encumbrance results in acute respiratory failure and tracheostomy or death.46,47

**Conclusion**

We have shown that the decompensatory events of coughing and choking in MND are multifactorial in origin. Various combinations of upper and lower motor neuron dysfunction result in respiratory muscle weakness, dysphagia and laryngeal dysfunction resulting in a range of different factors which may promote the need to cough but impair efficacy of coughing; the relative contributions and clinical importance of volitional and reflex (including emotional) activation to the swallowing, laryngeal and respiratory impairments is often unclear in MND patients. There is a need for a more detailed and ongoing medical assessment of distress caused by coughing and choking. The careful assessment of the individual in terms of delineating the motor, sensory and central deficits both for breathing and swallowing holds out the best chance of intervening with the most effective and appropriate treatment. Such treatments may range from advice about what to do during an attack of coughing or choking, to the use of drugs and suction devices to control secretions or cough, alternative routes of feeding, airway diversion and ventilation.

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**References**


