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REVIEW ARTICLE

A Review- Mechanism Of Cough

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ABSTRACT

Today cough is the major persisting problem in the world. The current mortality statistics reveal the weighted average is 0.3 deaths per 1 million. 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, dysphasia 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. The cough reflex has both sensory (afferent) and motor (efferent) components. In auricular branch of the vagus nerve supplying the ear may also elicit a cough.

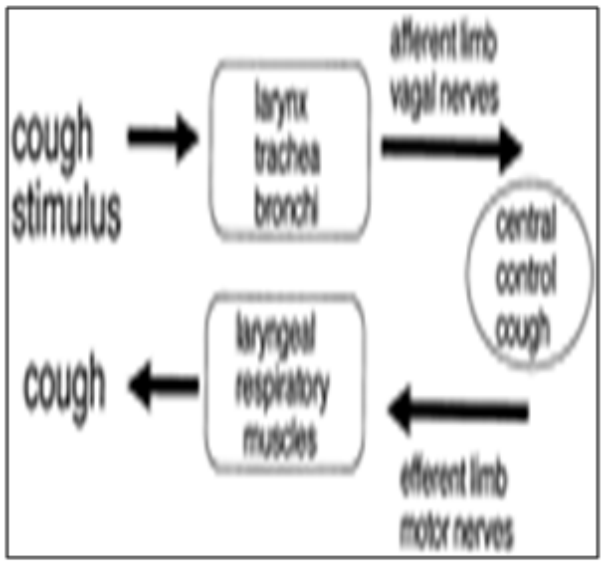
Key word: Mechanism, Cough, Cough mechanism

INTRODUCTION

A short inspiration, closure of the glottis, forcible expiratory effort, and then release of the glottis, with a rush of air at a flow rate of 3,000 to 4,000 cc/sec. A cough is essentially used or regarded as a process for removing foreign material from the lungs. It involves two phases. In the first, the combined action of the cilia and bronchiolar peristalsis moves the material up to the main bronchi and the bifurcation of the trachea. Further movement out of the respiratory system depends on the cough mechanism (**Sesuka et al.**). In all medical conditions in which this mechanism is abolished or reduced, secretions and foreign material accumulate in the alveoli, with a resultant reduction in the aerating surface and a predisposition to infection. Since ventilation of the lungs depends on a patent airway, the cough mechanism should always be used by patients whose inadequate ventilation of lungs may be related to obstruction of the airway [16].

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

Fig 1: The cough reflex.



The cough reflex has both sensory (afferent) and motor (efferent) components. Pulmonary irritant receptors (cough receptors) in the epithelium of the respiratory tract are sensitive to both mechanical and chemical stimuli [18]. Stimulation of the cough receptors by dust or other foreign particles produces a cough, which is necessary to

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remove the foreign material from the respiratory tract before it reaches the lungs.

The cough receptors, or rapidly adapting irritant receptors are located mainly on the posterior wall of the trachea, pharynx, and at the main carina, the point where the trachea branches into the main bronchi. The receptors are less abundant in the distal airways, and absent beyond the respiratory bronchioles. When triggered, impulses travel via the internal laryngeal nerve, a branch of the superior laryngeal nerve which stems from the (vagus nerve) (CN X), to the medulla of the brain [10]. This is the afferent neural pathway. Unlike other areas responsible for involuntary actions like swallowing, there is no clearly identifiable area that can be labeled as the cough center in the brain [1].

The efferent neural pathway then follows, with relevant signals transmitted back from the cerebral cortex and medulla via the vagus and superior laryngeal nerves to the glottis, external intercostals, diaphragm, and other major inspiratory and expiratory muscles [12]. The mechanism of a cough is as follows:

- Diaphragm (innervated by phrenic nerve) and external intercostal muscles (innervated by segmental intercostal nerves) contract, creating a negative pressure around the lung.
- Air rushes into the lungs in order to equalise the pressure.
- The glottis closes (muscles innervated by recurrent laryngeal nerve) and the vocal cords contract to shut the larynx.
- The abdominal muscles contract to accentuate the action of the relaxing diaphragm. Simultaneously, the other expiratory muscles contract.
- The increases the pressure of air within the lungs.
- The vocal cords relax and the glottis opens, releasing air at over 100 mph.
- The bronchi and non-cartilaginous portions of the trachea collapse to form slits through which the air is forced.
- This clears out any irritants attached to the respiratory lining.

Stimulation of the auricular branch of the vagus nerve supplying the ear may also elicit a cough [5]. This is known as Arnold's reflex. Respiratory muscle weakness, tracheostomy, or vocal cord pathology (including paralysis or anesthesia) may prevent effective clearing of the airways [9].

The reflex is impaired in the person whose abdominals and respiratory muscles are weak. This problem can be caused by disease condition that lead to muscle weakness or paralysis, by prolonged inactivity, or as outcome of surgery involving these muscles. Bed rest interferes with the expansion of the chest and limits the amount of air that can be taken into the lungs in preparation for coughing, making the cough weak and ineffective. This reflex may also be impaired by damage to the internal branch of the superior laryngeal nerve which relays the afferent branch of the reflex arc. This nerve is most commonly damaged by swallowing a foreign object, such as a chicken bone, resulting in it being lodged in the piriform recess (in the laryngopharynx) or by surgical removal of said object.

- Coughing is an airway reflex mediated by airway receptors that react to either pressure or chemical stimuli. In several cardiopulmonary diseases, such as left atrial enlargement, tracheal collapse and primary neoplasms, coughing is primarily associated with mechanical compression of the airway. In other conditions a combination of inflammatory mediators stimulating irritant receptors, and airway exudates stimulating mechanoreceptors, results in coughing.
- Large numbers of cough receptors are located in the larynx, at the thoracic inlet and tracheal bifurcation. The numbers of receptors decrease further down the respiratory tract and there are no receptors present in the peripheral airways or alveoli.
- The cough reflex therefore functions mainly in the larger airways, although material from the lower airways and alveoli can move to the level of the larger airways where coughing will help to remove it[11]
- The function of coughing is to assist the removal of material from the airways. This material may have been inhaled or produced in the airways. Coughing also prevents additional inhalation of material, or movement of inhaled material into the peripheral airways.
- With respiratory diseases, airway defense mechanisms result in increased production of mucus from goblet cells and mucous glands in the airway. Respiratory diseases will also result in inflammatory exudates entering the respiratory tract [4]. This material can accumulate in the lower airways and alveoli.
- Alveolar and lower airway material is usually removed through phagocyte

Sis by alveolar macrophages, but because of the presence of the surface tension reducing agent surfactant in the alveoli, this material can also move cranially by a capillary action.

- Once material comes in contact with ciliated epithelium, it is transported by ciliary beating towards the trachea where there is the highest density of cough receptors [7] .
- Coughing then propels the material into the oropharynx where it is swallowed.
- Considering these factors it can be appreciated that coughing is an extremely important protective mechanism for the respiratory system.
- However, coughing caused by mechanical compression of the airways has no protective function, may cause airway epithelial damage and should be controlled, particularly if it is causing exhaustion.

Cough In Motor Neuron Disease

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 [8]. 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.

Central control of the cough reflex:

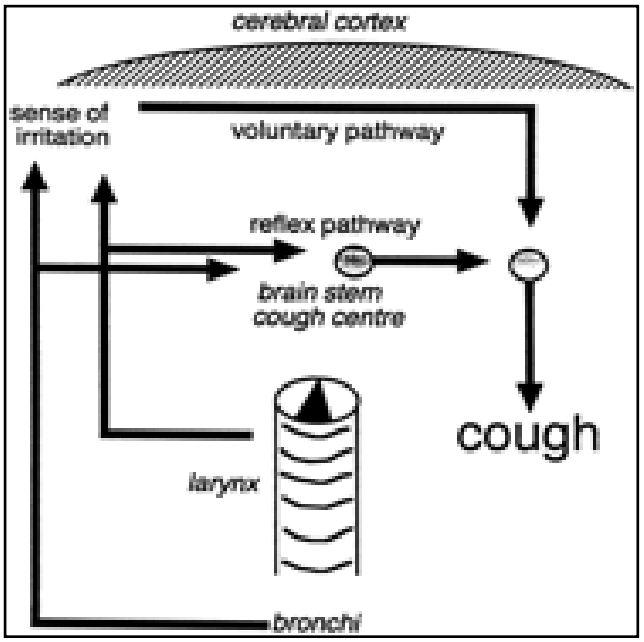
Various clinical observations and experimental studies identify the brain stem as the site of the cough motor generator. Whether the cough motor pattern is produced by the same brainstem neurons that generate the normal respiratory rhythm or by a separate `cough centre' is unclear. Efferent respiratory activity from the `respiratory centre' in man mainly passes in crossed pathways in the ventrolateral cervical cord adjacent to the spinothalamic tracts[3]. 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 [[14]. 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[14] . 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 man oeuvre, despite adequate spontaneous ventilation, tidal volume responsive to 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 [14] . 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. 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,[3] but there is no evidence to support an antitussive action of codeine for cough associated with upper respiratory tract infection (URTI)[14] . 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. 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. A possible model to illustrate the voluntary and reflex pathways involved in the control of cough is shown in (**Fig 2**).

Fig.2 A possible model of the voluntary and reflex pathways involved in cough control.



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 militated fibres, and the pulmonary and bronchial C fibre receptors with non-militated afferent fibres[18] . 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 defense 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 hyper reactivity of the cough reflex [16].

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 before expulsion by forced expiration [18].

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 [11]. 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 subglottal 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 [15].

Some findings have been contradictory concerning the larynx and the cough reflex. Experiments in healthy awake subjects whose cough was elicited by inhaled nebulae 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 vigil 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 [6].

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[17]. 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 manoeuvers in which the glottis is open. The main muscles involved are the lateral cricoarytenoids and the transverse arytenoid innervated by the recurrent laryngeal nerve [13].

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. 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. Secondarily, they vibrate the lung and airway tissues, causing the characteristic coughing sound [2]. The coughing sequence may be repeated rapidly several 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 [19].

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. 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.

CONCLUSION

Coughing is an important way to keep your throat and airways clear. However, excessive coughing may mean you have an underlying disease or disorder. Some coughs are dry, while others are considered productive. A productive cough is one that brings up mucus. Mucus is also called phlegm or sputum. The recent increased interest in cough reflex sensory neurobiology has unveiled a previously unrecognized complexity in the interacting roles of multiple afferent nerve subtypes in regulating this defensive reflex. However, further careful dissection of the cough sensory pathways is still required for the identification of future therapeutic targets for the effective treatment of cough disorders. There is a need for a more detailed and ongoing medical assessment of distress caused by coughing and choking.

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