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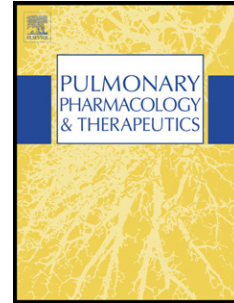
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Voluntary and Reflex Cough: Similarities and Differences

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Abstract

Cough is defensive airway reflex subjected to a high degree of cortical control. Not surprisingly, all cough motor patterns can be mimicked and reflex cough be inhibited up to complete suppression, at least to a certain extent. Reflex cough differentiates from other airway reflex responses for its characteristic 3-phase motor pattern, and such pattern is maintained when coughing is produced voluntarily. Despite these and some other similarities, voluntary and reflex cough differ in many important respects, suggesting different neural control of the respiratory and non-respiratory musculature implicated in the generation of the cough modalities. This paper focuses the motor features that differentiate voluntary and reflex cough efforts, and highlights the importance of functional assessment of coughing in the diagnostic workup of respiratory and extra-respiratory diseases affecting the production of voluntary and reflex cough.

Introduction

Cough is an expulsive respiratory motor act normally elicited through the activation of a specific reflex pathway [1]. A peculiar aspect of the cough reflex is the high degree of voluntary (cortical) control to which it is subjected, so that all possible cough patterns can be mimicked and the frequency and intensity of spontaneous cough be modulated up to complete suppression [2]. Accordingly, in physiology textbooks cough is defined as a respiratory expulsive reflex consisting of three phases, with a preparatory inspiration followed by compressive and expulsive phases [3]. However, recent guidelines have proposed a definition of cough only based upon its acoustic features, i. e. an expulsive airway reflex accompanied by a characteristic sound [4]. Although this definition may simplify the work of clinicians involved in the recordings of cough sounds, we believe that such definition fails to differentiate coughing from other important airway expulsive reflexes. In fact, abundant literature is available on how the typical 3-phase motor sequence differentiates coughing from the so-called expiration reflex, in which the preparatory inspiration is lacking [3]. The lack of an inspiratory phase is not the only distinguishing feature of the expiration reflex: its pharmacological and neural controls appear to differ considerably from those of cough, as do the functions the two reflexes are thought to subserve [3].

It seems worth noting that if one is invited to perform a voluntary cough, the resulting motor pattern is invariably 3-phased, as we have repeatedly assessed in our laboratory. Thus, in the brain region[s] where the *cough* motor pattern is “stored” for voluntary reproduction, it is comprised of three distinct phases as reported above.

In the light of the above considerations, the fact that cough and the expiration reflex produce a similar expulsive sound should rather be regarded as a confounding factor, as witnessed by a small

survey demonstrating the inability of lay people to distinguish between the two reflexes on a merely acoustical ground [5].

The well-established notion that the motor patterns of cough can be mimicked so accurately probably contributed to the widespread conviction that the motor features of voluntary and reflex cough are similar, though virtually no experimental evidence supports this view. Indeed, whilst many previous studies have provided a detailed description of the motor components of cough efforts produced voluntarily, only a few studies have attempted at comparing the patterns of voluntary and reflex cough efforts in the same individuals; especially of the preparatory [i. e. inspiratory] and compressive phases of voluntary and reflex cough. More information can be found in the literature on the motor features of the expulsive phase of voluntary and reflex cough efforts. For instance, some investigations carried out in normal subjects [6] and in patients with neurological [7, 8] or upper airway disorders [9] have compared the intensity of expulsions produced voluntarily or in response to threshold and supra-threshold cough stimuli. A recent electromyographic study [10] is notable for the evaluation of the pattern of activation of the respiratory musculature of reflex and voluntary cough efforts in a group of normal subjects. Nonetheless, a systematic, comparative analysis of the various motor components of spontaneous coughing with those of coughing produced voluntarily is still incomplete. Since all phases of the cough reflex eventually contribute to optimise expulsion [11 for Refs], it seems obvious that efforts should be devoted to better understanding the mechanics and the neural control mechanisms subserving all cough phases, especially if one wishes to assess cough impairment in patients with respiratory and extra-respiratory diseases. In this paper, we will review available information on the motor pattern of coughing produced either voluntarily or reflexly by normal subjects or patients with respiratory and extra-respiratory disorders. Emphasis will be placed on motor features of single cough efforts, in an attempt to highlight similarities and differences that may provide insights into the mechanisms activated to generate each cough modality.

The 3-phase motor pattern of voluntary and reflex coughs

The inspired volume and the rate of the inspiratory flow of a voluntary cough effort have been investigated in detail. Studies in normal subjects who were instructed to cough voluntarily suggest that the inspiratory volume relates to the anticipated forcefulness of the subsequent expulsive effort [12, 13]. With a “gentle” cough effort, the mean volume of inspired air has been shown to be about 0.4 l, whereas with a maximum cough effort the mean inspired volume was 2.5 l. The mean time required for air intake varied to a much lesser extent, being 0.75 s and 0.65 s with a gentle and a maximum cough, respectively. In consequence, also mean inspiratory flow rate varies considerably in relation to the pre-programmed intensity of the subsequent expulsion.

Much less information is available on the preparatory volume of induced and/or spontaneous cough. Unpublished evidence indicates that, with coughing induced by inhalation of a tussigenic agent, the magnitude of the inspired volume relates to the intensity of the stimulus causing cough [Davenport P, personal communication]. However, no information is available on how the amount of air intake and the rate of inspiratory flow of reflex coughs produced in response to stimuli of variable strength compares with that of voluntary cough efforts of graded intensity.

Preparing to expel: inspiratory and compressive phases

Closure of the glottis by adduction of the ventricular folds and covering of the laryngeal inlet by the epiglottis marks the onset of the compressive phase of cough. Several mechanistic studies have shown that contraction of the expiratory muscles against a closed glottis leads to the development of high abdominal, pleural, alveolar and subglottic pressures, all of which contribute to the mechanical efficiency of coughing [11]. What is disappointing with this crucial cough phase is that even in the most respectable textbooks its duration is laconically reported to be “~0.2 s”, mainly with reference to efforts produced voluntarily. We are not aware of studies reporting a comparative analysis of the

duration of the compressive phase of voluntary and reflex cough efforts, particularly those evoked by a tussigenic stimulus of threshold intensity. A notable exception may be represented by a recent study also aimed to compare the duration of compressive phase of maximum voluntary cough efforts in normal children and in sex- and age-matched patients with congenital central hypoventilation syndrome [8]. The syndrome is characterised by lack of automatic breathing when the neural drive from the reticular substance drops below a certain level as in the case of non-REM sleep, and previous investigations suggested that the children also suffered from an impaired cough sensitivity [14]. In contrast, the study by Lavorini et al. [8] demonstrated normal cough sensitivity and activation of the expiratory musculature in the children during cough challenge testing, along with a normal expulsive cough mechanism. Noticeably, the Authors were also demonstrated severe reduction or complete absence of respiratory sensation during inhalation, along with remarkable inter-patient variability in the duration of the compressive phase of voluntary cough [8]. Duration of the compressive phase of reflex cough efforts could not be assessed for technical limitations. In more detail, it was found that patients' mean compression time was very similar to that of controls [197.1 vs 203.0 ms]; however, individual values ranged 20-420 ms in the former and 180-230 ms in the latter. On one hand, the findings point to a relatively small variability of compression time of maximum voluntary cough in normal subjects of pediatric age; on the other hand, the results reveal significant variability of cough compression time in patients with a major disturbance of central respiratory control [8]. Taken together, the result suggest that evaluation of the duration of compression may reveal deficits of the neural mechanism subserving the sequencing and timing of voluntary cough phases.

Although glottic closure is generally considered a prerequisite for developing the high intra-thoracic pressures of cough, some lines of evidence seem to deny this. For instance, the study of Gal [15] showed that, in subjects who performed maximum voluntary cough efforts prior to and following tracheal intubation, cough pressures were the same or even greater after intubation. However, intubation prevented narrowing of the airway promoted by the increased intra-thoracic

pressure, a phenomenon that would result in a significant reduction in cough flow velocity and impaired clearing effectiveness. The findings of Gal [15] obtained in intubated patients are in keeping with the reduced volume acceleration values later recorded in laryngectomised patients [9]. Whether a functioning larynx positively contributes to cough flow velocity in voluntary and reflex cough efforts has not been established.

The cough job: expulsion

The expulsive phase is that of the cough cycle during which the airways are cleared of secretions, debris, and foreign material. The importance of abdominal muscles in the production of the cough expulsive force is well known, and it has been confirmed by many electromyographic (EMG) studies [6-10]. For instance, several human investigations have shown activation of the rectus abdominis, internal oblique, external oblique, and transversus abdominis muscles during voluntary cough [16-17]. Furthermore, abdominal muscle activation has been found to be proportional to cough flow rate, and a linear relationship has been demonstrated between increases in EMG activity and voluntary cough flow rates [18, 19]. In addition to abdominal muscles, EMG bursts over the latissimus dorsi and pectoralis major muscles have been demonstrated during voluntary cough efforts in healthy volunteers and tetraplegic subjects in whom corticospinal abdominal inputs were interrupted [20, 21].

At variance with the inspiratory and compressive phases, several comparisons of the motor features of the expulsive efforts of cough produced voluntarily and reflexly in the same subjects can be found in the literature. A recent study analysed motor activation patterns of voluntary and reflex cough adjusted for flow rates. Activation of the expiratory musculature, (rectus abdominis, obliques, lower intercostals) and accessory (trapezius, pectoralis major, deltoid, latissimus dorsi) muscles was assessed by surface EMG [10]. Again, the main findings were that intensity of

activation and burst duration of expiratory and accessory muscles during voluntary cough increased in proportion to cough flow and that substantial co-activation of the expiratory and accessory musculature occurs during both voluntary and reflex cough efforts. However, the study also demonstrated for the first time that voluntary cough was associated with coordinated activation of expiratory and accessory muscles, with a progressive increase in EMG activity and burst duration proportional to cough flow; lower cough flow rates were produced mainly by the activation of expiratory muscles, whereas accessory muscles were sequentially and increasingly recruited for the generation of higher flow rates [10]. With reflex cough, a simultaneous onset of EMG activity in expiratory and accessory muscles increased EMG activity of all muscle groups and shorter EMG burst duration was observed, suggesting rapid, simultaneous activation of all muscle groups [10]. Taken together, these important findings point to different neurological control of the respiratory musculature during voluntary and reflex coughing. In this connection, Addington et al [18] evaluated the physiological characteristics of intra-abdominal pressure changes generated during voluntary cough and reflex cough of laryngeal origin, which provides efficient neurophysiological airway protection in humans [18 for Refs]. It was found that reflex cough generated significantly higher peak intrabdominal pressure and larger overtime intrabdominal pressure changes compared to maximum voluntary cough. The different motor behaviours of laryngeal vs voluntary cough may be due to the continual and simultaneous activation of cough-associated expiratory muscles with rapid and repeated glottal closure with laryngeal cough compared with voluntary cough, the latter being mainly characterized by brief and often single event of brief glottal closure [18]. The differences between the two types of cough provide a new perspective to study the neurophysiological differences between these two events. Voluntary cough appears useful in clearing the vocal cords for speech and clearing the airways once material is present in the tracheobronchial tree.

Comparisons of motor patterns during voluntary and reflex cough have provided insights into pathogenetic mechanisms that may be relevant to the genesis of potentially lethal respiratory

infections in patients. For instance, respiratory complications, particularly aspiration pneumonia, are a common feature of Parkinson's disease and are the most common cause of death [23]. Respiratory alterations include disturbances of ventilation and breathing pattern, EMG abnormalities of laryngeal muscles, respiratory disrhythmias, respiratory muscle weakness, chronic or recurrent airflow obstruction; Some lines of evidence have favoured an upper airway muscles dysfunction as the major cause of airflow limitation in these patients [for Refs see 7]. A study performed on a relatively large group of Parkinson's disease patients of varying severity and sex- and age-matched control subjects demonstrated disease-specific alterations in the motor pattern of voluntary and reflex cough efforts [7], and indicated that the central neural mechanisms subserving the recruitment of motor units and/or the increase in their frequency of discharge during voluntary and reflex are impaired in these patients. Of note, such impairment was much more prominent during reflex than voluntary coughing. On one hand, the results demonstrate that Parkinson's disease features a generalised impairment of autonomic reflexes such as, for instance, the pharyngeal phase of swallowing [18] and the cough reflex. On the other hand, the findings also suggest that the evaluation of the cough motor pattern provides useful information on the central mechanisms subserving this crucial reflex response; in more details, it seems likely that impaired expiratory muscle recruitment during voluntary and, more markedly reflex cough reflect one of the most prominent functional disturbances of patients with Parkinson's diseases, i.e slowness of movement that is ongoing, or bradykinesia [7]. The phenomenon may reduce the effectiveness of cough as an airway clearing mechanisms and account for the increased prevalence of serious pulmonary infections in Parkinson's disease patients.

Recently, comparison of voluntary and reflex cough efforts in patients with acute hemispheric stroke revealed that voluntary and reflex cough are both impaired [25]. Impairments of respiratory muscle function when measured by volitional tests and reductions in voluntary cough flows and gastric pressure in stroke patients have been described previously[26, 27], but demonstration of a cough deficit, which may be considered more important for airway protection and clearance, is

novel. An interesting finding was that despite patients achieved normal reflex cough gastric pressures, flow rates and expired volumes for reflex cough were both decreased. A likely explanation may be that brain injury affected the coordinated activation of the upper airway muscles with the abdominal and thoracic muscles used for cough production.

Some years ago, Fontana et al compared several aspects of voluntary and reflex coughing in laryngectomised patients [9]. The study was prompted by the well established notion that the larynx is crucial for compression and that it not clear if and to what extent laryngectomy affects the expulsions of voluntary and reflex cough efforts. One important finding was a reduction of abdominal muscle contraction as assessed by surface EMG and expiratory flow during coughing elicited by stimuli of threshold intensity, suggesting an important by laryngeal sensor in expiratory muscle recruitment during exposure to threshold stimuli for the cough reflex. Overall, the pattern of voluntary cough was significantly less affected by laryngectomy than that of reflex cough efforts at threshold. The findings confirm that analysis of the cough motor pattern by means of simple techniques such as surface EMG and expiratory flow recording allows one to disclose important motor differences between voluntary and reflex cough efforts in patients with major upper airway disease.

Comparisons of voluntary and reflex cough efforts consistently display a common feature: if one considers a single, individual cough effort (i .e. not a cough epoch) the intensity of expulsion attained for stimuli of threshold intensity corresponds to approximately 80% of that attained during maximum voluntary cough. This appears to be independent of what variable is chosen to grade effort intensity, with expiratory flow rates and abdominal muscle EMG-related variables behaving comparably, and of the stimulating agent used [21]. Thus, it seems logical to conclude that the reflex cough activation recruits a considerable portion of the contractile mechanism already at threshold level, thus providing a substantial safety factor in airway clearing. Further needs for

airway clearing may be coped with by little further recruitment of motor units in the contracting muscles and by increasing the number of cough efforts.

Conclusions

The bulk of available evidence indicates that voluntary and reflex cough share common features, including the 3-phase pattern and the involvement of a large amount of the respiratory musculature. The noise produced by voluntary and reflex cough is also acoustically indistinguishable. On the other hand, it is becoming increasingly apparent that the neural mechanisms subserving muscle recruitment and, in consequence, the motor pattern and mechanical characteristics of the two cough modalities not only differ considerably but also are differentially affected in disease. The functional evaluation of cough needs to be encouraged in view of a better understanding of cough pathophysiology.

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