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PPT Special Issue: Cough.**Workshop: Cough: exercise, speech and music**

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Abstract

Twelve distinguished scientists attended the workshop, heard three presentations, and took part in the discussions. Fontana first described his unpublished studies on cough in exercise and during hyperventilation with healthy subjects. Both activities depressed cough induced by inhalation of distilled water aerosol (fog). The possible mechanisms were discussed. Gibson then described the successful use of speech therapy to treat chronic cough, and discussed the possible mechanisms, centering on the role of the larynx and its neural control. A comparison was made with the ability of speech and laughter to precipitate cough. Widdicombe discussed the scanty literature on the effect of singing and playing wind instruments on cough, most of the evidence being anecdotal. In the discussion periods several matters for future study arose. It is usually not clear if the modulation of cough, its depression, enhancement or excitation, arose primarily at peripheral sites (reflexes from the airways), or at a cortical level, or both. Nor is it clear whether the same results would be obtained with provoked cough and with spontaneous cough. But all three aspects of 'behavioural' changes in cough sensitivity (exercise, speech and music) could be further explored, and current techniques should make this possible.

Keywords: cough, exercise, speech, music, laughter.

1. Introduction

John Widdicombe introduced the workshop. He pointed out that, although cough was (with pain) one of the two commonest medical afflictions of mankind, and had been exhaustively studied in the clinic and the basic science laboratory, we know little about its interaction with human activities. Although its diurnal variation and inhibition in sleep are well documented, what happens during activities such as exercise, talking, laughing, singing, playing wind instruments, eating and drinking, has been little studied, although there are some clues in the literature and some anecdotal evidence. Many, but not all, athletes say that when they have a cough it does not stop them running; indeed it seems to be inhibited during the run, although it may occur with a vengeance during post-exercise hyper-reactivity. There are a number of comments in the literature that talking can precipitate cough, and speech therapy can effectively treat chronic cough, presumably at least in part by controlling the pattern of breathing during talk so that cough is not activated. Laughter is a well-established trigger for cough in asthmatics and non-asthmatics. Many singers say that a cough, if not too strong, does not stop them singing, although the purity of their notes may be affected and they may have to cough discretely between songs.

Some of the above statements have a small degree of documentation in the medical literature, but many do not. Even if the cause and effect of the cough are established, the neural mechanisms of trigger and response (positive or negative) have not been determined.

The workshop heard three brief presentations of cough in exercise, speech, and music, respectively, with discussions after each presentation and a general discussion at the end of the workshop.

1. Cough in exercise

Giovanni Fontana presented evidence (Lavorini, F, Fontana, G, Widdicombe JG, unpublished results; see also [1]) that during exercise in healthy subjects the cough threshold to distilled water aerosol (fog) was increased, and the same was true with isocapnic hyperventilation without exercise; in other words cough is depressed when ventilation is increased voluntarily or reflexly. The mechanisms of these changes were discussed.

The cough reflex is not static, but rather the pathways for cough strongly exhibit plasticity at sensory, ganglionic and central nervous levels [2,3]. This usually consists of a sensitization (up-regulation) of the reflex, but down-regulation may also occur [4]. Factors implicated in the modulation of the cough reflex, either enhancing or inhibiting it, have been extensively reviewed [4-6], but not in relation to exercise.

Physical activity of variable intensity is intrinsically related to everyday life, and represents a condition during which profound cardiorespiratory adjustments occur. The adaptive responses to exercise include, to mention but a few, changes in the pattern of breathing, activation of airway, lung, and chest wall nervous sensors ('receptors'), alterations in the composition and physical characteristics of the airway surface liquid, and airway heat loss. Exercise is also associated with increased

sympathetic activity and plasma catecholamine concentrations, as well as with the release of inhibitory neurotransmitters that are co-localized with noradrenaline in sympathetic nerves [7-9]. These phenomena have been implicated in the genesis of the bronchodilator response that appears *during* the exercise of normals and asthmatics [7-9]. Francois Marchal and colleagues have shown that rabbits exhibit bronchodilation during muscular activity [8], and that bronchodilation is also induced by deep lung inflations such as would occur in exercise [10]. Bronchoconstriction is well recognised as a stimulus to cough, so one might expect bronchodilation to down-regulate cough, although studies on this possibility do not seem to have been done.

In the literature little information is available regarding the effects of exercise on the sensitivity and intensity of cough; furthermore, the available information is often contradictory. For instance, cough and bronchoconstriction are common features of asthmatic subjects *after* exercise (post-exercise hyperreactivity) [11,12]; however, questioning athletes provides anecdotal evidence that subjects with cough may find it reduced *during* exercise, suggesting down-regulation [4]. The study of the influences of exercise on coughing is potentially important to improve our understanding of the mechanisms subserving cough. The putative influences of some of the phenomena brought into action by exercise and/or hyperventilation on cough regulation are shown briefly in Table 1.

Table 1 near here

An important aspect of cough physiology may be related to the biochemical and physical changes occurring within the airway during hyperventilation or exercise. Postexercise hyperreactivity, and the sequence of events involved in its genesis, have

been reviewed recently in detail [11,12]. More specifically, it has been pointed out that the hyperventilation of exercise causes dehydration of the airway surface liquid (ASL) which, in turn, may result in increased mucus production and hyperosmolality of the ASL. Animal experiments have demonstrated that changes in lower airways' osmolality can initiate reflex responses, possibly contributing to the genesis of cough [13]. Both increased mucus production and ASL hyperosmolality are effective tussigenic stimuli also in normal subjects [14]. It has also been shown that, in normal subjects who reported coughing *after* exercise, the frequency of cough evoked by voluntary hyperventilation with poorly conditioned air is related to the degree of the hyperventilation and rate of overall respiratory water loss [15]. On the basis of this information, one would conclude that some of the phenomena related to exercise, namely hyperventilation, water and heat loss, exert a facilitatory action on cough.

Airway slowly adapting stretch receptors (SARs) play a key role in the mediation of many respiratory and cardiovascular reflexes [6]. Adequate stimuli, such as for instance lung inflation due to the deep breaths of exercise, result in an increased SAR discharge in myelinated afferent fibres. The nerve impulses arising from the receptors provoke an array of respiratory and cardiac reflex actions that have been the object of several important reviews (see e.g. [5]). Although it is commonly thought that activation of SARs facilitates the cough reflex [16,17], other studies seem to provide evidence against this possibility [18,19]. Nishino et al. [16,17] showed that, in anaesthetized humans, lung inflations with continuous positive airway pressure (CPAP) increased the strength of the cough reflex. Conversely, in anaesthetized animals, application of CPAP stimulating SARs had the opposite effect [18]. Furthermore, enhanced stimulation of SARs due to airway occlusion at the end of

inspiration and throughout the subsequent expiratory effort did not affect expiratory muscle activity during mechanically-induced cough [19]. Thus it seems likely that SARs play an important but still poorly defined role in modulating the cough reflex when the depth of breathing is augmented, such as during exercise or voluntary hyperventilation.

Exercise augments cardiac output and leads to an increase in pulmonary blood flow [20]. In the cat, marked increases in pulmonary blood flow stimulate the normally silent pulmonary C-fibre receptors, formerly termed “J receptors” [21], and lead to reflex inhibition of inspiratory and expiratory muscles [22]. Since in experimental animals both pulmonary [23] and bronchial [24] C-fibres inhibit cough, activation of these nerve terminals by the increased pulmonary blood flow of exercise may result in inhibition of cough.

Activation of chest wall and limb afferents has repeatedly been demonstrated to affect breathing [25]. On the other hand, little information is available as to whether signals originating from these receptors can influence the cough reflex. In anaesthetized rabbits, Javorka et al. [26] showed that during stimulation of airway, lungs and chest wall receptors by high-frequency jet ventilation causing inhibition of spontaneous breathing, mechanical stimulation of the nasal, laryngeal and tracheal mucosa was still able to provoke defensive responses, namely sneezing and coughing. Interestingly, the inspiratory component of all the evoked reflexes was inhibited, and the overall intensity of coughing and sneezing was reduced [26]. In healthy humans, chest wall vibrations applied bilaterally over the 7th to 10th intercostal spaces significantly inhibit the volume and time components of the breathing pattern [27]. By

using a similar technique, Kondo et al. [28] provided evidence that cough threshold to citric acid is significantly increased during chest wall vibrations, suggesting that inputs from intercostal muscles and/or costovertebral joints have an inhibitory effect on cough sensitivity. Taken together these results point at the possibility that signals arising from chest wall joint and muscle receptors partially inhibit the cough reflex. Thus, it can also be hypothesized that the large chest wall displacements provoked by the hyperventilation of exercise and subsequent receptor stimulation activate similar cough inhibitory mechanisms.

In Fontana et al.'s unpublished work the inhalation of tussigenic aerosols to assess cough sensitivity was used. No published information seems to be available regarding the impact of voluntary or exercise-induced hyperventilation on the sensory-motor components of coughing evoked by inhalation of tussigenic agents. Previous studies on induced bronchoconstriction have repeatedly shown that the pattern of aerosol inhalation, particularly the inspiratory flow rate, is a major factor influencing the airway response to both bronchodilator and bronchoconstrictor agents [29]. Some studies [30,31] have shown that when inspiratory flow rate is increased the ratio of central-to-peripheral distribution of deposited aerosol is larger, pointing at the possibility that the increased ventilation induced by exercise would favour a more central deposition of an inhaled aerosol. Interestingly, neuroanatomical and physiological studies have consistently shown that the majority of airway receptors putatively involved in cough mediation are located in the proximal portion of the tracheobronchial tree [32]. Therefore, it seems logical to predict that coughing induced by tussigenic aerosols would be up-regulated when these are inhaled at higher inspiratory flow rates.

The mechanisms of cough induced by exercise at high altitude have been studied by Mick Mason [33] but remain controversial; at high altitude excitatory or sensitizing factors seem to outweigh the inhibitory effect of cough on exercise at sea-level, and the underlying mechanisms clearly need more study. Temperature and osmolality changes are potentially important.

Although the available information on the effects of exercise and hyperventilation on cough sensitivity and motor pattern is very limited, present knowledge on the physiological mechanisms subserving cough allows one to predict that many of the adaptive responses brought into action by physical activity, or even voluntary hyperventilation, have the potential of modulating the cough reflex. The observation that some of the exercise-related influences seem to be mainly inhibitory to cough, whereas others have the potential of up-regulating the reflex, is *per se* interesting. There is little doubt that future studies aimed specifically at clarifying the modalities with which the various exercise-induced adjustments can influence the sensory-motor components of coughing are strongly needed, and have the potential of clarifying important aspects of cough control.

3.Cough and Speech

Peter Gibson discussed the interactions of speech and cough. Cough and speech are two key motor functions of the larynx. People with chronic cough often experience abnormalities of voice and other laryngeal motor functions. Similarly, speech is a common trigger for cough [34]. In addition to cough, other inputs to laryngeal motor functions include breathing, breath-holding, swallowing and laughter. The symptoms

of laryngeal motor dysfunction can be thought of in terms of the key motor functions of the larynx and include: cough, from increased sensitivity of the cough reflex; dysphonia, from disordered phonation; dyspnoea, usually on inspiration, from disordered breathing; dysphagia from disordered swallowing; and apnoea with laryngeal spasm from disordered breath-holding [35]. Many of these symptoms occur in patients with chronic cough or voice disorders. A further example of laryngeal dysfunction is seen with gastro-oesophageal reflux (GOR). GOR can input to the larynx and cause cough, and can be induced by respiratory and postural changes. Conversely cough can cause GOR.

Speech is a common trigger for cough. The important components of speech include articulation, resonance, phonation, and breathing. Phonation represents an interaction of vocal fold vibration and airflow through the larynx. Typical rates of vocal fold vibration in men are 100 cycles/s, and in women 200 cycles/s. In chronic cough, there are perceptual abnormalities of voice that include increased breathy features, increased roughness, increased strain, and glottal fry. Oates and Russell [36] define glottal fry as characterized by the impression of a rapid series of low-pitched ‘pops’ or ‘taps’ and a creaky quality. The physiological basis for glottal fry is thought to be a longer closed phase of vocal fold vibration, low frequency of vocal fold vibration, tightly adducted vocal folds with flaccid free edges and low subglottal pressure [37,38]. These abnormalities correspond to changes in laryngeal function. With glottal fry the voice has a ‘creaky sounding’ quality due the adduction of the arytenoid cartilages and consequent tight vocal fold compression that results in vocal fold vibration about two octaves below normal vocal frequency. It is associated with low subglottic pressure to support phonation. Breathiness represents incomplete vocal fold

adduction, strain occurs with increased vocal fold tension and supraglottic constriction, and roughness occurs with aperiodic vocal fold vibration. Other acoustic abnormalities include reduced maximum phonation time, increased jitter, which represents an increase in the acoustic cycle-to-cycle variation, and reduced closed phase of vocal fold vibration. These changes are examples of the alterations in various aspects of laryngeal motor function that can occur in patients with chronic cough. Since many of these changes respond to speech pathology management, they suggest a basis for using speech therapy to treat chronic cough [39].

Speech can trigger cough during normal 'tidal speech', or during extended speech, when the phonatory apparatus is pushed to the limits of performance [34]. This may be by extremes of pitch, loudness, or vocal projection. Vocal projection represents a number of elements including auditory-perceptual aspects, acoustic aspects, and physiological aspects. The auditory-perceptual aspects of increased voice projection involve increases in volume and oral resonance that result in a voice that carries a greater distance and can be heard over background noise. The acoustic aspects of voice projection involve increased amplitude and greater energy in the 3rd and 4th formants. The physiological aspects involve an increased duration of closed phase of vocal fold vibration, greater amplitude of vocal fold vibration, vocal folds that are closed along the entire edge, i.e. no glottic chinks or bowing, increased respiratory support, increased aryepiglottic narrowing (this provides an additional resonance chamber) and potentially increased tongue tension.

Several of these changes are limited in chronic cough, which means that cough patients have limited ability to manage voice projection, and that voice tasks may

trigger cough. An important aspect of this relationship between voice projection and cough is the concept of 'vocal load'. This refers to the load placed on the phonatory system by vocalization tasks. Vocal loading is a combination of prolonged voice use and additional loading factors (e.g. background noise, acoustics, air quality) affecting the fundamental frequency, type and loudness of phonation or the vibratory characteristics of the vocal folds as well as the external frame of the larynx [40]. Certain occupations are associated with increased vocal loads, with teachers being a prime example. For this reason, cough and voice symptoms are common among members of the teaching profession [41]. Telemarketers also experience a significant incidence of vocal abuse [42]. In addition to dysphonia, they also report increased symptoms of a 'choking sensation', throat clearing, and frequent coughs and colds.

The mechanisms by which speech pathology management is effective in chronic cough are yet to be defined. Several mechanisms have been hypothesized including reduced cough reflex sensitivity, improved voluntary control over coughing, reduced laryngeal irritation through improved vocal hygiene practices and effective treatment of coexisting paradoxical vocal fold movement.

In discussion it was pointed out that laughter, as well as speech, can induce cough, especially in asthmatics [43,44]. The big question is why does laughter sometimes induce cough and sometimes not? At a TV or theatrical comedy there may be widespread hearty laughter but virtually no obvious coughing. The mechanisms have not been identified or studied, but there seem to be the two same possibilities that also apply to cough and speech. That the vigorous respiratory and laryngeal movements of laughter [45,46] activate cough sensors in the airways to reach central nervous threshold; or that cerebral cortical mechanisms, activated by particular patterns of

humour, sensitize neural cough pathways to reach threshold. Anecdotally voluntarily mimicing the vigorous respiratory patterns of laughter does not induce coughing in a subject who coughs in response to bizarre hilarious stimulants. This seems a field wide open for very enjoyable research.

4. Cough and music

John Widdicombe introduced the subject. There has been little study of the relationship between cough and singing. He had consulted a number of professional singers and they all agreed that only if the cough were severe would they not sing. Milder degrees of cough seemed to be inhibited during the singing although the purity of notes might be affected. Apart from causing or sensitizing cough, prior laryngeal inflammation might affect the purity of the singing notes. Although there were a number of studies of the patterns of breathing during singing [47,48], none of these mentioned coughing, either its induction or its suppression during the activity.

Peter Gibson commented that singing is an important human activity that requires heightened performance of the vocal apparatus. A study of Italian opera singers found an increased prevalence of cough and dysphonia (compared with non-singers), that was also accompanied by increased gastro-oesophageal reflux symptoms of heartburn and regurgitation [49]. Classically trained singers employ a range of vocal techniques to enhance performance, and presumably to manage the increased vocal load requirements [50]. In contrast, other singing groups may not use these techniques and their singing voice more closely resembles their speaking voice, but at an increased

vocal load [51]. There is a need to investigate further symptoms of cough, laryngeal motor dysfunction and cough reflex sensitivity in relation to vocal performance.

A further mystery related to singing is whether and how the ingestion of milk products adversely affects singers' performances, including by causing cough. Some singers are convinced of this process, others think it is a myth. Workers on the production line of a powdered milk factory complain of cough and wheezing far more than those in adjacent offices [52], but this is probably not surprising and may be irrelevant to singing.

Coughing while playing a wind instrument (e.g. flute, clarinet or trumpet) would be highly undesirable, but there seem to be no studies on the effect of these activities on subjects with cough. Patterns of breathing while playing a wind instrument are well documented (53,54) and they somewhat resemble those of talking, singing and laughing: deep inspirations followed by long and fluctuating or interrupted expirations.

There seem to be no reports of any relationship between whistling and cough; whistling combines some features of speech, singing and wind instrument playing (the lips), but is probably little practiced nowadays.

4. General Considerations

In general cough can be inhibited or enhanced by two types of mechanism: by changes in peripheral nervous sensor activity either due to tidal volume and flow variations or to the sensitization of airways sensors for cough, including their

activities in brainstem pathways for cough; or by upper neural influences, especially in the cerebral cortex, a zone which is established as a potential site for initiation and augmentation of cough or its inhibition [4,5]. In the conditions considered at this workshop it proved difficult to apportion responsibility between the two areas of activity.

The influence of cortical 'distraction', 'meditation', or 'deliberate conditioning' on cough was considered. Chronic cough can be inhibited by deliberate (conscious) suppression [55]. 'Meditation' can suppress induced cough [56,57]. 'Distraction' can increase the threshold to pain [58]. Background music can lessen the cough (and also the discomfort) of patients undergoing bronchoscopy [59], presumably by 'distraction'. To what extent these mechanisms apply to the reduced cough in exercise, speech therapy and music does not seem to have been studied.

Two problems were discussed in relation to further research. Firstly, recent studies consisted of two general methods: those on patients with chronic cough, and those on healthy subjects with cough induced by, for example, aerosols of capsaicin, citric acid or distilled water (fog). There seemed to be no agreement as to whether tests with the two methods should give equivalent results or, if not, which method was more relevant to pathophysiological studies. And secondly, with chronic cough, changes in frequency (but not intensity) might be detected accurately by cough counting methods. However induced cough might be difficult to access since the methods usually involved face masks or mouth pieces which would interfere with some behavioural activities such as talking, singing or playing wind instruments. It was

suggested (Paul Davenport) that these tests could be conducted with the subject in a body-box or plethysmograph, which would also allow recording of breathing patterns.

The workshop discussed methods for measuring and assessing cough in the various behavioural studies. Jacky Smith and Surinder Birring and colleagues had developed automated audiovisual methods for cough-counting [59-61], and they both felt confident that their methods would accurately measure cough sounds polluted, for example, by the noise of exercise hyperpnoea, talk, laughter, singing and wind instrument playing.

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Table 1. Putative mechanisms implicated in the regulation of cough during exercise

Down-regulation of cough		Up-regulation of cough
SARs activation		SARs activation
C-fibre activation		Heat loss
Chest wall sensor activation		Hyperosmolality
Increase in plasma catecholamine levels		Increased central deposition of tussives

ACCEPTED MANUSCRIPT