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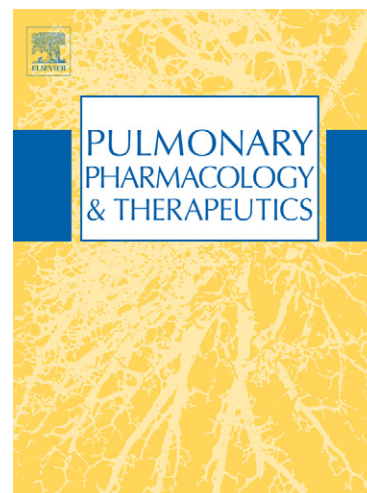
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What is cough and what should be measured?

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Abstract

Cough is usually defined as a three-phase event, although for convenience clinicians may prefer to define it as only the expiratory expulsive efforts. Cough may occur as a single event or as a cough ‘epoch’ (or ‘bout’ or ‘attack’) that includes several or many expiratory efforts in a single episode. The distinction between a single cough and a cough epoch is important, both in mechanistic and clinical implications, since the latter may include many ‘expiration reflexes’ (ERs), for which the functions and neural mechanisms are different from those of the cough reflex. We describe the various ways in which cough can be assessed. For simplicity in clinical work the main methods are patient scores or automated cough counters; these assess only one aspect of the complex changes in cough. For analytical and basic medical studies other facets of cough need to be included: expiratory EMGs, respiratory pressures, airflows and lung volume changes. Cough ‘intensity’, a much used expression, needs to be defined in terms of the facets of cough which are being measured.

Keywords: Cough frequency, cough intensity, cough sound, measurement of cough, cough epochs.

1. What is cough?

Cough is defined in the dictionary as ‘A violent expulsion of air from the lungs with a characteristic sound’ [1], a description favoured by some clinicians [2]. However textbooks and reviews make it more complicated. They identify three phases: an initial inspiration (the inspiratory phase), followed by closure of the glottis and a forced expiratory effort (the compressive phase), followed by opening of the glottis and vigorous expiration (the expulsive phase) [e.g. 3]. Fig.1 is a well known illustration of these three phases. Some descriptions identify a ‘fourth phase’. This is the inspiration subsequent to the expulsive phase, and is ‘restorative’. However it may also be the initial phase of the next cough, and the expression is not commonly used.

In practice the cough often occurs in epochs (sometimes called ‘bouts’ or even, harmoniously, ‘peals’; the patient usually refers to them as ‘attacks’). Their nature will be discussed below.

1.2. Spontaneous cough.

Many (over 100) pathological conditions, usually of the respiratory system, are associated with cough. It is said to be restricted to tissues innervated by the vagus nerves, but not all of them can give rise to cough, e.g. the abdominal viscera. In animals different parts of the respiratory tract cause different patterns of cough. For example in cats the coughs due to mechanical stimulation of the laryngopharyngeal area have pronounced inspiratory phases, while those from the trachea and bronchi are predominantly expiratory [4]. Whether this applies to humans is uncertain and has seldom been

investigated. It is not even known, for example, whether cough due to laryngitis has the same pattern as that occurring in asthma or COPD, although the coughs sound different, perhaps because of the presence of mucus in the lower airways or of bronchoconstriction. One study with cough induced in humans with a bolus of water showed almost identical patterns of cough from the larynx and from the trachea [5].

The sensors (sensory nerve receptors in the airway walls) and patterns of discharge in vagal fibres thought to mediate cough have been extensively studied [see 6,7]. Since the initiation of cough involves several types of sensor and nerve fibre, it would not be surprising if the pattern of cough varied with the balance of activities of the sensors. In animals, many of the sensors show some activity 'at rest', i.e. during quiet non-coughing breathing. The intensity of their discharge has to reach a central nervous threshold for cough to occur. However, the number of receptors involved seems to be almost irrelevant. A punctuate stimulus to the larynx or to the tracheal bifurcation, that can only reach a minute proportion of all the cough sensors, will induce as vigorous a cough as will inhalation of a strong irritant that may reach them all. It has been suggested that the brainstem neural areas responsible for cough may be influenced by the patterns of discharge of sensors as well as by total action potential number [8]. It may be that a few sensors discharging at high frequency with appropriate patterns of discharge are more effective in inducing cough than a large number of sensors discharging at low frequencies and/or with inappropriate patterns, although the total number of impulses per second may be much greater for the second category.

1.2. Induced cough

Cough is often induced to test the sensitivity of the reflex [9]. Capsaicin and citric acid aerosols are usually used, although fog (i.e. distilled water aerosol), tartaric acid, acetic acid and hypertonic solutions have also been administered. Cough number or frequency is usually measured, and a few papers show patterns of response [5,8,10-12]. Even fewer papers have shown the responses in the same subjects or patients when two different stimuli are used; but when this has been done, for example with fog and with capsaicin, the general patterns of the two coughs are very similar [10].

At threshold stimulus intensity, inhaled capsaicin seems to induce a greater number of coughs (possibly resembling an epoch) than does fog; however, the mean intensities of capsaicin- and fog-induced cough efforts do not differ when assessed in terms of abdominal muscle activity or peak expiratory flow rate [10]. Subjects reported stronger sensations with capsaicin than with fog but these were described as being qualitatively similar with both agents and included irritation, burning, choking and, mainly, urge to cough [10].

Even when cough is artificially induced in patients with spontaneous cough due to disease, there seem to be no descriptions of the two patterns of cough (artificial and spontaneous) and their related sensations.

Presumably the afferent inputs for cough are integrated in the brainstem and then trigger off a more-or-less stereotyped motor cough response. If the motor output is stereotyped one would expect all coughs to have the same general pattern, but the question does not seem to have been often asked (see also below).

1.3. Voluntary cough

Cough can be voluntarily caused or suppressed [13]. Spontaneous and induced coughs are associated with the sensation ‘urge-to-cough’, which may have a lower threshold than cough itself, and usually precedes it [8,10,12,14]; or with unpleasant sensations, usually irritation or even pain [10]. These results suggest that the cerebral cortex is involved. This view is supported by studies in humans using functional magnetic resonance imaging (fMRI) [S. Mazzone, personal communication; see also 15]. However the exact sites in the cortex still need to be delineated, and compared with those for other unpleasant sensations, such as dyspnoea and pain [16]. The pattern of voluntary cough is very similar to that of induced cough, although the former may be associated with greater muscular activities. Studies involving the use of capsaicin [10] and fog [10,17] as tussigenic agents have shown that cough intensity, assessed by expiratory muscle electromyograms (EMGs), at threshold level approaches 80% of that of maximum voluntary cough (MVC) efforts. Supra-threshold stimuli cause stronger coughs that attain intensities similar to that of MVC [11]

The neural connections for cough between the cortex and the brainstem have not been worked out. Decerebrate animals can cough vigorously with an irritant stimulus [18], so at most the cortex can induce or facilitate cough (or inhibit it). It seems likely, although unproven, that the cortex can switch on or off the cough reflex, or else modulate the strength of a stereotyped and complex pattern of cough based on the brainstem neural pathways [13].

Some insight into the cortex/brainstem interconnections is seen in the study of children with congenital central hypoventilation syndrome (CCHS). These patients can

voluntarily produce cough, just as they can voluntarily control breathing. However although their involuntary chemical control of breathing is lost, they usually still possess an active reflex cough mechanism [G. Fontana, unpublished].

1.4. Cough epochs

So far we have talked of cough as though it is a ‘simple’ three-phase event. In practice it often occurs as an epoch (or a bout or an attack), where an initial inspiration is followed by a series of glottal closures and expiratory efforts, sometimes with interspersed inspirations [4,19]. Whether an epoch should be described as a single cough or a series of cough has caused some contention, which will be discussed later. The semantics probably do not matter very much, provided it is clear what is being measured and described [19]. However in terms of mechanisms the cough epoch has interesting features. Why, for example does the glottis usually only close for the initial expiratory efforts, but seems to remain open for later ones, at least as judged by the ‘second cough sound’ (Fig. 2) [20]? If, in the course of a cough epoch, a second inspiration is taken, is this another ‘true’ cough, or is it that the vigorous expirations have so lowered lung volume that an inspiration is the only way to go? It probably doesn’t matter except to those interested in neural mechanisms.

One advantage of calling a cough epoch a cough epoch (rather than a cough), is that it leads us to consider the expiration reflex.

1.5. *The expiration reflex*

The expiration reflex (ER) was first described by Williams in 1841 [21], and extensively studied by Korpas and his colleagues in the 1960's [4]. It consists of a glottal closure and forced expiration followed by glottal opening and expulsive airflow, in response to irritation (mechanical or chemical) of the vocal folds or trachea. In other words it is like the second and third phases of the cough reflex (Fig. 3). However it is *not* the cough reflex. The distinction is not pedantic. An initial reflex inspiration (cough) and an initial expiration (ER) must activate fundamentally different neural mechanisms, and this has been confirmed by Shannon and colleagues in extensive neurophysiological studies on the brainstem [22,23]. But, perhaps more important from a clinical viewpoint, the two reflexes have very different physiological and pharmacological properties [4,19]. They also have quite different functions: cough will clear the lower airways of debris including mucus, while the ER will prevent aspiration of material into the lungs. These differences have been fully discussed elsewhere [4,19].

From the practical point of view, isolated coughs and ERs are easy to distinguish, although perhaps not by acoustic methods alone. But in a cough epoch it may be difficult to distinguish coughs and ERs, although it can be done [see 8,12 in this Special Issue]. This consideration will be developed below.

2. **What may be measured?**

Since cough (and the ER) have many facets, there are many parameters that may be measured. In analytical studies of cough and its mechanisms, as many of these parameters as possible should be considered. In clinical studies it is usually appropriate

and desirable, for reasons of simplicity, to measure only one or two of the parameters, usually including cough frequency assessed acoustically. The methods chosen should depend on the question being asked.

2.1. Frequency

The frequency of expiratory efforts can be measured manually by listening to cough sounds, with a high degree of accuracy. However the method is labour-intensive and probably impractical in ambulatory conditions. For these reasons automated audiometric methods have been devised [24-26]. These are dealt with in detail elsewhere in this Special Issue [27].

The main problem with the automated audiometric method is that it only records expiratory efforts, and therefore cannot distinguish between cough and the ER. Although the inspiration of cough causes a sound that can be recorded, it is weak and has not yet been used to distinguish coughs from ERs. Furthermore the identified expiratory efforts cannot easily be separated into those of isolated coughs and those in cough epochs. (It is of course a semantic point as to whether a cough epoch should be identified as a single cough or multiple coughs, but the use of the term ‘cough’ needs to be defined.) These ‘defects’ in the audiometric method are of little relevance to most clinical studies [27]. However in studies of the mechanisms of cough, a cough epoch can be divided into ‘coughs’ and ‘ERs’ provided not only expiratory frequency but also another parameter of cough (EMGs or airflows, for example) is measured. This technique has been largely developed by Davenport and Bolser and colleagues [8,12]

Other methods of assessing cough, by airflow, intra-abdominal or intra-oesophageal pressure, electromyographic (EMG) activity, and lung volume changes, will also allow measurement of the frequency of cough, even in the absence of sound, and will be considered below.

2.2. *Intensity*

‘Intensity’ is a generic word which, in relation to cough, includes muscular activity, pressures in the abdomen, chest and infralaryngeal airways, airflow velocities, lung volume changes and sound. Essentially ‘you pays your money and you takes your choice’ (Old English Unscientific Saying).

2.2.1. *Muscular activity*

The expiratory muscles of the abdomen and chest wall are primarily responsible for the ‘intensity’ of cough, although other muscles, such as the inspiratory ones and those in the larynx, are also involved.

The motor pattern of coughing involves the co-ordinated activation of several muscles exerting their action on the upper airways or chest wall. Upper airway muscles (nose, mouth and larynx) can greatly influence airflow, and their activation needs to be synchronized with that of the respiratory muscles to control upper airway patency and to produce the cough airflow output.

Activation of the inspiratory muscles (mainly the diaphragm and the external intercostals) during the preparatory inspiration of cough has a major impact on cough intensity (see below). During voluntary cough efforts, the inspiratory volume is related to

the anticipated forcefulness of the subsequent cough effort [reviewed in 11]. However, little is known about the regulation of inspiratory volume during the inspiratory phase of reflex cough but it may be related, at least in part, to the intensity of the stimulus causing cough (G. Fontana, unpublished observations).

The expiratory muscles of the ventrolateral aspect of the abdominal wall are intensely activated during both the compressive and expulsive phases of cough [28] and the ER [8,12]. The chief expiratory muscles are the internal intercostals, the oblique (external and internal) muscle, the transversus abdominis, and the rectus abdominis [see 29]. EMGs of the expiratory muscles have been used not only to study the neural mechanisms of cough but also to assess its intensity [8, 10-12].

It has been demonstrated that the rate of rise of the integrated EMG activity reflects the rate of recruitment of motor units, as well as of the increase in their firing frequency, while the peak of the integrated EMG activity is an expression of the total number of units recruited and of their maximum firing frequency [30]. Thus, EMG recordings of expiratory muscle output during cough can provide insights into the neural mechanisms activated during voluntary and reflex cough and during the ER. Since the magnitude of EMG activity correlates with the force produced by the contracting muscle [31], recordings of EMG activity of human abdominal muscle activity have been used to assess the intensity of induced cough efforts [see 32, and for further refs]. In particular, the ‘moving average’ integrated EMG activity of the obliquus externus muscle, perhaps the principal muscle implicated in the production of cough force, has been used to evaluate the intensity of voluntary and reflex cough efforts in humans [11,17].

EMGs have the advantage that they are a direct indicator of the primary expiratory neural output of cough; pressures, flows, volumes and sounds are secondary outputs, and may be modified by, for example, degrees of glottal closure, initial lung volumes and coincident diaphragmatic activity.

Interestingly, the peak and rate of rise of the obliquus externus integrated EMG activity correlates with both the intensity of the cough stimulus, and the cough maximum expiratory flow [31]. As mentioned above, the integration of EMG activity per expiratory effort is a good index of expiratory driving force [31].

One important aspect of using EMGs to assess cough is that they give important information about cough in neuromuscular diseases, such as stroke, Parkinson's disease and motoneurone disease, where cough may be severely affected [33].

2.2.2. Pressures

Intra gastric, intravesicular or intrarectal pressures give good indices of the expiratory efforts in voluntary or induced coughing [34,35], and may be important in assessing the risk and causes of vesicular incontinence due to cough. They have been rather neglected, presumably for practical reasons, in studies on the causes and mechanisms of cough. Intraoesophageal pressure has been usefully applied as an index of cough [20].

In experimental animals expiratory pressures (including intrapleural and intraoesophageal pressures) have been extensively used to assess the intensity of cough [4], but the invasive nature of the techniques may limit their applicability to humans.

2.2.3. *Airflows*

Measurement of inspiratory and, especially, expiratory airflows can characterize cough and are fairly easy to apply [8,17]. Their limitation is that they are secondary indices of the intensity of cough and their values will depend on such factors as the degree of closure of the larynx as well as the force of contraction of the expiratory muscles.

2.2.4. *Volume changes*

Lung volume changes associated with cough can be measured either with a body inductance vest, or its equivalent, or by integrating an airflow signal from the mouth. Both methods have advantages and disadvantages.

The inductance vest is probably inaccurate during the vigorous movements of the torso in coughing; however, cough expiratory flow and volume during voluntary or induced cough efforts can be measured fairly accurately using a calibrated pneumotachograph [17]. Since the force developed during the expulsions of cough largely depends upon the magnitude of the preceding inspiration [11], measurements of cough inspiratory volume might also represent a useful indicator of cough intensity.

Both the pneumotachograph and the inductance vest have the advantage that they allow identification of the inspiratory, as well as the expiratory, phases of cough, and are essentially non-invasive. For research into volume changes in cough, it might be useful to recall the old rigid neck-down body plethysmograph, the 'Drinker respirator', if any can still be found.

2.2.5. *Sound*

The integrated expiratory sound of cough has been used as an index of the intensity of cough [36,37]. It has the advantage that, with modern methods for automated recording of cough sounds, it is simple to integrate them and use the resultant as an index of cough intensity. The problem is that the intensity of cough sound has never been correlated with more basic measures of cough intensity such as muscular activity or evoked pressures. By analogy one might question how the intensity of a *cri du coeur* is related to the importance of the message it transmits. This seems to be an important field for future research.

3. **How and when may cough be measured?**

As discussed elsewhere [19], the answer depends on the question being asked. The ‘simple’ question, ‘is the cough getting better or worse?’, may be answered by a cough questionnaire or by an automated audiometric device. More complicated questions, such as those that ask about the mechanisms of the cough, require more complicated methods [19]. To give one of many examples [see 19 for others]: gastro-oesophageal reflux is one of the commonest causes of cough. There is dispute as to whether the cough is due to acid in the lower oesophagus stimulating sensors there, or to acid reaching the larynx, and possibly being aspirated, and thus stimulating airway receptors. As far as we can see, no-one has attempted to answer the question by comparing cough reflex patterns from the two sites. An automated audiometric device would, if alone, be inadequate for this purpose.

4. Conclusions

Cough is a complex phenomenon, and different basic and clinical scientists may give different definitions of it. This doesn't matter very much provided the definition is clear. There are many methods for measuring and assessing cough. Each has advantages and disadvantages, and the choice of them, apart from practical and financial considerations, must depend on the question being asked.

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Figure legends.

Fig. 1. Diaphragmatic representation of the changes of the following variables during a typical cough: sound level, volume, subglottic pressure and flow rate. During inspiration the flow rate is negative; as the glottis closes the flow rate is zero; and during the expiratory phase the flow is positive. The last phase can be divided into three parts: growing, constant and decreasing. The cough sound and the pressure and flow rates suggest the glottis partially closed for a second time during the expiratory phase. [From 38]

Fig. 2. Voluntary coughs and a cough epoch in a female subject. Traces, from the top: time in s, cough sound, airflow (expiration upwards) thoracic/oesophageal pressure (positive upwards) and abdominal pressure (positive upwards). On the left are two voluntary coughs. They are followed by a spontaneous involuntary cough epoch consisting of an initial inspiration and then four compressive and expulsive phases without intermediate inspirations. Vertical lines indicate equal time points. Note the second cough sound (closure of the larynx?) occurs in the voluntary coughs and in the first two expirations of the cough epoch. [From 20]

Fig. 3. Respiratory response to laryngeal stimulation by injection of distilled water (at arrow) in an awake human subject. The injection was given via a nasal endoscope. Pressure, airflow and end-tidal carbon dioxide tension were recorded via a face mask.

Note that there are three initial expirations (the ER) followed by an inspiration and two expirations (the cough reflex). [From 5]

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