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PERSPECTIVE

Cough: what's in a name?

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ABSTRACT: **The cough reflex (CR) and the expiration reflex (ER) are two defensive reflexes from the respiratory tract, the latter mainly from the larynx. Both are elicited by mechanical and chemical irritation of the airway mucosa, and are a characteristic of airway diseases, but they have different functions. The CR first draws air into the lungs, to accentuate the subsequent expulsive phase; the ER consists of a strong expiration, to prevent aspiration of material into the lungs. They have different sensory pathways, central nervous circuits, and physiological and pharmacological modulations. In practice, coughing often consists of a combination of the two reflexes, a cough bout, epoch or attack. Articles on cough usually do not distinguish between the two reflexes, or whether the coughs are single events or epochs; they usually only measure frequency of expiratory efforts, and neglect other aspects. Current methods for measuring and assessing cough are described, with indications of when the use of these methods may be important.**

KEYWORDS: **cough, expiration reflex, larynx, trachea, bronchi**

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Our shelves are filled with many files of reprints of research papers about cough, going back to 1841; we have Medline versions of many recent papers, hundreds in total. There has not been time to check them all, but 60 were pulled out at random for the period 1929–2005. They have two features in common: all of them are about cough, and cough is defined in virtually none of them (including many papers by one of the present authors, J. Widdicombe), except for those by a small number of authors (including some papers by one of us, G. Fontana) [1–3]. In contrast, reviews usually include a textbook definition of cough, and a comprehensive book on cough admirably describes several different patterns of cough [4].

We are confident from memory that the lack of definitions applies to nearly all those research papers we have not checked, as well as the ones we have checked. Does it matter? Of course it does! Otherwise we don't know what we're talking about.

Cough can be elicited from the larynx, trachea or bronchi. It is clearly defined in the textbooks: an inspiratory effort (inspiratory phase), followed by a forced expiratory effort against a closed glottis (compressive phase) followed by opening of the glottis and rapid expiratory airflow (expulsive phase) (fig. 1) [5]. The literature on cough goes back to Hippocrates. It is one of the defensive reflexes of the respiratory tract.

A second defensive reflex is the expiration reflex (ER). This is induced by mechanical or chemical irritation of the vocal cords [4, 6] or of the trachea [7, 8], and consists of a forced expiratory effort (without preceding inspiration) with closure of the glottis, followed by opening of the glottis and an expulsive phase (fig. 2). The ER from the larynx was first described (but not named) by WILLIAMS [9] in 1841, who pushed his finger up the opened trachea of a dog and noted that, when the finger tip reached the larynx, the dog made a series of convulsive expiratory efforts. Later, the reflex was named, and its importance and mechanisms were extensively analysed by KORPAS and colleagues [4, 6]. Figure 2 is taken from their pioneering studies. They distinguished the ER from the cough in many ways, in addition to its different respiratory patterns. However, the literature in general ignores or confuses the distinction between cough and the ER. Both reflexes can be elicited either from the larynx or from the trachea, but the physiological mechanisms that determine the responses are still not fully clarified.

The distinctions between cough and the ER are important for several reasons:

1) Their functions are distinct and diametrically opposed. The cough reflex (CR) will draw air into the lungs to augment the force of the subsequent expulsive phase, promoting clearance of mucus and material from the tracheobronchial tree and

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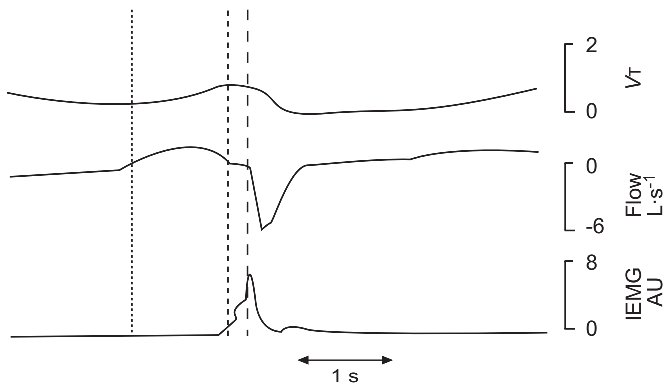

FIGURE 1. Original recordings obtained from one normal subject showing a single cough effort induced by inhalation of the threshold concentration of ultrasonically nebulised distilled water for the cough reflex. Traces are tidal volume (V_T; inductive plethysmography), airflow (derived electronically from the V_T signal), and the integrated electromyographic activity of the right abdominal oblique muscle (IEMG). Note zero airflow during the compressive phase. ······: onset of the inspiratory phase; ------: compressive phase; and – – –: expulsive phase of cough. AU: arbitrary units.

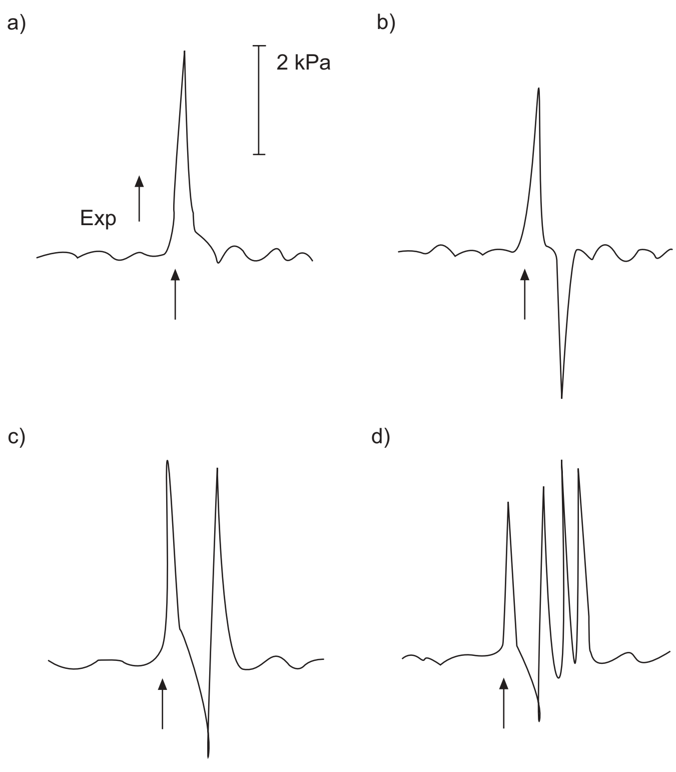

FIGURE 2. The expiration and cough reflexes induced by touching the vocal folds with a nylon fibre (at arrows) in an anaesthetised cat. The record is of intrapleural pressure with positive expiratory pressure upwards. Time intervals of 1 s are indicated by the scale bar at the bottom. a) A single expiration reflex (ER). b) An ER followed by an inspiration without cough. c) An ER followed by a single cough. d) An ER followed by a single cough and then two further ERs. Exp: expiration. Reproduced from [6] with permission.

lungs. The ER from the larynx will prevent the entry of material into the tracheobronchial tree and lungs. The function of the ER from the trachea is less obvious. (Those who believe in ''intelligent design'' might say that humans should have been designed without a CR from the larynx and without an ER from the trachea).

2) The two reflexes must have fundamentally different afferent (sensory) pathways, since one starts with an inspiration and the other with an expiration, unless there is a brainstem switch that determines the response, in which case, what sensory input activates the switch?

3) The brainstem neural pathways for the two reflexes are distinct [10–12], as are the neural ''gating'' mechanisms that ''permit'' cough or an expiratory effort to replace quiet breathing [13].

4) The physiological modulations of the two reflexes are often different. For example: a) activation of the Hering–Breuer inflation reflex by lung inflation strongly augments the ER (there is a paradox here because in practice there is no preliminary inspiration to augment the reflex), but has only facilitatory or inconsistent actions on the CR [14]; b) high levels of carbon dioxide in arterial blood depress the cough but not the ER [15]; c) in slow-wave sleep, cough, but not the ER, is depressed [16,17]; d) in neonates, the ER appears during development before the CR [18]; e) unlike in sleep, anaesthesia depresses the ER more than the CR [2] (see later); f) anecdotal evidence suggests that the full effort of a cough can be voluntarily produced, but the full explosive effort of the ER cannot; g) cough is associated with a sensation, an urge-to-cough [19], but if the ER has a similar sensation it has not been described.

5) The pharmacological inhibitions of the two reflexes are different; for example, codeine has no action on the ER in doses that inhibit cough [20]. This, in the future, could have considerable implications for the preferential therapy of different types of cough.

The above studies are based mainly on animal experiments, but there is some human research that supports them.

The plot thickens! Two cough-like defensive reflexes have been described, but in practice many coughs consist of cough epochs or bouts or, as usually called by the patient, cough attacks. There seem to be three patterns of these cough epochs, as follows.

1) A single textbook cough, but with the glottis briefly closing again during the expulsive phase and interrupting expiration and giving a second cough sound, or even repeated closures during a single expiratory effort of cough with multiple sounds (fig. 3) [21]; the mechanism of these closures is obscure. These patterns were analysed by YOUNG *et al.* [1] in 1987; figure 3 is from this study. Should the spontaneous cough illustrated in figure 3 be defined as a single cough or as four coughs? There was an initial large inspiration before only the first expiratory effort, so are the last three expiratory efforts ERs induced by the first cough? Note the cough sound patterns: the voluntary coughs produce a single sound, the first two efforts in the cough epoch produce double sounds, and the last two efforts single sounds. Presumably the second cough sounds are due to

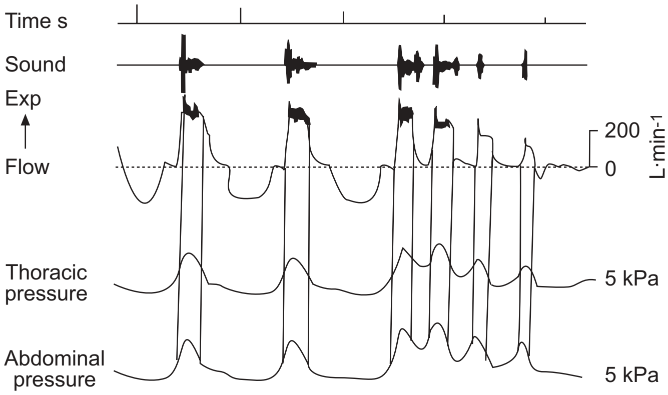

FIGURE 3. Voluntary coughs and a cough epoch in a female subject. Traces, from the top: time in s, cough sound, airflow (expiration upwards), thoracic/oesophageal pressure (positive upwards), and abdominal pressure (positive upwards). On the left are two voluntary coughs. They are followed by a spontaneous involuntary cough epoch consisting of an initial inspiration and then four compressive and expulsive phases without intermediate inspirations. Vertical lines indicate equal time points. Exp: expiration.

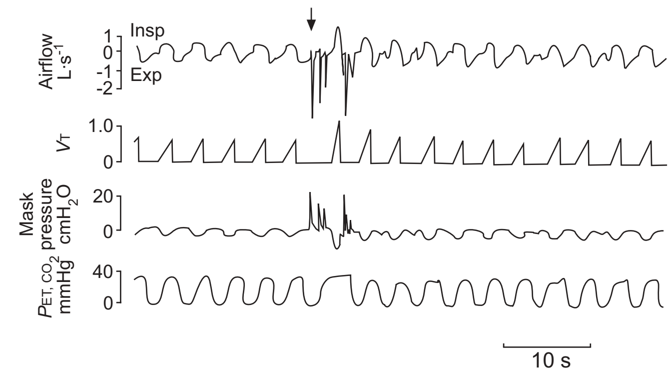

FIGURE 4. Respiratory response to laryngeal stimulation by injection of distilled water (at arrow) in an awake human subject. The injection was given *via* a nasal endoscope. Pressure, airflow and end-tidal carbon dioxide tension (P_{ET,CO_2}) were recorded *via* a face mask. V_T: tidal columе; Exp: expiration; Insp: inspiration. Reproduced from [2] with permission.

closure of the glottis. What is the mechanism for these differences?

2) The textbook cough followed by repeated and distinct expiratory efforts with compressive and expulsive phases due to glottal closure(s), and then further coughs (with inspiratory efforts) within a single cough epoch [1, 2].

3) An initial ER followed by textbook coughs and more ERs and coughs, as seen when food or possibly gastric reflux enters the glottis, and presumably preventing or limiting its aspiration and inhalation.

Note that patterns 1 and 2 above start with an inspiration, whereas pattern 3 starts with an expiration. It should also be noted that repeated ERs have not been seen from the trachea but only from the larynx.

There have been very few records similar to figure 2 in humans, except for the extensive studies by NISHINO and colleagues [2, 22]; figures 4 and 5 are taken from these articles. Figure 4 shows the response to application of distilled water to the larynx of a non-anaesthetised subject: there are three ERs followed by a cough (note the deep inspiration) followed by another ER. Figure 5 shows the response to the same stimulus in a lightly anaesthetised subject: there is an ER, followed by eight coughs and, after a pause, another ER. Although there are very many more records of animal coughs than human coughs, there is no reason to expect fundamental difference in patterns.

It should be noted that repeated expiratory efforts, as shown in figure 4, are bound to be followed by a compensatory deep inspiration that may be the first phase of a cough.

It is obvious that the neurological mechanisms underlying these various patterns of cough must differ in fundamental ways. Stimuli that induce cough excite a variety of afferent (sensory) nervous inputs from the airways [23, 24], which must interact to produce the common systems of motor outflow. These inputs enter a complex brainstem respiratory mechanism [10–13], the delineation of which will not be attempted here. The brainstem pathways have some different features for the cough and ERs [25]. The inputs relay up to the cerebral cortex where they may be associated with sensation and the urge-to-cough [19, 26].

In view of the neurological differences of the reflexes, it is not surprising that the patterns of spontaneous and evoked cough and of the ER may vary in the following conditions.

1) The presence of sleep depresses cough more than the ER [16, 17, 27]. For anaesthesia, the pattern is the opposite [2]. For clinical coma, which depresses cough, there seem to have been no detailed observations.

2) The strength of the stimulus: weak chemical stimuli in the larynx may cause glottal closure without respiratory muscle changes [28]; stronger stimuli cause cough [27]; even stronger chemical stimuli cause the ER (sometimes inaccurately called the laryngeal cough ER [29]) and glottal closure. In the context of the current Perspective, it is important to emphasise that a clear ER (as distinct from a cough) is seen in tests for aspiration risk in patients after stroke or with Parkinsonism, and its latency and characteristics have been studied [29–31].

3) The sensation that accompanies the defensive reflexes: urge-to-cough [19], irritation, even pain, may influence cough threshold and pattern.

4) The voluntary control of cough: this can either induce or inhibit it [32]; it is not known to what extent voluntary control can influence a strong ER, although obviously it can powerfully affect throat clearing or a ''huff'', which may be an example of a weak ER, either initiating or suppressing it.

5) The actions of antitussive drugs in experimental animals may be quite different on cough and the ER [20].

Two examples can be given to illustrate ignorance about the role of the two reflexes in clinical conditions.

1) Current views on the mechanisms of cough due to gastro-oesophageal reflux (GOR), one of the three commonest causes of chronic cough [33], include two possibilities: that it is due to activation of oesophageal sensory receptors responsive to acid

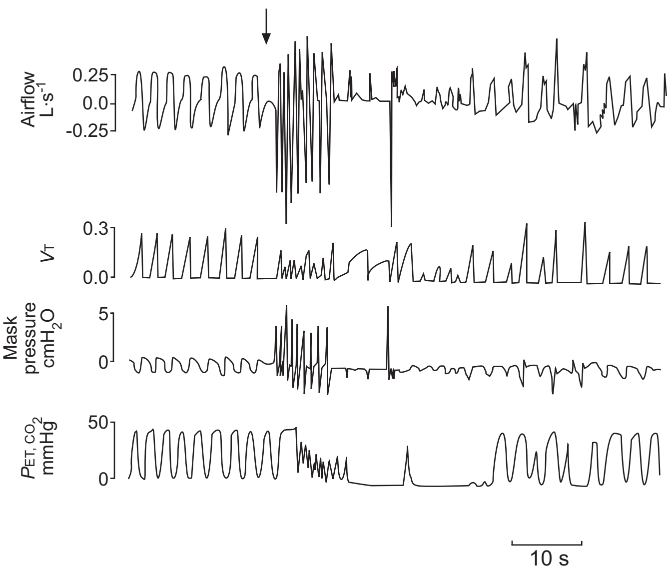

FIGURE 5. The procedure was carried out as described in figure 4, but the subject was lightly anaesthetised with propofol. P_{ET,CO_2}: end-tidal carbon dioxide tension; V_T: tidal volume. Reproduced from [2] with permission.

or gastric contents in the lower oesophagus, or that it is due to gastric contents irritating the larynx and perhaps being aspirated [34]. Both possibilities may apply. One might expect the two mechanisms to elicit different responses: the oesphageal response might be a textbook cough and the laryngeal/aspiration response primarily an ER. Yet the present authors' limited literature survey suggests that no one studying GOR-induced cough has accurately described the patterns of response.

2) Post-nasal drip syndrome (PNDS) is also one of the three most common causes of cough [33]. It could be due either to mucus draining to the larynx and mechanically setting up a throat-clearing or huff, presumably an ER; or to mediators in the nasal mucus causing inflammation of the laryngeal mucus membrane perhaps inducing a ''true'' cough; or both [35]. Yet the present limited literature search suggests that no one writing about the cough due to PNDS has accurately described the pattern of the cough response.

Those authors who assess cough by measuring its frequency, who are in the majority, seldom comment on its strength or its pattern in a cough epoch. It might be worth counting both the numbers of true coughs and also the numbers of expiratory efforts not preceded by inspirations (since they probably have different mechanisms), and expressing them as, for example, CRN_1 and ERN_2, where N_1 and N_2 are the respective numbers of the coughs and the separate expirations in a single cough epoch (P. Davenport, Dept of Physiological Sciences, University of Florida, FL, USA, personal communication). If this is done for figure 2c, and figures 4 and 5, the CRN_1/ERN_2 ratios are 1:1, 1:4, and 8:2, respectively. An alternative, although not quite the same thing, is for the cough epoch to be expressed as IN_1 and EN_2, where N_1 and N_2 are the numbers of inspiratory and expiratory efforts in a cough epoch. Again, if this is done for figure 2c, and figures 4 and 5, the IN_1/EN_2 ratios would be 1:2, 1:5 and 9:10, respectively.

Do these sophisticated types of analysis need to be applied to clinical conditions? It depends on what question is being asked. The question ''Is the patient coughing more or less?'' can be answered by a ''simple'' cough monitor or even a subjective questionnaire. The question ''Is there a difference between the cough of post-nasal drip and that of post-viral infection?'', both of which arise from the larynx and may require different therapeutic approaches, may need sophisticated methods of analysis for an answer. Similarly, if one asks ''Is the cough in asthma essentially the same or different from that in chronic obstructive pulmonary disease (COPD)?'', cough scores and cough counts may not be adequate methods of analysis. The question ''Does elevated arterial arterial carbon dioxide tension in severe COPD affect either the CR or the ER or both?'' seems worth asking by using sophisticated methods, since the answer may point to a risk of aspiration.

In terms of clinical management, the identification of a spontaneous ER may raise the possibility of aspiration, with appropriate clinical precautions, and certainly implicates the larynx and possibly the trachea as the source of the reflex input.

How are these counts to be made? If they are done by observation, does one distinguish a single cough from a cough epoch and, if the epoch is analysed, how quickly do the ear and the eye break it down into components? The solution is an automated cough counter, several of which have been used in ambulatory conditions [34–38]. However, they are all based only on acoustic signals and therefore record only expiratory efforts. They could be programmed to allocate all the expiratory efforts in a cough epoch to a single cough, or all the efforts to separate coughs. However, they cannot distinguish between cough and the ER. One device quantifies coughing in terms of the amount of time spent coughing, *i.e.* the number of seconds that contain at least one cough [39], but does not distinguish between the two reflexes. It is also possible to assess the inspiratory and expiratory forces of the efforts, and their timings and relationships, from the electromyographic (EMG) activity of the expiratory muscles [40]. However, EMG records are limited in interpretation by the nonrespiratory actions of the abdominal muscles and by posture, and the inspiratory phase of the cough efforts is not recorded. Airflow can be recorded, which will give inspiratory and expiratory phases [2, 8, 28]. Inductance plethysmography could be used but practical factors may limit its usefulness. Invasive techniques such as recording oesophageal or gastric pressure could be informative but are not applicable to long-term monitoring. Clearly there is no ''best-buy'' but all these methods give valuable information to supplement a patient's questionnaire.

There have been very few assessments of the sensation associated with cough: irritation, urge-to-cough and even pain, yet these may be more important symptoms for patients with laryngitis or post-viral cough than the cough itself. Urge-to-cough may have a lower sensory threshold than cough itself [19, 26]. As far as can be seen, there have been no reports of the sensory corollary of the ER. It is not known whether patients can distinguish between the two reflexes, or their relative importance in a cough attack, but they have probably never been asked. The patients' perceptions of cough and its associated sensations comprise a potentially valuable field of study. Such studies have been carried out with dyspnoea, but this is a ''slow'' phenomenon and relatively easy for the subject to describe.

The present authors suggest that it does not much matter what one calls a cough, provided it is defined. And it cannot be defined unless it is carefully described and measured. There is an analogy with the description of the afferent (sensory) receptors that are thought to cause cough. They have been given many overlapping and somewhat-confusing names: irritant receptors, rapidly adapting receptors, cough receptors, deflation receptors, nociceptors, J-receptors, pulmonary and bronchial C-fibre receptors, Aδ nociceptors, but this does not matter greatly because the writers have nearly always clearly defined what they are describing; indeed, the need to define the true cough sensor(s) is stimulating much valuable research [22, 23].

The same is not true for cough itself, since it is seldom defined. The present authors' plea is this: when writing about cough, say precisely what is meant by it and identify as many of its facets as possible. Gertrude Stein would have been wrong if she had said ''a cough is a cough is a cough''; so would Shakespeare if he had written ''a cough by any other name would sound as sweet''. But they might be excused because they were not scientists.

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