Physiology of the Cough Reflex: Sensory and Mechanical Features

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1.1 General Features

Cough is one of the most important airway defensive act aimed at removing foreign particles or endogenously produced materials from airways and serves as a vital defensive mechanism for lung health [1, 2]. It can be an adequate reflex in response to nociceptive stimuli applied to the airways, i.e., stimuli that may actually or potentially damage tissues (e.g., [3, 4]), but can also be voluntary or behavioral. The cough reflex involves the activation of one or more subsets of airway afferent fibers. The importance of an intact cough mechanism is reflected in the occurrence of pulmonary problems when cough is inefficient. Noticeably, cough is the most common symptom for which patients consult a doctor. Cough reflex is purposeful and useful under many circumstances ("appropriate cough"), but is without an apparent benefit or even with clear physical and psychological complications in cases of persistent or chronic cough ("inappropriate cough"). This latter greatly decreases patient's quality of life and may lead to secondary damage of the airway wall and ribcage. Antitussive drugs possess scanty efficacy, and their use is limited by severe side effects. Therefore, further research is necessary for a better understanding of the neural mechanisms involved in acute and chronic cough and to find reliable treatments [5]. However, it seems important to note that not only upregulation but also downregulation of airway defensive reflexes is of clinical interest. In particular, an impairment of airway protective reflexes, including cough and swallowing, in some neurodegenerative diseases (e.g., Parkinsonism, Alzheimer's disease, fronto-temporal dementia) or following ictus could lead to

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high risk of aspiration and pulmonary infections with consequent life-threatening conditions (e.g., [5–9]). Studies on animal models of chronic cough or neurodegenerative diseases could be most appropriate to disclose novel therapeutic approaches. Nevertheless, also investigations on the basic neural mechanisms subserving the cough reflex performed on healthy preparations can provide useful hints for further cough researches and for the development of antitussive or protussive therapies (see, e.g., [7, 10]).

It is important to point out that, despite some differences, cough displays very similar mechanical and airflow features when produced reflexly or under voluntary control [11, 12]. Cough is produced by complex and sequential changes in several upper airway and chest wall muscles. These muscles are responsible for normal eucapnic breathing and their activity depicts a respiratory cycle divided into three phases: inspiration, postinspiration, and expiration (see, e.g., [13]). Similarly, cough that consists mainly of a modified respiratory act (e.g., [1, 14]) includes at least three phases: inspiratory or preparatory, postinspiratory or compressive (glottal closure), and expiratory or expulsive (see also below). A fourth cessation phase has also been described. Both mechanical and chemical perturbations within the airways can evoke coughing bringing into action cough-related afferents that elicit coughing either by reflexively reconfiguring the brainstem respiratory network or via ascending pathways to the cerebral cortex to produce perceivable sensations associated with airway irritation that promote irrepressible coughing (behavioral cough; see Chap. 3 in this book). In fact, a characteristic aspect of human cough motor responses in both acute and chronic conditions is the "urge-to-cough" caused by a tickling sensation in the upper airways that leads to behavioral coughing [15, 16]. Reflex and voluntary cough present similarities, but also different features. In addition, the cough reflex is under a high degree of voluntary control that can modulate its expression up to complete suppression [11, 12, 17–19].

The contribution of higher brain structures to the control of the cough reflex is also clearly reflected in its relationship with sleep and anesthesia. This reflex very strongly depends on the sleep-wakefulness state. In dogs, laryngeal or tracheobronchial stimulation causes coughing during awakefulness, but not during slow-wave sleep (SWS) or rapid-eye-movement (REM) sleep. Only when the intensity of tussigenic stimuli becomes sufficient to induce arousal, the cough reflex develops, i.e., it always follows arousal. The intensity of laryngeal stimulation required to produce arousal and coughing is higher in REM sleep than in SWS [20, 21]. Other reflexes of laryngeal origin (apnea, bradycardia, expiration reflex) can be evoked without arousal. This suggests that only the cough reflex relies on supra-medullary neural processes active only during wakefulness. Similarly, anesthesia deeply affects respiratory reflex responses to stimulation of the tracheobronchial tree. For instance, under the highest levels of anesthesia, the patients do not cough, rather they respond with a prompt apnea. On the other hand, the cough reflex is progressively more frequent by reducing the level of anesthesia, while the apneic response shows an opposite trend [22].

1.2 Cough-Related Afferents

Reflex cough is mediated by vagal afferents from the upper airways and the tracheobronchial tree [19, 23, 24]. Also some other extrarespiratory sources of cough are supplied by vagal afferents, such as the external acoustic meatus (auricular branch of the vagus nerve, Arnold's or Alderman's nerve) that mediates the Arnold's ear-cough reflex [25–27]. Other tussigenic areas may be the visceral pleura and the esophagus (for review see [28]). Gastroesophageal reflux seems to be a factor in some airway disorders associated with cough and bronchoconstriction [29–31].

1.2.1 Tracheobronchial Tree

The general characteristics of airway vagal afferent neurons, mainly derived from studies in cats and rodents (guinea pigs, rats and mice), have been extensively reviewed by Sant'Ambrogio and Widdicombe [32], Lee and Yu [28], and Mazzone and Undem [19]. The cell bodies of vagal sensory fibers innervating the respiratory tract arise from two distinct ganglia, i.e., the nodose ganglion and the jugular ganglion, and have their first central station in the nucleus tractus solitarii (NTS). The nodose and jugular afferent fibers differ in several characteristics, including distinct molecular phenotypes, peripheral distribution to the tracheobronchial tree, and projections to brainstem structures (see [19]). Sensory nerve terminals can be found widely distributed throughout all the levels of the airway tree and in association with the various tissue types of the airway wall and with different end-organs. Afferent receptors described as present within the tracheobronchial tree and lung parenchyma are divided into three broad classes: slowly adapting stretch receptors (SARs), rapidly adapting stretch receptors (RARs), and bronchial and pulmonary endings of C-fibers. There are, in addition, slow adapting nociceptors innervated by Aδ and C fibers and the polymodal neuroepithelial bodies. However, their involvement in the cough reflex is at present obscure. Some important features of these receptors have been reported in several reviews [19, 25, 32–34]. This classification is based on a variety of properties such as adaptation during sustained lung inflations and conduction velocity of related afferent fibers. The main receptors implicated in the cough reflex are SARs, RARs, and bronchial and pulmonary C-fibers.

Cough-related receptors mainly located in the large extrapulmonary airways (trachea, carina, main bronchi) belong to the wide family of pulmonary RARs innervated by Aδ fibers, possibly including the so-called "cough receptors" described in the guinea pig larynx and rostral trachea [35–37]. RARs are a heterogeneous family of polymodal receptors and some of them are particularly sensitive to various kind of mechanical stimuli of the airway mucosa or airway muscular walls (rapid inflation and, especially, deflation) and to chemical irritant stimuli, such as citric acid, ammonia, and cigarette smoke, as well as to hyper- or hypoosmotic solutions (e.g., distilled water, mainly because of a lack of permeant anions, in particular chloride). Activation of RARs in the deep intrapulmonary airways usually

provokes hyperpnea/tachypnea, augmented breaths, bronchoconstriction, laryngeal closure, but very rarely cough. Further evidence for their role in coughing comes from studies of vagal cooling, which blocks cough at temperatures that selectively abolish activity in myelinated fibers (including Aδ afferent fibers from RARs) while preserving C-fiber activity [34, 38].

The abovementioned "cough receptors" described in guinea pigs [35–37] are innervated by slowly conducting Aδ-fibers that arise from nodose ganglia. They are sensitive to punctate mechanical stimuli of the epithelium overlying the sensory endings, and to rapid changes in luminal pH (acidification) or to hypotonic solutions (e.g., distilled water) due to the expression of acid sensing ion channels (ASICs) and Ca^{++}-activated chloride channels, respectively. However, they are unresponsive to capsaicin, bradykinin or hypertonic saline, smooth muscle contraction, and changes in airway luminal pressure. Furthermore, the "cough receptors" possess stimulus specificity. For example, ATP activates RARs, but not Aδ nodose fibers, and is relatively ineffective at evoking cough in anesthetized animals (for further details see [19]). Like other mechanosensors in the lung, a single myelinated axon can give rise to one or several unmyelinated arborized terminals that lay above the airway smooth muscle, but below the epithelium basement membrane. This location for cough receptor terminations may explain their relative insensitivity to airway smooth muscle contractions [19, 25]. Like Aδ RARs, they do not express transient receptor potential vanilloid type 1 (TRPV1) channels under normal healthy conditions, but only when airway inflammation is present. Recent results on the antitussive effects of long-acting muscarinic receptor antagonists (LAMAs) are consistent with the possible role of this type of receptors in cough production both in awake and anesthetized rabbits [10, 39]. However, their presence in the tracheobronchial tree of this animal species remains to be ascertained. The results of these studies strongly suggest that other membrane receptors, in addition to the TRPV1 channels, as shown by Birrell et al. [40] in guinea pig, should be taken into consideration in the mediation of LAMA antitussive effects, such as ASICs and mechanoreceptors of cough-related afferents.

SARs, corresponding to a great extent to pulmonary stretch receptors, are highly sensitive to lung inflation and are the primary afferent fibers involved in the Breuer-Hering inflation reflex, which terminates inspiration and initiates expiration when the lungs are sufficiently inflated. Their activity increases during inspiration, reaching a maximum just prior to the beginning of expiration. SARs are primarily associated with smooth muscle in the tracheobronchial tree. They may have a permissive role in the cough reflex (absence of cough reflex responses when they are selectively blocked) only in some animal models, e.g., in rabbits, but not in dogs (see, e.g., [41–43]). Their action may be due to their facilitatory influences on expiratory motoneurons and, therefore, on the reflex activation of expiratory muscles during coughing [24, 32, 44]. Interestingly, other studies in guinea pigs found no evidence for a permissive effect of SARs in cough production [45]. Admittedly, the role of pulmonary stretch receptors and, in particular, of volume-related feedback in the regulation of the cough reflex is controversial [46–49]. Recently, Poliacek et al. [50] have reported that modified lung inflations during coughing and/or additional

expiratory airflow resistances in the cat alter the spatiotemporal characteristics of the cough motor pattern through volume-related feedback mechanisms similar to those operating during eupneic breathing. They also have suggested a significant contribution of both SARs and RARs in shaping the cough reflex.

The majority (80%) of bronchopulmonary vagal afferent nerves are unmyelinated C-fibers and cough-related afferents may originate from bronchopulmonary C-fiber endings; their sensory neurons are located both in nodose and in jugular ganglia [24, 25, 37, 45, 51–56]. Vagal afferent C-fibers are distinguished from lung stretch receptor afferents (SAR afferents) not only for their conduction velocity (<2 m/s) but also by their relative insensitivity to mechanical stimulation and lung inflation. C-fiber endings are further differentiated from lung stretch receptors by their direct sensitivity to bradykinin and activators of both the TRPV1 channels (e.g., capsaicin and protons) and the transient receptor potential ankyrin 1 (TRPA1) channels (e.g., ozone and allyl isothiocyanate). C-fiber stimulation (e.g., capsaicin inhalation) has consistently failed to evoke coughing in anesthetized animals. In addition, the cough reflex can be inhibited owing to the activation of a subset of pulmonary C-fibers in dogs, cats, and guinea pigs ([25, 38, 42, 45, 51, 57, 58]; see also [19]). The same is true for stimulation of bronchial C-fibers in dogs [38, 58]. In particular, it has been reported that cough is abolished during apnea, i.e., the initial phase of the pulmonary chemoreflex due to C-fiber receptor stimulation, and significantly reduced during the rapid shallow breathing that immediately follows apnea. These respiratory effects were accompanied by marked bradycardia and hypotension. However, at variance with previous findings, Mutolo et al. [59] have shown that tracheobronchial cough is not significantly reduced in the rabbit during the pulmonary chemoreflex, thus suggesting that species differences should be taken into consideration. Further support for the inhibitory role of vagal C-fibers on mechanically induced cough in anesthetized cats has recently been derived from the study by Simera et al. [60]. However, some studies have suggested that in anesthetized guinea pigs [61, 62] C-fiber activation does not evoke cough, but consistently reduces the threshold for coughing evoked by other receptors sensitive to both electrical and mechanical stimuli. All these findings indicate that C-fibers may be especially relevant to coughing associated with airway inflammation and inhalation of environmental irritants.

In conclusion, the role of bronchopulmonary C-fibers in the cough reflex has been the subject of considerable debate ([19]; see also [63]). Bronchopulmonary C-fibers represent a very wide family, and different subtypes have been described in different animal species (e.g., [56, 64]). In guinea pigs, C-fiber subtypes may have different origin (nodose vs. jugular ganglia), sites of peripheral airway termination (extra- vs. intrapulmonary), expression of neurokinins, and responsiveness to some neuroactive agents such as adenosine, 5-HT_3 receptor, and ATP/$P2X_{2/3}$ receptor agonists [56, 65, 66]. Recently, in agreement with previous results, it has been reported that airway C-fibers arising from the jugular ganglion initiate or sensitize the cough reflex, and that the intrapulmonary C-fibers arising from the nodose ganglion inhibit cough induced by citric acid and electrical stimulation in anesthetized animals or by capsaicin in awake animals [63]. It is unclear whether the C-fiber subtypes with

opposing effects on cough in species other than the guinea pig also arise from distinct vagal ganglia ([63] also for further Refs.). In the light of the present knowledge on the role of sensory afferents from the respiratory tract, it seems conceivable that Aδ cough-related afferents are mainly involved in the production of the cough reflex, while C-fiber cough-related afferents are mainly implicated in the generation of airway sensations, such as, for instance, chest pain, dyspnea, and the "urge-to-cough," that is characteristic of awake animals and humans and may lead to the behavioral act of coughing (see also [19, 39]).

1.2.2 Larynx

In this context, it is important to mention that laryngeal receptors are a very important source of airway defensive reflexes and, in particular, of the cough reflex [28, 44]. The main source of afferent laryngeal fibers is the internal branch of the superior laryngeal nerve. The cell bodies of these laryngeal afferents are located in the two vagal sensory ganglia, with a majority of them in the nodose ganglion. Recordings from the peripheral stump of the superior laryngeal nerve in animals spontaneously breathing through their upper airway show the presence of afferent activity with marked respiratory modulation. This respiration-related activity derives from different types of receptors: (1) receptors activated by the inspiratory cooling of the laryngeal lumen ("cold" or "flow" receptors); (2) receptors detecting either negative or positive transmural pressure in the larynx ("pressure" receptors); and (3) receptors stimulated by the contracting intrinsic laryngeal muscles and by passive movements of the larynx ("drive" receptors). Cough-related laryngeal receptors apparently display analogies with the RARs located in the tracheobronchial tree ([1, 14, 32, 34, 44] also for further details). Cough-related laryngeal receptors innervated by myelinated Aδ fibers are activated by mechanical and chemical stimuli and are often called "irritant receptors." They possibly include the "cough receptors" described above. A large proportion of "irritant" receptors responds to water or water isosmotic solutions lacking chloride ions. C-fiber activation has also been reported to have a role in cough production and it seems plausible that specific second-order neurons for cough-related laryngeal afferents exist. In this regard, Widdicombe [34] proposed a putative model of the central pathways for the cough reflex where laryngeal RARs project to their own laryngeal relay NTS neurons that have separate connections with the cough generating mechanism in the brainstem. Although the central pathways have not been investigated in detail, they are probably similar to those displayed by tracheobronchial cough afferents ([67–70]; see Chap. 3 in this book). In addition, "irritant" receptors may evoke other airway protective reflexes such as glottal closure, apnea, bronchoconstriction, mucus secretion, the expiration reflex and the swallowing reflex as well as various cardiovascular reflexes [1, 14, 19, 32, 71–73]. The expiration reflex closely resembles cough responses, but it consists of a pure expiratory effort evoked by the mechanical stimulation of the vocal fold mucosa in the absence of a preparatory inspiratory phase [1, 32, 74]. The expiration reflex can be also evoked by the

stimulation of the tracheobronchial tree [75–77]. Glottal closure and the expiration reflex can be regarded as the first level of airway defense since they prevent penetration of foreign bodies into the airways. The other laryngeal receptor afferents mediate different respiratory reflexes (see, e.g., [14, 44]). For further details on cough peripheral afferent pathways and related cough-inducing mechanisms, see Chap. 2 in this book.

1.2.3 Bronchoconstriction and Cough

Cough and bronchoconstriction are often associated. They are, however, distinct mechanisms that can be separately brought into action and differentially inhibited by drugs. Inhalation of nebulized water is well known to elicit cough and bronchoconstriction in humans. However, cough depends on a lack of permeant anions (e.g., chloride), while bronchoconstriction depends on the osmolarity of the inhaled solution. Furthermore, the effects of bronchodilating drugs on cough suggest that changes in airway tone are not involved in cough production. It is also apparent that the bronchomotor tone can be altered by inputs that do not cause cough, such as chemoreceptor stimulation and irritation of the nose or nasopharynx. Both cough and bronchoconstriction are mediated by the central nervous system, but bronchoconstriction may also be elicited by the release of mediators from afferent nerve fibers (for review see [44]).

1.3 Bronchopulmonary Sympathetic Afferents

Sensory information generated by mechanical and chemical stimuli applied to the airways and lungs is also conveyed by sympathetic afferents to the central nervous system (for review see [28]). It is generally believed that sympathetic afferents are less important than their vagal counterparts since most of the known airway reflexes can be essentially suppressed by bilateral vagotomy. However, possible interactions between these two afferent systems should be considered. In general, sympathetic afferents travel in association with sympathetic efferent fibers. Their cell bodies are located in the dorsal root ganglia and reach the paravertebral ganglia and the prevertebral ganglia through the white ramus communicans. Bronchi and lungs are supplied by fibers derived from the middle cervical ganglia, the stellate ganglia, and the upper thoracic ganglia. Central pathways may terminate at thoracic segments T1-T6 and also up to C7 and down to T8. Part of neurons in the dorsal root ganglia may contain TRPV1 and substance P. So far, sympathetic sensory receptors have not been divided into different categories. They are a heterogeneous group sensitive to mechanical stimuli (e.g., lung hyperinflation) and chemical stimuli (e.g., ammonia and smoke) and comprise polymodal nociceptive receptors. Their stimulation alters the breathing pattern in vagotomized animals. For example, bradykinin injected into the bronchial artery evokes sustained inspiration, while injected into the right atrium stimulates breathing, and applied to the lung parenchyma produces marked

respiratory excitation or inhibition as well as bradycardia and hypotension. Noticeably, both vagal and sympathetic afferents contain both TRPV1 and substance P. Sympathetic afferents contribute with vagal afferents to the genesis of respiratory sensations, especially pain arising from the pleural region [78]. The viscerosomatic and visceroviscerall convergence is probably relevant to cardiopulmonary reflexes and to chest pain originating from trachea and lower airways. It may be involved in reciprocal phenomena of sensitization (e.g., noxious damage and related pain in one organ may influence pain threshold and associated pathological responses in the other). Respiratory sensations such as dyspnea, air hunger, airway irritation, and "urge-to-cough" are generated by sensory signals arising from peripheral and central chemoreceptors or from respiratory structures, including airways, lungs, and chest wall. In particular, not only vagal afferents but also sympathetic afferents may contribute to these respiratory sensations.

It seems appropriate to recall that the solitary tract neurons receive the converging input of both somatic skeletomuscular (small myelinated and unmyelinated fibers) and vagal afferents, thus indicating that they are involved in the mediation of somatosympathetic reflexes. This viscerosomatic convergence may be the anatomical substrate of cardiorespiratory responses to muscle activity [79–82] and of central sensitization phenomena.

1.4 Respiratory Muscles

As already mentioned, the same muscles engaged during eucapnic breathing also participate in the cough motor pattern. Respiratory muscles are involved not only in lung ventilation, but also in other functions such as postural adjustments, movements of the trunk, expulsive maneuvers (cough, sneezing, emesis, defecation) and behavioral functions (sniffing, speech, and vocalization). Respiratory muscles that are similar to the other skeletal muscles comprise "pump" muscles that are responsible of inspiratory and expiratory activity and determine lung inflation and deflation, respectively. During quiet breathing the diaphragm, the parasternal intercostals, scalene (always in humans), and probably part of the external intercostal muscles produce active inspiration. Under the same conditions, expiratory muscles are generally silent, i.e., expiration is a prevailing passive event. During increased ventilation, for instance because of exercise, hypercapnia or hypoxemia, also other respiratory muscles are recruited, such as all the intercostals as well as abdominals, scalene, sternocleidomastoids, erector spinae, trapezius muscles, pectoralis muscles and other accessory muscles, including for instance those of the upper airways (for details see below).

The diaphragm is innervated by the two phrenic nerves that originate from C_3, C_4, and C_5 roots. It is anatomically unique among skeletal muscles in that it separates two body cavities and its muscle fibers radiate from a central tendinous structure to insert peripherally into skeletal structures. Diaphragm contraction produces very complex actions. The dome of the diaphragm descends relative to the costal insertions of the muscle and expands the thoracic cavity along its craniocaudal axis.

Hence, pleural pressure falls and depending on whether the airways are open or closed, lung volume increases or alveolar pressure decreases. Furthermore, it causes a caudal displacement of the abdominal viscera and an increase in abdominal pressure which, in turn, pushes the ventral abdominal wall outwards and contributes to rise the lower rib cage, i.e., that located in the "apposition zone" between the diaphragm and thoracic wall. In addition, owing to its insertion on the lower six ribs and the cranial orientation of its fibers, it lifts and rotates them outward, thus increasing the thoracic volume. As a result of the contraction of the diaphragm, the thoracic pressure decreases with a possible inward movement of the sternal portion of the thoracic wall, which however is counteracted by the activity of the parasternal intercostals.

In the electromyographic (EMG) activity of the diaphragm as well as in the electroneurogram of the phrenic nerve (but not in the EMG of intercostal inspiratory muscles) after the end of inspiration (marked by the change in the direction of the airflow), there is a short period of silence followed by a resumption of inspiratory activity during expiration. This diaphragmatic activity is called "postinspiratory inspiratory activity" or more simply "postinspiratory activity" and allows to recognize three phases in respiratory activity (Fig. 1.1), i.e., inspiration, postinspiration or E1 phase, and expiration or E2 phase characterized by the possible appearance of expiratory activity and therefore also called "active expiration" [13]. This triphasic feature can also be recognized in the organization of the central pattern generating mechanisms (for review see, e.g., [13, 83–85]). Postinspiratory activity provides a mechanism to mechanically brake the expiratory airflow and comprises glottal closure due to the activation of vocal fold adductor muscles innervated by the inferior or recurrent branches of the vagal nerves (see Fig. 1.1). This phase is of great importance for the mediation of various protective reflexes, such as glottal closure, sneeze,

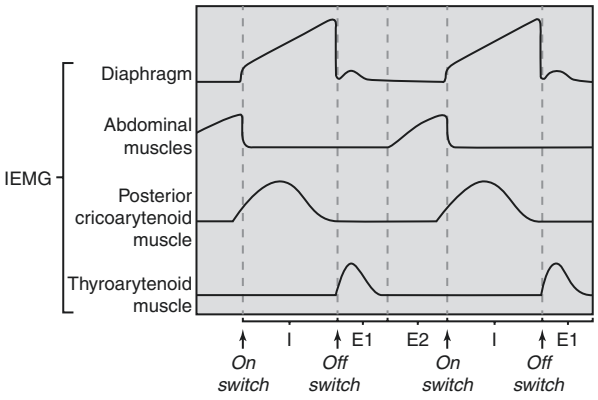

Fig. 1.1 Diagrammatical representation of the three phases of the respiratory cycle, depicted by the integrated electromyographic activity (IEMG) of the diaphragm, abdominal muscles, and thyroarytenoid muscle (larynx adductor). The activity of the posterior cricoarytenoid muscle (larynx abductor) has also been reported. *I* inspiratory phase, *E1* expiratory phase 1 or postinspiratory phase, *E2* expiratory phase 2 or active expiration

cough, and swallowing, that ensure protection against penetration of potentially harmful foreign substances into the airways [8, 86].

The diaphragm can be actually considered composed of two distinct muscles: the sternocostal and the crural or lumbar portion, respectively. These two portions have different embryonic origin and innervation, a different number of slow fibers (higher in the crural portion), different actions on the thoracic wall, and, in addition, differential activation in some motor behaviors that require a separate control of the esophageal hiatus (expulsion phase of vomiting, swallowing, belching). For instance, during the expulsion phase of vomiting, crural fibers that surround the esophagus are silent, while sternocostal fibers are active along with abdominal muscles. Proprioceptive reflexes and postural activity are poorly represented in the diaphragm. At variance with intercostals and other respiratory muscles, the diaphragm contains a few muscle spindles, which are mainly concentrated in the crural portion.

The respiratory function of intercostal muscles has been controversial throughout medical history. The theory of Hamberger (1749) deserves special mention because it provides the basis for the conventional current concepts concerning the action of intercostal muscles. He argued that external intercostals are inspiratory muscles and the internal intercostals are expiratory muscles, with the exception of the intercartilaginous (parasternal) portion which is inspiratory. According to this theory, because the fibers of external intercostals slope caudad and ventrally from the rib above to the rib below, their lower insertion is further from the center of rotation of the ribs (costovertebral articulation) than their upper insertions. When these muscle fibers contract exerting equal and opposite force at the two insertions, the torque acting on the lower rib, which tends to raise it, is greater than that acting on the upper rib, which tends to lower it. The opposite is true when the fibers of the internal intercostals contract since they slope in the opposite direction. As to the parasternal internal intercostals, they raise the ribs since their action should be referred to the sternum rather than to the vertebral column. However, for many reasons the Hamberger theory is incomplete and cannot entirely describe the action of intercostal muscles. Studies by De Troyer and coworkers in humans have shown that in the dorsal half of the second interspace the external intercostals have a large inspiratory effect, which decreases rapidly in the caudal and ventral direction [87, 88]. Thus, the effects become expiratory in the ventral half of the sixth and eighth interspaces. Furthermore, the internal intercostals have been shown to have a large expiratory effect in the ventral half of the sixth and eighth interspaces, but this effect decreases dorsally and cranially. The distribution of EMG inspiratory and expiratory activities is consistent with these results ([89]; for review see [90]). Human parasternal intercostal muscles are active during inspiration and their mechanical respiratory effect diminishes from the first to the fifth muscles with a parallel decrease in the phasic drive (EMG activity) and an increase in tonic activity [91]. During coughing, mid-thoracic external and internal intercostal muscles discharge synchronously with the diaphragm and abdominal muscles, respectively. On the contrary, both caudal external and internal intercostal muscles discharge simultaneously with abdominal muscles [92, 93]. The triangularis sterni or transversus

thoracis muscle is usually inactive during resting breathing, but contracts during voluntary and involuntary expiratory efforts, including cough. It pulls the ribs caudally and deflates the rib cage, together with the expiratory internal intercostals.

The abdominal muscles with significant respiratory function in humans are the rectus abdominis, the external oblique, the internal oblique, and the transversus abdominis. As they contract, they pull the abdominal wall inward and produce an increase in abdominal pressure. This causes the diaphragm to move cranially into the thoracic cavity with a consequent increase in pleural pressure and decrease in lung volume. These muscles, owing to their insertions on the ribs, pull the lower ribs caudally and deflate the rib cage. This action is, however, partially counteracted by the concomitant raise in abdominal pressure that exerts an inspiratory function since it expands the lower rib cage at the level of the "apposition zone."

In the upper airways there are multiple muscles at each of five major sites: the pharynx, soft palate, larynx, nose, and mouth. Their major respiratory functions are to optimize airway patency during inspiration, regulate the rate of airflow during expiration, and partition ventilation between nasal and oral routes. Among the muscles that assure the airway patency there are alae nasi muscles, that dilate the nares, the genioglossus muscle, that is the major protrusor of the tongue, the muscles that are directly or indirectly mechanically attached to the hyoid bone (geniohyoid, sternohyoid, sternothyroid, thyrohyoid muscles) which are generally believed to dilate the pharynx. Their activity precedes by a few milliseconds that of the diaphragm, reaches a maximum during the first part of the inspiratory flow, and then decreases. Laryngeal muscles produce large changes in the size and, hence, resistance of the laryngeal aperture through the inspiratory abduction and the expiratory adduction of the vocal cords. Vocal cord abduction during inspiration occurs even during quite breathing (posterior cricoarytenoid muscle contraction). Adduction of the larynx regulates the rate of airflow during expiration (relaxation of posterior cricoarytenoid muscle and contraction of adductor muscles, such as the thyroarytenoid muscle) in concert with the postinspiratory activity of the diaphragm (Fig. 1.1).

The activation of some upper airway muscles also regulates the route of airflow that, with increased ventilator demand (exercise, respiratory diseases), requires a reduction in the level of resistance and breathing occurs no more through the nose, but through the nose and mouth or only the mouth. For a more extensive account on respiratory muscle function see De Troyer and Loring [87], Sieck and Prakash [94], Duron and Rose [95], Bishop [96], van Lunteren and Dick [97], De Troyer [98], and De Troyer et al. [90]. Respiratory muscles are illustrated in Fig. 1.2.

1.5 Phases of Cough and Expiratory Flow

Cough consists of a modified respiratory act that includes three or four phases: inspiratory or preparatory, postinspiratory or compressive (glottal closure), expiratory or expulsive and phase of cessation (e.g., [1, 14, 99]). Coughing usually occurs not as a single cough, but as a succession of cough (interrupted expirations) starting

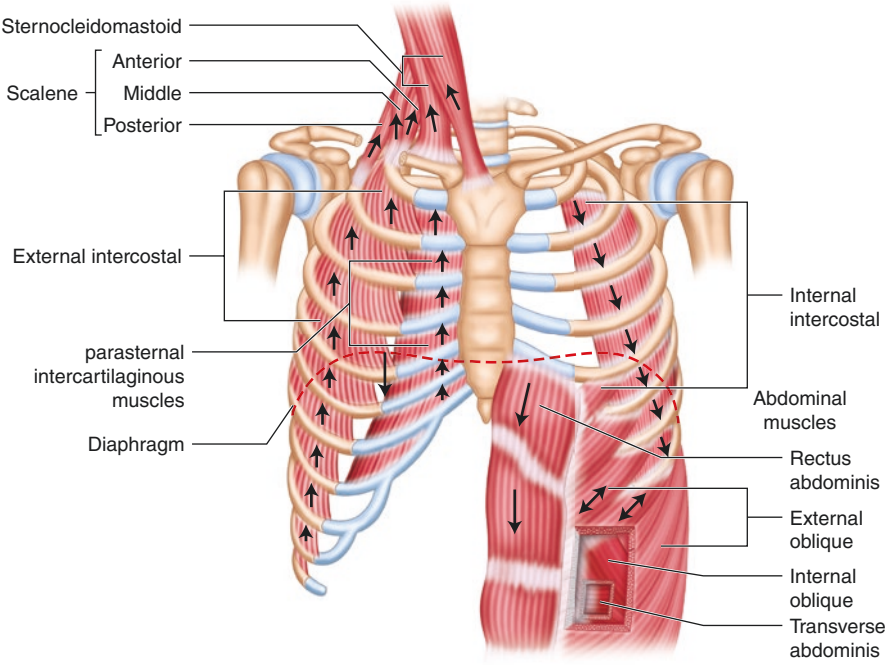

Fig. 1.2 The main inspiratory and expiratory muscles involved in coughing. (From Netter FH, Respiratory system, Publisher Ciba-Geigy Corporation)

after a deep inspiration and ending at residual volume. This pattern probably provides a better clearing mechanism in which rapidly changing swings in transmural pressure act on the wall of the tracheobronchial tree and help to loosen the mucus there accumulated.

1.5.1 Inspiratory or Preparatory Phase

Cough characteristically begins with a brief inspiration (inspiratory phase) and the opening of the glottis by contraction of the abductor muscles of the arytenoid cartilage. The volume of inspired air is variable, but usually greater than that under eucapnic breathing. The increase in lung volume may enhance the mechanical efficiency of the subsequent expiration by different means: optimization of the tension-length relationship of the expiratory muscles resulting in greater intrathoracic and abdominal pressures, and activation of pulmonary stretch receptors by lung distension leading to central facilitation of cough [100]. Although the precise mechanism responsible for the regulation of the inspired volume is not known, it should depend on the intensity of the tussigenic stimulus for reflex cough, while on the expected

forcefulness of the expiratory phase for voluntary cough. Yanagihara et al. [101] observed that when subjects were instructed to produce a single, gentle cough effort, they inspired an amount of air approximately equal to the tidal volume. When subjects were instructed to cough three times with maximal expiratory efforts, they inspired much more deeply, as much as 50% of their vital capacity [102].

1.5.2 Postinspiratory or Compressive Phase

The inspiratory phase is followed by expiration against a closed glottis (compressive phase), which produces large increases in intrapulmonary pressure. Closure of the glottis is achieved by contraction of the adductor muscles of the arytenoid cartilage. This is reinforced by apposition and displacement downward of the ventricular or false folds, except in a very gentle cough. In addition, often the epiglottis covers the laryngeal opening. The glottis remains closed for a short and variable time (often indicated as about 0.2 s) during which the abdominal, pleural, alveolar, and subglottic pressures raise rapidly, and lung volume decreases owing to the compression of alveolar gas. During the compressive phase of cough, intrapleural pressure becomes greater than atmospheric pressure, and alveolar pressure, due to the elastic recoil of the lung, will be even greater than pleural pressure. The rate and extent of the change in lung volume during this time may be surprisingly great. For example, if thoracic gas volume is initially 5 L and if intrathoracic pressure rises to 200 cmH_2O in 0.2 s, the reduction in volume due to compression is about 1 L and the mean rate of change due to compression is 5 L/s. Expiratory muscle length and contraction velocity are related to the thoracic gas volume and to the expiratory flow, respectively. Furthermore, the force-length and force-velocity relationships of the expiratory muscles are like those of other skeletal muscles. Thus, taking into considerations that force and velocity are inversely related and that in a three-dimensional structure like the thorax, force corresponds to pressure and velocity to airflow, the contractile force and therefore the intrathoracic pressure achieved would be much greater during a closed-glottis maneuver (isometric or nearly isometric conditions) than throughout an open-glottis maneuver (e.g., forced expiration). The higher pressure and the consequent higher flow presumably enhance cough effectiveness.

1.5.3 Expiratory or Expulsive Phase

The expiratory phase is the most characteristic of the reflex. The effectiveness of coughing depends essentially upon the velocity at which air flows through the airways. This depends on the total cross-sectional area of airways (i.e., velocity = airflow rate/cross-sectional area) that becomes progressively smaller from the alveoli towards the larynx. Therefore, the linear velocity of flow must be, in general, greater in large than in small airways. This phase initiates with the active opening of the glottis (abduction of the vocal folds) in 20–40 ms. The pressure in

the central airways falls abruptly towards atmospheric levels, whereas pleuric and alveolar pressures remain high or continue to rise. At the beginning, while pressure at the airway opening (mouth) remains atmospheric, pressure in the airways (alveolar level) is still greater than pleural pressure and keeps the airways distended. During air movement, intraluminal pressure decreases from the alveoli to the airway opening (due to the encountered resistances), while pleural pressure remains approximately equal throughout the intrathoracic cavity that represents the external side of all intrathoracic airways. According to the "airway dynamic compression," there must be a point along the tracheobronchial tree where pleural and intraluminal pressure are equal (equal pressure point). Upstream to this point (towards the alveoli) airways are distended, while downstream to this point (towards the mouth) airways are compressed. Thus, during this phase of coughing both trachea and main bronchi undergo considerable narrowing with corresponding increases in linear velocity of expired air, which improve the scrubbing action of this reflex. Two related but distinct events occur simultaneously. Expiratory flow from the lung periphery rises rapidly to maximal values because of the pressure gradient between alveoli and airway opening, while central intrathoracic airways abruptly collapse (due to the rapid opening of the glottis), causing volume decrements. These modest (about 100 mL) but very rapid decrements generate transient "supramaximal" flow spikes superimposed on the flow coming from the lung parenchyma and limited by the airway dynamic compression. In conclusion, the instantaneous flow through the airway opening is the sum of two flows, i.e., the expiratory flow and the transient "supramaximal" flow spikes. These events are accompanied by intense accelerations of airway wall movements and contribute to the formation and suspension of droplets. After airway collapse, there may be a phase of maintained expiration during which airway walls may flutter. All these events are of importance for airway clearance. During this phase, characteristic sounds are present with a decrementing trend, related to the intensity of airflow.

1.5.4 Cessation Phase

Cessation of cough is characterized by expiratory muscle relaxation. This sometimes occurs with the onset of (or an increase in) inspiratory muscle activity. Alveolar and pleural pressures decline towards ambient pressure. As final event, the glottis may close or on the contrary there may be a terminal expressed sound related to flow or a quiet cessation of flow with a concomitant fall of alveolar pressure to ambient pressure. For further details see, e.g., Leith et al. [99] and Sant'Ambrogio [44]. Neurophysiological and mechanical events that characterized the different phases of cough are schematically illustrated in Fig. 1.3.

Details on the cough motor pattern and the analysis of cough responses mainly derived from experiments on anesthetized cats can be found in Chap. 4 in this book.

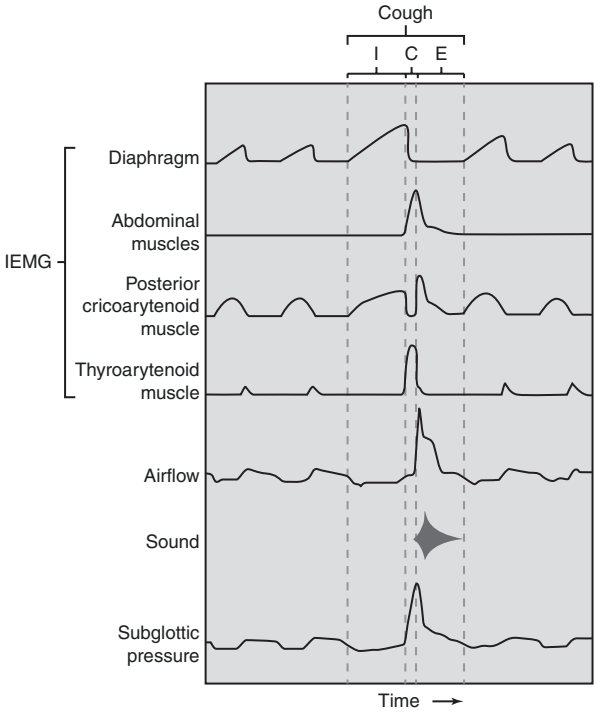

Fig. 1.3 Schematic representation of the motor pattern during a single cough along with flow at airway opening (airflow), subglottic pressure, and sound level. I, C, and E indicate inspiratory, compressive, and expiratory phases marked by vertical dashed lines. Note that laryngeal muscles are active also during eucapnic breathing and rhythmically abduct (posterior cricoarytenoid muscle) and adduct (thyroarytenoid muscle) the vocal folds. Muscle activity is reported as "integrated" electromyographic (IEMG) activity (integration of raw EMG activity is usually performed by a low-pass RC filter, time constant 100 ms)

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