

Physiological and Pathophysiological Implications of Upper Airway Reflexes in Humans

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Abstract: The upper airway is a vital part of the respiratory tract. Although the upper airway serves several functions, protection of the airway and preservation of airway patency are the most essential functions subserved by upper airway reflexes. Various types of nerve endings have been identified in and under the epithelium of the upper airway, and afferent nerve endings are the natural starting of all reflex activity. The upper airway reflexes consist of many different types of reflex responses such as sneezing, apnea, swallowing, laryngeal closure, coughing, expiration reflex, and negative pressure reflex. Although the activation of upper airway reflexes does not necessarily occur at one particular site of the respiratory tract, individual reflex response is usually considered to be highly specific for the particular

respiratory site which has been affected. The upper airway reflexes are modified by many factors such as sleep, anesthesia, and background chemical ventilatory drive. Both depression and exaggeration of upper airway reflexes cause clinical problems. Depression of upper airway reflexes enhances the chance of pulmonary aspiration and compromises the maintenance of the airway, whereas exaggeration of airway reflexes such as laryngospasm and prolonged paroxysm of cough can be harmful and dangerous. In this review, various aspects of upper airway reflexes are discussed focusing on the functions of upper airway reflexes in humans and some pathophysiological problems related to clinical medicine. [Japanese Journal of Physiology, 50, 3–14, 2000]

Key words: airway patency, airway protection, upper airway receptors, upper airway reflexes.

The upper airway, which is a vital part of the respiratory tract, is composed of the nose, pharynx, larynx, and extrathoracic portion of the trachea. The anatomy of the upper airway is very complex and its structural complexity reflects diverse functions such as phonation, olfaction, air conditioning, digestion, preservation of airway patency, and protection of the airways (Fig. 1). Among these functions, preservation of airway patency and protection of the airways are the most essential functions subserved by upper airway reflexes. Since these two aspects of upper airway functions are of most interest to respiratory physiologists and physicians in respiratory care, this review will describe basic characteristics, the function of upper airway reflexes, and some pathophysiological problems related to clinical medicine.

Basic Characteristics

Like many other respiratory and cardiovascular reflexes, the upper airway reflexes consist of a nervous receptor, afferent pathway, central synapses, motor pathway, and effector organs (Fig. 2). Although the general patterns of reflex processes are common to most sites in the upper respiratory tract, there are important differences for each component of the upper respiratory tract. Since the types of upper airway reflexes vary with the site of stimulation, upper airway afferents from each component of the upper respiratory tract are to be described first.

Upper airway afferents

Nose. The sensory innervation of the nasal mucosa is supplied by the trigeminal nerve through branches of the anterior ethmoidal and maxillary nerves. Although non-myelinated endings in and

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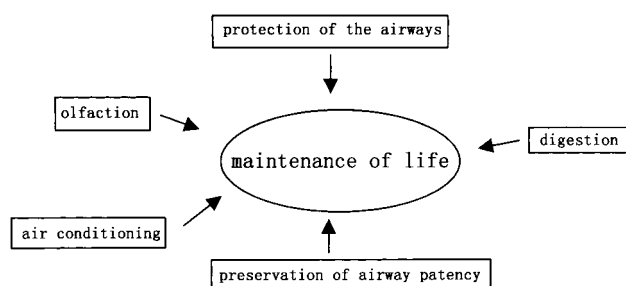


Fig. 1. Functions of the upper airway.

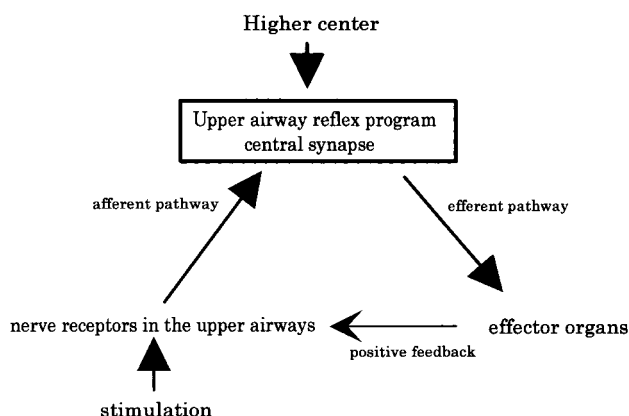


Fig. 2. Simplified model of upper airway reflex system.

under the epithelium are presumed to mediate mainly the nasal reflexes, no structurally differentiated sensory end-organs have been identified in the nose. Dawson [1] and Ulrich *et al.* [2] showed that airborne chemical irritants cause discharges in the trigeminal nerves. These responses are presumably responsible for nasal reflexes such as sneezing and apnea. More recently, several investigators showed that ethmoidal nerve endings are strongly stimulated by different kinds of chemical substances including aldehyde gases [3], ammonia [4, 5], and nicotine and capsaicin [5]. The presence of other types of nasal receptors such as cold receptor and pressure-responsive receptors has also been demonstrated in the ethmoidal nerve of cats [5]. These receptors can sense changes in temperature and pressure within the nasal cavity, respectively.

Pharynx. The sensory innervation of the nasopharynx is supplied by the maxillary nerve, whereas the glossopharyngeal nerve, through the pharyngeal branch, provides sensory innervation to the mucous membrane below the nasopharynx. Information about pharyngeal receptors is scanty and only one type of pharyngeal receptor seems to have been described morphologically [6]. This is a non-myelinated ending found under the epithelium of the nasopharynx, corresponding to myelinated fibers of the glossopharyngeal

nerve. Nail *et al.* [7] showed that the glossopharyngeal nerve of the cat contained fibers that gave rapidly adapting responses to mechanical deformation of the pharyngeal mucosa. Hwang *et al.* [8] also showed that the glossopharyngeal nerve of the cat contained fibers from slowly adapting receptors that responded to maintained inflation and deflation of the pharyngeal airway: several tonically active receptors that responded to both positive and negative pressures have been recorded from glossopharyngeal afferents in the cat. These receptors may influence upper airway patency. However, it is not clear to what extent these receptors relate to the maintenance of upper airway patency. Although receptors with non-myelinated fibers have not been described, it is likely that the pharyngeal wall contains receptors with non-myelinated afferent fibers corresponding to “nociceptive” endings since pharyngeal pain is a common symptom.

Larynx. The innervation of the larynx is provided mostly by the superior laryngeal nerve (SLN), and to a minor extent, the recurrent laryngeal nerves (RLN). The internal branch of the SLN is mainly composed of afferent fibers from the cranial portion of the larynx. The RLN provides the afferent innervation of the subglottal portion of the larynx, although this nerve contains primarily efferent fibers which control all intrinsic laryngeal muscles except the cricothyroid muscles. The larynx has been the subject of most of the studies on defensive and regulatory roles of the upper airway since it has a major role in the maintenance of upper airway patency and in airway defense. The majority of the cell bodies of laryngeal afferents are located in the nodose ganglion and the central projections of these afferents synapse with cells of the nucleus tractus solitarius (NTS).

Numerous afferent terminals have been described in the larynx: free endings, distributed among the epithelial cells, having either myelinated or non-myelinated fibers, as well as more organized structures like corpuscles and taste buds [6, 9]. With single-unit action potential recordings, Sant’Ambrogio *et al.* [10] showed in the dog that there were different groups of receptors that are classified on the basis of their responses to airflow and mechanical changes (Fig. 3). These are: (1) cold receptors which are affected by changes in temperature, (2) pressure receptors which are sensitive to changes in laryngeal transmural pressure, and (3) drive receptors which are affected by laryngeal motion. The cold receptors adapt rapidly to a maintained stimulus and may have smaller fiber diameters than the pressure and drive receptors. The pressure and drive receptors are respiratory-modulated mechanoreceptors and are active in eupneic respira-

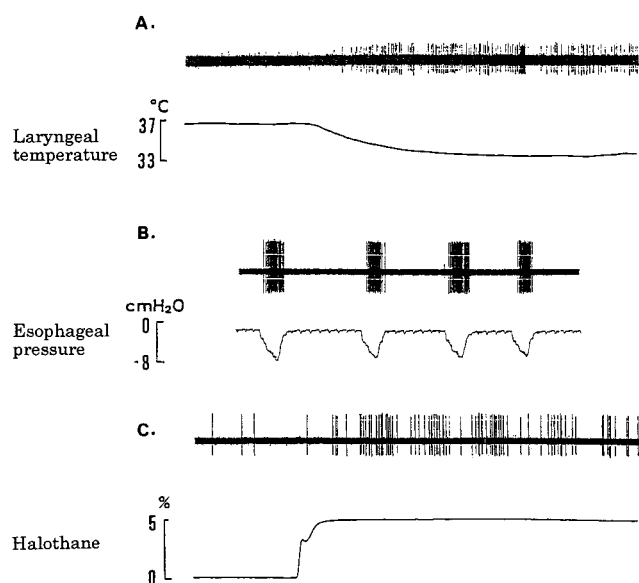


Fig. 3. Laryngeal receptors responding to various stimuli. **A:** Cold receptor responding to changes in laryngeal temperature. **B:** Respiratory modulated mechanoreceptor responding to upper airway negative pressure. **C:** Irritant receptor responding to administration of halothane into the larynx.

tion with their phasic discharge predominantly in inspiration, but the firing of drive receptors is prevented by the blocking of the motor nerves to the larynx. In addition, there are free nerve endings with myelinated afferent nerve fibers under the epithelium of the larynx which show rapidly adapting response to maintained mechanical deformation [11]. These nerve endings are especially sensitive to chemical and mechanical stimulation and are classified as laryngeal irritant receptors. Laryngeal irritant receptors are also stimulated by water solutions lacking chloride anion, but not by hypotonic solution [12].

Extrathoracic trachea. The afferent supply to the extrathoracic portion of the trachea is provided by SLN, RLN and the pararecurrent nerve. Although there is physiological evidence for the presence of slowly adapting stretch receptors (SARs) in the extrathoracic trachea [13], much less is known about rapidly adapting receptors and c-fiber receptors. As elsewhere in the trachea, SARs are localized uniquely in the membranous posterior wall within the trachealis muscle [14].

Central integration

It is surprising that we know little about the central mechanisms responsible for the elicitation of upper airway reflexes. This is because our understanding of the medullary pathways and the ascending and descending central connections of the upper airway re-

flexes is still fragmentary.

Primary afferents from the receptors in the upper respiratory tract travel in the trigeminal, glossopharyngeal, and vagus nerves, respectively, and converge in the solitary tract destined for synaptic contact with second-order neurons in the NTS. The NTS is not only an afferent portal but has interneurons that play a crucial role in the genesis of upper airway reflexes. There may be some centers in the brainstem which regulate and program the types of respiratory responses to airway stimulation although there has been no substantial evidence to suggest the existence of such centers to date. In contrast, there are some studies to suggest that upper airway reflexes may be produced by the medullary neural network alone without considering the existence of separate centers [15, 16]. However, the central neuronal network mechanisms that process upper airway receptor inputs and produce appropriate changes in respiratory muscle activity are far from clear. The higher center seems to play some role in the modification of upper airway reflexes. For example, induced and natural coughing in humans can be suppressed voluntarily [17], suggesting the presence of inhibitory pathways from the higher center to the brainstem where the existence of a cough center is postulated.

Motor pathways and effector organs

Upper airway reflexes usually involve several principal muscles of inspiration (diaphragm and intercostals) and the muscles of expiration (internal intercostals and abdominals). These muscles are innervated by spinal motoneurons. The upper airway muscles also appear to play an integral role in various airway reflexes. There are more than 20 pairs of muscles located around the upper airway. Most of these muscles probably have some respiratory role but only a few muscles have been studied. The upper airway muscles participate not only in respiratory tasks but also in non-respiratory tasks such as mastication, vocalization and deglutition. The motor innervation of the upper airway muscles is very complex [18]. For example, the alae nasi, which acts as nasal dilator, is innervated by the facial nerve and most of the tongue muscles are innervated by the hypoglossal nerve, while most of the laryngeal muscles are innervated by the vagus nerve. All the palatal muscles, except the tensor veli palatini, are innervated by the vagus nerve through the pharyngeal plexus. The mandibular branch of the trigeminal nerve supplies the tensor veli palatini. Motoneurons of the intrinsic and extrinsic laryngeal muscles are located in the brainstem within the nucleus ambiguus and the adjacent nucleus

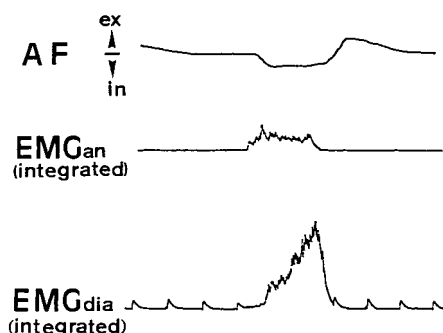


Fig. 4. Electromyographic activity of alae nasi (EMGan) and diaphragm (EMGdia) during quiet breathing are shown together with airflow (AF). Onset of EMGan occurs prior to onset of EMGdia.

retroambigualis, while those of pharyngeal and nasolabialis muscles are in the intermediate and rostral parts of the ventral respiratory group. Motoneurons of the tongue are found in the hypoglossal nucleus. In general, the inspiratory activity of upper airway muscles during normal breathing precedes the activity of the diaphragm, reaches a peak earlier, and starts to decline well before the end of inspiration (Fig. 4). The activation of upper airway muscles prior to inspiration is suited to the respiratory function by stiffening the upper airway walls against the collapsing forces of inspiratory efforts by the diaphragm and chest wall muscles. In humans, a sequence of inspiratory muscle activation is more clearly evident during sleep or progressive hyperoxic hypercapnia than during quiet breathing [19]. Thus, central control of the upper airway seems to play an important role in the sequence of inspiratory muscle activation in relation to intrathoracic mechanical events.

Stimulation of the upper airway mucosa often produces cardiovascular and bronchomotor reflexes as well as reflex mucous secretion, indicating that not only the skeletal muscles (chest wall and upper airway) but also the smooth muscles innervated by the autonomic nervous system are involved in reflexes from the upper airway.

Upper Airway Reflexes

The upper airway reflexes consist of many different types of reflex responses such as sneezing, coughing, apnea, swallowing, and so on (Fig. 5). Although the activation of upper airway reflexes does not necessarily occur at one particular site of the respiratory tract, individual reflex response is usually considered to be highly specific for the particular respiratory site which has been affected.

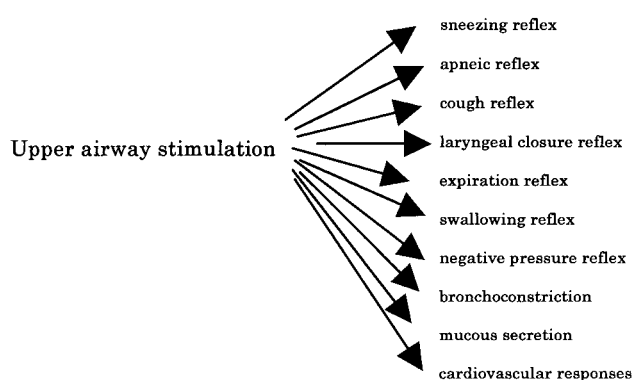


Fig. 5. Various reflex responses elicited by upper airway stimulation.

Sneezing

In humans, mechanical stimulation and a wide variety of chemical irritants applied to the nasal mucosa can cause sneezing. The inhalation of drugs such as histamine into the nose and nasal mucus secretion are also effective stimuli [20]. The respiratory changes in sneezing consist of an initial deep inspiration followed by forced expiration against a closed glottis. The glottis then opens permitting a forced expiratory blast of air. The sneeze has many features in common with the cough except that, during the expulsive phase, the pharynx seems to be constricted and the forced expiration is via both the nose and mouth. The sneeze provides an effective clearance mechanism for the nose and nasopharynx, whereas the cough contributes a similar clearance mechanism for the larynx and lower airway. Information as to the sneezing reflex is scanty because this reflex is easily suppressed by general anesthesia and is rather difficult to study in anesthetized animal preparations.

Apnea

Apnea can be derived from all parts of the upper airway, but the nose and larynx are the most sensitive areas for the elicitation of the apneic reflex (Fig. 6). During apnea elicited by stimulation of the upper airway, breathing usually stops in the expiratory phase with relaxation of the inspiratory muscles. However, in some instances, there may be tonic contraction of the expiratory muscles.

The apneic reflex from the larynx can be elicited at thresholds lower than those required to cause coughing [21]. The apneic reflex mechanism is possibly related to "the diving reflex" observed in aquatic mammals [22]. Although the distinction between the apneic reflex from the nose and the diving reflex is not clear, there is little reason to believe that the apneic reflex elicited by nasal irritation differs fundamentally

Upper Airway Reflexes

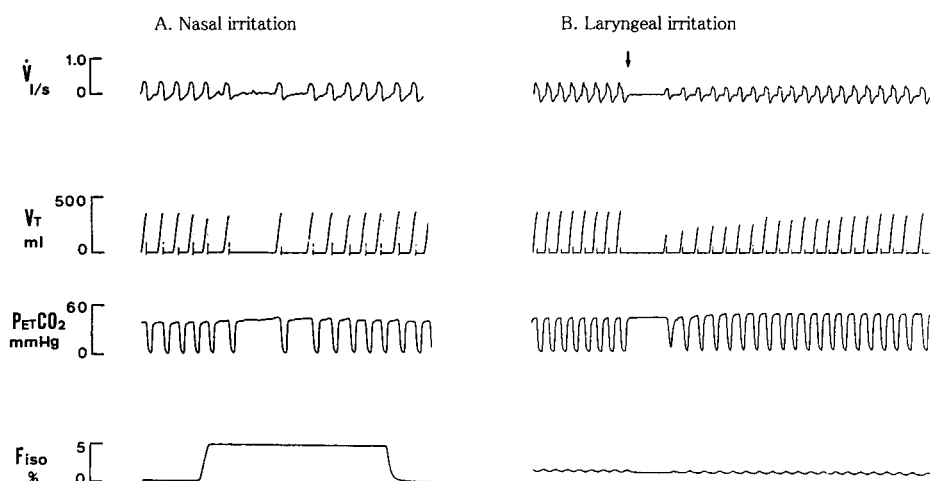


Fig. 6. Apneic reflex response to nasal irritation and laryngeal irritation. Nasal irritation was produced by insufflation of isoflurane into the nose and laryngeal irritation was produced by the injection of distilled water into the larynx in an anesthetized man. At arrow, 0.5 ml of distilled water was injected. \dot{V}_I , airflow; V_T , tidal volume; P_{ETCO_2} , end-tidal PCO_2 ; F_{iso} , isoflurane concentration.

from the diving reflex. It is also worthy to note that the apneic reflex is more resistant to deepening anesthesia than the sneezing and coughing reflexes [23]. The physiological role of the apneic reflex is not entirely clear, but it is conceivable that it may be functional in preventing the aspiration of foreign materials in the respiratory tract.

Swallowing

Although the main function of reflex swallowing is the propulsion of food from the oral cavity into the stomach, it can also serve as a protective reflex for the respiratory tract [24]. The act of swallowing requires not only the integrated action of the respiratory center but also the coordination of the autonomic system within the esophagus. In general, swallowing can be divided into three stages: (1) the initial oral preparatory stage, (2) the subsequent pharyngeal stage, and (3) the esophageal state. Of the three stages, the involuntary control of the pharyngeal state of swallowing is the most important stage from the standpoint of protection of the airway. Swallowing results in reflex closure of the glottis, which is the single most vital function of the larynx. Strong adduction of the true vocal cords is supplemented by closure of the false cords and approximation of the aryepiglottic folds, although adduction of the true cords alone suffices to prevent that which is swallowed from entering the trachea.

Swallowing must interact with respiration so that a swallow causes minimal or no disturbance of continual respiration [25]. In awake human adults, approximately 80% of swallows occur during the expiratory phase, and respiratory movement resumes after a swallow in the same expiratory phase as has been interrupted [26]. In contrast, in unconscious adult humans, swallows occur with equal incidence during inspiratory and expiratory phases, suggesting that the preponderant coupling of swallows with the expira-

tory phase may be associated with consciousness [27]. This preponderant coupling of swallows with the expiratory phase when in the conscious state may be a useful mechanism for clearing the airway of foreign materials before the subsequent inspiration, and thus may exert a physiologic role in preventing low-grade recurrent aspiration. In contrast with the particular relationship of swallowing to the respiratory cycle observed in conscious human adults, 80 to 94% of swallows occurred during or at the peak of inspiration in anesthetized animals [28] or unanesthetized chronically prepared animals [29]. Furthermore, it has been reported that, in unanesthetized human infants, swallows were initiated during all phases of the respiratory cycle with no preponderant occurrence during a certain phase [30]. All of these observations indicate not only that the relationship of swallowing to the respiratory cycle is markedly affected by consciousness and age but also that considerable differences exist among species regarding the relationship between swallowing and the respiratory cycle.

Laryngeal closure reflex

Although laryngeal closure is an important component of the coughing and swallowing reflexes, mechanical or chemical irritation of the laryngeal mucosa causes laryngeal adduction even if the stimuli are too weak to cause coughing or respiratory changes. Laryngeal closure reflex is associated with increased activity in the thyroarytenoid muscles and expiratory motor fibers in the recurrent laryngeal nerve. In exaggerated form, it produces life-threatening laryngospasm. It is also worthy to note that human babies have no laryngeal adductor response at birth [31].

Coughing

The coughing reflex is one of the most typical defensive reflexes elicited from the upper airway. The

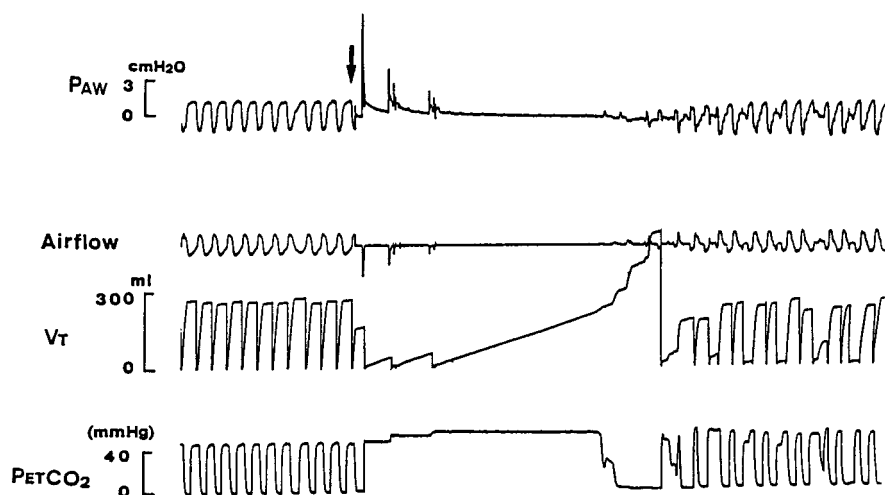


Fig. 7. Expiration reflex produced by the injection of distilled water into the larynx (at arrow) in an anesthetized man. PAW, airway pressure; VT, tidal volume; $PETCO_2$, end-tidal PCO_2 .

larynx and trachea are the areas most sensitive to mechanical and chemical stimuli. Coughing has an obvious function in clearing materials which might otherwise be aspirated into the airway or are already present in the airways. Several upper airway and chest wall muscles are activated in a well-coordinated and fixed pattern during coughing, suggesting the presence of specialized centers.

Although the nature of laryngeal receptors mediating cough remains unclear, the rapidly adapting receptors activated by known tussigenic stimuli are generally considered as the probable source [32]. A cough starts with an inspiratory phase during which a volume of air generally larger than the resting tidal volume is rapidly inspired because of contraction of the diaphragm and other inspiratory muscles. This is followed by a brief compressive phase in which the glottis is closed and the expiratory muscles contract forcefully while the diaphragm remains active. An expulsive phase follows immediately when the glottis is suddenly reopened and the expiratory muscles are strongly active in concert with the diaphragm, allowing expulsion of a blast of air. Although laryngeal closure is an integral part of coughing, effective clearance is not entirely dependent on glottis closure. For example, patients with tracheotomies [33] or patients with endotracheal tubes in place [34] are still capable of effective coughing. Coughing elicited from the larynx appears to be similar in its fundamental characteristics to that evoked from the trachea. However, it has been shown in animal studies that the pattern of coughing from the larynx is slightly different from that induced from the trachea [35].

Expiration reflex

The expiration reflex consists of a brief expiratory effort without preceding inspiration, which may be

followed by coughing or apnea (Fig. 7). It seems to be a reflex distinct from the laryngeal coughing reflex. Although it has been considered that the site of origin of this reflex is specially the vocal folds [36], recent studies in humans showed that the expiration reflex can be elicited not only from the larynx but also from the lower part of the respiratory tract [37, 38]. Like coughing, its function is presumably to prevent the entry of foreign materials into the lower respiratory tract. However, it is more resistant to general anesthesia and to antitussive drugs than is the coughing reflex.

Upper airway negative-pressure reflex

Until recently, only the defensive role of the upper airway reflexes has been studied in detail, although it has been known for many years that pressure and airflow in the upper respiratory tract can change breathing [39]. The results of recent studies which analyzed the mechanisms of sleep apnea and sudden infant death syndrome indicate that upper airway pressure reflexes have important actions on the musculature of the pharynx, and therefore on its patency, breathing, and arousal. For example, negative pressure in the upper airway produces an excitatory effect on upper airway dilating muscles while exerting an inhibitory effect on breathing patterns by prolonging inspiratory and expiratory durations and decreasing the rate of rise of diaphragmatic activity [40–43].

Both the excitatory influences on the upper airway controlling muscles and the inhibitory influences on chest wall muscles can be interpreted as contributing to airway stability in that they increase the dilating forces and reduce the collapsing forces, respectively. The negative upper airway reflex can be abolished by the mucosal application of topical anesthetics or by cutting the superior laryngeal nerve [41, 44] and the

elimination of sensory feedback from the upper airway impairs the ability of upper airway muscles to respond to adverse conditions such as airway obstruction [45].

Switching of breathing route

The acute obstruction of nasal passages leads to opening the mouth and oral breathing. The ability to change from the nasal route of airflow to the oral route during nasal obstruction is crucial for the maintenance of adequate ventilation. Two major muscles responsible for the switching of breathing route are the palatoglossus muscle, which directs the soft palate caudally and ventrally, and the levator veli palatini, which pulls the soft palate cephalad in the dorsal direction. Activation of these muscles results in nasal breathing and oral breathing, respectively. Consciousness is an important factor in the control of the route of breathing, but the switching of breathing route can also be triggered by some reflex mechanisms. In fact, there is evidence to suggest that the sensory information from receptors in the nasal passage of humans has an important role in controlling shifts in the breathing route [46].

Other reflexes

Mechanical and chemical irritation of the upper airway mucosa causes a variety of cardiovascular and bronchomotor reflexes [47]. The cardiovascular reflexes are most often represented by hypertension due to sympathetic stimulation, but hypertensive response varies with the site of stimulation and decreases from the epipharynx to the nose and larynx.

Manipulation in and around the larynx has occasionally been found to cause cardiac arrhythmia and even cardiac arrest in patients [48]. Irritation of the nasal mucosa may cause either bronchoconstriction or bronchodilatation, whereas the bronchomotor response from laryngeal irritation is a constriction.

Coughing and reflex bronchoconstriction often occur simultaneously and have been considered closely related. However, accumulating data indicate that coughing and bronchoconstriction are separate airway reflexes having separate afferent neural pathways [49]. They can be induced individually and can be differentially inhibited by drugs. The role of reflex bronchoconstriction is not clear. However, bronchoconstriction may render the airways less susceptible to collapse during forced expiratory efforts, decrease the dead space, and increase the impaction and absorption of extraneous particulates and aerosols in the larger airways.

Clinical Considerations

Depression of upper airway defensive reflexes

Obviously, the depression of upper airway defensive reflexes is a clinical problem. In the absence of adequate activity of the defensive reflexes, the chance of pulmonary aspiration is greatly enhanced. Impairment of the upper airway reflexes may result from a defect or disorder in any part of the reflex arc of the upper airway reflexes. Afferent nerve endings are the natural starting of all reflex activity. Thus, it is natural that impairment of triggering upper airway reflexes occurs after the application of local anesthetics into the upper airway. Nerve blocks of the afferent pathway with local anesthetics are useful in the elimination of various upper airway reflexes. For example, the superior laryngeal nerve block may be the choice of technique to minimize the adverse effects of upper airway reflexes during endotracheal intubation in conscious subjects [50]. The superior laryngeal nerve may also be blocked by the application of gauze pads soaked with lidocaine deep in the pyriform fossa [51].

The impairment of upper airway reflexes may occur in the central nervous system. It is a commonplace observation that general anesthesia depresses the different types of upper airway reflexes in a dose-dependent manner. In fact, it has been suggested that the differences in sensitivity of different types of reflex responses to anesthesia may be a valuable sign in the clinical assessment of depth of anesthesia [23]. Among different types of reflex responses, the coughing reflex is the most sensitive and the apneic reflex is the most resistant to deepening anesthesia. However, these observations were obtained from anesthetized humans and information concerning airway reflex responses obtained in anesthetized conditions may not be applicable to awake conditions. It has been shown in a recent study [52] that laryngeal stimulation in awake humans elicits vigorous responses of expiratory efforts including the expiration reflex and coughing while other types of responses are scarcely observed. In addition, the duration of these responses is remarkably short compared with more variant, prolonged, and exaggerated responses observed during a light depth of anesthesia. Thus, it is possible that anesthesia may potentiate, or consciousness may attenuate responses to airway irritation. The mechanisms of enhancement of reflex responses under an anesthetized condition are not clear. However, considering the high sensitivity of the higher center to anesthesia, disinhibition of the inhibitory influence on the airway reflex program in the brainstem from the higher center may

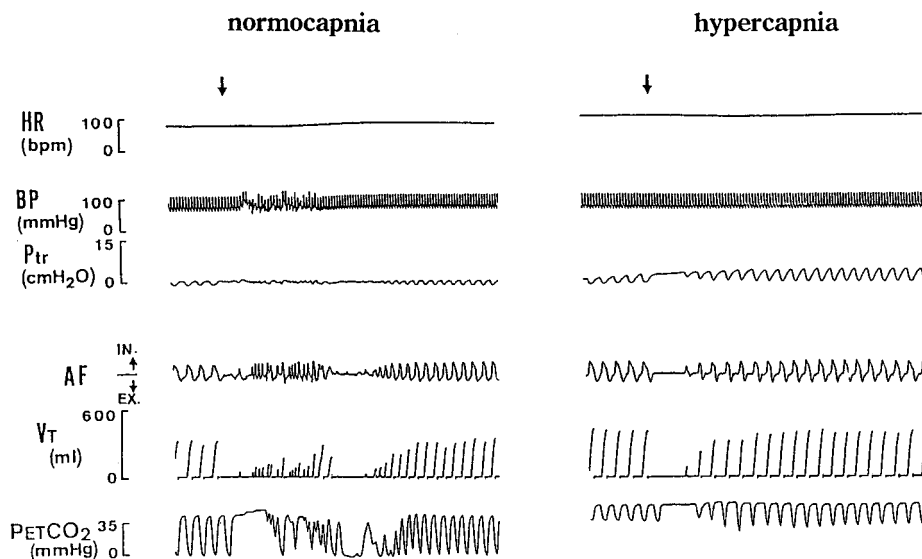


Fig. 8. Inhibitory effects of CO₂ on airway reflex responses. Note that vigorous and prolonged responses were produced by the injection of distilled water into the larynx (at arrow) during normocapnia, whereas the same stimulation caused only a short apneic response during hypercapnia.

be a possible mechanism.

Although changes in $PaCO_2$ and PaO_2 are known to influence the activity of the respiratory center, the effects of these factors on the upper airway reflexes have not been fully studied. Nevertheless, in anesthetized animals, there is some evidence to suggest that reflex responses to airway irritation interact with background chemical ventilatory drive. Kulik *et al.* [53] studied the coughing reflex during experimental hypercapnia in anesthetized cats and reported that tracheobronchial and laryngopharyngeal coughing are reduced during the inhalation of 10% CO₂ but not during the inhalation of 5% CO₂. Tartar *et al.* [54] also showed in anesthetized cats that hypoxia decreases the intensity of mechanically induced cough. Similarly, experimentally induced laryngospasm has been reported to attenuate during hypercapnia and hypoxia [55]. In anesthetized humans, an increase in CO₂ ventilatory drive decreases the degree and duration of respiratory responses to airway irritation (Fig. 8), whereas a decrease in CO₂ ventilatory drive has the opposite effect [56]. In addition, it has been reported in a recent study on conscious subjects that the CO₂ ventilatory response is not influenced by continuous reflex swallowing but hypercapnia decreases the frequency of swallows and increases the incidence of laryngeal irritation during continuous infusion of water into the pharyngeal cavity [57]. These observations suggest that the function of protecting the airway subserved by upper airway reflexes may be compromised during hypercapnia or hypoxia.

Depression of the upper airway reflexes can occur even during sedation or sleep, and there is some evidence to show that pulmonary aspiration occurs during sedation and sleep [58–60]. During sleep, the sleep state appears to play an important role in modifi-

cation of the upper airway responses. Sullivan *et al.* [61] studied ventilatory responses to laryngeal stimulation during wakefulness and sleep in dogs and showed that, during REM sleep, laryngeal stimulation causes prolonged apnea while arousal and cough responses to laryngeal stimulation are depressed. Thus, REM sleep, like anesthesia, may potentiate the airway reflexes. They also showed that during wakefulness, laryngeal stimulation invariably elicited the coughing reflex.

The intravenous administration of local anesthetics such as lidocaine has been shown to suppress both mechanically and chemically induced airway reflexes in a dose-dependent manner [62–64]. The mechanisms by which intravenous lidocaine suppresses airway reflexes are unknown. However, the rapid equilibration of local anesthetics between blood and brain suggest that a depressant effect on the central nervous system may contribute to this action [64].

Dysfunctions of the efferent neural pathway and effector organs may also seriously impair the upper airway reflexes. Muscle disorders, disorders of the neuromuscular junction, and disorders that affect peripheral nerves can all lead to the impairment of reflex responses and may result in pulmonary aspiration [65].

Exaggeration of upper airway defensive reflexes

Exaggeration of upper airway defensive reflexes is another clinical problem. An example of exaggerated reflex responses is laryngospasm. Laryngospasm consists of prolonged intense laryngeal closure in response to direct laryngeal stimulation from inhaled irritant agents, secretions or foreign bodies. Similarly, coughing can be harmful when it is nonproductive, painful, traumatic or dangerous, in other words when

the physiological defense activity of coughing turns into a pathophysiological one. During a prolonged paroxysm of coughing, the persistent high intrathoracic pressure may impede venous return so much that cardiac output falls and cerebral ischemia occurs.

Airway obstruction

The recognition of clinical problems such as obstructive sleep apnea has generated an immense interest in the patency of the upper airway in recent years. Upper airway collapse is often seen in anesthetized patients and in patients with obstructive sleep apnea syndrome. Upper airway obstruction in unconscious subjects has primarily been attributed to a result of the tongue falling back [66], but recent studies indicate that the most common site at which obstruction occurs is the pharynx [67, 68].

Upper airway obstruction occurs easily in older, male, and overweight patients who frequently have reduced pharyngeal size or structural abnormalities of the pharynx, suggesting that anatomical factors play an important role in initiating upper airway obstruction [69].

Upper airway patency during wakefulness is, in large part, attributable to continual control by the higher nervous system which regulates inspiratory motor output to the muscles of the pharynx and related structures. In addition to the effects of upper airway dilating muscles, the thoracic muscles may also influence the upper airway. During inspiration with the diaphragm, a negative pressure is generated in the pharynx (Fig. 9). The negative pressure in the pharynx during inspiration is considered to be an important factor in promoting occlusion of the upper airway, but a negative-pressure reflex would be initiated during upper airway obstruction and would tend to compensate for airway obstruction while increasing the pharyngeal size or stiffness.

In healthy subjects, nasal occlusion with large negative pressure does not collapse the upper airway, presumably because the collapsing effect of negative pressure is opposed by the action of airway dilating muscles. Moreover, in normal human subjects, topical anesthesia of the upper airway increases the incidence of episodes of airway obstruction during sleep, particularly if the pharynx is anesthetized [70]. Thus, at least in some circumstances, upper airway reflex responses may contribute to upper airway patency.

Patients with OSA have small pharyngeal size and thus may have greater changes in upper airway pressure with ventilation, and hence, reflex activation of the airway muscles. However, any pressure reflex is not adequate to keep the upper airways patent in ob-

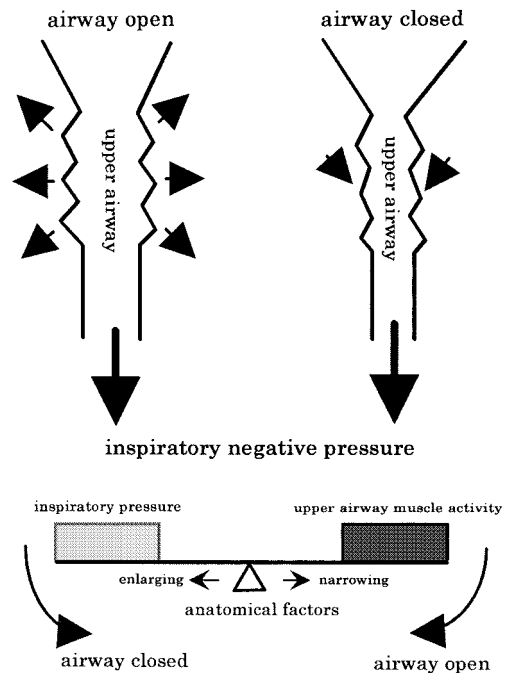


Fig. 9. The balance of forces leading to patency versus closure of the upper airway. Upper airway dilator muscles counteract inspiratory negative pressure generated by chest wall muscles while maintaining the upper airway patency. A loss of upper airway muscle activity, resulting in an imbalance between dilating and collapsing forces, predisposes airway closure. Underlying anatomical factors also influence the size or compliance of the upper airway.

structive sleep apnea.

Although anesthesia or sedation often reduces respiratory drive and airway reflex activity, the reduction in activity of upper airway muscles seems to be greater than in the diaphragm [71]. Thus, it is possible that the imbalance between dilating and collapsing forces may be a precipitating factor of upper airway obstruction.

The majority of awake patients are nasal breathers during quiet breathing. Thus, it is possible that, even in the presence of a patent upper airway, airway obstruction may occur if the ability to change from the nasal route of airflow to the oral route in response to nasal obstruction is impaired. The change of breathing route would depend, not only on reflexes, but also on voluntary control of the palatal muscles. It has been shown that the ability to maintain adequate ventilation by switching from the nasal to oral route in response to nasal occlusion is greatly impaired during sedation in human subjects [72]. Additionally, it has been reported that, in sedated human adults, nasal packing for the control of epistaxis causes hypoxemia [73].

Conclusion

It is obvious that maintenance and protection of the

airways are the most important functions subserved by the upper airway reflexes. Although there has been a tremendous amount of work on upper airway reflexes in the past, most of the information was obtained using anesthetized animals and relatively few studies have evaluated the role of upper airway reflexes in humans. In experimental studies, different types of receptors have been identified in the upper airway, and their properties have been clarified based on single-fiber recordings. There is no doubt that these receptors are responsible for elicitation of the upper airway reflexes. The significance of upper airway reflexes in respiratory and nervous disease must be considerable. However, information as to the modification of upper airway reflexes in disease processes has been neglected except for acute pathological conditions studied in experimental animals. Although it remains to be determined whether the results obtained from animal studies can be extended to human subjects, the application of experimental studies to pathophysiology in human subjects and patients would be rewarding and important. A better understanding of the upper airway reflexes is essential for the better management of patients who need respiratory care.

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