HIGHLIGHTED TOPIC | Reflexes from the Lungs and Airways

Modulation of upper airway muscle activities by bronchopulmonary afferents

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Bailey, E. Fiona, and Ralph F. Fregosi. Modulation of upper airway muscle activities by bronchopulmonary afferents. J Appl Physiol 101: 609–617, 2006; doi:10.1152/japplphysiol.00204.2006.—Here we review the influence of bronchopulmonary receptors (slowly and rapidly adapting pulmonary stretch receptors, and pulmonary/bronchial C-fiber receptors) on respiratory-related motor output to upper airway muscles acting on the larynx, tongue, and hyoid arch. Review of the literature shows that all muscles in all three regions are profoundly inhibited by lung inflation, which excites slowly adapting pulmonary stretch receptors. This widespread coactivation includes the recruitment of muscles that have opposing mechanical actions, suggesting that the stiffness of upper airway muscles is highly regulated. A profound lack of information on the modulation of upper airway muscles by rapidly adapting receptors and bronchopulmonary C-fiber receptors prohibits formulation of a conclusive opinion as to their actions and underscores an urgent need for new studies in this area. The preponderance of the data support the view that discharge arising in slowly adapting pulmonary stretch receptors plays an important role in the initiation of the widespread and highly coordinated recruitment of laryngeal, tongue, and hyoid muscles during airway obstruction.

tongue; larynx; hyoid; vagus

INTEREST IN THE RESPIRATORY-related discharge of upper airway muscles has grown exponentially since the classic review by Bartlett (10), published in the Handbook of Physiology. This growth reflects the realization that abnormal control of these muscles may contribute to obstructive sleep apnea. Accordingly, research interest has focused on the control of upper airway muscles by chemoreceptors and mechanoreceptors, their sleep-state dependence, and their potential to regulate the geometry and biophysical properties of the glottis, pharynx, and nose. In regard to mechanoreceptors, those of the nose, pharynx, and larynx have attracted much more interest than the pulmonary receptors responsive to lung inflation or bronchial and parenchymal irritation. The paucity of data on the modulation of upper airway motor output by bronchopulmonary airway afferents is surprising, given their key role controlling the rate and depth of breathing movements and in airway defensive reflexes.

In this review, we seek to shift the reader’s attention back to the reflex control of upper airway muscles by slowly adapting pulmonary stretch receptors (PSR), rapidly adapting “irritant” receptors, and bronchopulmonary C-fiber receptors. Unfortunately, page limitations prevent us from including some outstanding work that examines the regulation of upper airway muscles in development, sleep, and in coordinated functions such as cough and swallowing, and permit us to cover only the respiratory-related control of muscles of the larynx, tongue, and hyoid arch in this review (Fig. 1). For a more detailed coverage, we direct the reader to several excellent reviews (10, 39, 60, 71, 77). Our goal is to paint as complete a picture as possible, while identifying gaps that are physiologically important and ripe for experimentation. The review does not address the central processing of this information, only the reflex response of upper airway motoneurons to pulmonary afferent input. Information on the former subject is provided in two excellent recent publications (26, 67a). We begin with a brief overview of the characteristics of three pulmonary receptors and the techniques commonly used to stimulate or inhibit their activity.

PULMONARY RECEPTORS

Slowly Adapting PSRs

PSRs are the afferents responsible for the Hering-Breuer inflation reflex: their mounting discharge in inspiration acts as an inspiratory off-switch. This off-switch function is dramatically demonstrated when the lungs of an anesthetized animal are prevented from emptying by occluding the tracheal airway at end inspiration. This maneuver leads to marked prolongation of expiratory time, a steady discharge of PSRs with only slow adaptation, and elimination of inspiratory efforts; this is the classic inflation reflex, first described by Hering and Breuer in 1868.

PSRs lie in close association with airway smooth muscle and respond to stretch of the airway wall (21, 83). They display static and dynamic properties, i.e., some fire throughout the respiratory cycle (tonic activity) and others burst in response to lung inflation (phasic activity) (10, 78), with progressive increases in discharge rate as a function of lung volume.

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PSR modulation of upper airway muscle activities has been assessed via two very different approaches. The classic approach is to stimulate the PSRs via sustained pulmonary inflation delivered at end inspiration, as described above; this stimulates the PSRs tonically and profoundly inhibits upper airway muscle activities.

The magnitude of the inhibition by phasic PSR inputs is typically assessed by preventing lung inflation, either by occluding the extrathoracic airway for a single breath, or by stopping mechanical ventilation, thereby eliminating the change in lung volume and hence stimulation of the PSRs. The difference between upper airway motor activities during the occluded breath and the preceding breath provides an index of phasic PSR modulation of upper airway motor output (7, 14, 67, 113). Importantly, neither maneuver is effective following bilateral cervical vagotomy, confirming that these reflex changes are mediated by pulmonary afferents with axons in the vagus nerves.

In addition to PSRs that discharge with lung inflation, many PSRs discharge tonically at or below functional residual capacity (10, 87). Tonic activities exert a subtle yet significant influence on respiratory-modulated activities of upper airway muscle motoneurons that persist even during tracheal occlusion (84, 113). The magnitude and influence of the tonic PSR discharge may be assessed via application of positive end-expiratory pressure (PEEP), which causes a sustained increase in lung volume. Because this manipulation maintains the lungs at a constant transmural pressure (and volume), rapidly adapting receptors (RARs) and bronchopulmonary C-fibers are not stimulated, and the inflation-mediated responses are eliminated (97). Thus one can differentiate the effects mediated by slowly adapting PSRs that respond either to phasic inflation of the lungs or to maintained lung inflation at levels above the normal functional residual capacity.

RARs

RARs are found throughout the tracheobronchial tree (concentrated in the larger airways), primarily in and under the epithelium in close approximation to bronchial venules (65, 88) and have vagal myelinated fibers of Aδ diameter (110). They are exquisitely sensitive to mechanical stimuli and respond with a rapidly adapting discharge to large and rapid lung inflations and deflations (109). RARs are also stimulated or sensitized by intraluminal chemical irritants, smoke, dust, and environmental toxins, and because of these properties they are also known as irritant receptors. Significantly, the inhalation of high concentrations of sulfur dioxide (SO2) leaves RAR activities intact but (reversibly) blocks phasic and tonic PSR activities in the rabbit (22, 23) but not in the cat (11) or dog (89). Carbon dioxide also inhibits PSR discharge frequency (13), although the action of SO2 is considerably more powerful (22). The combined application of SO2 (to block the slowly adapting PSRs) with brief pressure pulses (100 ms) has been used to assess the contribution of RARs to the breathing pattern in rabbits (22).

Bronchopulmonary C-Fiber Receptors

Pulmonary C-fiber receptors are located between the alveolar epithelium and the pulmonary capillary (81). Bronchial C-fiber receptors lie in the walls of the conducting airways, and their endings extend into the space between epithelial cells or form a plexus immediately beneath the basement membrane (1, 8, 66). Both C-fiber receptor types are innervated by nonmyelinated vagal afferent fibers and discharge irregularly and at low frequency in eupnea, although the discharge of pulmonary C-fiber receptors is greater than that of the bronchial C-fiber receptors under these conditions (21).
Although stimulation of either RARs or C-fiber receptors can induce rapid, shallow breathing and apnea, many of the reflex responses elicited by selective stimulation of RARs and C-fiber receptors are distinctly different. For example, C-fiber receptor activation (either pulmonary or bronchial) evokes inhibitory effects (apnea or bradypnea; hypotension and bradycardia), whereas RAR stimulation, in general, elicits excitatory effects (augmented breath, tachypnea) (21). Accordingly, anodal depolarization (42) and cooling techniques (31) have been used to selectively block myelinated vagal fibers, leaving the nonmyelinated C-fiber receptors partially (i.e., 40%) blocked (64). The ventilatory effects of pulmonary C-fiber receptor stimulation have been studied by injecting phenyl diguanide (22), capsaicin (3, 20, 49, 74, 94), or histamine into the right atrium or pulmonary artery, although it is also possible to stimulate RARs inadvertently with this technique, via secondary effects on airway epithelium (63, 94, 109).

**BRONCHOPULMONARYafferent modulation of upper airway muscles**

Muscles of the Larynx

In this section, we examine how reflexes initiated by receptors in the pulmonary airways modulate laryngeal motor activities and how these effects translate into alterations in laryngeal airway resistance. We have focused on the intrinsic laryngeal musculature and nerve supply, including the posterior cricoarytenoid, lateral cricoarytenoid, and thyroarytenoid muscles innervated by the recurrent laryngeal nerve, and the cricothyroid muscle innervated by the superior laryngeal nerve.

**Modulation of laryngeal motor activities by PSRs.** Much of what we know about the PSR modulation of upper airway motor activities came from early recordings of the whole recurrent laryngeal nerve or the posterior cricoarytenoid muscle in decerebrate or chloralose anesthetized animal preparations. These studies report profound inhibition of recurrent laryngeal nerve (19, 69, 95, 96, 105) and posterior cricoarytenoid muscle activities (34, 41) when lung inflation is maintained at the end-inspiratory level. Significantly, PSR-mediated inhibition of laryngeal motor output consistently exceeds the inhibition of the diaphragm or of phrenic motoneurons (19, 105), with the strength of the reflex varying as a function of the volume and timing of lung inflation. Several studies report a range of reflex effects associated with lung inflation, including abolition of phasic posterior cricoarytenoid activities (34, 41), while inflation delivered at end expiration evoked tonic expiratory posterior cricoarytenoid activation and sustained decreases in end-expiratory laryngeal airway resistance (9, 12, 79). The discrepant nature of the findings is somewhat confusing but can be attributed to methodological differences, including species, anesthesia, the volume and timing of the inflation, and whether recordings were of laryngeal resistance, whole recurrent laryngeal nerve (or individual nerve fiber) activities, or laryngeal muscle electromyographic (EMG) activities.

The elimination of phasic PSR activity via end-expiratory airway occlusions held for one or two breath cycles offers additional insights into the PSR modulation of upper airway activities. For example, in eupneic breathing, recurrent laryngeal nerve or posterior cricoarytenoid muscle activities peak very early in inspiration with a steeply augmenting rate of rise, followed by a plateau or decrementing phase (19, 36, 69, 95, 96), whereas the phrenic nerve or diaphragm EMG burst is steadily augmenting, not reaching a peak until late inspiration (19, 105). However, when lung inflation is withheld, the laryngeal motoneuron burst changes to an augmenting pattern, whereas the phrenic motoneuron burst is prolonged but otherwise unaltered (19, 105). Thus the effects of PSR input on laryngeal motoneurons are significantly more pronounced than those on phrenic motoneurons. Moreover, PSR input changes both the spatial and temporal characteristics of laryngeal motoneuron activities, unlike the effect on phrenic motoneuron activities that are manifest largely as a timing change. The fact that laryngeal motoneuron activities attain peak amplitude so early in inspiration in eupnea, and that peak amplitude is delayed when lung inflation is prevented, suggest that PSRs facilitate laryngeal motoneuron discharge, possibly by synchronizing the activation of a large proportion of the laryngeal motoneuron pool. In addition to delaying the time to peak activity, PSR input also attenuates laryngeal motor output. Thus withholding lung inflation results in significantly greater increases in laryngeal compared with phrenic motoneuronal activities (105). Moreover, studies in spontaneously breathing dogs (105) and cats (69) show that the inhibition of peak laryngeal motor output occurs at lower average lung volumes than the inhibition of peak phrenic motoneuron output (i.e., 41 vs. 94% of tidal volume).

In addition to the clear effects of PSR activity on inspiratory laryngeal motoneuron activity, there is good evidence that phasic PSR feedback also affects laryngeal motor activities in the subsequent expiration. Huang and colleagues (54) (see Fig. 2) have shown that the thyroarytenoid muscle (a primary laryngeal adductor) motoneurons discharge in early expiration. When phasic PSR activity is abolished by withholding lung inflation, there is a dramatic increase in the peak amplitude and duration of the subsequent expiratory phase (see text). [Adapted from Huang et al. (54), reproduced with permission of the authors and publisher.]

![Fig. 2. Influence of withholding pulmonary inflation on phrenic and laryngeal motor nerve activities. Moving-time-averaged recordings of the whole recurrent laryngeal nerve, as well as the branch to the TA muscle, are shown. The recurrent laryngeal nerve supplies the PCA muscle, which is active in inspiration, and the TA, which is active in early expiration (Fig. 1). Records were obtained under normocapnic conditions in a decerebrate, paralyzed cat that was mechanically ventilated in phase with phrenic nerve activity, using a servorespirator. Note that withholding lung inflation increased peak phrenic and whole recurrent laryngeal nerve activities and evoked a massive recruitment of TA muscle motoneurons. In addition to demonstrating the profound inhibition of upper airway motoneurons by lung inflation, the TA recording also shows that inhibitory input in the inspiratory phase can influence events in the subsequent expiratory phase (see text).]
duration of expiratory thyroarytenoid muscle motoneuron activity (95). Thus the expiratory activity of the thyroarytenoid muscle appears to be “conditioned” by the activities of PSRs in the preceding inspiration, similar to the observations in abdominal motoneurons (32).

Like thyroarytenoid, the cricoarytenoid muscle is considered a laryngeal adductor as it tilts the thyroid cartilage ventrally, lengthening and slightly adducting the vocal cords (80). Yet both inspiratory and expiratory cricoarytenoid activities have been observed in humans (107, 108) and in anesthetized animals (44, 75) and, when coactivated with the posterior cricoarytenoid, appear to contribute to glottic opening (114). The observation that only inspiratory-related cricoarytenoid activities increase during tracheal occlusion in anesthetized dogs (2, 75) and cats (111) indicates that there are different thresholds for phasic PSR-mediated inhibition of inspiratory and expiratory cricothyroid motoneurons. Although inhibition of inspiratory cricothyroid activities by PSRs would contribute to glottic opening during inspiration, the fact that there is any cricothyroid activity during inspiration is more difficult to reconcile. One possibility is that coactivation of the cricothyroid and posterior cricoarytenoid muscles reduces inspiratory laryngeal resistance (17, 67).

Not all alterations in laryngeal upper airway motor output are attributable to changes in phasic PSR discharge. Tonic discharge of PSRs has also been shown to modulate laryngeal upper airway motor output. For example, St. John and Zhou (97) demonstrated substantial reductions in peak phasic inspiratory and expiratory laryngeal motoneuronal activities with application of (1–6 cmH2O) PEEP in decerebrate cats. This is of course opposite to the well-known activation of spinal expiratory motor output by PEEP (16). However, others report that PEEP has no effect on posterior cricoarytenoid activities (48, 61) and increases cricothyroid activities in spontaneously breathing, anesthetized dogs (61). Although species differences and/or anesthesia likely contribute to these different findings, the significance of tonic PSR influences in modulating laryngeal upper airway activities remains ripe for investigation.

**Modulation of laryngeal motoneuron activities by RARs.** The modulation of laryngeal upper airway muscle activities by RARs is poorly understood, despite the fact that these receptors are thought to be responsible for cough, mucous secretion, and bronchoconstriction. Stransky et al. (99) using phenyl diguanide in cats shows tonic inspiratory and expiratory laryngeal motoneuron activities during the period of tachypnea that follows the brief apnea evoked by the phenyl diguanide injection. Similarly, Glogowska and colleagues (40) induced pulmonary edema in cats via intravenous injection of fatty acids, which led to apnea with concomitant tonic activation of expiratory laryngeal motoneurons. The elegant work by Remmers and colleagues (45, 51) offers additional insights into C-fiber receptor modulation of laryngeal motor output. Using a technique first described by Hammouda and Wilson (43), they paired selective stimulation of the central end of the cervical vagus nerves with vagal cooling to block conduction of A-fiber traffic while leaving C-fiber conduction partially intact. These interventions evoked tonic discharge in thyroarytenoid, posterior cricoarytenoid, and diaphragm muscles, with recruitment of phasic expiratory thyroarytenoid bursts (51). Most recently, Lu et al. (74) injected capsaicin into the right atrium of anesthetized rats and observed glottic narrowing, an increase in expiratory thyroarytenoid activity, and a reduction in laryngeal abductor activity. In this instance, C-fiber receptor stimulation coactivates laryngeal abductor and adductor muscles, which closes the airway and protects the respiratory system against inhalation of gaseous irritants.

**Muscles of the Tongue**

The relatively recent recognition that tongue position plays an important role in the pathophysiology of obstructive sleep apnea has stimulated intense investigation of the inspiration-related function and control of tongue muscles. The great majority of the work has focused on the inspiration-related activity of the genioglossus. In this section, we broaden the focus to include all hypoglossal innervated musculature, including intrinsic (inferior and superior longitudinalis, transversus, verticalis) and extrinsic (genioglossus, hyoglossus, and styloglossus) tongue muscles (Fig. 1).

**Modulation of tongue muscles by PSRs.** Withholding lung inflation results in a marked and consistent increase of hypoglossal nerve (14, 18, 56, 69, 70, 95, 115) and genioglossus muscle activities (7, 105). More recent studies have shown that the hypoglossus muscle behaves similarly (4, 7) (see Fig. 3), as do the intrinsic tongue muscles whose fibers originate and terminate within the body of the tongue (4). These observations support the concept that all tongue muscles are activated in an integrated manner during breathing, although subtle differences in the PSR modulation of the different muscle groups do exist as outlined below.

Steady-state increases in end-expiratory lung volume with PEEP have no significant effects on hypoglossal nerve activi-
ties in the cat (97) or genioglossus and hyoglossus activities in the rat (7). Although attempts have been made to study the influence of elevated lung volume on tongue motor output in human subjects, the results are equivocal because elevations in lung volume also elevate upper airway transmural pressure. Thus it is unclear whether pulmonary or upper airway (pharyngeal/laryngeal) afferents are driving the observed reflex responses (98). Importantly, vagotomy results in additional increases in the activity of extrinsic and intrinsic tongue muscles over and above those evoked by withholding pulmonary inflation (4, 6, 7, 33, 35) (Fig. 3). The latter observations suggest that hypoglossal motoneurons receive input from a class of PSRs that respond to end-expiratory lung volume and discharge tonically.

Interestingly, the rise in extrinsic and intrinsic tongue muscle activities evoked by bilateral vagotomy is not immediate (37) but builds over time in the absence of a systematic change in blood gases (4). Moreover, unilateral vagotomy had no effect on intrinsic tongue muscle activities but a profound effect on extrinsic muscle output. The reasons for these phenomena are uncertain; however, several mechanisms have been postulated (4). First, the absence of an effect of unilateral vagotomy on intrinsic muscle activities suggests some redundancy in vagal inputs onto hypoglossal motoneurons. The selectivity of the effect may be ascribed to differential vagal modulation of intrinsic and extrinsic hypoglossal motoneuronal activities. The latter possibility is of particular interest, given anatomic evidence of distinct medullary projections onto intrinsic and extrinsic hypoglossal motoneuron pools (101). The progressive increase in intrinsic tongue muscle activities after vagotomy may be due to accommodation of intrinsic muscle motoneurons to the removal of vagal input, or to the persistence of vagal inhibition onto intrinsic but not extrinsic hypoglossal motoneurons. There is evidence that such persistence or “memory” arises in PSRs, evoking a short- or intermediate-term inhibition of activities that lasts beyond the actual period of stimulation (30, 112). This same mechanism may explain long-lasting reductions in extrinsic tongue protruder and retractor muscle activities observed following augmented breaths (62).

Modulation of tongue muscle activities by RARs. To our knowledge, the only study that reports on RAR modulation of tongue muscle activities was conducted by Haxhiu et al. (47) in thiopental-chloralose anesthetized dogs. The authors’ report that methacholine induced bronchoconstriction increases upper airway EMG activities with the most profound (fourfold) increase evident in peak genioglossus activities. The effects on upper airway muscles are effectively blocked after bilateral vagotomy, indicating that vagal afferents are responsible for augmenting upper airway dilator muscle activities. Such activation may serve to decrease upper airway resistance and partially offset increases in pulmonary resistance and/or modulate airflow patterns during bronchoconstriction (47).

Modulation of tongue muscles by bronchopulmonary C-fiber receptors. Lee et al. (73) studied changes in respiratory-related hypoglossal nerve activity by injecting capsaicin into the right atrium of anesthetized rats. Capsaicin reduced phrenic and hypoglossal nerve activities at low doses, whereas at high doses it reduced phasic hypoglossal activity, increased tonic hypoglossal discharge, and increased phrenic nerve activity. Significantly, over the first few minutes following capsaicin injection, the peak hypoglossal output (tonic plus phasic discharge) during inspiration was significantly reduced, while phrenic activity was still elevated. These data suggest that stimulation of pulmonary C-fiber receptors may put the upper airway at risk by causing a simultaneous increase in inspiratory pressure produced by the diaphragm, with a reduction of...
activity in the tongue muscles. Similarly, Haxhiu et al. (46) showed that injection of capsaicin into the right atrium slightly raised nasal resistance, suggesting a lack of compensatory upper airway dilator muscle responses to the bronchoconstriction associated with C-fiber receptor stimulation. Interestingly, when respiratory drive was elevated in hypercapnia, all responses were attenuated, with the exception of nasal resistance. These data suggest differential influences of C-fiber receptor stimulation on chest wall and upper airway muscles, with physiologically significant consequences.

Despite some important temporal differences in the response to vagotomy, the data overwhelmingly demonstrate that PSRs strongly inhibit the activity of all hypoglossal motoneurons. Such observations support the concept that the central nervous system activates the various extrinsic and intrinsic tongue muscles in an integrated manner. Studies of the effects of tongue muscle coactivation on pharyngeal mechanics and geometry demonstrate that such integration has important physiological consequences (5, 27–29, 38, 68, 72, 90–92).

Muscles of the Hyoid Arch

The hyoid arch is located in the hypopharynx, caudal to the base of the tongue, and narrowing of this region is implicated in obstructive sleep apnea (55). Although there is species variation, about a dozen muscles insert or originate on the hyoid bone (Fig. 1). Van de Graaff et al. (102) and Roberts et al. (85) have shown, in anesthetized dogs and rabbits, respectively, that electrical stimulation of hyoid muscles or ventral traction on the hyoid bone significantly reduces upper airway flow resistance, indicating that activation of these muscles dilates the hypopharynx. But despite the importance of these muscles in determining hypopharyngeal size and stiffness, our understanding of the modulation of these muscles by bronchopulmonary afferents is modest. By far the majority of the information on the respiratory-related control of the hyoid muscles has been obtained from recordings of geniohyoid, sternohyoid, and thyrohyoid muscle activities.

Modulation of muscles of the hyoid arch by PSRs. Withholding pulmonary inflation for a single breath cycle increases the activities of the geniohyoid and sternohyoid muscles (104) and increases the discharge rate of geniohyoid muscle inspiratory motor units, while reducing the discharge rate of motor units with an inspiratory-expiratory (“phase-spanning”) pattern (103) in anesthetized cats. These observations are consistent with a task-specific control of geniohyoid muscle motor units by PSRs. Similarly, Van De Graaff et al. (102) recorded the activities of the thyrohyoid, geniohyoid, and sternohyoid muscles in anesthetized dogs, noting higher peak activities of all three muscles and prolonged discharge duration in the absence of lung inflation. In addition, airway occlusion at end inspiration inhibits or abolishes the activity of all three muscles. Interestingly, the rate of rise of the moving-time-averaged muscle activities declines when lung inflation is withheld, suggesting that PSRs may promote synchronous activation of hyoid muscle motoneurons (102). The increase in peak activity when lung inflation is withheld is largely a consequence of the delayed inspiratory off-switch that allows more of the motoneurons to be recruited as the breath cycle continues. Thus PSR input onto pharyngeal motoneurons appears to modulate both recruitment and the extent of synchronization of the motor unit pool.

Modulation of muscles of the hyoid arch by RARs and C-fiber receptors. We are unaware of any data on modulation of hyoid muscles by RARs or C-fiber receptors.

CONCLUSION

The respiratory-related recruitment and control of the upper airway muscles are closely monitored by slowly adapting PSRs. Inadequate lung inflation reduces PSR activity and initiates rapid and powerful increases in neural drive to all upper airway motoneurons by releasing them from inhibition. This is most dramatically demonstrated when lung inflation is prevented in anesthetized or decerebrate, tracheotomized animal preparations. Similarly, observations showing that elevations in end-expiratory lung volume systematically inhibit upper airway motor activities provide further support for the idea that lung volume is a potent stimulus for respiratory-related activation of upper airway motoneurons.

An important caveat here is that most of these conclusions are drawn from experiments conducted in anesthetized animal preparations. This is because isolating the effects of phasic lung volume feedback on ventilatory output has proven all but impossible in human subjects with intact airways, because changes in lung volume are transmitted to both the upper and lower airways. For example, reducing lung volume via negative extrathoracic pressure in humans also makes upper airway pressure more negative (98). Thus it has not been possible to confidently delineate the site of the stimulus (i.e., pulmonary vs. upper airway mechanoreceptors). Nevertheless, studies conducted in human subjects (15, 52, 53, 59), in anesthetized rabbits (86), and in decerebrate anesthetized cats (57, 58) clearly demonstrate the potent effect exerted by upper airway receptors on upper airway muscle activities.

In our view, the reduced rate of lung inflation that accompanies upper airway occlusion provides an equally critical stimulus for the initiation of reflexes that activate upper airway muscles and reduces the probability of airway collapse. Yet it is also clear that, while the upper airway muscles may prevent complete airway collapse, their coactivation does not preclude the airway narrowing that accompanies negative pharyngeal transmural pressures. This is evident from a recent study in human subjects showing that reductions in lung volume are associated with increases in upper airway resistance, despite activation of the genioglossus muscle and presumably many other upper airway muscles (98).

In conclusion, there are still large gaps in our knowledge of the modulation of upper airway muscles by respiratory reflexes in general, and by bronchopulmonary afferents in particular. Nevertheless, some important concepts are emerging from recent studies in animal models. This work indicates that upper airway muscles act in a highly integrated and complex manner to stabilize and change the shape of the oral cavity, pharynx, and larynx and that the slowly adapting PSRs provide an important afferent input for the initiation of the widespread and coordinated recruitment of laryngeal, tongue, and hyoid muscles during airway obstruction. Whereas the notion of coactivation of antagonist muscles is not new (25, 33), evidence of coactivation that occurs within a given muscle’s primary airway region (e.g., coactivation of protrudor and retractor mus-
cles of the tongue) and across airway regions (e.g., laryngeal muscle activation contributing to pharyngeal airway opening) is both new and exciting. On the basis of these observations, we suggest that airway defense can no longer be attributed to the activation of a single muscle, e.g., genioglossus or geniohyoid, but rather should be considered as the product of a complex interplay between many upper airway muscles. According to this view, the upper airway comprises an integrated system wherein muscles are recruited and coactivated within and across airway regions in an effort to adjust airway shape, size, and stiffness, thereby optimizing respiratory airflow resistance.

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REFERENCES
PULMONARY AFFERENT MODULATION OF UPPER AIRWAY ACTIVITIES


