



Molecular and physiologic basis of obstructive sleep apnea

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This is an exciting time to be involved in the study of the obstructive sleep apnea-hypopnea syndrome (OSAHS) because characterization of the diverse manifestations of this disorder continues to evolve. One may be certain that the characterization of this highly prevalent and disabling disorder is not complete. There are many reasons why the definitions and descriptions of the OSAHS will continue to evolve. The syndrome-in-progress status may be attributed, in part, to the relative newness of the initial characterization of the OSAHS three decades ago [1,2]. A more important reason, however, is that this disease process, with repeated systemic oxyhemoglobin desaturations followed by reoxygenation events and sleep disruption, has the potential to place a substantial oxidative burden on many, if not all, physiologic systems. Recently, researchers have begun to recognize that included in the physiologic systems impacted on by the repeated airway occlusions and hypoxia/reoxygenation events are the upper airway soft tissues and muscles and neural control mechanisms. The disease process itself may alter the molecular and physiologic mechanisms involved in OSAHS.

This article summarizes the pathophysiologic mechanisms of OSAHS and complements the physiologic information with data concerning molecular mechanisms involved in OSAHS and newer information regarding the mechanisms through which the disease process may alter obstructive sleep-disordered breathing. An understanding of the pathophysi-

ology [3,4] has brought therapies such as continuous positive airways pressure [5,6], surgical therapies for the upper airway [7–10], and oral mandibular advancement devices [11,12]. An understanding of the molecular mechanisms may provide unique approaches to therapies for this prevalent disorder, including pharmacotherapies, and at the same time, a comprehension of the molecular mechanisms may afford insight into the differential vulnerability in the severity and diverse manifestations of OSAHS, so that we may better understand who is at risk for this disease and its many morbidities.

An overview of the pathophysiology of obstructive sleep apnea-hypopnea syndrome

One of the most remarkable features of the OSAHS is the state dependency of this disorder. Specifically, in persons with isolated OSAHS, ventilatory patterns and arterial oxygen values during wakefulness are completely normal. In contrast, during sleep, the upper airway of persons with OSAHS narrows or collapses or both [4], which results in upper airway occlusion with large intrathoracic and upper airway intraluminal pressure swings [13,14], oxyhemoglobin desaturations [4], hypercapnia [15], increases in sympathetic drive [16–18], and ultimately, arousal with larger sympathetic surges [4] and massive increases in upper airway dilator muscle activity, which restores airway patency [4].

This state dependency in upper airway patency and respiratory function suggests that state-dependent changes in neural drive to the upper airway dilator and pump muscles prompt obstructive upper airway events. It is important to recognize that state-dependent changes in neural drive to respiratory muscles are not unique to sleep apnea. State-dependent reduc-

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tions in respiratory muscle activity are a normal phenomenon of sleep [19,20]. The unique features in individuals with OSAHS are a reliance on upper airway dilator muscle activity and lung volume and a greater magnitude of sleep state-dependent reductions in muscle activity [20,21]. For these reasons, the impact on airway caliber is larger [22–25].

State dependency of disease is a unique and clinically important characteristic because it implies that this disorder should be readily amenable to pharmacologic therapies that effectively target state-dependent neural changes. Understanding the mechanisms underlying OSAHS is essential for elucidating safe, effective therapies for this syndrome. The key components of this pathophysiology are (1) state-dependent changes in respiratory drive to the upper airway and pump muscles, (2) upper airway anatomy, (3) upper airway mechanics, and (4) upper airway muscle function.

Neural mechanisms underlying state-dependent changes in upper airway and pump muscle activity

State-dependent upper airway obstruction in OSAHS occurs most commonly within the pharynx in the retropalatal or retroglottal regions or both [26,27]. During inspiration, negative intraluminal pressures in these regions exert centripetal forces that

must be countered by centrifugal forces of the upper airway dilator muscles, particularly in persons with upper airway narrowing or increased collapsibility. The neurochemical control of upper airway motoneurons is complex, and in this section the author works backward from the upper airway dilator motoneurons to reflexes and upper respiratory neural drive to describe what is known of the neural and neurochemical mechanisms that may contribute to state dependency of the upper airway for each neural mechanism.

Many muscles contribute to centrifugal forces in the upper airway (Fig. 1), whereas other muscles that are important in phonation, deglutition, and respiratory breaking act as constrictors within the upper airway. When discussing neural mechanisms, it is important to recognize that most upper airway motor nuclei (cranial nuclei, V, VII, X, XI, and XII) house motoneurons for upper airway dilators and constrictors. Many researchers, including the author, have chosen to focus first on XII, the hypoglossal nucleus, because this collection of motoneurons innervates the largest upper airway dilator muscles in humans with OSAHS: the genioglossus and geniohyoid [4,20]. The hypoglossal motoneurons also innervate many more dilators than constrictors [28]. The information gained concerning the state-dependent control of hypoglossal motoneurons ultimately must be addressed for other populations of motoneurons, however. Recently, Kuna showed that

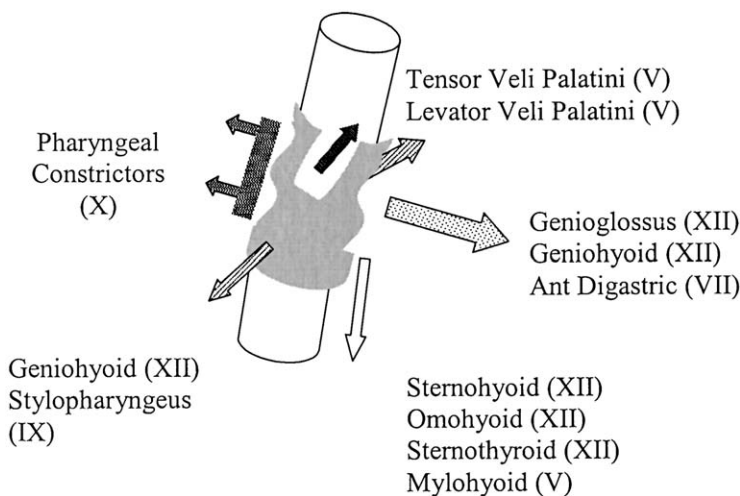


Fig. 1. Schematic of potential upper airway dilators in humans. Muscles surrounding the upper airway have the potential to dilate or stent the upper airway in many different directions. Represented in this drawing are the force vectors for activation of specific muscle groups. As a collapsible tube (gray), oropharyngeal patency is most effectively achieved by simultaneous activation of muscles with vectors in different directions. As discussed in the text, elongation of the airway along with widening of the lateral walls may be most effective in rendering the airway less collapsible.

electrical stimulation of the glossopharyngeal nerve causes marked dilation of the pharynx (Fig. 2) [29].

Many excitatory and inhibitory neurotransmitters and neuromodulators contribute to the activity of hypoglossal and other upper airway dilator motoneurons. Serotonin and its co-localized neuropeptides, substance P, thyrotropin-releasing hormone, and noradrenaline, orexin, acetylcholine (nicotinic receptors), and glutamate may contribute to upper airway motoneuronal excitation, whereas acetylcholine (through different receptor subtypes), glycine, GABA, and perhaps enkephalin may contribute to upper airway motoneuronal suppression [30–44]. Sleep state-dependent reductions in upper airway motoneuronal activity may reflect changes in inhibitory, excitatory, or both inputs. One model used to explore the neurochemical changes in motoneurons during sleep has been the pontine carbachol model of rapid eye movement (REM)-associated atonia. This model produces many of the phenomena of REM sleep, including suppression in respiratory muscles in a manner similar to natural, or spontaneous, REM sleep (upper airway muscle activity is more suppressed than diaphragmatic activity) [32–35].

In models of carbachol REM atonia, serotonin and noradrenaline delivery are reduced to hypoglossal motor neurons coincident with upper airway motor neuron suppression [32,35]. Kubin et al have shown that carbachol suppression of hypoglossal nerve activity may be largely prevented by pretreating the hypoglossal nucleus with serotonin [31]. Further evidence that sleep-dependent serotonin withdrawal contributes to suppression of upper airway dilator activity is shown in research on adult rats, in which serotonin delivered by way of a chronic microdialysis probe into the hypoglossal nucleus largely prevents genioglossus suppression in spontaneous NREM sleep and reduces the suppression in REM sleep, albeit to a lesser extent [45]. Serotonin is important for the maintenance of patent airways in an animal model of obstructive sleep-disordered breathing, the English bulldog [46], and a combination of serotonergic drugs that increase serotonin production and release within the brain and target multiple serotonin receptor subtypes reduces obstructive sleep-disordered events in the bulldogs [47]. Serotonin may have excitatory and inhibitory effects at motoneurons and on respiration [48,49], and there are at least 15

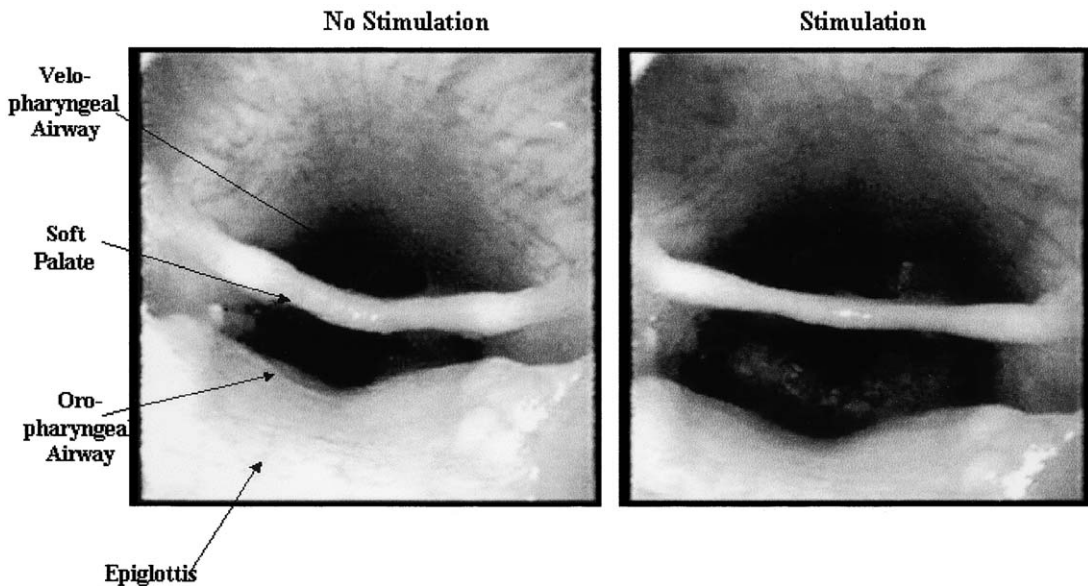


Fig. 2. The effects of glossopharyngeal nerve stimulation on pharyngeal patency in a decerebrate cat. Caudal view from pharyngoscopy in a tracheostomized cat. The left panel shows velopharyngeal and oropharyngeal patency in the absence of nerve stimulation. The right panel illustrates the large effect of glossopharyngeal nerve stimulation on the patency of the velopharynx and oropharynx. Stimulation of the glossopharyngeal nerve extends most pharyngeal dimensions. Although this nerve innervates primarily the stylopharyngeus, it also contributes to the innervation of the anterior digastric, levator palatine, and stylohyoid, a collection of muscle that would extend all airway dimensions. (Courtesy of Sam Kuna, MD, University of Pennsylvania, Philadelphia, PA)

unique serotonin receptor subtypes within the central nervous system in mammals [50]. Researchers recently identified which excitatory serotonin receptor subtypes are involved in postsynaptic serotonergic excitation of hypoglossal motor neurons [51,52]. 5-HT_{2A} and _{2C} are the excitatory 5-HT receptors transcribed in hypoglossal motoneurons and the only functional excitatory receptors [51,52]. Kubin et al identified α_{1B} as the main postsynaptic noradrenergic receptor subtype that mediates excitation [53]. Substance P excites hypoglossal motoneurons through activation of the natural killer-1 receptor [42].

Glutamatergic excitation of hypoglossal motoneurons involves multiple receptor subtypes in the hypoglossal nucleus [54,160–163], and although reports have identified the presence of many different receptor subtypes [55–59], it remains unclear what the relative role of each subtype is. Recent studies suggested that N-methyl-D-aspartate (NMDA) receptor subtypes are particularly vulnerable to nitrosative and oxidative stress and that the excitability of this receptor is reduced in oxidative stress through nitrosative and oxidative changes in the sodium channel, a mechanism believed to be protective in preventing glutamatergic excitotoxicity [60]. Because glutamate is involved in the respiratory drive to hypoglossal and other respiratory neurons, it is essential to understand glutamatergic control of upper airway motoneurons and how OSAHS impacts on glutamate receptor function [159].

Although glycine plays a major role in REM sleep postural muscle suppression, it does not seem to contribute significantly to either the pontine carbachol REM suppression of hypoglossal activity [61] or spontaneous REM suppression of brain stem motor reflex activity [62]. There are large hyperpolarizations of brain stem motor neurons during phasic REM sleep [63], which may occur when glycine contributes to upper airway dilator muscle suppression [64].

In summary, recent studies have identified the subtypes for monoaminergic excitatory inputs to hypoglossal motoneurons in an effort to identify drug targets. Unfortunately, the predominant and non-rapidly desensitizing serotonin receptor subtype involved in excitation of hypoglossal motoneurons in normal mammals, 5-HT_{2A}, is not an ideal target for pharmacotherapies, because activation of this receptor subtype has been implicated in vasoconstriction of the systemic and pulmonary beds, bronchospasm, and thromboembolic disease [65]. The adrenergic receptor subtype involved in hypoglossal excitation, α_{1B} , is also implicated in vasoconstriction [66]. A thyrotropin-releasing hormone analog has been tried in the English bulldog model of sleep-disordered breathing

and found to increase wakefulness without improving sleep-disordered breathing (S.C. Veasey, unpublished observations). To date, there are no ideal receptor targets for pharmacotherapeutics for OSAHS.

With the certainty that the clinical description of the manifestations of OSAHS is not complete, one also may be sure that the list of neurochemicals involved directly in the control of upper airway motoneurons is not complete. Many “orphan” G protein-coupled receptors and other potential targets for drug therapies for OSAHS exist. Researchers currently are probing upper airway motoneuronal tissue for novel receptors with activity at upper airway dilator motoneurons because they may provide additional avenues for pharmacotherapies for this disorder.

It is crucial to determine how OSAHS alters neuronal function. There are recent reports of long-term intermittent hypoxia inducing neuronal injury and reducing excitatory responsiveness in hippocampal neurons [67,68]. There is at least one report of patients with OSAHS showing delayed phrenic nerve conduction, which is associated with severe oxyhemoglobin desaturations [69], suggesting that perhaps oxidative injury occurs to the respiratory motor neurons with severe OSAHS. Motor neurons are sensitive to oxidative stress, and one likely mechanism of disease progression in persons with OSAHS is oxidative injury to respiratory neurons and upper airway dilator motor neurons. Advancing knowledge concerning the neurochemical control of upper airway dilator motor neurons in sleep requires an understanding of the major inputs to motor neurons.

Respiratory neural inputs to the upper airway motoneurons are numerous and include reflexes, respiratory drive, and other central inputs. Responses to reflexes may be excitatory or inhibitory, fast or slow adapting responses. There is evidence that sleep may modulate upper airway activity through many of these mechanisms [70–88]. Readers are referred to excellent review chapters [89]. One example in which a rapid reflex response may play an important role in upper airway patency in sleep is the immediate response (first 200–300 milliseconds) to increased respiratory loads. This augmentation of upper airway muscle activity is not evident in non-REM sleep [70]. Loss of an initial powerful excitatory drive to the upper airway muscles could reduce substantially the effectiveness of pump muscle activity. In the English bulldog model of obstructive sleep-disordered breathing, the lead-time for upper airway muscles before diaphragmatic activation that occurs upon waking is lost in non-REM and REM sleep [21]. The relative role that this reflex plays in waking respiratory drive to upper airway muscles in persons with OSAHS is

largely unknown. There is evidence for a significant contribution of a slow adapting reflex response, mechanoreceptor reflex activation, to waking dilator muscle activity in persons with OSAHS. When topical anesthesia is applied to the pharyngeal mucosa, electromyographic activity of upper airway dilators and airway caliber declines in normal persons and persons with OSAHS [71,72]. In both groups, the apnea-hypopnea index increases [71,72].

Sleep also affects the pharyngeal muscle reflex response to negative pressure [73–81]. Evidence that this reflex contributes to waking genioglossus activity is apparent because the application of positive pressure abruptly (within a reflex latency) drops genioglossus activity in persons with OSAHS [75,81]. Effects of sleep on suppression of the negative pressure reflex are more pronounced in REM sleep than in non-REM sleep [77,78]. It is unclear, however, whether the sleep effect is a primary effect on reflex inactivation or whether this is secondary to sleep-induced reductions in upper airway motor neuron excitability [79].

There is some evidence that reflex responses may be impaired in persons with OSAHS. One recent report suggested that long-term severe OSAHS is associated with swallowing dysfunction [79]. The swallowing reflex impairment was associated with more frequent severe oxyhemoglobin desaturations and is improved in patients after successful continuous positive airway pressure (CPAP) therapy [79]. The negative pressure reflex response is also impaired in OSAHS and improves with CPAP therapy [80]. It is likely that in addition to impairments in respiratory motor neurons, OSAHS may result in impairments in important upper airway reflex responses. This is an area in need of further exploration.

Another group of neurons affected by sleep and likely by OSAHS is the upper respiratory neurons. Collectively, the work from many studies suggests that sleep may have larger suppressive effects on pontine respiratory neurons [84,87], some of which rely on serotonergic inputs [86]. There are little to no suppressive effects on medullary neurons; in cats, medullary respiratory neurons may increase firing during REM sleep [83,85]. The large changes in upper airway motor activity in sleep are most consistent with tonic reductions in monoaminergic inputs from nonrespiratory groups and perhaps phasic increases in glycinergic drive through activation of glycinergic interneurons. The reduced chemosensitivity in sleep is also poorly understood. It is not because of sleep-related effects on nucleus tractus solitarius response to hypercarbia [88]. Medullary serotonergic neurons are chemosensitive, and because

firing of these neurons occurs less during sleep, this could contribute to reduced chemosensitivity in sleep. OSAHS may injure upper respiratory neurons and alter drive to dilator and pump muscles. In neonatal rats exposed to intermittent hypoxia, nucleus tractus solitarius neurons show substantial injury, including apoptosis [68]. Functional magnetic imaging in adults with OSAHS reveals loss of grey matter in brain regions involved in respiratory drive [90]. Whether this is a consequence of OSAHS, or whether the lesions render persons more vulnerable to OSAHS, is presently unknown. The above referenced study in young rats suggested a narrow window of increased vulnerability, and whether clinically significant injury may occur at later stages is presently unknown.

Overall, upper airway and other protective respiratory reflexes are lost in sleep, and reduced or absent reflex responses and respiratory neuronal injury may contribute to the pathogenesis of OSAHS. How much of a role these reflexes play remains unknown. It is important to determine how much waking upper airway dilator muscle activity is present because of specific reflex activation in humans with OSAHS. This is important to determine in persons with OSAHS because the neurochemical control of reflex activity may differ significantly from the neurochemical control for central mechanisms. If reflexes contribute substantially to upper airway activity in persons with OSAHS, then the neurochemical basis for significant reflexes may be determined in animals and targeted to provide therapeutic targets. Differences among patients in relative roles of reflex and central inputs may explain partly the differential responses to pharmacotherapies. At the same time, it is important to understand which neurons are injured by OSAHS and how this injury occurs.

The neurochemical control of upper airway reflexes is not well delineated, but it seems that noradrenaline and serotonin may contribute to inhibitory [91,92] and excitatory upper airway motor responses for trigeminal nerve reflexes [93]. Serotonin does not seem to contribute to the superior laryngeal nerve stimulatory response of hypoglossal motor neurons [94]. Glutamate contributes to excitatory responses [95,96]; however, few other upper airway motoneuronal excitatory receptor targets have been excluded from reflex contribution, and this is an area in need of further study.

Upper airway anatomy

One of the challenges for studying upper airway anatomy in persons with OSAHS has been the state

dependency of the upper airway anatomy. Specifically, the upper airway is sufficiently patent in wakefulness to allow normal ventilatory function, and it is only during sleep, or anesthesia, that airway collapse manifests. The following studies describe the anatomy of the upper airway in awake normal subjects and distinguish the unique features of the waking upper airway in persons with OSAHS before characterizing the features of the sleeping upper airway anatomy in persons with OSAHS.

The upper airway extends from the nares to the vocal cords. Upper airway collapse, however, occurs most frequently within the oropharynx, which extends from the posterior edge of the hard palate to the level of the cervical esophagus and glottic inlet [97,164]. The anatomy described in this section is the anatomy of the oropharynx with an emphasis on the two more collapsible segments, the retropalatal and retroglossal airway, both of which are surrounded by abundant soft tissues. The hypopharynx has been identified as a site of collapse. Typically, however, the hypopharynx is not a primary site of collapse. The posterior wall of the oropharynx is comprised of mucosal tissue encompassed by various posterior pharyngeal constrictors (muscles that narrow the airway somewhat but also stiffen the wall). The lateral walls of the oropharynx include mucosal folds, a continuation of the constrictor muscles, tonsils, tonsillar pillars, other lymphoid tissue, and the parapharyngeal fat pads. The anterior wall of the oropharynx consists of mucosa, the soft palate, and the tongue. Many of the soft tissues that surround the upper airway are surrounded, in turn, by fixed skeletal structures, including the skull base, maxilla, mandible, and cervical vertebral column. There are many potential causes of upper airway compromise, and many anatomic variations have been associated with OSAHS, including retrognathia, maxillary retropositioning, intranasal obstruction, caudal displacement of the hyoid bone, macroglossia, a low-lying or enlarged soft palate, enlarged lymphoid tissue in the upper oropharynx, and brachycephalic posture [97–99].

Evidence supports the hypothesis that genetic variations in skeletal head and neck structures contribute to the likelihood of OSAHS. Several genetic disorders with craniofacial anomalies are associated with an increased risk of OSAHS, including craniofacial microsomia, Down syndrome, Pierre Robin syndrome, Nager syndrome, Treacher Collins syndrome, and cri du chat syndrome [100–102]. There are racial differences in the skeletal anomalies associated with OSAHS. Hispanics, relative to white adults, have on average smaller anteroposterior and

lateral dimensions for the maxilla and mandible [98]. Support that the smaller facial bones may contribute to a predisposition to OSAHS stems from the increased prevalence for OSAHS in Hispanics [98,103]. In many patients with OSAHS, however, obvious craniofacial anomalies are not evident [98]. For example, African Americans have on average larger mandibular and maxillary inner dimensions relative to whites, but the median respiratory disturbance index is higher in African-American adult men compared with white adult men [104]. Collectively, these data suggest that the skeletal predispositions to OSAHS are multifactorial; there are genetic influences on facial skeletal structure that might increase the likelihood of developing OSAHS, but skeletal structural variances cannot explain all cases of OSAHS.

In addition to skeletal anatomic variations, there are soft tissue differences in persons with OSAHS (Fig. 3), and significant evidence supports the hypothesis that changes in the upper airway soft tissue anatomy also may predispose an individual to the pathogenesis of OSAHS [98,99]. As with skeletal changes, the sources of soft tissue abnormalities in persons with OSAHS are numerous. It is difficult, however, to determine which of the soft tissue changes contribute to the disease process and which are secondary to repeated upper airway obstruction. For example, one tissue change in OSAHS is edema, not only in the mucosa and submucosa but also in the upper airway muscles, as evidenced by MRI of the pharynx and neck muscles with T_2 relaxation measurements [105]. Edema could be caused by upper airway negative pressure trauma but also could worsen OSAHS by reducing airway caliber. Fatty infiltration of upper airway soft tissues is likely to play a causal role in upper airway compromise. Obesity is a significant risk factor for OSAHS [106], and significant weight loss in obese persons with OSAHS reduces the severity of sleep-disordered breathing [107]. Of obesity parameters, neck size is the strongest predictor of OSAHS [108,109], and neck circumference correlates with increased dimensions of the parapharyngeal fat pads [110]. Increased weight gain not only augments fat in mucosal tissue but also increases adipose tissue within upper airway muscles [111]. Weight gain may jeopardize the upper airway caliber by increasing soft tissue confined by skeletal structures surrounding the airway and causing potentially deleterious effects on muscle function. A larger upper airway soft tissue volume in men may contribute to the increased prevalence of OSAHS in men compared to women [112].

One of the most striking differences in persons with OSAHS in wakefulness is a marked narrowing

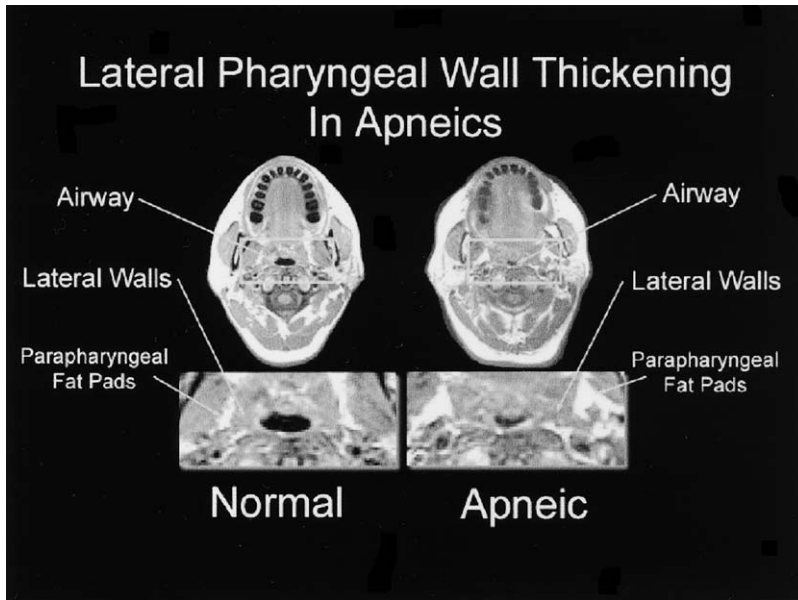


Fig. 3. Axial MRIs of the pharynx and all surrounding skeletal, soft tissue structures in a normal individual (*left*) and a person with severe OSAHS (*right*). Notice the increased fat pads (*white*) in the person with OSAHS and compromise of the anterior posterior and lateral pharyngeal walls. (Courtesy of Richard Schwab, MD, University of Pennsylvania, Philadelphia, PA)

of the lateral airway walls (Fig. 3) [113]. An increase in the size of the parapharyngeal fat pads may contribute to airway narrowing, but because the increase in fat pad size cannot explain fully the marked narrowing, there also must be an increase in soft tissue edema or mucosa [158]. It is conceivable that persons with mild upper airway narrowing manifest a progression of OSAHS from soft tissue stress-induced mucosal growth. Several growth factors in mucosa elsewhere in the body respond to tissue distortion with increased growth factor transcription [114]. This concept has not been explored in human upper airway soft tissues, however. Increased surface area of mucosa would increase tissue collapsibility. CPAP clearly affects soft tissue structures, and at pressures effective to treat OSAHS, CPAP increases the lateral wall soft tissue cross-sectional area more so than anterior or posterior soft tissue, which suggests that this region is more distensible in humans with OSAHS [115]. An increase in upper airway mucosal surface area may contribute to lateral wall increased collapsibility in persons with OSAHS.

State-dependent imaging of the upper airway has provided more clues concerning the pathogenesis of OSAHS. By imaging persons during sleep, it is possible to discern which structures surrounding the upper airway might contribute to airway collapse or

narrowing. In normal persons, consistent with the reduced upper airway muscle activity during sleep, the upper airway dimensions decline in sleep [116]. The decline may be attributed to posterior positioning of the tongue and soft palate and narrowing or folding in of the lateral walls [116]. The posterior and lateral changes are less likely to be explained by activity reduction in one muscle. Presumably the narrowing results from simultaneous reductions in several of the following muscles: genioglossus, geniohyoid, tensor veli palatini, and levator palatini. Similar dimensional changes have been observed in persons with OSAHS [117–119]. The reductions in upper airway caliber, however, are more pronounced in persons with OSAHS [117]. The larger changes in persons with OSAHS may occur because of larger reductions in upper airway muscle activity but also may occur as a consequence of smaller lung volumes, which may shorten the upper airway and allow the lateral walls to collapse inward [120].

Imaging studies of the upper airway in persons with and without OSAHS, particularly imaging studies performed during sleep, have provided a characterization of many abnormalities of skeletal and soft tissue origin that may contribute to OSAHS. The abnormalities in waking are not sufficient to allow diagnosis or consistently reliable predictions concern-

ing which patients may benefit from various surgical and nonsurgical therapies. Future imaging studies in sleeping persons with OSAHS will be tremendously insightful when measurement of specific muscle activity and lung volume may be acquired simultaneously with dynamic breath-to-breath imaging across states. The insight gained into neural control of the upper airway and upper airway anatomy in persons with OSAHS must be complemented with data on mechanics to begin to approach unanswered questions concerning state-dependent changes in upper airway mechanics, because muscle activity over several breaths before upper airway collapse may not change in parallel with progressive reductions in upper airway caliber.

Upper airway mechanics

This article highlights the sleep state-dependent reductions in upper airway dilator activity as normal neurologic phenomena and phenomena that are more pronounced in persons with OSAHS and result in repetitive upper airway occlusions only in persons with OSAHS. The author has discussed several anatomic changes, including several genetically determined bone and soft tissue features that may predispose an individual to require increased upper airway dilator activity to maintain a patent upper airway. However, anatomy and muscle activity alone are insufficient to explain fully the complicated pathogenesis of OSAHS [121]. The mechanics of the upper airway, particularly forces that alter compliance and upper airway collapsibility, are equally important in determining which patients snore and which patients have occlusive apneas [122–124]. It is difficult to predict reliably OSAHS severity with either imaging or electromyographic studies. In contrast, several studies of upper airway biomechanics help to distinguish snorers from persons with hypopnea and persons with apnea [124–126].

The retropalatal and retroglottal regions of the upper airway act much as a Starling resistor, a collapsible passageway [127]. The clinical significance of Starling properties is that variations in intraluminal pressures, resistance, and airway collapsibility influence upper airway flow so that despite a high pulling pressure (from inspiratory muscle activity), flow may become limited [127,128]. Several factors influence maximal flow in the upper airway through the collapsible area [128]. First, a greater upstream (nasal) driving pressure increases flow, because flow is somewhat proportional to the pressure gradient (nasal pressure minus the critical closing pressure) [129].

Through this mechanism, positive airway pressure therapies (CPAP, BiPAP, mask ventilation) work. The increased driving pressure increases inspiratory flow [130,131]. Nasal pressure does not differ in normal persons and persons with OSAHS, however; at end-expiration, this is simply atmospheric pressure.

One factor that varies among persons with and without OSAHS is nasal or upstream resistance, and as a Starling resistor, maximal flow is limited by upstream resistance. If this resistance is too great, flow ceases. In this manner, nasal obstruction may contribute to OSAHS [132,133], although correction of nasal resistance only rarely results in substantial reductions in apnea/hypopnea frequencies [134]. The third—and perhaps most influential—factor in persons with OSAHS is the specific collapsing pressure of the Starling segment [127,128]. This pressure is termed the critical pressure, P_{crit} , and is defined as the upper airway pressure (nasal pressure) at which air flow ceases in the collapsible segment. The upper airway muscles come into play, and P_{crit} is affected by sleep state [121]. The dilator muscles act with centrifugal force to produce a more negative closing pressure, a less collapsible segment. Even in normal persons, the effects of sleep are pronounced on upper airway collapsibility and may change the P_{crit} from -40 cm H₂O when awake to -15 cm H₂O during sleep [121]. In sleep the P_{crit} can be used to distinguish types of obstructive sleep-disordered breathing. Snorers have a P_{crit} closer to -6 cm H₂O, whereas in persons with hypopnea, the P_{crit} is more positive, closer to -2 cm H₂O. In persons with predominantly apneas, the P_{crit} actually may be above atmospheric pressure during sleep [121]. The frequency of obstructive sleep-disordered breathing events correlates somewhat with the P_{crit} [123].

Collapsibility of a Starling resistor also may vary with lengthening or shortening of the tube (pharyngeal mucosa/submucosa). The collapsible portion of the upper airway may be thought of as a tube that, under some circumstances, is too long for the space within it is housed, and under these circumstances the walls of the tube are redundant with many folds of tissue. The upper airway space may be shortened by reductions in lung volume [135–142]. Sleep may impose reduced lung volume through two mechanisms: reducing end-expiratory lung volume and reducing tidal volume [120,143]. Functional residual volume or end-expiratory volume may be reduced in sleep because of supine posturing and less activity to tonic respiratory muscles, including the external intercostals [143]. Phillipson et al examined the upper airway in awake subjects with OSAHS and in controls at several lung volumes using acoustic reflection, and they found

reductions in pharyngeal cross-sectional area in normal persons and in persons with OSAHS from total lung capacity to residual volume [120]. The reduction was greater in persons with OSAHS [120].

Begle et al extended these findings to show that increasing lung volume (0.5 L) reduces the pharyngeal resistance in non-REM sleep despite reductions in genioglossus electromyographic phasic and tonic activity [137]. Increasing the functional residual capacity reduces obstructive sleep-disordered breathing event frequency [135]. A major effect of CPAP therapy is pneumatic splinting [140]. The second mechanism through which sleep reduces lung volume is reduction in tidal volume [143]. Tidal volume is reduced in non-REM sleep and reduced even further in REM sleep in persons with OSAHS [144]. Sleep-related reductions in lung volume impose additional challenges on an already highly vulnerable airway in persons with OSAHS. Through reduction in lung volume it is possible to reduce the upper airway caliber profoundly.

The effect of supine positioning on the pharyngeal cross-sectional area is independent of the lung volume and is likely additive [145,146]. It is surprising that little is known about the effects of upright posturing on OSAHS (many patients prefer this sleeping position). In one small study, resolution of OSAHS was shown in half of the subjects, whereas the rest of the subjects had significant reductions in sleep-disordered breathing [147]. It is more likely that upright posture for sleep might represent a supplemental therapy for patients in whom high positive airway pressures are required or in whom other therapies are only partially effective.

An additional factor for upper airway mechanics is upper airway hysteresis. This is a minimally explored area, with the exception of several topical oropharyngeal lubricant therapy studies for sleep-disordered breathing. In the upper airway, particularly in the oropharynx, there are redundant folds. With airway collapse and even with end-expiration when the upper airway is smallest, the number of folds or contact areas increases. Each of these folds represents a potential contact area for the development of hysteresis. Part of the airway compromise relates to sleep state-dependent changes in upper airway dilator activity [148]. Progressive hysteresis within the upper airway would partially explain the dissociation between upper airway dilator activity and upper airway caliber in the last few breaths preceding an apneic event [121,149,150]. Lubricants that may reduce surface tension on pharyngeal mucosa have been shown to reduce apneic and hypopneic events and snoring [151,152].

Upper airway muscle function

Many muscle disorders predispose to sleep apnea, including OSAHS [153]. Evidence also exists that the disease process itself may result in injury to the upper airway dilator muscles. In individuals with OSAHS, upper airway dilator muscle activity is required for airway patency. In quiet wakefulness, the drive to upper airway muscles is relatively constant compared to sleep. During sleep, the drive to upper airway muscles fluctuates with each obstructive event, sometimes reaching tremendously high levels of activity at the termination of an event. Intense activation of upper airway muscle activity at a time when intraluminal pressure is low may cause muscle injury. That is, the centrifugal force of the dilator muscles is opposed by the centripetal force of negative intraluminal pressure. Mechanical lengthening of a muscle during contraction (eccentric contraction) may injure the muscle [154].

Petrof hypothesized that eccentric contraction may occur in persons and in English bulldogs with OSAHS and that evidence of eccentric contraction injury should be seen on biopsy specimens of upper airway dilator muscles. Petrof also observed an increased proportion of fast twitch fibers, increased inflammation throughout the upper airway dilator muscles, increased connective tissue, and a significant reduction in muscle fibers in bulldog compared to control dog airway muscles [155]. These findings are consistent with an overuse injury [154] to upper airway muscles in the bulldog. The increase in myosin type II fibers in the sternohyoid muscle is consistent with resistive load training of this dilator muscle [156]. There were no differences in myosin type in a non-upper airway striated muscle, the anterior tibialis. Petrof concluded that eccentric contraction of upper airway muscles over a long time, seen particularly in older dogs, may result in muscle injury, which could help explain progression of disease. Injury specific to upper airway muscles rather than diffusely has been shown by Dr. Schotland and colleagues [165]. Intermittent hypoxia also may increase fatigability of upper airway dilator muscle, as shown recently in adult rats exposed to 5 weeks of intermittent hypoxia [157].

Summary

Obstructive sleep apnea-hypopnea syndrome occurs because of various combinations of anatomic, mechanical, and neurologic anomalies that jeopardize ventilation only when normal state-dependent reduc-

tions in drive to upper airway respiratory muscles and pump muscles occur. A well thought out and carefully described infrastructure of the normal and abnormal physiology in persons with OSAHS has been developed over the past few decades, which enables the development of innovative and largely effective therapies. The most recent data complement the infrastructure with the neurochemical changes underlying the state-dependent respiratory disorder and observations that the disease process itself can impair muscles, neural inputs, and soft tissue in a manner that has the potential to worsen disease. Oxidative and nitrosative stress from the repeated oxyhemoglobin desaturations and re-oxygenations is implicated in the injury to these tissues. An improved understanding of the mechanisms through which OSAHS progresses may lead to alternative therapies and aid in the identification of persons at risk for disease progression.

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