Pathogenesis of obstructive sleep apnea

Clodagh M. Ryan and T. Douglas Bradley
Sleep Research Laboratory of Toronto Rehabilitation Institute and Centre for Sleep
Medicine and Circadian Biology, Department of Medicine, Toronto General Hospital/
University Health Network, University of Toronto, Toronto, Ontario, Canada

The pathogenesis of obstructive sleep apnea (OSA) has been under investigation for over 25 years, during which a number of factors that contribute to upper airway (UA) collapse during sleep have been identified. Structural/anatomic factors that constrict space for the soft tissues surrounding the pharynx and its lumen are crucial to the development of OSA in many patients. Enlargement of soft tissues enveloping the pharynx, including hypertrophied tonsils, adenoids, and tongue, is also an important factor predisposing to UA collapse, as much as this can impinge on the pharyngeal lumen and narrow it during sleep. Other factors, including impairment of UA mecanoreceptor sensitivity and reflexes that maintain pharyngeal patency and respiratory control system instability, have also been identified as possible mechanisms facilitating UA instability. This suggests that OSA may be a heterogeneous disorder, rather than a single disease entity. Therefore, the extent to which various pathogenic factors contribute to the phenomenon of repetitive collapse of the UA during sleep probably varies from patient to patient. Further elucidation of specific pathogenic mechanisms in individuals with OSA may facilitate the development of new therapies that can be tailored to individual patient needs according to the underlying mechanism(s) of their disease.

upper airway; upper airway resistance; pharynx; respiratory control system; hypopnea

OBSTRUCTIVE SLEEP APNEA (OSA), defined as ≥15 apnea and hypopneas per hour of sleep (apnea-hypopnea index) (1), occurs in ~9% of men and 4% of women in the middle-aged American population (155). It adversely affects quality of life and is a risk factor for hypertension and, possibly, cardiovascular diseases (3, 77). Despite progress in elucidating several aspects of its pathogenesis over the last 25 years, its etiology remains elusive. Progress is hampered by the occurrence of OSA only during sleep, making invasive and interventional studies difficult to perform while maintaining the sleep state. The critical pathophysiological feature of OSA is sleep-related collapse of the upper airway (UA) at the level of the pharynx. Essentially, pharyngeal collapse occurs when the normal reduction in pharyngeal dilator muscle tone at the onset of sleep is superimposed on a narrowed and/or highly compliant pharynx. This highlights the interaction of anatomic and neural state-related factors in causing pharyngeal collapse. Our objective, therefore, is to review the anatomic and pathophysiological factors that predispose to UA collapse in adults with OSA.

Anatomic Factors

The pharyngeal airway is enclosed along its length by bones, including the nasal turbinates, hard palate of the maxilla, mandible, hyoid, and cervical vertebrae, and by soft tissues, including the tongue, soft palate, tonsillar pillars, pharyngeal mucosa and muscles, epiglottis, pharyngeal fat pads, and blood vessels of the neck. In general, the ratio of UA soft tissue mass is disproportionately high for the space made available by the bony structures enveloping the pharynx in OSA patients. Thus an excess of soft tissue and/or a small bony cage impinges on the pharyngeal lumen in most OSA patients.

Sites of UA collapse. Obstructive apneas and hypopneas occur because of intermittent complete and partial collapse of the pharynx, respectively, during sleep. The pharynx can be divided into four segments: 1) the nasopharynx, which extends from the nasal turbinates to the superior part of the soft palate, 2) the retropalatal pharynx, from the hard palate to the caudal margin of the soft palate, 3) the retroglossal segment, from the caudal margin of the soft palate to the tip of the epiglottis, and 4) the hypopharynx, from the epiglottis to the larynx. The retropalatal and retroglossal pharynx are often referred to together as the oropharyngeal segment and the junction of the retropalatal and retroglossal pharynx as the velum. The sites of collapse during sleep have been assessed with a variety of techniques, including pharyngeal pressure catheters placed at various sites in the UA, cine fluoroscopy, video endoscopy,
computerized tomography, and MRI. Pharyngeal collapse can occur at end expiration or at the beginning of inspiration (84, 135). The collapse starts initially in the retropalatal/oropharyngeal areas in most (56–75%) OSA patients (57, 127). This is followed by caudal extension of the collapse to the base of the tongue in 25–44% of patients (57, 127) and, finally, to the hypopharyngeal region in 0–33% of patients (8, 50, 127, 135). In a minority of patients, the initial site of collapse is the hypopharynx (8). The extent of the collapsed segment varies between sleep stages, with a more caudal extension often occurring during rapid eye movement (REM) sleep (128). In OSA patients with more severe disease, the primary site of collapse is reproducible from night to night in ~80% of patients (103). Airway reopening at the termination of apnea usually occurs during inspiration, its onset is sudden in half of cases and gradual in the other half, and it extends from the caudal to the cranial portion of the occluded segment (97).

**UA configuration.** Compared with normal subjects, habitual snorers with or without OSA have a generalized narrowing of the pharyngeal lumen, whether or not they are obese (13). The pharyngeal lumen of normal subjects is generally elliptical in shape, with the long axis in the lateral dimension (Fig. 1). In contrast, the lumen of snorers and OSA patients during wakefulness and sleep is circular or elliptical, with the long axis in the anterior-posterior dimension as a result of medial displacement of the lateral pharyngeal walls. These differences in shape are most pronounced at the retropalatal level (116) and are most notable when subjects are asleep (135). Accordingly, structures adjacent to the lateral pharynx displace the lumen medially, indicating that these structures play an important role in narrowing the pharyngeal lumen.

**Skeletal structures.** Abnormalities of the bony cage enveloping the oropharyngeal cavity are frequently observed in OSA patients. The most common abnormalities are hypoplasia and/or retrodisplacement of the maxilla and mandible, restricting space in the oropharyngeal cavity (26, 144) (Fig. 2). As a consequence, the tongue, soft palate, and soft tissues surrounding the UA are displaced posteriorly, impinging on the lumen. Extreme examples of such abnormalities occur in subjects with congenital craniofacial dysplasia, such as those with Aperts, Pierre-Robin, and Treacher-Collins syndromes (53, 82, 130). These syndromes cause maxillary and/or mandibular hypoplasia and are associated with very high prevalence of OSA.

Cephalometric studies have shown subtle retropositioning and shortening of the mandible and maxilla, even in the absence of distinct craniofacial abnormalities, in OSA patients compared with normal subjects (26, 52, 144). Shorter and more posteriorly displaced mandibles have been confirmed in up to two-thirds of OSA patients and correlate with decreased pharyngeal size (102, 124). Medial displacement of the mandibular rami may also occur and reduce intramandibular volume (124).

Displacement of the hyoid bone may also contribute to the pathogenesis of OSA (154). In contrast to most other mammals, the hyoid bone of humans is not attached to the cervical spine. This detachment of the hyoid appears to be related to the development of speech (22) but makes the UA much more compliant and susceptible to collapse in humans than in other mammals because of the lack of rigid bony support. Furthermore, compared with normal subjects, the hyoid bone is displaced inferiorly in OSA patients (101). This inferior displacement of the hyoid bone is accompanied by an inferior displacement of the tongue into the hypopharyngeal area: the

![Fig. 1. Magnetic resonance images of transverse sections of pharynx (arrowheads) in a normal subject (left) and a patient with obstructive sleep apnea (OSA, right). Note smaller pharyngeal lumen and more medially displaced lateral pharyngeal walls in OSA patient than in normal subject. [Reproduced with permission from Rodenstein et al. (102a).]](image-url)
more inferiorly displaced the hyoid, the greater the apnea-hypopnea index (154). Whether caudal displacement of the hyoid bone in OSA patients is the result of the inferior shift of the tongue is not clear (144). All these anatomic variations reduce the size of the UA in OSA patients. However, the reduction in mandibular length appears to be the most common and, probably, most important skeletal abnormality predisposing to OSA (81). This point is emphasized by the observation that mandibular advancement by appliances or surgery increases the size of the pharyngeal lumen and reduces the severity of OSA (56, 98).

Soft tissues. Soft tissues form the walls of the pharynx and include the tongue, uvula, tonsillar pillars, soft palate, blood vessels, lymphoid tissue, pharyngeal fat pads, UA muscles, pharyngeal mucosa, and lateral pharyngeal walls. Enlargement of the soft tissues through hypertrophy, inflammation, or edema may reduce the diameter of the UA. MRI studies have demonstrated increased soft tissue mass surrounding the UA and, hence, reduced UA size in the retropalatal and, to a lesser extent, the retroglossal area of OSA patients compared with control subjects (115–117). The larger the volumes of the lateral pharyngeal walls, tongue, and total soft tissue, the greater are the odds of OSA (117). Thickening of the lateral pharyngeal walls appears to be the predominant factor in OSA (112).

Although the lateral pharyngeal fat pads in OSA patients are enlarged compared with those in control subjects (45, 125), these fat pads do not necessarily impinge on the UA lumen (116). UA edema, especially in the lateral pharyngeal walls, has been demonstrated on tissue specimens and with MRI scanning and can contribute to soft tissue enlargement in OSA patients (2, 114). Nuchal or pharyngeal mucosal edema could result from distension of and/or increased pressure in the neck veins, edema formation from vascular congestion or inflammation secondary to the trauma caused by vibration of tissues during snoring, or pulmonary hypertension from recurrent hypoxic pulmonary artery vasoconstriction (14). The jugular veins are located adjacent to the lateral walls of the pharynx, and because these walls appear to be the most compliant part of the pharynx (69), they would be most susceptible to medial displacement in the face of jugular venous distension in fluid-overload states, such as biventricular heart failure, cor pulmonale, and renal failure (Fig. 3) (126). The soft palate and tongue are also enlarged in OSA patients (14). In adults and, particularly, children, adenotonsillar hypertrophy may increase the risk of OSA (35).

The length of the pharynx may also be a significant predisposing factor for OSA. Cephalometric studies demonstrate a lengthening of the pharynx in men with OSA compared with those without OSA (92), which may predispose to UA collapse by increasing the length of the collapsible portion of the lumen (74). A reduction in the distance from the soft palate to the posterior oropharyngeal wall, which is partly a result of retrodisplacement of the maxilla, has also been observed in OSA patients. A thickening of the soft palate (46) and enlargement of the uvula have been noted in OSA patients (131).

The UA begins in the nares, and nasal obstruction may play a role in UA collapsibility; however, this remains a point of...
conjecture. Nasal obstruction can be caused by a deviated nasal septum or mucosal swelling from allergic or nonallergic rhinitis. This causes an increase in airflow resistance upstream from the collapsible portion of the pharynx. As a result, the degree of negative collapsing pressure is increased on inspiration, rendering the pharynx more collapsible. Indeed, experimentally induced nasal obstruction can induce sleep-disordered breathing (137). Increased nasal airflow resistances due to allergic rhinitis can induce or worsen OSA and can be alleviated by intranasal steroids or spontaneous resolution of rhinitis (58, 79). However, surgical correction of a deviated nasal septum does not consistently alleviate OSA, although it may reduce continuous positive airway pressure (CPAP) requirements in patients with severe OSA (59). Although nasal obstruction may contribute to UA collapsibility, data are insufficient to clarify its role in the pathogenesis of OSA.

The significance of the combination of skeletal and soft tissue factors in predisposing to UA obstruction is highlighted by observations in subjects with acromegaly, in whom prevalence of OSA is increased (36). In acromegaly, a dorsocaudal rotation of the mentum with posterior-cranial repositioning of the angle of the mandible causes retrodisplacement of an enlarged tongue (40). Treatment of acromegaly may cause regression of some of the soft tissue changes (particularly the macroglossia), but because the skeletal abnormalities are permanent, OSA often persists (47).

**Pharyngeal Collapsibility**

**Compliance and critical closing pressure.** In addition to reduced UA caliber, UA collapsibility is also increased in OSA patients. In general, UA collapsibility is a function of the balance of surrounding tissue collapsing pressure, intraluminal pressure, and compliance of pharyngeal walls (16). Pharyngeal compliance is expressed as the change in volume or cross-sectional area per unit change in pressure and is an indicator of the ease with which an airway can be deformed (15). Because compliance is usually considered to reflect the passive properties of the tissues, it is difficult to quantify because of the difficulty in ensuring that UA muscle activation is not contributing to such measurements. Greater UA compliance is related to greater collapsibility of the UA in OSA patients than in control subjects (66). Passive collapsibility of the UA has been assessed during natural or benzodiazepine-induced sleep and during muscular paralysis by vecuronium (48, 85). Under these conditions, the UA is stabilized with CPAP. Passive UA collapse is induced by a sudden reduction in CPAP or application of negative pressure while nasal or pharyngeal pressure is recorded (48, 85). The pressure at which the UA collapses is the critical collapsing pressure (Pcrit). In patients with severe OSA, Pcrit is positive, indicating a more collapsible UA than in normal subjects, in whom it is markedly negative. The combination of obesity and craniofacial anomalies, on the one hand, and increased pharyngeal compliance, on the other, may act synergistically to increase Perit (144). In men there is a graduated increase in UA collapsibility from younger to older healthy subjects to OSA patients. This may indicate that with normal aging the UA becomes smaller and/or more collapsible, thus approaching the characteristics of OSA patients (29, 31).

**Pharyngeal muscles.** Although anatomic factors play an important role in the pathogenesis of UA occlusion in OSA patients, because OSA occurs only during sleep, neuromuscular factors must also be involved. Such factors include UA muscle tone, sensation, and function.

The pharyngeal muscles are responsible for movement of the tongue, soft palate, uvula, hyoid bone, and pharynx and subserve multiple functions, including respiration, phonation, deglutition, and coughing. There are many pharyngeal dilator muscles, but the most studied are the genioglossus (GG) and tensor palatini (TP). The GG is responsible for protrusion and depression of the tongue, and its activity is mainly phasic on inspiration (110). The TP tenses the soft palate, and its activity tends to be more tonic throughout the respiratory cycle (38). These muscles have been studied during wakefulness and sleep in normal subjects and OSA patients. Previous studies have demonstrated the important role of the UA dilator muscles in maintaining airway patency. However, whether they dilate or simply stabilize the airway, preventing collapse, remains uncertain (62). It seems likely that the TP stabilizes, while the GG dilates, the UA. The importance of the GG in maintaining UA patency has been previously demonstrated by the observation that activation of the GG through stimulation of the hypoglossal nerve during sleep increased UA diameter and improved OSA (25, 118).

The activity of pharyngeal muscles is elevated during wakefulness in OSA patients compared with normal subjects (27). At sleep onset in normal subjects, there is an initial fall in UA muscle activity due to a reduction in central respiratory drive (150). However, this fall in muscle activity is transient in the phasic muscles; subsequently, during non-REM (NREM) sleep, phasic GG activity is increased, but tonic TP activity continues to fall (138). In OSA patients at sleep onset, there is a greater reduction in GG activity, which may predispose to pharyngeal collapse (80). Over the course of an obstructive event, the GG activity increases in response to the rising PCO2, until the patient awakens, GG activity is suddenly augmented, and airflow resumes (5).

The control of the UA dilators is through a number of pathways: 1) central respiratory pattern-generating neurons located in the ventral medulla that respond to changes in PCO2 and Po2 (9, 2) vagal input due to changes in lung volume (4), 3) the wakefulness drive to the muscles mediated through the state-sensitive neural systems (91), 4) reflex activation in response to negative intrapharyngeal pressure, and 5) mucosal mechanoreceptors (24).

Local mechanoreceptor-mediated reflexes influence the activity of the UA dilator muscles. The application of negative pressure to the UA in humans leads to a substantial increase in the activity of the GG as well as other UA muscles (44, 76). This is proportional to the increasingly negative epiglottic pressure and UA resistance (UAR). Local topical anesthesia attenuates this reflex (6, 7, 28, 147). Although CPAP reduces UAR and phasic and peak GG activity, GG activity remains higher than in healthy men (29, 80). In tracheostomized OSA patients, GG activity is reduced when ventilation is switched from nasal breathing to breathing through the tracheostomy, indicating that sensing of pressure and/or flow in the UA elicits this reflex GG activity (73). However, during sleep in normal subjects, the response of these local mechanoreceptors to negative pressure is diminished, as demonstrated by the decline in the slope of the correlation between peak GG activity and epiglottic pressure, pharyngeal airflow resistance (30, 75), and...
P\textsubscript{CO}_2 from wakefulness to NREM sleep (29). During NREM sleep, the ability of the GG to respond to brief pulses of negative pressure, elevated P\textsubscript{CO}_2, or inspiratory resistive loading is diminished (43, 73, 146).

It is known that chronically increased muscle activity can lead to histological changes in muscles that may adversely affect function (108). Chronic trauma to UA structures by low-frequency vibration due to snoring may also play a role (32). In OSA patients, there are inflammatory T lymphocytes within the UA mucosa (CD4 and CD8) and musculature (predominantly CD4). Inflammatory cell infiltration in skeletal muscle can cause contractile dysfunction through a direct effect on the muscles or through a toxic neural effect causing denervation (12). Increased fatigability of the UA dilators or constrictors has been suggested as one possible factor in OSA that prevents dilator activity from maintaining patency in response to high UAR (111). This may arise, in part, from an abnormally high ratio of type IIa fatigue-susceptible to type I fatigue-resistant fibers (123), which is supported by the observation that treatment of OSA by long-term CPAP reduces the proportion of these type IIa fibers (19). Intermittent hypoxia may provoke the shift to a more fatigable fiber type in OSA patients (93). A more recent study demonstrated similar GG contractile endurance (fatigability) but increased time to recovery of strength in OSA patients compared with control subjects after induction of fatigue (11). Increased recovery time is an early sign of fatigue and could herald impending contractile impairment of the UA dilators. The cause of this impaired recovery of contractile strength remains to be determined.

**Sensory changes.** The pharyngeal muscles are sensitive to local stimuli and, in particular, negative intrapharyngeal pressure, which causes activation of these muscles (see Pharyngeal muscles). Inasmuch as topical UA anesthesia induces apneas and hypopneas during sleep in normal subjects and OSA patients, impairment of UA mucosal sensory function could contribute to UA collapse during sleep (20, 78). Therefore, inability to detect mechanical stimuli, such as increased UAR, may reduce dilator muscle activity, leading to UA collapse. Impairment of sensation in the UA may be primary or secondary to trauma or inflammation from vibration and suction pressure on the UA soft tissues from snoring and repetitive UA collapse. Degenerative neural changes have also been shown in biopsy specimens from the uvula and soft palate mucosa (33, 149). This sensory dysfunction has also been demonstrated on direct testing of sensitivity to vibration, two-point discrimination, temperature thresholds, and vascular reactivity in the pharyngeal mucosa (34, 60, 68).

**Respiratory influences on the UA.** As with the intrathoracic airways, UA size varies with lung volume: it increases during inspiration and decreases during expiration. The degree of lung volume dependence of UA cross-sectional area is increased in OSA patients compared with normal subjects (42). This lung volume dependence is greatest below functional residual capacity, so the pharynx has a greater tendency to collapse at low lung volume in OSA patients than in control subjects (13, 107). Increases in lung volumes may also affect pharyngeal stiffness through caudal traction on the trachea, which can tether the pharynx and make it more resistant to collapse (104).

In several respects, the UA behaves as a Starling resistor during sleep; i.e., it collapses when the intraluminal pressure falls below the extraluminal tissue pressure (113, 120). In OSA patients, pharyngeal occlusion usually occurs above atmospheric pressure (49, 129). The pharynx can collapse at end expiration or at the beginning of inspiration (84, 135). Collapse at end expiration indicates passive collapse when phasic pharyngeal dilator muscle activity is at its lowest or is absent (133). This is consistent with the observation in many OSA patients that Pcrit is positive (113). On the other hand, the observation that UA collapse can occur at the onset of inspiration indicates that, in some instances, negative intraluminal suction pressure is an important collapsing factor in which Pcrit would be less than or equal to atmospheric pressure (27, 120).

**Effects of Sleep on UA Function**

Central drive to the respiratory pump and the UA dilator muscles is reduced at the transition from wakefulness to NREM sleep. This leads to reduced UA cross-sectional area and increased UAR, which render the UA more susceptible to collapse. The drive to the UA dilators is further reduced at the transition from NREM to REM sleep. As a consequence, the UA is most susceptible to collapse during REM sleep, which is the state during which obstructive apneas are most often observed (21). In some OSA patients, there appears to be an imbalance between the high neural input to the inspiratory pump muscles and the lower input to the UA dilator muscles, which contribute to UA collapse by increasing collapsing pressure without increasing UA dilator activity (121).

**Respiratory Control System Instability in OSA**

The significance of ventilatory instability in the pathogenesis of OSA is a matter of debate. The presence of ventilatory instability in OSA patients was first noted when periodic breathing, accompanied by central apneas, occurred after tracheostomy (90). However, over time, periodic breathing resolved, suggesting that periodic breathing and respiratory control system instability may have occurred as a consequence, rather than as the cause, of OSA. On the other hand, induction of periodic breathing during sleep by hypoxia, but only in the presence of inspiratory resistive loading, can induce UA obstruction in normal subjects (89).

The possibility that respiratory system instability is present in some OSA patients has been tested more directly by Younes and colleagues (153). They assessed the degree of respiratory control system instability by quantifying loop gain (LG), which is the ratio of a corrective response (ventilation) to a disturbance (ventilatory perturbation that instigated the response). At LG > 1, respiration is unstable, and periodic breathing tends to occur. Younes et al. found that LG, assessed during sleep as the degree of ventilatory assist (applied by a proportional-assist ventilator) required to cause ventilatory overshoot, triggering a fall in P\textsubscript{CO}_2 below the apnea threshold and, thereby, precipitating periodic breathing, was greater in patients with severe OSA than in those with mild OSA (151). Wellman and colleagues (145) found that LG was greatest in OSA patients in whom Pcrit was close to atmospheric than in those in whom Pcrit was negative (less pronounced UA collapsibility) or positive (greater UA collapsibility) (145). However, neither study established whether LG contributes to the pathogenesis or is a result of OSA. Thus the extent to which augmented LG...
and respiratory control system instability contribute to the pathogenesis of UA obstruction in OSA remains unclear.

Younes (152) also proposed that arousals might augment LG and, thereby, precipitate periodic breathing and UA collapse during the waning phase of hyperpnea. Traditionally, arousal has been viewed as a defense mechanism that augments UA dilator muscle tone at the termination of obstructive apneas to facilitate airflow. However, if arousals cause ventilatory instability by triggering ventilatory overshoot, they might increase the tendency for repetitive UA collapse in some OSA patients. Although increasing airway collapsibility during sleep in normal subjects with sleep fragmentation has been demonstrated (122), there is no clear evidence that arousals from sleep play an important role in the causation of OSA.

Other Potential Mechanisms for UA Collapse

Surface tension. The stability of the UA may be influenced by surface adhesive forces and fluid elasticity. During UA collapse, apposition of pharyngeal mucosa may lead to mucosal desiccation and/or trauma, which could reduce surface tension and/or increase mucous adhesiveness. Such factors could facilitate and/or maintain collapse of the UA by increasing the dilator muscle activity required to restore UA patency. Indirect evidence for the role of surface tension in maintaining UA patency was initially demonstrated by a reduction in the incidence of snoring (41) and an increase in resistance to collapse of the airway in awake human subjects due to the topical application of surfactant (141). Furthermore, in sleeping OSA patients, application of lubricant and surfactant to the UA mucosa reduced the frequency of obstructive events over short periods (54, 61). The reduction in the severity of OSA correlated with the reduction in UA mucosal surface tension during wakefulness. These observations suggested a role for reduced surface tension in the pathogenesis of OSA (61).

Central neurotransmitters. Central neurotransmitters can inhibit or excite the hypoglossal motor neurons and the GG (65). Animal studies have demonstrated that the neurotransmitters norepinephrine and serotonin are excitatory (51) and that glycine and GABA are inhibitory to the hypoglossal motor neurons (63), whereas acetylcholine has mixed effects (71). However, receptor antagonism of these neurotransmitters in animals has produced inconsistent results (86, 87), raising the following question: What, if any, role do these neurotransmitters play in activation and inhibition of UA dilators? Furthermore, the use of the serotonin-enhancing agents fluoxetine and protriptyline did not significantly improve OSA in humans (39, 64). More recently, it has been shown that although the selective serotonin reuptake inhibitor paroxetine increases GG activity during wakefulness in healthy humans (134) and during NREM sleep in OSA patients, it had no effect on the severity of OSA (8). Thus there is no evidence that central neurotransmitters that affect UA dilator muscles play a role in the pathogenesis of OSA.

Influence of Gender, Obesity, and Racial Factors

OSA is two to three times more prevalent in men than in women (99, 155). Although the reasons for this are not entirely

Table 1. Factors affecting pharyngeal patency

<table>
<thead>
<tr>
<th>Factors Maintaining Patency</th>
<th>Factors Facilitating Collapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal factors</td>
<td>Skeletal factors: constricted pharyngeal envelope</td>
</tr>
<tr>
<td>Normal craniofacial structure</td>
<td>Maxillary and/or mandibular hypoplasia or retrodisplacement</td>
</tr>
<tr>
<td>Soft tissue factors</td>
<td>Inferior displacement of hyoid</td>
</tr>
<tr>
<td>Normal volume of soft tissue surrounding the pharynx</td>
<td>Soft tissue factors</td>
</tr>
<tr>
<td>Increased volume of soft tissue</td>
<td>Increased volume of soft tissue</td>
</tr>
<tr>
<td>Adenotonsillar hypertrophy</td>
<td>Adenotonsillar hypertrophy</td>
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<tr>
<td>Macroglossia</td>
<td>Macroglossia</td>
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<tr>
<td>Thickened lateral pharyngeal walls</td>
<td>Thickened lateral pharyngeal walls</td>
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<tr>
<td>Increased fat deposition</td>
<td>Increased fat deposition</td>
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<tr>
<td>Increased vascular volume</td>
<td>Increased vascular volume</td>
</tr>
<tr>
<td>Pharyngeal inflammation and/or edema</td>
<td>Pharyngeal inflammation and/or edema</td>
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<tr>
<td>Increased muscle volume</td>
<td>Increased muscle volume</td>
</tr>
<tr>
<td>Pharyngeal compliance</td>
<td>Pharyngeal compliance</td>
</tr>
<tr>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Pharyngeal muscle factors</td>
<td>Increased Pharyngeal muscle factors</td>
</tr>
<tr>
<td>Normal strength and function of pharyngeal dilators and fixators</td>
<td>Impaired strength and endurance of pharyngeal dilators and fixators</td>
</tr>
<tr>
<td>Sensory factors</td>
<td>Sensory factors</td>
</tr>
<tr>
<td>Normal mechanoreceptor sensitivity</td>
<td>Impaired mechanoreceptor sensitivity</td>
</tr>
<tr>
<td>Brisk pharyngeal dilator reflexes</td>
<td>Impaired pharyngeal dilator reflexes</td>
</tr>
<tr>
<td>Lung volume dependence of UA XSA</td>
<td>Lung volume dependence of UA XSA</td>
</tr>
<tr>
<td>Normal</td>
<td>Increased below FRC</td>
</tr>
<tr>
<td>Respiratory control system factors</td>
<td>Respiratory control system factors</td>
</tr>
<tr>
<td>Stable respiratory control</td>
<td>Unstable respiratory control</td>
</tr>
<tr>
<td>Normal ventilatory responses and LG</td>
<td>Increased ventilatory responses and LG</td>
</tr>
<tr>
<td>Gender factors</td>
<td>Gender factors</td>
</tr>
<tr>
<td>Female influences</td>
<td>Male influences</td>
</tr>
<tr>
<td>Peripheral pattern of obesity</td>
<td>Centripetal pattern of obesity</td>
</tr>
<tr>
<td>Presence of progesterone</td>
<td>Absence of progesterone</td>
</tr>
<tr>
<td>Absence of testosterone</td>
<td>Presence of testosterone</td>
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<tr>
<td>Weight</td>
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</tr>
<tr>
<td>Normal</td>
<td>Obesity causing peripharyngeal fat accumulation</td>
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UA XSA, upper airway cross-sectional area; FRC, functional residual capacity; LG, loop gain.
clear, two factors seem to be important: the pattern of fat distribution and differences in sex hormones.

Obesity is by far the most common predisposing factor for OSA (154). A centripetal pattern of obesity, with fat preferentially distributed to the abdominal viscera, upper body, and neck, is more closely linked to OSA than a peripheral pattern of obesity, in which fat is preferentially distributed to the subcutaneous tissues of the hips and thighs (143, 156). Inasmuch as obese men have increased centripetal fat distribution, they are at increased risk of developing OSA, most likely through fat deposition in the neck, causing narrowing of the pharyngeal lumen (23, 88). Weight loss in obese men with OSA attenuates OSA in association with an increase in the UA cross-sectional area (106, 119). Obese women are less susceptible to the development of OSA than obese men, most likely because of less fat deposition in the neck (148). Nevertheless, as women go through menopause, fat distribution takes on a more centripetal pattern, which is associated with a greater tendency to develop OSA (155).

Comparisons of the UA between the genders in OSA patients are few. Once differences in body size are accounted for, UA cross-sectional area is similar in men and women. However, in men with OSA the UA is more collapsible during NREM sleep (i.e., higher Pcrit) in than body mass index-matched women with OSA, in whom OSA is also less severe (37, 83). Thus it appears that women are protected from OSA, partly because their UA is less collapsible than in men for a given body mass index. No consistent differences in UA at the onset of sleep have been observed between healthy men and women (105, 139, 140).

Because of the greater risk of OSA in postmenopausal than in premenopausal women, low progesterone/estrogen or high testosterone has been implicated in the pathogenesis of OSA (10). Progesterone is a respiratory stimulant and may stabilize the respiratory control system and protect against OSA. Testosterone, on the other hand, contributes to fat deposition in the neck and may contribute to the development of OSA through reduced UA size. In support of this hypothesis is the increased prevalence of OSA in women with high endogenous levels of testosterone (142) and the induction of OSA through administration of testosterone to women and hypogonadal men (109). However, androgen blockade did not affect OSA in men (132).

Because of the greater risk of OSA in postmenopausal than in premenopausal women, low progesterone/estrogen or high testosterone has been implicated in the pathogenesis of OSA (10). Progesterone is a respiratory stimulant and may stabilize the respiratory control system and protect against OSA. Testosterone, on the other hand, contributes to fat deposition in the neck and may contribute to the development of OSA through reduced UA size. In support of this hypothesis is the increased prevalence of OSA in women with high endogenous levels of testosterone (142) and the induction of OSA through administration of testosterone to women and hypogonadal men (109). However, androgen blockade did not affect OSA in men (132).

Therefore, the role of mechanisms of sex hormones in OSA is unclear and requires further investigation.

Epidemiological studies suggest some differences in factors contributing to the pathogenesis of OSA among racial groups (17, 94, 95). For instance, for a given degree of severity of OSA, Asians have shorter maxillae and mandibles, smaller anterior-posterior facial dimensions, and lower BMI than Caucasians (67, 70, 72). This suggests that constriction of the bony cage is of greater importance than obesity and soft tissue factors in the pathogenesis of OSA in Asians than in Caucasians. On the other hand, soft tissue factors, including increased tongue area and increased soft palate length, play a greater role in susceptibility to OSA in African-Americans than in Caucasians (18, 100). The potential role of gender, racial, and genetic factors in the pathogenesis of OSA is described in greater detail elsewhere (55, 96, 136).

Future Directions

Although the critical pathophysiological feature of all OSA patients is partial or complete collapse of the pharynx during sleep, as outlined in this review, many factors, alone or in combination, can contribute to this collapse. These are summarized in Table 1. These observations suggest that OSA may be a heterogeneous disorder, rather than a single disease entity. Therefore, one of the main objectives of future research in OSA should be the elucidation of the relative contributions of different pathophysiological factors to the development of recurrent sleep-related collapse of the pharynx in individual patients. Such an approach could lead to the development of new treatments for OSA that would target specific pathways that lead to UA collapse and provide alternatives to CPAP and oral appliances.

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Invited Review


