Anatomy and Physiology of Obstructive Sleep Apnea

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KEYWORDS

• Obstructive sleep apnea • Pathophysiology • Anatomy • Hypoglossal nerve • Pcrit • Ventilator control • Pharyngeal • Risk factors

KEY POINTS

- The oropharynx is the most common site of airway collapse in obstructive sleep apnea (OSA), and enlarged parapharyngeal fat pad, thicker lateral pharyngeal walls, and increased tongue volume play key roles.
- Pharyngeal closing pressure is influenced by craniofacial abnormalities, soft tissue crowding from obesity, caudal traction, and lung volumes.
- Reversible heightened arousal threshold in apneic patients combined with high loop gain ventilator response to arousals contribute to ventilatory instability.
- Obesity, sex, and age are pathophysiologic factors that promote OSA.

ANATOMY

This article reviews how the upper airway anatomy influences the pathophysiology of obstructive sleep apnea (OSA), and the pertinent anatomy.

The upper airway is a common passageway for digestive, respiratory and phonatory systems. Traditionally it is divided to 3 sections: the nasopharynx, oropharynx, and hypopharynx.

The nasopharynx extends from the posterior margin of the nasal turbinates; it sits above the soft palate and continues inferiorly with the oropharynx. The posterior wall is occupied by adenoids, which when inflamed can partially obstruct the upper airway. The soft palate, a nearly vertical flap, extends from the posterior edge of hard palate and terminates in the uvula. All the muscles of the soft palate are innervated by the pharyngeal branch of vagus nerve except the tensor veli palatini, which is innervated by the medial pterygoid nerve. A posterior elevation of the soft palate toward the posterior pharyngeal wall can cause enlargement of the oral cavity during swallowing and produce narrowing of the nasopharynx. Adenotonsillar disease can lead to sleep-disordered breathing. Polysomnography in children with allergic rhinitis and adenoidal hypertrophy found that 66% have mild apnea.[1] In fact in children, tonsillectomy and/or adenoidectomy is the first therapeutic modality to be considered for the treatment of OSA.[2]

Humans naturally breathe through the nose, particularly during sleep, when the daily oral fraction of breathing, estimated at 7%, drops to 4% during sleep.[3] Although during wakefulness both nasal and oral resistances are equal, nasal resistance is lower than the oral at night,[4] but increases in the supine position.[5] Hippocrates[6] first mentioned the connection between the nose and breathing in sleep when he described a role of

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Sleep Med Clin 8 (2013) 425–431
http://dx.doi.org/10.1016/j.jsmc.2013.07.016
1556-407X/13/$ – see front matter

nasal polyps in restless sleep. Nasal obstruction can occur secondary to deviated septum, chronic rhinosinusitis, and nasal polyps. Nasal congestion has been associated with a 3-fold increase in the incidence of snoring and daytime sleepiness.[7] Earlier studies indicate that acute nasal obstruction could increase the apnea-hypopnea index (AHI), prolong rapid eye movement (REM) latency, and increase non-REM (NREM) sleep.[8] However, nasal obstruction alone is not thought to cause any moderate or severe OSA.[6,9]

The hard and the soft palate form the roof of the oral cavity, and the lingual mucosa covers the floor. The lateral part of the oral cavity is covered by buccal mucosa and anterior pillars of palatine tonsils, which define the junction with oropharynx. The tongue, which occupies the major part of the oral cavity, has both extrinsic and intrinsic muscle groups. The 4 extrinsic tongue muscles are the genioglossus, hyoglossus, palatoglossus, and styloglossus. The genioglossus is the largest and most-studied pharyngeal dilator muscle. All of these muscles are innervated by the hypoglossal nerve except the palatoglossus, which is innervated by the vagus nerve. The intrinsic muscles of the tongue (superior and inferior longitudinal, transverse, and vertical muscles) are confined to the tongue. The anterior two-thirds of the tongue is innervated by the facial nerve, whereas the posterior one-third is innervated by cranial nerve IX. The size of the tongue is an important risk factor for OSA.[10]

An increase in the size of type II muscle fibers is seen in OSA compared with normal subjects, which could represent a response to vibratory strain or perhaps neuronal activity.[11,12]

The hypoglossal nerve is a critical component in the motor control of upper airway dilatation. The muscle fibers in the posterior part of the tongue are fatigue-resistant, thereby sustaining the forward tongue position and preventing its collapse into the retroglossal area. Using this mechanism, the therapeutic effect of proximal hypoglossal nerve stimulation can be used to treat OSA.[13]

The oropharynx extends from the soft palate to the epiglottis. The anterior part of oropharynx is formed by the posterior part of the tongue and the soft palate, whereas the posterior part is formed by the pharyngeal constrictor muscles. The lateral pharyngeal walls are formed by the pharyngeal constrictors, muscles of the extrinsic tongue, muscles of the soft palate, and the larynx. Other structures that contribute to upper airway lumen, located in the retropalatal area, are the palatine tonsils and parapharyngeal fat pads.

A magnetic resonance imaging (MRI) study revealed a smaller minimum airway area in patients with OSA in the retropalatal region, and particularly in the lateral dimension, compared with individuals with normal breathing.[14] The volume of the tongue and lateral walls have been shown to independently increase the risk of OSA.[15]

The oropharynx is the most common site of airway collapse in patients with OSA,[16] which is more likely to occur during REM sleep.[17] A recent study evaluating the role of parapharyngeal fat in the predisposition to OSA used MRI to examine pharyngeal anatomy. Patients with retropalatal airway closure had a higher percentage of parapharyngeal and soft palate fat, whereas patients with retroglossal airway closure had an increased volume of the tongue and parapharyngeal fat pad (**Fig. 1**).[18]

The caudal portion of the upper airway is the hypopharynx, which extends from the superior border of the epiglottis to the inferior border of the cricoid cartilage. It is formed anteriorly by the base of the tongue and the epiglottis, and

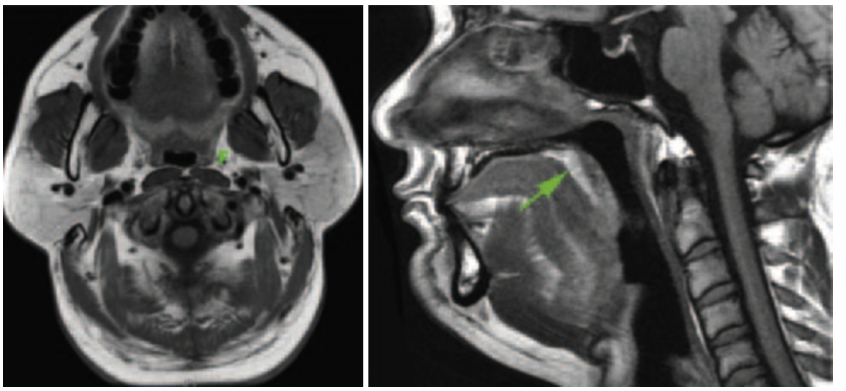

Fig. 1. Parapharyngeal fat pad and fat tissues in the soft palate (*green arrow*). (*From* Li Y, Lin N, Ye J, et al. Upper airway fat tissue distribution in subjects with obstructive sleep apnea and its effect on retropalatal mechanical loads. Respir Care 2012;57(7):1100; with permission.)

postero-laterally by the inferior pharyngeal constrictor. Obstruction at the level of the hypopharynx is less common than at the oropharynx. The structures in the hypopharynx, such as the lingual tonsils, can have a potential role in OSA.[19] In children with tonsillar hypertrophy, tonsillectomy is an effective treatment for snoring and OSA.[20] Epiglottic prolapse during inspiration has been described as a cause of OSA, with a partial laser epiglottidectomy reported as a cure.[21]

PATHOPHYSIOLOGY

The pathophysiology of OSA is multifactorial, with much individual variability. The complex interaction among pharyngeal dilator tone, arousal threshold, respiratory control instability, and changes in lung volume during sleep plays an important role in OSA. Considerable heterogeneity exists in the mechanism of OSA in patients.[22] This section focuses on how these and other factors interact to cause obstruction of the upper airway during sleep, but does not dwell on the pathophysiologic consequences of OSA on the body.

Upper Airway Collapsibility

The vulnerable airway extends from the hard palate to the larynx, and can collapse during sleep. This collapse can occur because of variations in transmural pressure, such as decreased intraluminal pressure or increased external tissue pressure, or a reduction in the longitudinal tension on the pharynx. MRI studies indicate that the apneic airway is different from the normal airway because of thicker lateral pharyngeal walls with an anterior-posterior elliptical configuration, unlike the horizontal configuration in the normal airway. This thickened anatomy seems to be more important than the enlargement of parapharyngeal fat pads in causing airway narrowing in apneic patients.[14] The minimal airway area is also smaller in apneic patients, contributing to the airway collapse. The threshold pressure required to maintain patency of the upper airway is called the *pharyngeal closing pressure* (Pcrit). Pcrit has been shown to correlate with OSA severity.[23]

When the principles of a Starling resistor are applied, the pharyngeal airway can be conceptualized as a collapsible tube surrounded by tissue within a bony box.[24] The luminal size is determined by the properties of the tube and the transmural pressure, which is the difference between pressures inside and outside the tube. Increase in the outside tissue pressure will promote luminal narrowing. Pcrit will increase as tissue pressure increases, which could occur from a reduction in size of the bony box from micrognathia, a high arched palate, or mid-face hypoplasia, or from soft tissue crowding caused by macroglossia, adenotonsillar hypertrophy, and central adiposity.[25] Obesity acts synergistically with narrowing of the bony box. The receded mandibles in apneic patients contribute to increased tissue pressure[26] and, consequently, pharyngeal collapse. Conversely, weight loss has been shown to reduce Pcrit,[27] and the resolution of sleep-disordered breathing depends on the degree of Pcrit reduction. Similarly, a stepwise advancement of the mandible in apneic patients leads to dose-dependent reductions in Pcrit.[28]

Effect of Lung Volumes

Caudal traction and elongation of the airway reduces Pcrit through stiffening the airway and mitigating the surrounding tissue pressures.[29,30] The supine position reduces lung volumes in apneic patients, which decreases caudal traction on the airway. An increase in end-expiratory lung volume using continuous positive airway pressure (CPAP) has been shown to substantially reduce apnea severity and improve sleep architecture.[31] Improvement in caudal traction on the trachea is one mechanism involving in achieving this goal. Apnea severity has also been shown to improve with sleeping in the semi-recumbent position, which would occur through improved caudal traction.[32]

Upper Airway Dilator Muscle Activity

Collapsing forces related to tissue pressure and intraluminal negative pressure are offset by pharyngeal dilator muscle activity. The genioglossus is the largest and most extensively studied pharyngeal dilator.[33] Upper airway dilator tone is high during wakefulness, and this maintains an open airway. With sleep onset, a decrease in the tone of the genioglossus muscle occurs. In apneic patients who are relying on a heightened genioglossus tone to support the airway, this leads to airway instability.[34] The degree to which this occurs also depends on the sleep stage. Slow-wave sleep has been associated with heightened genioglossus tone, which might be protective against OSA.[35] During REM sleep, a reduction in tonic genioglossus activity occurs, which potentiates further apneas.[36] Local reflexes generated by negative pharyngeal pressure during sleep modulate an increase in both genioglossus and tensor palatine tone, especially in the supine position.[37,38] Genioglossus activity increases during inspiration but decreases during expiration.[33] More recently, a secondary suppression phase after an initial excitatory phase was shown in the

genioglossus, but not the tensor palatine, in response to negative pharyngeal pressure. Thus, the genioglossus has both excitatory and inhibitory responses to airway collapse, but the response is variable.[39]

Arousal Response in OSA

Most episodes of apneas are followed by arousals, which are thought to be mediated via negative intrathoracic pressure generation.[40] However, apnea termination can occur without arousals through the accumulation of stimuli, such as chemical drive and negative intrapharyngeal pressures.[41–43] OSA impairs the arousal threshold, and therefore apneic patients need greater inspiratory efforts to trigger an arousal.[44] This function likely represents an acquired response, and means that apneic patients experience prolonged event duration because of the heightened length of inspiratory effort required to trigger an arousal. Treatment with CPAP has been shown to reduce the heightened arousal threshold in apneic patients.[45] Slow-wave sleep may stabilize the breathing in apneic patients via the arousal threshold. Ratnavadivel and colleagues[46] showed that the arousal threshold is further increased in slow-wave sleep compared with N2 sleep, but they did not find evidence supporting increased ventilatory drive or increased upper airway responses during slow-wave sleep compared with N2 sleep.

Ventilatory Control Stability

Ventilatory control stability contributes to OSA pathogenesis but is incompletely understood.[22] The feedback loop that controls the respiratory response to airway collapsibility and arousal can be conceptualized as "loop gain," which refers to the magnitude of the response relative to the intensity of the input.[47] Apneic patients have an elevated loop gain, particularly those with severe OSA,[48,49] which translates into an overshoot of the ventilator response to apneas and arousal, leading to disproportionately lowered carbon dioxide (CO_2). In a recent study, Yuan and colleagues[50] found that obese adolescents with OSA had a higher sensitivity to CO_2 during wakefulness compared with the lean control group. However, in other studies, the ventilator response during wakefulness in OSA has been inconsistent.[51] Importantly, the sensitivity decreased during sleep in the apneic adolescents. This blunting would lead to prolonged obstructive events. However, the magnitude of the ventilatory response to spontaneous arousal may promote driving the CO_2 below the apneic threshold, leading to further sleep-disordered breathing.[50] In a novel study, Edwards and colleagues[52] showed that acetazolamide reduced the ventilator response to spontaneous arousal in patients with OSA treated with CPAP, and improved this ventilatory instability. They found that the ventilator response to spontaneous arousals correlated with the severity of OSA, further increasing the evidence regarding the role of post-arousal ventilatory instability in perpetuating OSA.

Pharyngeal Neuropathy

Pharyngeal neuropathy has been described in patients with OSA.[53–55] A selective impairment of the ability to detect mechanical stimuli in the upper airway of patients with OSA and snorers has been shown using 2-point discrimination and vibratory tests.[53] Abnormal laryngeal sensation has been shown in patients with OSA using air pressure pulses during endoscopy.[54] Inflammation and denervation affect the oral mucosa and upper airway muscles in patients with OSA.[55] Whether it is the vibratory strain[56] or intermittent hypoxia[57] that plays a major role in promoting the pharyngeal neuropathy remains unclear. A recent study found neurogenic changes in the genioglossus.[58] Using measurements of motor unit potentials, Saboisky and colleagues[58] reported evidence of collateral sprouting and reinnervation in the genioglossus, which correlated with lowest oxygen desaturation in patients with OSA. How this neuropathy affects upper airway function during sleep remains to be determined.

EFFECT OF RISK FACTORS ON OSA

Obesity

Obese patients with OSA have increased fat deposits in the soft tissue surrounding the upper airway, including in the soft palate.[59,60] Schwab and colleagues[14] indicated that fat deposits along the lateral pharyngeal wall and posterior tongue play an important role in OSA. Furthermore, the difference in upper airway soft tissue volumes between obese patients with OSA and nonobese controls was small (30 cm^3) compared with differences in body mass index.[14] This finding of a small increase in upper airway soft tissue volume in apneic patients compared with normal controls was confirmed in Japanese patients.[61] Furthermore, a small decrease of 17 cm^3 in upper airway volume from overall weight loss (average of 7.8 kg) led to a 31% decrease in the apnea-hypopnea index.[62] A reduction in functional residual capacity (FRC) is seen in obese individuals,[63] and decreased upper airway patency from low FRC is an additional mechanism contributing to OSA in obese patients.[64] Consequently, weight

loss and improvement in FRC would augment upper airway patency.

Male Sex

The upper airway was found to be longer in patients with OSA, and the length correlates with the severity.[65] An increase in pharyngeal airway length and soft palate area may explain the higher predisposition to pharyngeal collapsibility in men.[66] Arousals from sleep in men are associated with a greater ventilatory response and with hypoventilation on falling back asleep compared with women. This heightened propensity for ventilatory instability on arousal in men was shown to be further exaggerated in supine position.[67]

Age

The prevalence of OSA increases with age, with a plateau after 65 years of age.[68,69] In fact, the increased tendency for OSA has been observed even in otherwise healthy nonobese men older than 50 years.[70,71] Increased parapharyngeal fat and upper airway narrowing has been observed in elderly patients.[72,73] Whether age predisposes to increased upper airway collapsibility is unclear, but studies indicate that patients have an increased vulnerability from longer airways with age.[74,75]

SUMMARY

Understanding of the pathogenesis of OSA is evolving. Airway obstruction can occur at several sites in the upper airway, with the oropharynx the most common. The hypoglossal nerve is a key player in upper airway dilator function. Retrognathia, adenotonsillar hypertrophy, enlarged tongue, lateral pharyngeal wall thickening, and parapharyngeal fat pads are important anatomic risk factors. The arousal response is heightened in apneic patients. Elevated loop gain leads to an overshoot of ventilator response in OSA, contributing to ventilator instability. The role of pharyngeal neuropathy in the pathophysiology of OSA is being investigated.

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