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CME Review

The nose, upper airway, and obstructive sleep apnea

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- Review clinical studies evaluating the role of rhinitis and therapy of rhinitis in obstructive sleep apnea

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Introduction

The pathogenesis of obstructive sleep apnea (OSA) remains a conundrum. It appears multifactorial, and the relative roles of anatomic and neurohumoral factors remain unclear. One component of the pathophysiology of OSA that is among the least understood and studied is the role of the nose and syndromes of rhinitis in the evolution of OSA. It is unlikely that the first manifestation of OSA is intermittent snoring with nasal obstruction, often considered a coincidental finding. The authors propose that abnormal nasal physiology is a major mechanism of OSA and review the available information to support this hypothesis.

Obstructive Sleep Apnea

Obstructive sleep apnea is characterized by partial or complete cessation of airflow and oxygen desaturation during sleep owing to upper airway collapse. Repeated episodes of transient hypoxia during sleep is the key feature of OSA.[1] According to American Academy of Sleep Medicine scoring rules, an apnea is defined as a decrease in respiratory airflow of at least 90% during sleep for at least 10 seconds.[2] Oxygen desaturation is generally present during an apnea but is not required to define apnea. However, to score a hypopnea, it is required to have at least 4% desaturation and at least 30% decrease in respiratory airflow. The severity of sleep apnea is defined by the apnea-hypopnea index (AHI), which is the sum of the total number of apneas and hypopneas per hour of sleep. Upper airway collapse during sleep is a multilevel phenomenon that has been demonstrated by dynamic magnetic resonance imaging, acoustic analysis, sedation endoscopy, and pharyngeal pressure recordings.[3,4] Turbulence of airflow, or the level of resistance, at the nose, oropharynx, and hypopharynx determines the severity of OSA. Although the retropalatal region is the most common site of collapse, airway narrowing is a dynamic process, markedly varying within and among people. Anatomic optical coherence tomography, an endoscopic imaging technique, was used to compare shape, size, and length of the pharyngeal airway in patients with OSA vs without OSA. The study showed that people with OSA have a smaller velopharyngeal cross-sectional pharyngeal area compared with people without OSA. This suggests that the severity of sleep apnea is related to the abnormality of the size of the airway instead of the shape of the airway.[5] Since multilevel resistance in a dynamic process, healthy persons whose anatomy puts them at risk for OSA can maintain a normal patent airway during sleep by dynamically dilating the airway with an active genioglossus muscle.[6] Among the anatomic levels of the upper airway, the nose is the first port of entry and accounts for 50% of total resistance of the upper airway.[5]

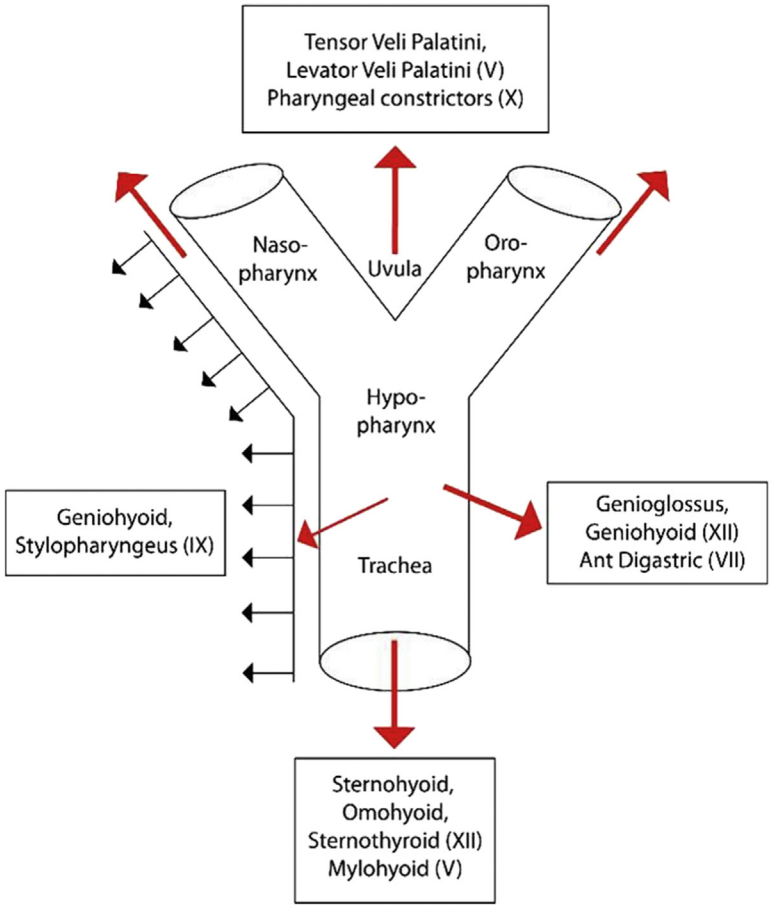

Figure 1. The tethered upper airway and forces that keep it patent during changes in internal pressures associated with respiration. Modified from Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010; 90:47–112.

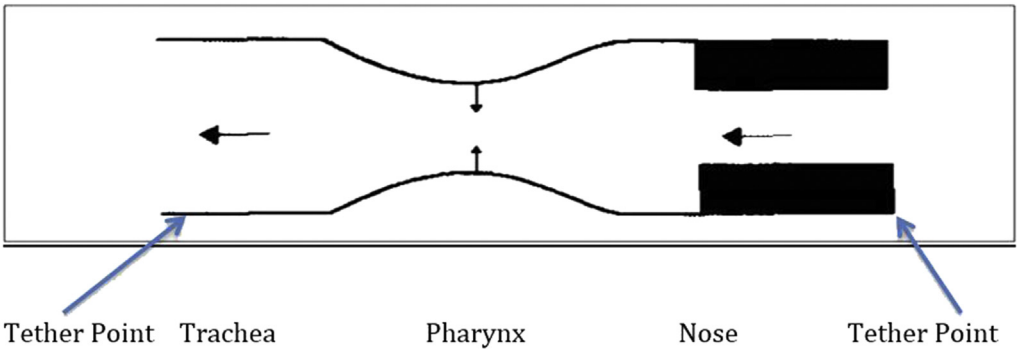

Figure 2. Inspiratory flow through the upper airway promotes closure of the airway. The luminal pressure at which the airway begins to close is the critical closing pressure. The patency of the nose (*left*) can influence the patency of the pharynx (*center*). Adapted from Gold AR, Swartz AR. The pharyngeal critical pressure. The whys and how of using nasal continuous positive airway pressure diagnostically. *Chest*. 1996; 110:1077.

Anatomic Considerations

The collapse of the airway during sleep in patients with OSA is clearly multifactorial. Obstruction can occur at more than 1 level simultaneously and is dynamic in nature.[6,7] The anatomic components of the upper airway include the nose, paranasal sinuses, nasopharynx, oropharynx, larynx, and trachea. The nose and paranasal sinuses function as the gateway to the upper airway and form a vestibule, providing heat, humidity, and filter function to the inspired air before its contact with the epithelium, smooth muscle, and the intricate capillary network below, where respiration occurs.

The upper airway is collapsible throughout, initially at the nasal valve formed by the nasal alae and then in the oropharynx (Fig 1).[6] These structures are subject to negative inspiratory pressure forces, which are transferred from the thoracic cavity in retrograde fashion to the upper airway.[8] The upper airway complex is suspended in the neck and chest and tethered to the skull, neck, and chest structures by muscle complexes that allow movement with cough or swallowing. Coordination of intrinsic and extrinsic airway muscles is required to maintain patency of the airway because the airway structures, with the exception of the trachea, have no rigid support except at the upper and lower extremes. Thus, there is a potential for airway collapse at any point along the airway.[8]

There are multiple factors that are associated with OSA. These include obstruction at the nasal level, small bony infrastructure, short or posteriorly placed mandible, large tongue, thick lateral pharyngeal wall, increased pharyngeal wall fat deposition, size of the pharyngeal airway, loss of muscle tone of the pharyngeal muscles, ventilatory control stability, and arousal threshold from sleep.[9,10] While awake, there is phasic increase in muscle tone of the genioglossus with each inspiration, which prevents the tongue from falling posteriorly in response to negative suction from the lower airway. The continual maintenance of the muscle tone of other pharyngeal muscles prevents the airway from collapse from negative intrathoracic pressure. Tonic and phasic activities in pharyngeal muscles decrease during sleep, more so during rapid eye movement (REM) sleep than non-REM sleep. Normal pharyngeal airway muscle function is decreased in patients with OSA, leading to intermittent partial or complete collapses of the pharyngeal airway during sleep.[6]

Mechanics of Pharyngeal Collapse and the Role of the Nose

The mechanism of nasal airway resistance can be explained by the *Starling resistance model* (Fig 2).[11] It is a term used to describe a highly collapsible tube having infinite compliance at one particular transmural pressure and low compliance at higher or lower transmural pressures.[6] The Starling model views the upper airway as a hollow tube, with a partial obstruction at the inlet, corresponding to the nose, and a collapsible segment downstream, corresponding to the oropharynx.[12]

The luminal pressure at which the airway shifts from a fully open to a fully closed status is referred to as the *critical closing pressure* (Pcrit). This pressure is less than approximately −10 cm H_2O in sleeping and paralyzed humans.[6] The Pcrit increases (to less negative or higher positive) as the resistance to flow increases, which is seen in OSA. Thus, the pharyngeal wall is more likely to collapse from negative intrathoracic pressure during inspiration when higher resistance exists at the inlet (nose). According to this model, partial obstruction at the inlet causes increased downstream suction forces that promote oropharyngeal collapse.[13] With nasal obstruction, the upstream pressure decreases, and when the upstream pressure approaches and decreases below the Pcrit, airflow decreases and can lead to a complete airway collapse.

The Pcrit is affected by sex and body mass index (BMI). Although not understood, men tend to have a higher Pcrit than women. This could be related to longer upper airways, increased fat deposition, and other upper airway anatomic differences found in men.[14,15] As BMI increases, fat deposition in the pharyngeal wall results in an increased extrinsic force on the upper airway, thereby increasing the Pcrit required to keep the airways open. Neck circumference has been reported to be a stronger predictor of AHI than BMI.[13]

Other Factors That Contribute to Airway Collapse When the Nasal Airway Is Compromised

Although the Starling resistance model appears to explain a large component of OSA, it does not explain the entire mechanism.[16] Other factors are known to contribute to airway dysfunction in OSA.

One of these factors is the switch from nasal to oral breathing. Healthy individuals breathe predominantly through the nose during sleep. During normal nasopharyngeal breathing, negative pressure stimulates upper airway afferent nerves that increase the upper airway dilator muscle activity. This is known as the *negative pressure reflex*.[17,18] In the presence of nasal or upper airway congestion, nasal airflow decreases and oral breathing becomes predominant. Oral breathing fails to activate upper airway dilator muscles by activation of the negative pressure reflex, leading to an increased tendency to upper airway collapse.[19–21]

The nasal ventilation reflex is another factor not accounted for in the Starling resistance model. During sleep, the nasal ventilation reflex increases respiratory rate and minute ventilation in healthy people. The absence of nasal airflow, as seen in upper airway obstruction, decreases spontaneous ventilation during sleep.[22,23]

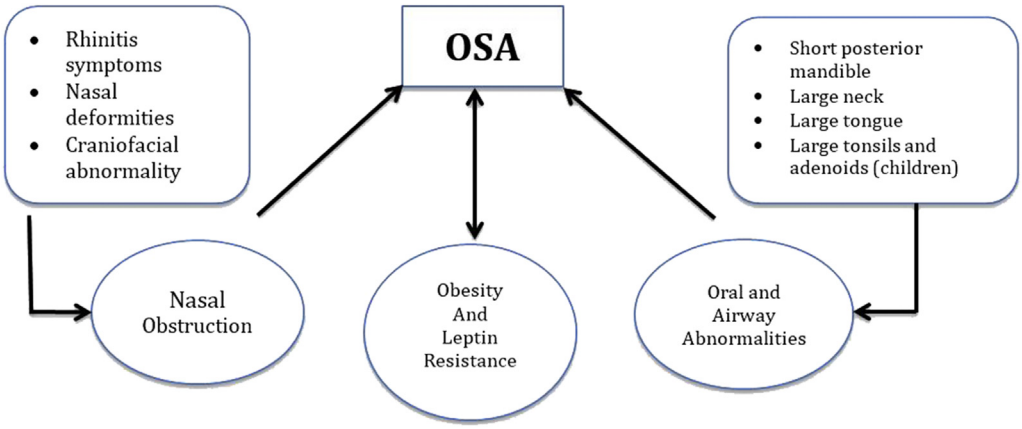

Figure 3. Factors likely to play an important role in the pathogenesis of obstructive sleep apnea (OSA).

The presence of a nasal ventilation reflex is supported by the observation that application of a topical anesthetic to the upper airway decreases arousal times.[23]

Additional areas of airway obstruction represent the third factor. There are multiple areas of normal anatomic airway constriction in the nose, mouth, and hypopharynx. In OSA, these areas also could cause worsening airway obstruction with increased turbulent airflow.[16] This contribution to OSA is different from that proposed in the Starling resistance model because it is not related to pressure gradients, but to loss of laminar airflow.

The role of nasal nitric oxide could be another factor. Nitric oxide is an aero-transmitter between the nose, pharyngeal musculature, and lungs. Oral nitric oxide levels are elevated in OSA and oropharyngeal inflammation.[16,24] These correlate with the AHI. Moreover, elevated levels of plasma inflammatory cytokines have been reported to be present in OSA. Data on the role of inflammatory cytokines in sleep disorders are accumulating. For example, tumor necrosis factor-α levels correlate with sleep time and hypoxemia in OSA, whereas levels of interleukins-1, -4, and -10 correlate with polysomnographic abnormalities in patients with allergic rhinitis.[25,26]

Role of the Pharynx in Adults vs Children

Pharyngeal airway diameter affects the airway patency. Enlargement of soft tissue structures within and surrounding the airway contributes to pharyngeal airway narrowing. Adipose deposition and pharyngeal muscle hypertrophy might contribute. Adipose deposits under the mandible and within the tongue, soft palate, and uvula contribute to extrinsic compression of lateral airway walls.[27] Compensatory pharyngeal muscle hypertrophy can result and further compress lateral pharyngeal walls, narrowing pharyngeal airway diameter.[28–31]

In children, the major contributor to airway narrowing is hyperplasia of pharyngeal tonsils and adenoids.[32] In adults, this obstruction is multilevel and dynamic. Subtle craniofacial abnormalities, such as a high arched palate, long soft palate, large tongue, moderately retro-placed mandible, redundant tissues in retropalatal, or hypopharyngeal region, can play a role in the obstruction of OSA. Decreased contractility of upper airway dilator muscles also can affect the level of obstruction. To improve the success rate of surgery, drug-induced sleep endoscopy is being used more commonly to detect the dynamic changes occurring during sleep before proceeding for a corrective surgery.[33]

The decrease in muscle tone in the pharyngeal musculature during sleep is more prominent in REM sleep than in non-REM sleep.[34] This explains the higher AHI seen in some individuals during REM sleep than during non-REM sleep. Use of alcohol, opioids, and muscle relaxants in patients with sleep apnea generally worsens the problem. Continuous positive airway pressure (CPAP), which is the gold standard treatment of OSA, works as a pneumatic stent to prevent collapse of the pharyngeal walls secondary to the decreased muscle tone occurring during sleep.

Airway edema and surface tension also appear to contribute to OSA. The severity of sleep apnea has been compared between supine and lateral positions in patients with severe sleep apnea (AHI >70/h, $n = 30$). Apneic events are more frequent and prolonged in the supine than in the lateral position.[35] Different approaches, such as elevating the head of the bed to 30° or sewing a tennis ball to the back of a shirt, have been used to avoid the supine position.[36] An accumulation of even small amounts of edematous fluid (up to 200 mL) can enlarge the upper airway soft tissue and promote airway collapse, as with recumbency and the displacement of fluid from the lower extremities to the interstitial tissue of the upper airway. Vascular engorgement while in the supine position increases the thickness of the airway surface. Edema in the mucosa of the pharyngeal wall creates a higher surface tension, resulting in increased airway resistance.

Fat, Respiration, and Leptin

Fat deposits are a rich source of humoral mediators and inflammatory cytokines, which can affect the neural pathways for respiratory control.[37] Leptin, an adipocyte-derived factor, plays a key role in appetite and satiety regulation by interacting with receptors in the hypothalamus. It also affects muscle fiber and adipose distribution in normal people. Leptin directly promotes skeletal muscle lipid oxidation and insulin-mediated glucose uptake.

Leptin also acts as a respiratory stimulant. Obese individuals develop leptin resistance and exhibit respiratory depression. Measurement of respiratory function in the mouse has associated profound obesity with impaired respiratory mechanics and depressed respiratory control, particularly during sleep. Experimental data also suggest that sleep fragmentation, hypoxia, altered glucose metabolism, and leptin resistance in OSA might contribute to elevated serum leptin, promoting body fat deposition and an increase in obesity.[38] Circulating leptin concentrations in patients with OSA, independent of BMI and age, are significantly higher than levels in nonapneic controls, and there is a positive relation between leptin concentrations and the severity of sleep apnea. Neck circumferences (>17 inches for men and >16 inches for women) and BMI (>35 kg/m^2) have been consistently used as screening tools for OSA.[39]

Losing weight lessens the severity of sleep apnea, but a recent study has reported that the change in central adiposity is more closely associated with improvement in AHI than overall weight loss.[40] Decreases in AHI after a weight-loss trial have been correlated with a decrease in upper airway length and abdominal adiposity. Leptin levels appear to correlate with BMI and with total abdominal and subcutaneous fat in untreated OSA. After 8 weeks of treatment of OSA with CPAP, a significant decrease in leptin levels occurred, without a concomitant decrease in BMI.[41] These studies support a role for leptin in the pathophysiology of obesity and OSA and logically fit into models of the pathogenesis of OSA (Fig 3).

Clinical Studies Evaluating the Role of the Nose in OSA

Importance of Nasal Airway

The nasal airway comprises nearly two thirds of the airway resistance during normal breathing. Levels of resistance vary during respiration.[5] A high nasal resistance is one contributing factor in the pathogenesis of OSAs in general,[42] and daytime nasal obstruction is an independent risk factor for OSA.[38] Nasal obstruction can increase the frequency of respiratory events during sleep or increase arousals from sleep even without respiratory events, leading to sleep fragmentation. Any factor causing nasal obstruction will lead to an increase in negative pressure in the upper airway and thus promote inspiratory collapse at the pharyngeal level.

Unilateral and bilateral elevations of nasal resistance can lead to severe snoring or apnea, and supine nasal resistance is closely related to sleep-disordered breathing. Various fixed and dynamic obstructions, including engorgement of blood vessels in the middle and inferior turbinates, nasal septal deviation, congenital and acquired upper airway malformations, nasal polyps, and other mucosal abnormalities from chronic inflammation, result in worsening nasal obstruction, and this has been associated with snoring and daytime sleepiness.[16] Apneas, sleep arousals, and loss of deep sleep also have been reported to develop in normal individuals from nasal obstruction during upper respiratory infections.[43]

Allergic Rhinitis

Chronic nasal inflammation appears to play a role in upper airway obstruction in OSA. Patients with allergic rhinitis have poorer sleep compared with healthy controls,[16] and numerous studies have demonstrated that allergic rhinitis can predispose to or worsen the symptoms of OSA. Subjects who experience nighttime symptoms of rhinitis (≥5 nights a month) are more likely to demonstrate habitual snoring (>3 nights/week), chronic daytime sleepiness, or nonrestorative sleep than subjects who rarely or never had symptoms.[44] That study also reported that subjects with persistent nasal congestion owing to allergy are 1.8 times more likely to have moderate to severe sleep-disordered breathing than those without nasal congestion from allergy.

Low levels of nocturnal cortisol can affect inflammatory mediators and contribute to increased nasal mucosal inflammation.[45,46] Use of nasal corticosteroids improved oxygen saturation and supine AHI in patients with OSA and allergic rhinitis, but there was no improvement in the group without allergic rhinitis.[47] Nasal decongestants, such as oxymetazoline, used in conjunction with nasal steroid sprays also have been evaluated in the treatment of patients with perennial rhinitis symptoms. These nasal sprays provide alleviation of nasal congestion without causing the unwanted side effects of rhinitis medicamentosa when used in conjunction with nasal steroid sprays.[48] Although nasal decongestants can improve quality of life and compliance with CPAP, reports of their efficacy in OSA have been inconsistent.[49–51] Nasal dilators also can be used to improve nasal congestion, thereby possibly improving CPAP compliance, although these have never been demonstrated to improve the objective indicators of OSA.[16]

A randomized, placebo-controlled, crossover study of 24 snorers with rhinitis showed a significant decrease in AHI and snoring after treatment with intranasal fluticasone for 4 weeks.[52] In another placebo-controlled trial (n = 25) with nasal fluticasone in a pediatric population with allergic rhinitis, the frequency of obstructive apneas decreased.[53] Subjects with seasonal allergic rhinitis and no increased nasal resistance out of season developed increased nasal resistance, fragmented sleep owing to OSA, and decreased stage 3 sleep in season. This resolved when allergic symptoms subsided.[42]

Patients with perennial allergies often complain of daytime fatigue and sleepiness, which often can be attributed to factors such as the side effects of medications. However, 1 study indicated that this can result in nasal congestion and associated sleep fragmentation, with a decrease in these symptoms after using topical nasal corticosteroids.[54] Another report showed that allergen specific IgE was detected by radioallergosorbent testing more frequently in children with habitual snoring and was associated with a higher prevalence of OSA (57% vs 40%; $P < .01$). Nasal obstruction also forces one to use the oral airway to maintain breathing during sleep and induces a switch from nasal to oral breathing that also is associated with OSA. The combination of nasal obstruction and a crowded oropharynx (with Mallampati score 3 or 4) have been found to double the risk of having OSA compared with those with no nasal obstruction.[55]

Nonallergic Rhinitis

There are only a few studies that have evaluated the role of nonallergic rhinitis (NAR) in OSA. One observational study found that NAR was associated with impaired sleep quality and that NAR was more likely to be correlated with OSA than allergic rhinitis. Patients with NAR had more impaired polysomnographic variables, more frequent sleep symptoms (particularly apnea), and higher scores on the Epworth Sleepiness Scale. One randomized, placebo-controlled trial to evaluate the effectiveness of fluticasone nasal spray on sleep quality in OSA included patients with NAR or allergic rhinitis. The 2 groups of patients demonstrated a significant decrease in AHI and snoring after treatment.[52]

CPAP-Induced Rhinitis

Another commonly encountered problem in patients with OSA is CPAP-induced rhinitis. More than 50% of CPAP users will experience increased nasal congestion, dryness, or rhinorrhea.[16] Oral breathing owing to nasal congestion from rhinitis or an ill-fitted CPAP mask can contribute to drying of the nasopharyngeal passage. Although the CPAP reservoir is often colonized with various bacteria, this does not increase the risk of sinusitis and is not associated with an increase in symptoms. However, cold, dry air associated with CPAP use can increase inflammatory mediator release, and heated, humidified air can decrease symptoms and improve compliance with CPAP. Medications, such as nasal steroids, anticholinergic agents, and decongestants, also can help relieve symptoms associated with CPAP-induced rhinitis.

Nasal Surgery Effects

The authors are aware of no randomized controlled studies of surgery for OSA in adults. Some uncontrolled clinical studies have reported subjective and objective improvement of OSA after nasal valve rhinoplasty, septoplasty, turbinectomy, and polypectomy.[35] Dilating the narrow nasal valve area using external or internal nasal dilators improved snoring, the overnight nadir oxygen saturation, and the severity of obstructed breathing.[56] Others showed improvement in snoring and daytime somnolence after correction

Table 1
Risk factors for obstructive sleep apnea[64]

Non-modifiable risk factors	Modifiable risk factors
Increasing age (>40 y)	Obesity (BMI >35 kg/m^2)
Male sex	Large neck size (>16 inches in women, >17 inches in men)
Postmenopausal state	Alcohol intake
Race (African American, Asian)	Smoking
Congenital craniofacial abnormality	Hypothyroidism
Type 1 diabetes[65]	Acromegaly
ESRD[66]	Enlarged tonsils and adenoids
	Structural abnormality of nasal and oropharynx[67]

Abbreviations: BMI, body mass index; ESRD, end-stage renal disease.

of the nasal valve area obstruction in carefully selected patients with moderate to severe OSA.[57] Nasal septoplasty and turbinectomy also have been reported to decrease nasal resistance and improve the time in REM sleep. One study demonstrated an improvement in quality of life and snoring but failed to show any improvement in polysomnographic data.[58]

Depending on the severity of OSA, correction of a deviated septum could decrease the CPAP required and improve oxygen saturation. In addition, CPAP compliance could improve in many patients after turbinate reduction surgery secondary to a subjective improvement in nasal obstruction. In conclusion, although nasal surgery can improve quality of life, it does not cure OSA. High-quality controlled studies of surgical approaches to OSA are needed.

Children

Adenoidal and tonsillar hypertrophy are common causes of OSA in children. One study showed that children with OSA had larger adenoids and tonsils than age-matched children without OSA. In addition, children older than 5 years had more protrusion of the maxilla, in addition to adenoidal hypertrophy, indicating that adenoidal hypertrophy combines with bony changes to increase the risk of OSA in this age group.[59] Surgical procedures appear to be more effective for OSA in children than in adults. One study showed that more than 80% of children had improvement in OSA after adenotonsillectomy.[60] Another study, in which children underwent an adenoidectomy with or without tonsillectomy, showed a 75% decrease in AHI in 30 of the 35 children who had an AHI higher than 5.[61] One longitudinal study demonstrated continued improvement in baseline and median AHI and increased REM sleep in children over the course of 3 years after adenotonsillectomy.[62]

Unanswered Clinical Questions

Should all patients with rhinitis be screened for OSA, and vice versa? Given that nasal obstruction is associated with sleep disturbance, snoring, and OSA, it seems prudent to ask screening questions in patients with OSA or rhinitis, knowing that CPAP can induce so-called CPAP rhinitis.[35] Patients should be questioned regarding rhinitis symptoms, snoring, sleep quality, and daytime drowsiness. Patients with rhinitis who experience snoring and/or daytime fatigue should be considered for polysomnography. Regardless, the available data support evaluation and treatment of rhinitis in patients with OSA. The treatment of nasal congestion, although improving quality of life and snoring, should not be expected to resolve OSA.[16]

Should patients be given a treatment trial for rhinitis symptoms before evaluation for OSA? Because there is no linear correlation between the degree of nasal obstruction and the severity of OSA, treatment prior to polysomnography could obscure the diagnosis of OSA. However, there appears to be no reason to repeat polysomnography in patients with OSA after treatment of rhinitis symptoms, because objective measurements of OSA are unlikely to change.

What role does rhinitis play in CPAP adherence? More than 50% of CPAP users complain of nasal congestion, rhinorrhea, nasal dryness, and sneezing,[63] and treatment of symptoms could help improve compliance with CPAP. Finding the ultimate answers to these questions is dependent on ongoing research to answer basic science and clinical aspects of OSA (Table 1).[64–67] There is much we do not know.

Conclusion

There are multiple pathways to OSA, and upper airway disease plays a role. Nasal obstruction of any cause can induce sleep-disturbed breathing, and treatment of rhinitis in patients with OSA alleviates symptoms but does not resolve OSA. It is the authors' assessment that nasal obstruction, although not linearly correlated with OSA, should be considered a risk factor and a mechanism for OSA and a condition that negatively affects quality of life of patients with it. Assessment of symptoms of rhinitis in those with OSA should identify those patients who will benefit from treatment of rhinitis. Detection and treatment of rhinitis in patients with OSA could improve the effectiveness and adherence of CPAP in patients with OSA.

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