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Upper airway function in the pathogenesis of obstructive sleep apnea: a review of the current literature

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Abstract

Purpose of review—Obstructive sleep apnea is an increasingly prevalent disease, with a considerable societal burden. The disease is defined by recurrent intermittent collapse of the upper airway. Understanding of and treatment for the disease is largely confined to relief of the mechanical obstruction of the upper airway by application of continuous positive airway pressure, and less commonly weight loss or surgery. However, recent work has focused on the function, rather than structure alone, of the upper airway.

Recent findings—The following contributors to upper airway structure and function have been studied: traditional fixed anatomical abnormalities, dynamic anatomical changes, upper airway dilator muscle dysfunction, lung volumes, and instability in control of breathing. In each patient with obstructive sleep apnea, the relative contribution of each of these components may be quite variable. The studies reviewed here describe methods to evaluate these factors, and some attempts at treatment.

Summary—Ongoing studies are attempting to classify patients on the basis of the underlying pathophysiology. This work suggests that obstructive sleep apnea is a heterogeneous disease with multiple root causes. Ultimately, such a classification may allow more individualized treatment, not only relying on mechanical relief of the upper airway obstruction.

Keywords

control of ventilation; lung; pharynx; upper airway; upper airway muscle activation

Introduction

Collapse of the upper airway during sleep is the hallmark of obstructive sleep apnea (OSA) [1,2]. Although anatomical characteristics can help determine pharyngeal collapsibility, several clinical observations suggest that anatomical factors alone do not cause OSA. For instance, various anatomical correlates are poor predictors of OSA prevalence or severity [3–5]. Moreover, obstructive events may occur only intermittently with most apnea patients having some periods of stable breathing [6,7•]. These observations suggest that there are

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nonanatomical, nonsleep stage-dependent functional changes that affect the propensity for upper airway collapse.

Mechanisms that might account for this variability include upper airway muscle activation, end-expiratory lung volume (EELV), central control of ventilation and the arousal threshold. The papers reviewed here help explain how these variables may contribute to clinical OSA.

Airway anatomy

Both fixed and dynamic elements contribute to the predisposition of the upper airway to collapse during sleep.

Assessment of the airway

A variety of methods exist to evaluate the upper airway and to investigate the severity and location of obstruction [8]. Several groups of investigators have studied the relationship between pharyngeal anatomy and polysomnography (PSG) measures of OSA. Kim *et al.* [9] used fiberoptic nasopharyngoscopy with Muller maneuvers and found that the degree and shape of pharyngeal narrowing correlated with the apnea-hypopnea index (AHI). However, the endoscope itself could in theory affect the outcomes of interest.

Perhaps clinically more relevant was the evaluation by Bachar *et al.* [10•] of those referred for upper airway obstruction with sleep endoscopy to look for the site of obstruction. Although the velopharynx was the most common site of obstruction (in 89% of patients), most patients (72%) had multiple sites of obstruction. The respiratory disturbance index (RDI) increased with the number of obstruction sites. These data may explain the poor predictive value of single measurements of airway anatomy and the relatively high failure rate of uvulopalatopharyngoplasty (UPPP) surgery. These results are supported by the meta-analysis by Lin *et al.* [11] in which patients who underwent multilevel surgery rather than UPPP alone had improved outcomes, although the level of evidence was quite low. These data are in agreement with modeling the upper airway as a Starling resistor. In physiology, the Starling resistor model of collapsible tubes suggests that collapse can occur in various different portions of the collapsible segment, making a targeted approach based on a single observation of narrowing unlikely to be successful.

Development and aging

OSA is more prevalent in men than in women, and the prevalence increases in both sexes with aging, independent of body weight. The difference in prevalence between the sexes cannot be explained by airway cross-sectional area or volume, which is actually larger in men than in women [12]. A more relevant measurement may be airway length, which is different between sexes and thought to be predictive of pharyngeal collapsibility based on experimental measurements and computational modeling [13,14,15•,16,17•]. Ronen *et al.* [17•] radiographically evaluated the upper airway in prepubertal and postpubertal boys and girls who underwent computed tomography for various reasons (usually for minor head trauma). Assessing airway length, the authors found equivalent lengths in prepubertal girls and boys, but mean airway length was greater in postpubertal boys than in girls, independent of systemic growth. Because a longer airway is more collapsible, pharyngeal airway length may explain at least in part the male predisposition to pharyngeal collapse and the increased risk of OSA in postpubertal but not in prepubertal boys as compared with girls. Kirkness *et al.* [18•] measured collapsing pressure of the upper airway (P_{crit}) with a method that minimized neuromuscular influences; their findings also supported an anatomical basis of sex differences in OSA prevalence.

In both sexes, OSA prevalence increases with age. Although there are a number of possible explanations, Eikermann *et al.* [19] found that pharyngeal closing pressure in healthy subjects increases with age, independent of sex or BMI. Kirkness *et al.* observed similar phenomena using different methodology [18••]. These data suggest that age-related changes in collapsibility are important in the propensity for pharyngeal collapse [20].

Dynamic changes

Dynamic changes in airway anatomy may also contribute to OSA. Redistribution of extracellular fluid in the supine position may cause airway narrowing. Chiu *et al.* [21] showed that lower body positive pressure increased neck circumference and pharyngeal resistance. Shiota *et al.* [22] used acoustic pharyngometry to demonstrate that lower body positive pressure reduced pharyngeal area by 9% at end-expiration. However, these studies were performed in awake participants.

Similarly, Iftikhar *et al.* [23] examined patients with OSA and compared those with and without leg edema (not due to cardiopulmonary disease). Patients with edema tended to be older and have more comorbidities such as diabetes and hypertension. However, even when adjusted for covariates, patients with edema had a higher AHI. However, the causal pathway is unclear, for example, sleep apnea could theoretically affect vascular permeability. Another cohort of patients frequently with edema – those with end-stage renal disease (ESRD) – were studied by Beecroft *et al.* [24]. Acoustic pharyngometry was used to assess the upper airway cross-sectional area (UA-XSA) in patients with and without ESRD and with and without OSA. The UA-XSA at functional residual capacity (FRC) was smaller in patients with ESRD than in those without and was smaller in both groups in patients with OSA. Lung volumes did not fully explain the differences in UA-XSA. The decrease in area may be due to upper airway edema, although other hypotheses include neuropathy or myopathy that arise as a result of ESRD [25]. In a follow-up study, to help assess clinical relevance, patients were converted from hemodialysis to nocturnal hemodialysis; a small subset of patients did show improvement in AHI [26•]. Responders showed an increase in pharyngeal area with the intervention; however, they also weighed less and showed an increase in the expiratory reserve volume, suggesting higher resting lung volume. Thus, the mechanism of improvement is unclear.

Other dynamic changes may result from the contents of the pharynx. For example, upper airway liquid surface tension has been linked with OSA and manipulation of surface tension has been shown to alter the upper airway closing pressure and AHI [27]. However, Hilditch *et al.* [28•] investigated Sjogren's syndrome patients and found differences in saliva characteristics but not in pharyngeal collapsibility and minimal difference in surface tension between groups. The clinical implications of these findings remain unclear.

Gastroesophageal reflux disease (GERD) and OSA are frequently comorbid conditions and are believed to exacerbate one another. Treatment of OSA with continuous positive airway pressure (CPAP) has been shown to decrease GERD symptoms [29,30]. Proposed mechanisms that may explain GERD worsening OSA include increased arousals with reflux, reflux causing bronchoconstriction and lower lung volumes subsequently decreasing upper airway stability, or direct tissue damage and edema [31]. Dickman *et al.* [32•] studied patients selected for esophageal reflux and found important interactions between sleep quality and GERD [33]. Friedman *et al.* [34•] studied OSA patients who were not on CPAP therapy with esophageal pH monitoring. Those with GERD were treated with proton-pump inhibitor therapy. In those patients whose pH improved on therapy, the AHI, snoring and subjective sleepiness also improved. The trial was small with only 29 patients completing the protocol (of the 146 referred for assessment and 52 of those with a positive pH study) and did not include a placebo arm. However, given the high prevalence of GERD in patients with OSA, even without symptoms,

acid suppression remains intriguing as a potential intervention. Randomized trials will be required to make any definitive recommendations (such a trial is ongoing by the same authors).

Upper airway muscle activation

Against any tendency toward collapse, upper airway patency is maintained by activation of dilator muscles. These muscles are driven by mechanoreceptors and chemoreceptors and also have a state-dependent drive. The most well studied are the genioglossus and tensor palatini [35]. Anatomic airway narrowing is likely offset by increased activation of upper airway muscles in awake patients. Pierce *et al.* [36•] tested this hypothesis by measuring closing pressure (P_{crit}), activity of genioglossus and tensor palatini muscles and pharyngeal resistance in OSA. These measurements confirmed that in awake OSA patients, activation of the genioglossus was proportional to P_{crit} . Furthermore, increasing muscle activation was sufficient to decrease upper airway resistance. Although this provides further understanding for a basic model of OSA, it does not explain what functional changes in dilator muscles may occur that predispose to collapse with sleep.

Loss of normal activity

Such changes might include loss of normal upper airway reflexes, change in central respiratory drive or even OSA-induced neuropathy or myopathy. Evidence suggests that patients with OSA may have diminished neuromuscular responses to maintain upper airway patency. McGinley *et al.* [37••] studied OSA patients and controls and measured genioglossus activity, maximal inspiratory airflow and transmural pharyngeal pressure during periods of induced airway collapse. With repeated upper airway obstruction, controls generated greater increases in tonic genioglossus activity, inspiratory flow rates and transmural pharyngeal pressure than did OSA patients. Their findings suggest that neuromuscular responses protect individuals without OSA from developing pharyngeal obstruction during sleep. Conversely, OSA patients may have dampened upper airway reflexes during sleep that predispose them to OSA. Work by Younes and coworkers [38,39••] highlighted the concept that recovery from hypopnea or apnea does not always require an arousal. Using varying degrees of CPAP and constant negative airway pressure (CNAP) to induce hypopneas, both OSA patients and controls were able to recover without arousal, but OSA patients were less often able to do so compared with controls [7•]. Although this study may implicate a decreased arousal threshold in OSA (see below), it may also be interpreted that OSA patients have less robust activation of protective reflexes during sleep. Finally, the observation that some controls have a positive P_{crit} [18••] suggests that other factors beyond anatomical compromise are important in OSA pathogenesis. Further studies are needed to understand the pathological mechanisms that account for these observations.

One such study could examine the impact of wakefulness stimulus on upper airway muscle activity. As shown by Lo *et al.* [40], using a technique that minimized changes in mechanical or chemical stimuli, wakefulness alone mediates changes in dilator muscle activity. However, the degree of influence was only measured in healthy volunteers and the response in patients with OSA is unknown. Controversy also exists as to whether the decreased protective responses seen in OSA patients could be due to, or exacerbated by, an acquired myopathy [25,41]. Proponents argue that repetitive injury (such as vibration) or oxidative stress may cause muscle damage that prevents adequate pharyngeal dilation. In this hypothesis, the increased tonic muscle activity seen during wakefulness reflects a compensatory increase in signaling to damaged muscle. In a rat model of intermittent hypoxemia, Dunleavy *et al.* [42] performed ex-vivo testing of sternohyoid muscle showing decreased endurance. This was exacerbated by treatment with a glutathione synthesis inhibitor and ameliorated by *N*-acetylcysteine, suggesting hypoxemia-mediated pathogenesis.

End-expiratory lung volume

Upper airway resistance is also affected by lung volume. Increases in lung volumes likely exert caudal traction on the upper airway, preventing its collapse [43]. This observation may help explain the link between obesity and OSA and other clinical observations such as the improvement in OSA when sleeping upright. Kairaitis *et al.* [44•] directly manipulated the upper airway in rabbits and showed that caudal traction did lower upper airway closing pressure (i.e., prevented collapse).

Research has shown that increasing FRC during sleep decreases the amount of CPAP needed to prevent flow limitation and pharyngeal collapse [45,46]. These experiments were performed in an iron lung; the authors hoped to reproduce this effect with the more easily tolerated and available expiratory positive airway pressure (EPAP). However, EPAP did not significantly change lung volume, but rather led to changes in breathing pattern that preserved lung volume [47]. This finding suggests that other nonmechanical factors help regulate lung volumes during sleep. Thus, if EELV is important in sleep apnea pathogenesis in some patients, a practical therapeutic mechanism still needs to be developed.

Control of ventilation and arousal threshold

The probability of OSA increases with certain anatomical conditions and deficiencies of the normal neuromuscular reflexes that maintain airway patency. Central neuronal output to these structures can also be abnormal and lead to obstructive episodes. Fluctuations in central respiratory pattern may be one explanation why OSA patients can develop stable patterns of breathing in the same position and stage of sleep as when they also develop an apneic episode. This concept was explored by Wellman *et al.* [48] who used proportional assist ventilation (PAV) to measure loop gain as a marker of ventilatory control and stability in OSA. Interestingly, the highest correlation between loop gain and AHI occurred in patients with P_{crit} near atmospheric pressure. This is likely because patients with very high P_{crit} will obstruct at almost any level of loop gain, whereas patients with low P_{crit} are relatively protected from airway obstruction regardless of other physiological parameters.

Other investigators have examined control of breathing in OSA. Ibrahim *et al.* [49••] measured instability around sleep wake transitions and found that it was correlated with AHI. Even when normalizing for covariates, the degree of variability was still predictive of OSA severity. At least in some cases, central respiratory instability may cause or contribute to OSA. Thus, patients with a decreased anatomical tendency toward obstruction (lower P_{crit}) may have more severe AHI if they have greater ventilatory instability. Using various mixtures of air and CO₂ bled into CPAP, prior to performing pressure drops to induce flow limitation, Younes [39••] observed respiratory instability in OSA. There were marked differences among individuals in response to increases in inhaled CO₂, as well as in the arousal threshold. Those with exquisite chemoresponsiveness and low arousal threshold had more instability. These are two additional variables that may explain some of the heterogeneity in OSA and may represent targets for intervention in some patients. Imadojemu *et al.* [50•] provided evidence that impaired reflexes may be a result, rather than simply a cause, of OSA. Using peroneal microneurography to study sympathetic nerve activity in patients with OSA and controls, the authors found both an increase in basal activity and a greater response to intermittent hypoxia in OSA patients. The effects were somewhat mitigated after treatment with CPAP.

These findings offer targets for pharmacological rather than mechanical therapies. Donepezil affects sleep in a variety of ways, playing a role in maintaining central sleep drive, upper airway muscle tone and sleep stage. When studied in patients with Alzheimer's disease, the drug lowered the AHI and improved oxygen desaturation [51•]. Similarly, mirtazipine was studied after 1 week of administration and shown to reduce AHI by 50% [52]; although other

unpublished reports did not show this effect. Trazodone, in a proof-of-concept study, raised the arousal threshold to hypercapnia (though not to mechanical stimuli using decremental CPAP) [53•]. Whether patients with a low arousal threshold as a major mechanism of OSA benefit from hypnotic therapy is unclear. In theory, raising the arousal threshold among the subgroup of OSA patients with robust muscle recruitability but low arousal threshold would allow stabilization of breathing by allowing sufficient time to achieve a stable airway.

Conclusion

Research over the last year has helped challenge the belief that OSA is a disease defined solely by the fixed anatomy of the upper airway. Other factors are now known to modulate the function of the upper airway. This paradigm shift may help further delineate OSA subtypes, and tailor therapy.

References and recommended reading

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