Tailored treatment strategies for obstructive sleep apnea

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Abstract

Obstructive sleep apnea (OSA) is characterized by repetitive collapse of the upper airway (UA) during sleep and is associated with chronic intermittent hypoxemia, catecholamine surges, and sleep disrupt. Multiple pathophysiological risk factors have been identified and contribute to OSA, including anatomical abnormalities (elevated UA mechanical load), compromised UA dilators, increased loop gain (unstable respiratory control), and decreased arousal threshold. These factors may contribute to the pathophysiology of sleep apnea in different individuals and recent evidence suggests that treatment may be targeted towards underlying pathophysiological mechanism. In some cases, combination therapy may be required to treat the condition.

Keywords

Sleep; Apnea; Lung; Airway; Muscle

1. Introduction

Obstructive sleep apnea (OSA) is a serious condition with major consequences and its prevalence is increasing. Obstructive sleep apnea is defined by repetitive collapse of the pharyngeal airway during sleep [1], which results in ongoing respiratory effort during pharyngeal collapse. This situation is in contrast to central apnea, which occurs with minimal or no respiratory effort. The prevalence of OSA has been debated because estimates have widely varied, largely because they are dependent upon equipment and the OSA criteria used [2]. Young et al. [3] previously estimated that approximately 4% of men and 2% of women in the United States (US) have at least 5 breathing abnormalities per hour of

sleep and excessive daytime sleepiness. More recently, Peppard et al. [4] reported that 13% of men and 6% of women in the US have at least 15 breathing events per hour of sleep. However, Heinzer et al. [5] recently estimated that, in Switzerland, up to 50% of men from a community sample had clinically important OSA (based on an apnea hypopnea index [AHI] above 5 events per hour and associated daytime consequences). Reasons for the increasing prevalence are complex, but likely reflect the obesity pandemic [6], diagnostic technology improvements [2], population aging, and other factors [7]. Similar figures have been estimated from other countries [8], even though the prevalence of obesity is generally lower than that of the US. Further data are clearly required, particularly given the importance of the condition being evaluated.

1.1. Pharyngeal collapse has two major consequences

Narrowing of the pharyngeal lumen leads to disturbances in gas exchange, including hypoxemia and hypercapnia, which can have end-organ consequences [9]. In addition, to restoring pharyngeal patency, arousals from sleep (plus intermittent hypoxia) lead to sleep fragmentation and associated neurocognitive sequelae [10]. Catecholamine surges occur with each repetitive apnea, leading to sustained sympathoexcitation over time and cardiovascular sequelae, including hypertension [11-13]. Ongoing research is leading to a better understanding of OSA causal pathways, including why apnea occurs [14].

2. Pathogenesis and tailored treatment strategies for obstructive sleep apnea

The concept of precision or personalized medicine is gaining in popularity [15]. The notion that 'one size fits all' is being reconsidered with increasing enthusiasm for an individualized approach to therapy. A number of endotypes (causal pathways) for OSA have been identified. If the underlying mechanisms of each OSA patient could be identified, OSA treatments could be targeted to the underlying cause. Traditionally, OSA has been thought of as a disease of anatomical compromise coupled with dysfunction in pharyngeal dilator muscles during sleep [1]. However, recent evidence suggests that the pathophysiological traits underlying apnea are highly variable. Anatomical compromise of the pharyngeal airway may be the primary cause of OSA in some patients, but non-anatomical traits, including pharyngeal dilator muscle dysfunction, unstable ventilatory control (elevated loop gain), or a low arousal threshold from sleep threshold, are important contributors to the development of apnea in many patients [16] (Fig. 1). The pharyngeal lumen has been shown to be smaller in patients with OSA compared to matched controls, even during wakefulness [17-19]. Using sophisticated measurements of pharyngeal mechanics that were independent of neuromuscular activity, Isono et al. [20] showed that the upper airway of patients with OSA is more prone to collapse than matched individuals without OSA. Additionally, because of compensatory reflex mechanisms, upper airway muscle tone has been shown to be higher in people with OSA compared to people without OSA. Using quantitative electromyography, Mezzanotte et al. [21,22] showed that the genioglossus (a major upper airway dilator muscle) is highly active in awake patients with OSA so that to maintain the pharyngeal patency during wakefulness. However, with the onset of sleep, there is a fall in dilator muscle activity, which leads to pharyngeal collapse in patients who are anatomically

predisposed to this [23-25]. Recent studies suggest that the noradrenergic system is critical for augmented genioglossus activity during wakefulness and that intermittent hypoxia is a critical stimulus in mediating this effect [26]. Instability in ventilatory control (elevated loop gain) is also thought to be an important factor [27-31]. This traditional model of OSA pathogenesis has been conceptually helpful in advancing knowledge, but data are increasingly showing that mechanisms underlying OSA are highly variable.

2.1. Critical closing pressure

Based on pharyngeal anatomy, the critical closing pressure (Pcrit) quantifies the propensity of the pharyngeal airway to collapse[32,33]. Individuals with a highly positive Pcrit require a high transmural pressure to open the airway and have a highly collapsible airway. In contrast, people with a markedly negative Pcrit require substantial subatmospheric pressure to close the airway and have a relatively rigid or sturdy pharyngeal airway [34]. Interestingly, Pcrit values only account for about 20–25% of OSA pathogenesis variance, emphasizing the importance of non-anatomical variables in OSA development [35]. In other words, Pcrit values have considerable overlap between patients with OSA and matched controls [36]. This finding suggests that other factors must be considered when explaining why some people have OSA and others do not. Therapies involving anatomical manipulation, such as uvulopalatopharyngoplasty, are expected to benefit patients with compromised anatomy, particularly at the velopharynx level. However, patients with apnea predominantly caused by other factors might experience no major benefit from the surgery [37-40].

2.2. Upper airway reflex

Highly variable upper airway reflexes have been observed among the population [23,41-43]. The negative pressure reflex refers to the robust activation of pharyngeal dilator muscles in response to suction or sub-atmospheric pressure. This phenomenon is thought to be a protective reflex, which serves to maintain pharyngeal patency in the context of a collapsing perturbation. The upper airway reflex is attenuated during sleep (as compared to wakefulness), but the level of activity is also highly variable across individuals. Furthermore, some evidence supports upper airway dilator muscle activation with respiratory stimuli, which may yield robust pharyngeal dilator muscle activation during stable sleep [44-47]. For example, a combination of mechanoreceptor (negative pressure) and chemoreceptor (CO_2) stimuli have been shown to activate pharyngeal dilator muscles during stable sleep if the stimuli are present in sufficient magnitude for adequate duration. If a drug were available to augment negative pressure reflex activity, this approach could be helpful for the subset of patients who have attenuated reflexes during sleep [25]. Patients with robust reflex activity at baseline are likely to have no major benefit from this pharmacological approach. On the other hand, an augmented negative pressure reflex may destabilize ventilatory control because a strong reflex may produce exaggerated upper airway muscle activity and ventilatory instability in response to stimuli. This situation could theoretically lead to increased apnea in certain patients [48-50]. Therefore, selecting patients who may benefit from therapy that targets upper airway reflex augmentation may be a viable approach. Hypoglossal nerve stimulation was recently approved for augmenting upper airway dilator muscle activity and improving upper airway mechanics [51-55]. Selecting patients for

hypoglossal nerve stimulation is a complex process and is still being debated. However, there is likely a subset of patients who will respond to this intervention more than others. In theory, patients with an attenuated reflex may be most amenable to hypoglossal nerve stimulation since those with robust reflexes likely have other abnormalities contributing to OSA.

3. Elevated loop gain (unstable ventilatory control)

Elevated loop gain, or unstable ventilatory control, has been recognized and accepted as a potential pathogenic mechanism for both obstructive and central sleep apnea. Loop gain is an engineering term used to define the stability or instability of a negative feedback control system. Loop gain can be calculated as the ventilatory response divided by the ventilatory stimulus. A system with a high loop gain is prone to instability and a system with a low loop gain is intrinsically stable. One way to understand negative feedback control is to consider an analogy describing the regulation of room temperature. An example of a system with a high loop gain is an overly sensitive thermostat or too powerful furnace [56], these system properties would lead to marked fluctuations in room temperature. For ventilation, an increase in ventilation that occurs with apnea or hypopnea determines the loop gain of the system. For control of breathing, the system maintains PCO_2 of 40 mmHg. If the system would have a high loop gain it would lead to marked fluctuations in response to slight CO_2 changes [57]. Fluctuations in output from the brainstem central pattern generator are characteristic of central apnea and result in Cheyne Stokes breathing [58]. However, oscillations in central output are also important in obstructive apnea. For example, central pattern generator output to the diaphragm also provides concomitant innervation to the hypoglossal nerve and thus determines upper airway muscle activity. The upper airway would theoretically be at risk for collapsing or closing when central pattern generator output to the hypoglossal nerve is at its nadir. Thus, elevated loop gain is likely important in both obstructive and central apnea, with underlying pharyngeal mechanics likely playing a major role in determining how the disease is clinically expressed [59-61].

Ventilation during non-rapid eye movement (NREM) sleep relies mainly on chemical feedback control, but ventilation during REM sleep is dependent on more variable non-chemical factors. Therefore, loop gain during the REM stage is relatively difficult to measure because of methodological issues, which need further investigation. It can be supposed that loop gain is quite low during REM sleep based on resolution of Cheyne Stokes breathing and periodic breathing during REM sleep [62]. Other factors, including upper airway dilator muscle tone, may be more critical than control of breathing during REM sleep. Thus, differences in sleep apnea severity among sleep stages may provide clues regarding the underlying pathophysiologic features of an individual. This information may be valuable to consider when tailoring treatment strategies for OSA.

Therapies that can alter loop gain are available. For example, oxygen therapy and acetazolamide have both been used to treat various forms of central apnea and periodic breathing [63-66]. These agents can lower loop gain via various mechanisms and may benefit patients who have apnea associated with an elevated loop gain. Current clinical trials remain small, but some data support the idea that therapy to lower loop gain is efficacious in

a predefined subset of OSA patients. Moreover, ongoing efforts are focusing on estimating loop gain using clinically available data obtained with polysomnography. This innovation would lessen the need for complicated overnight physiology studies to determine the optimal therapy for each individual [67].

4. Arousal threshold

Another important factor in OSA pathogenesis is the arousal threshold. The respiratory arousal threshold is defined as the intrathoracic pressure level at which a given individual wakes from sleep. Some patients have a high arousal threshold (sleep through major stimuli) and other patients have a low arousal threshold (wake up easily) [68,69]. For the case of ventilation, pharyngeal negative pressure is considered to be a critical stimulus for triggering arousal from sleep. On average, individuals with OSA have a higher arousal threshold than those without OSA, which presumably developed over time as a compensatory mechanism [70]. Indeed, continuous positive airway pressure (CPAP) therapy can lower arousal threshold. This finding supports the idea that OSA leads to an elevation in arousal threshold. However, a definable subset, roughly one third of OSA patients, have a low arousal threshold and may potentially be amenable to manipulation [71]. This subgroup of OSA patients is somewhat poorly defined because they may represent an earlier manifestation of the disease (i.e., before elevated arousal threshold has developed) and/or may have a different underlying genetic predisposition. Furthermore, Yanauchi [62] recently showed that patients with NREM predominant OSA have greater decreases in ventilation and dynamic changes of $PaCO_2$ in the transition from awake to NREM sleep. This finding may be helpful in identifying the clinical sub-group that should undergo treatment to stabilize ventilatory control by raising arousal threshold.

A pharmacological approach to raising the arousal threshold has been suggested, but outcome data remain limited. Trazodone and eszopiclone may be effective in raising the arousal threshold [72-74], which may allow the accumulation of respiratory stimuli (e.g., CO_2 and negative intrapharyngeal pressure) to reach a sufficient magnitude to activate dilator muscles without triggering arousal. On the other hand, raising arousal threshold may be deleterious in patients with unresponsive upper airway dilators because substantial hypoxemia may occur prior to arousal from sleep. Several studies have found that raising arousal threshold improves AHI in some patients. Fortunately, a theoretical deterioration in patients with OSA and worsening desaturations have not been observed. These findings suggest that combination therapy may be required for the treatment of sleep apnea by addressing more than one underlying pathophysiological mechanism. Future multicenter clinical trials are needed to assess the impact of various pharmacological interventions on OSA clinical outcomes.

5. Impact of comorbidities

Many comorbidities are associated with OSA, including hypertension, diabetes, chronic obstructive pulmonary disease, aging, impaired ventricular function, obesity, and others. These systemic factors also need to be considered when developing individualized treatment plans. These conditions represent OSA risk factors and any mechanistic approach to OSA

therapy must account for the fact that predisposing factors underlying apnea may vary based on predisposing factors. For example, if neuromyopathy could predispose diabetic patients to sleep apnea, then therapeutic measures that address upper airway dilator muscle function may be more effective than those that target other mechanisms. In addition, these factors may impact the consequences of OSA. Therefore, one approach to minimizing the impact of OSA may include addressing measures to reduce apnea complications. For example, antioxidant therapy has been suggested to ameliorate oxidative stress caused by frequent arousal and intermittent hypoxemia and potential treatment to minimize apnea complication in selected individuals.

6. Summary

A critical expansion of OSA knowledge has occurred over the past several years, allowing a mechanistic treatment approach to be considered. Although CPAP has transformative benefits for some OSA patients, some patients struggle with adherence to therapy or avoid the diagnosis entirely due to concerns for the eventual therapy. Because of the pathogenesis of OSA is multifactorial, the treatment of OSA should focus on the underlying causes of for each OSA patient. More research is needed to bring mechanistic treatment approaches from the research setting to the clinical setting and to discover new treatment approaches.

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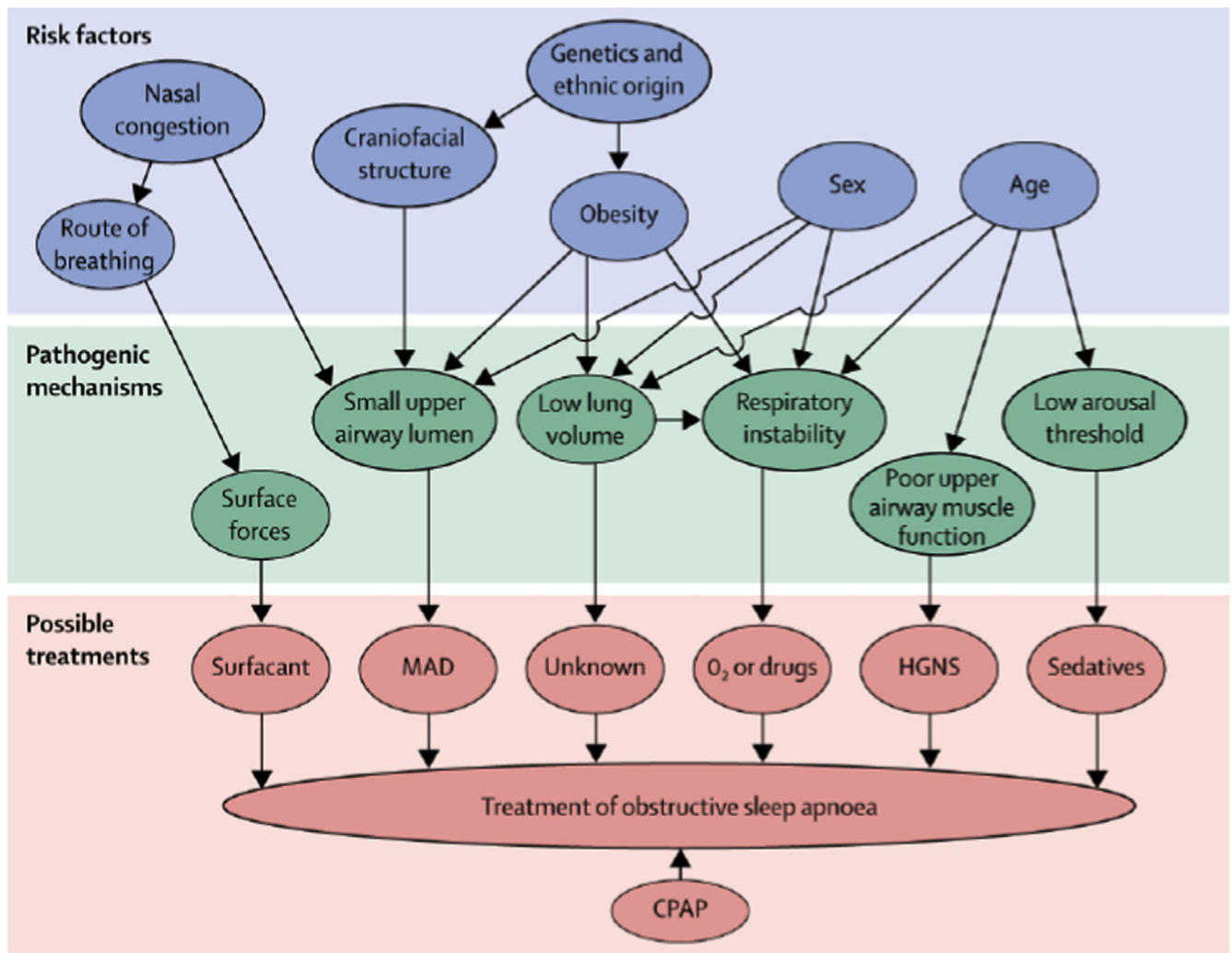
Fig. 1.
Risk factors, pathogenic mechanisms, and treatments for obstructive sleep apnoea Risk factors for obstructive sleep apnoea have long been recognised, but novel pathogenic mechanisms have now been detected in patients with the disorder. Although CPAP is the current treatment of choice irrespective of underlying cause, treatments based on tackling individual pathogenic mechanisms might prove a successful alternative approach in the future. CPAP=continuous positive airway pressure. MAD=mandibular advancement device. UPPP=uvulopalatopharyngoplasty. HGNS=hypoglossal nerve stimulation. Figure adapted from Jordan and colleagues, by permission of Elsevier.