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Review

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.

Contents

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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].