Obstructive sleep apnea (OSA) is a common disease with major consequences. Obesity and aging, as well as male gender, are recognized risk factors for OSA; however, the condition of OSA in women and the elderly has received only minimal attention. OSA in women is perhaps under-appreciated due to the traditional stereotype of an older obese man presenting with OSA. However, OSA in women, particularly post-menopause, can have important sequelae. Similarly, OSA in the elderly may have unique mechanisms, and the consequences are still debated. Further work is clearly needed to define the mechanisms and consequences of OSA in special populations.

**KEY WORDS:** Sleep, lung, apnea

Obstructive sleep apnea (OSA) is a very common condition with well-established neurocognitive and cardiovascular sequelae [1]. The prevalence figures vary in different studies and in different locations, but roughly 5%-10% of the general population is affected by this condition [2]. Established risk factors for OSA include male gender, aging, obesity, and menopausal status, among others. Despite recognition of the importance of this disease, the majority of patients remains undiagnosed and untreated, emphasizing the need for further efforts in this area. Nasal CPAP (continuous positive airway pressure) is the treatment of choice for this condition, but adherence is quite variable, suggesting the need for education on existing therapies plus research into new treatment options [3].

The mechanisms underlying OSA have been intensively investigated [4]. OSA patients have anatomical compromise, which increases the predisposition for pharyngeal collapse [5]. However, protective reflexes are present during wakefulness, which increases the activity of the pharyngeal dilator muscles and maintains pharyngeal patency during wakefulness [6]. However, with the onset of sleep, these protective reflexes are lost, leading to a fall in the activity of pharyngeal dilator muscles, yielding upper airway collapse in those who are anatomically predisposed [7]. Recent data have shown that the mechanisms underlying OSA are highly variable, such that one factor explains only a fraction of the variance in OSA occurrence [8]. Other factors of the importance in OSA pathogenesis include instability in ventilatory control [4], the propensity to wake up from sleep (arousal threshold) [9], end-expiratory lung volume, and tethering of the upper airway, among other factors. Some recent evidence suggests that there may be utility to defining the mechanisms underlying upper airway collapse, such that treatments can be directed to the underlying cause rather than a ‘one size fits all’ approach [4]. For example, uvulopalatopharyngoplasty may well be a therapy for the subset of OSA patients who have velopharyngeal compromise [10]. Patients with ineffective upper airway dilator muscle function may well respond to hypoglossal nerve stimulation [11]. Patients with a low arousal threshold may respond to pharmacological strategies, such as sedative/hypnotics, to reduce the propensity for arousal [12]. Delaying arousal may allow the accumulation of respiratory stimuli, such as carbon dioxide and negative intrapharyngeal pressure, which will allow recruitment of pharyngeal dilator muscle activity [13]. Instability in ventilatory control (also known as high loop gain) may respond to agents that stabilize ventilation [14-17]. For example, oxygen or acetazolamide can lower loop gain and thus reduce the propensity for apnea [18]. Some patients with multiple underlying mechanisms may well require combination therapy to eliminate OSA [4].

With regard to neurocognitive sequelae, OSA patients have impaired memory consolidation, excessive daytime sleepiness, reduced quality of life, and increased risk of motor vehicle accidents compared to people without OSA. Nasal CPAP (continuous positive airway pressure) is the treatment of choice for OSA based on randomized trials. CPAP has been shown to improve daytime sleepiness, improve quality of life, and reduce the risk of motor vehicle accidents [19].
the standpoint of cardiovascular sequelae, OSA has a causal link to the development of systemic hypertension and has strong associations with more serious adverse effects, such as myocardial infarction, congestive heart failure, and stroke [20,21]. The proof of causality for OSA and hypertension came from sophisticated animal models [22], large human epidemiological studies, and multiple randomized controlled trials. Nasal CPAP therapy reduces systemic blood pressure and helps to prevent the development of systemic hypertension compared to no therapy for OSA. Whether nasal CPAP prevents hard cardiovascular events remains unclear, but it is the subject of ongoing investigation.

What are the special considerations regarding OSA in women and in the elderly? Several points about sleep apnea in women deserve emphasis. First, men are at increased risk of sleep apnea as compared to women, although the risk of OSA in women increases following menopause [23]. For example, recent data have shown that OSA (as defined by apnea hypopnea index above 15/hr) is present in roughly 13% of North American men and 6% of North American women [1]. The mechanisms underlying the male predisposition to OSA have been debated but are likely complex and involve multiple anatomical and physiological factors [24]. Second, the symptoms of OSA may be somewhat different in men as compared to women, in part due to the reports of bed partners. While snoring is quite common in men, fatigue is a more common OSA manifestation in women, for instance.

Potential differences in the presentation of OSA across genders should be considered when evaluating patients at risk of OSA [25]. Similarly, the motivation for using continuous positive airway pressure (CPAP) may be different between various patients; such information can be helpful in the support of patients, particularly when struggling with issues around adherence to therapy [26]. Third, the consequences of OSA in women have been debated, since some have argued that the data are more compelling in men as compared to women. However, most, but not all, data point to similar consequences of OSA in men and women, and there is no strong biological rationale to suspect that women are protected from important hypoxemia [27,28]. Thus, OSA is an important disease in both men and women with OSA.

Regarding aging and OSA, several points deserve emphasis. Aging is a known risk factor for obstructive sleep apnea, although menopause also has important effects in women [29]. The mechanisms underlying the aging predisposition to OSA remain undefined, although some combination of anatomical susceptibility, impairment in upper airway reflexes, and instability in ventilatory control likely plays a role. The OSA history can be impacted by the absence of a bed partner in some cases or by impaired hearing and/or habitation over time, which may affect the reporting of snoring, for example. The consequences of OSA in the elderly have also been questioned, with some data actually suggesting a protective role for OSA in people over 80 years old [30]. If OSA consequences are truly reduced in the elderly, there are several possible mechanisms to explain this effect:

a) A survivor effect describes the possibility that the sickest patients will succumb before reaching advanced age, leading to the possibility that the healthiest patients (i.e., the survivors) are relatively resistant to OSA consequences. Some quantitative models have suggested that this possibility is unlikely (without exceedingly high OSA-attributable mortality), although further work is clearly needed in this area.

b) The mechanisms underlying apnea may be different in the elderly compared to younger patients. For example, the negative intrathoracic pressures are of lower magnitude in older OSA patients compared to younger OSA patients [31]. This negative intrathoracic pressure is a key determinant of cardiac wall stress (or afterload) [32]. Some data suggest that younger OSA patients may be anatomically predisposed, whereas older OSA patients may be at risk due to unstable ventilatory control. Thus, the causal pathway yielding apnea may be an important determinant of apnea consequences.

c) Proponents of theories on ischemic preconditioning suggest that intermittent hypoxemia (of mild intensity) may stimulate protective mechanisms, which may lessen subsequent risk of injury [33]. Some data have shown that mild OSA may actually be protective compared to more severe forms of the disease. Thus, the mild OSA commonly seen in the elderly may have some protective benefits, although such views remain theoretical at this stage.

Considerable progress has been made in our understanding and general awareness of the field of sleep apnea. Special populations, including both women and the elderly, have received less attention in the OSA field [34]. Further research into OSA is required in order for new treatment strategies to emerge.

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