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Editorial

Smoking and OSA: A Vicious Cycle and Synergistic Effects

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Editorial

Obstructive sleep apnea (OSA), characterized by recurrent intermittent hypoxia and sleep fragmentation, is recognized as a risk factor of morbidity and mortality, such as cardiovascular disease, cognitive impairment, metabolic dysfunction and cancer [1,2]. Age, excess body weight, male gender and craniofacial abnormalities are risk factors of OSA [3]. Smoking, a predisposing factor for cardiovascular and respiratory diseases, is also highly prevalent in patients with OSA [4]. Further, due to similar effects on multiple systems by smoking and OSA, it has become a great interest for researchers to investigate the possible interaction between smoking and OSA.

A vicious cycle between smoking and OSA

Cumulative evidence shows that smoking acts as a risk factor for OSA development [4-7]. The mechanisms of how smoking affects OSA may include the effects of nicotine on upper airway neuromuscular function, and smoking-induced upper airway inflammation and sleep disturbance.

The "rebound effect" of nicotine withdrawal is regarded as the main mechanism for the impact of smoking on sleep apnea. Early in 1963, nicotine was found to excite neural structures located close to the ventrolateral surface of the medulla and increase ventilation [8]. Further observation revealed that nicotine increased ventilation and upper airway muscle activity in animals [9,10]. Nicotine seems to be a potential benefit for OSA treatment. Indeed, administration of nicotine chewing gum before sleep decreased the number of obstructive and mixed apneas during sleep with reduced apnea duration in the first two hours of sleep, when blood nicotine levels were at their peak [11,12]. However, the obstructive and mixed apneas increased again in the second hour compared to the first hour, indicating that the beneficial effect of nicotine was transient. Then, as the nicotine levels continued to decline throughout the night, sleep apnea might increase due to the "rebound effect" of nicotine withdrawal *per se*.

Causal link was found between chronic smoking and reduced nasal cavity dimensions, low airflow and a less-compliant nasal mucosa [13]. Narrowing of the upper airway is considered to be a predisposing anatomic factor for OSA itself [14]. A cross-sectional prospective study showed that smokers were younger and were more likely to experience severe snoring with increased nasal obstruction, lower nasal volumes after decongestion and a longer soft palatal length compared to nonsmokers [15]. Furthermore, Kim *et al.* [16] reported that smoking OSA patients presented thicker lamina propria of the uvula compared to non-smoking OSA patients and the lamina propria thickness was positively related to smoking duration. They also observed that the adverse effect of smoking on histological changes of the uvular mucosa in OSA might be, at least partially, due to calcitonin gene-related peptide (CGRP)-related neuroendocrinologic inflammation in upper airway.

Sleep disturbance in smokers, including a longer latency to sleep onset, lower sleep efficiency and a shift toward lighter stages of sleep [17,18], can worsen the sleep quality of OSA. A study investigating effects of smoking on sleep disturbance in an OSA cohort showed that ever-smokers had a higher arousal index (AI), higher AHI and higher AHI with arousal than never-smokers did [19]. Recently, another study reported that severe smokers with OSA who smoked more than 20 pack-years presented a lower percentage of non-rapid eye movement (NREM) 3 stage and a higher percentage of NREM1-2 stages compared to mild smokers with OSA [20]. Smoking, via the stimulant effects of nicotine, nightly nicotine withdrawal and possible psychological disturbance [5], may exacerbate sleep fragmentation and arousal-related apneic events in OSA and worsen the consequence of OSA.

How does OSA affect smoking? Wetter *et al.* [5] believed that smoking might represent as a form of self-treatment of OSA patients, especially on daytime symptoms such as hypersomnolence, depression and cognitive dysfunction. The more severe these symptoms are, the more likely OSA patients are incompetent in their work and are ostracized by their peers. Since nicotine has been shown to cope with these symptoms, patients with severe untreated OSA may be encouraged to solve these social problems by smoking to maintain alertness and relieve stress. Further, a hypothesis, which remains untested, has been invoked to explain the possible effect of OSA on smoking addiction [21]. The nicotine addiction is dependent on dopamine (DA) system. Long-term hypoxia increases the release of DA in the carotid body [22]. When long-term hypoxia happens, smoking, which increases respiration and oxygenation, would stimulate the pleasure centers, and thus encourage the addiction and compulsive activity [21]. Among those untreated OSA patients with severe symptoms of depression and cognitive dysfunction, treating OSA may be a necessary precondition for smoking cessation.

Synergistic effect of smoking on outcome of OSA

Various Studies have demonstrated the adverse effects of OSA on multiple organ systems [23,24] and so is smoking [25,26]. Notably, OSA and smoking may share some common pathophysiological mechanisms contributing to those diseases or dysfunctions including

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oxidative stress and activation of inflammatory system, which led investigators to pay attention to the synergistic effects between smoking and OSA.

Lavie *et al.* [27] investigated oxidative stress and circulating inflammatory markers of cardiovascular disease in OSA patients, and found that smokers with OSA showed significantly higher levels of circulating triglycerides and inflammatory markers including C-reactive protein, ceruloplasmin, and haptoglobin and lower levels of high-density lipoprotein (HDL) cholesterol than non-smoking OSA patients. Another study demonstrated an association between smoking and nocturnal ventricular arrhythmias in a cohort of systolic heart failure and sleep apnea, with an OR up to 10, which was much higher than OR presented in other cohorts [28]. It is conceivable that smoking and sleep apnea share some similarities in adverse pathophysiologic consequences of cardiovascular system. In addition to the combined effects of smoking and OSA on systemic inflammation, smoking, through nicotine-mediated mechanisms, leads to coronary vasospasm and increased blood pressure, heart rate and myocardial oxygen consumption, which act synergistically with OSA-induced oxygen desaturation to exacerbate ventricular tachyarrhythmias [28]. Moreover, oxygen desaturation was found to be associated with smoking-related cancers in a large cohort of more than 10 000 patients who had suspected OSA, suggesting a possible amplifying effect of OSA-induced intermittent hypoxemia or inflammatory responses on cigarette smoke carcinogens [29]. Recently, we reported that smoking patients with OSA performed the worst on cognitive function tests including Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clock Drawing Test (CDT) and Verbal Fluency Test (VFT) than those smoking subjects without OSA and non-smoking with /without OSA [30]. Aksu et al. found that ex/current smokers with OSA had significantly higher plasma orexin-A levels than never smokers with OSA, while in the absence of OSA, plasma orexin-A levels were comparable between never smokers and ex/current smokers, indicating there might be some association between smoking and OSA on orexin-A levels [31].

In summary, there is a plausible reciprocal causal association between smoking and OSA, although the evidence is less than conclusive. Further studies are required to explore precise mechanisms underlying the interaction between smoking and OSA. Due to the possible vicious cycle between smoking and OSA, smoking cessation is recommended for treatment of OSA, which, in turn, may be a necessary precondition for smoking cessation.

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