Review Article

Asthma and Obstructive Sleep Apnea

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Abstract

Objective: To get a comprehensive understanding about the relationship between obstructive sleep apnea (OSA) and asthma by reviewing the epidemiology, pathophysiology, and clinical manifestation and then summarizing the latest progress on diagnosis and treatment.

Data Sources: Articles referred in this review were mainly collected from a comprehensive search of the PubMed published in English from 1990 to 2015 with the terms "OSA" and "asthma" as the main keywords. Highly regarded older publications were also included.

Study Selection: Information about the features of the two diseases in common, the pathophysiologic association between them and their current treatments from the literature search were identified, retrieved, and summarized.

Results: Both OSA and asthma are very prevalent conditions. The incidences of them have kept on rising in recent years. Asthma is often accompanied by snoring and apnea, and OSA often combines with asthma, as well. They have many predisposing and aggravating factors in common. Possible shared direct mechanistic links between them include mechanical effects, intermittent hypoxia, nerve reflex, inflammation, leptin, etc. Indirect mechanistic links include medication, nose diseases, smoking, obesity, and gastroesophageal reflux disease. Since OSA presents many similar features with nocturnal asthma, some scholars termed them as a sole syndrome – "alternative overlap syndrome," and proved that asthma symptoms in those patients could be improved through the treatment of continuous positive airway pressure.

Conclusions: OSA and asthma are closely associated in pathogenesis, symptoms, and therapies. With the growing awareness of the relationship between them, we should raise our vigilance on the coexistence of OSA in those difficult-to-control asthmatic patients. Further studies are still needed to guide the clinical works.

Key words: Asthma; Continuous Positive Airway Pressure; Gastroesophageal Reflux Disease; Obesity; Obstructive Sleep Apnea

Introduction

Both obstructive sleep apnea (OSA) and asthma are prevalent diseases, and the incidences of them have shown a gradual increase recently. OSA usually involves the upper airways (nasal, oral, and pharyngeal passages), manifested with inspiratory flow limitation and repeated airway collapse during sleep, in combination with many daytime symptoms such as sleepiness, morning headaches, depression, concentration difficulties, and memory loss. Asthma is usually characterized by chronic inflammation, airway hyperresponsiveness (AHR), and reversible expiratory flow limitation. Recently, massive researches have been done on the interaction between the two diseases, but still reached no consensus. This review has presented multiple acknowledged connections on epidemiology, pathophysiology, clinical manifestation, and the latest progress on diagnosis and therapies. Theoretically, OSA and asthma are closely associated in those respects.

Epidemiology

OSA has been recognized as a major public health problem. It is a disease prevalent in middle-aged males and is estimated to affect 2–4% of the adult population.[1] Asthma is one of the most common chronic respiratory system diseases, and

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Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.167361

Received: 08-06-2015 **Edited by:** Yuan-Yuan Ji
How to cite this article: Qiao YX, Xiao Y. Asthma and Obstructive Sleep Apnea. Chin Med J 2015;128:2798-804.

as of 2004, it was estimated that as many as 300 million people of all ages suffer from it.[2]

Previously, numerous studies have demonstrated the high prevalence of OSA in asthmatics. In a prospective cohort of Australian Busselton Health Study, asthma emerged as one of the independent risk factors for the development of habitual snoring (relative risk, odds ratio (*OR*) = 2.8).[3] A questionnaire survey done by Ekici *et al.* showed that asthma was associated with a higher likelihood of snoring and apneas versus those in controls (54.0% vs. 16.7% and 41.4% vs. 7.0%, respectively), and these symptoms mentioned above could cause further impairment in health-related quality of life.[4] Auckley *et al*. also reported that asthmatics posed a high risk of self-reported snoring and daytime sleepiness when compared with the general internal medicine population (18.5% vs. 8.0% and 46.1% vs. 34.3%, respectively) independent of the severity of asthma (P = 0.183).[5] However, Julien *et al*. came to a different conclusion on this issue through the polysomnography (PSG) device that OSA seemed to be more prevalent among patients with severe asthma versus those moderate and controlled ones, thus revealed the potential pathophysiologic interaction between OSA and asthma severity.[6] Despite the prevalence of OSA in asthma, patients with OSA were also reported with many asthma symptoms. Alharbi *et al*. investigated 606 patients with OSA and demonstrated a high prevalence of asthma (35.1%).[7] OSA was proved to be significantly associated with asthma exacerbation. Ten Brinke *et al*. regarded OSA as one of the key determinants of recurrent asthma attacks (*OR* = 3.4).[8]

Pathophysiology

Recently, there have been numerous reports in the literature, suggesting an association on pathophysiology between OSA and asthma. Though the definite relationship has not been established, several theories have been proposed. Based on the pathways, it could be classified as direct or indirect effects.

Direct Effects

Mechanical effects

Mechanical effects between OSA and asthma are bidirectional. Previously, Ballard *et al*. found that the functional residual capacity of the asthmatics fell during sleep, which might partly contribute to the nocturnal increase in airway resistance.[9] This could attenuate the caudal traction on upper airways and induce airway collapse.[10] On the other side, patients with OSA often present habitual snoring. The intermittent vibration caused by turbulent air leads to local inflammation and edema around the uvula, soft palate, and upper airway, which increase the airflow resistance and then trigger or aggravate asthma. Previous studies held the idea that the airway collapse in OSA during sleep was mainly due to the increasing inspiratory resistance. However, there has been a growing experimental support for the viewpoint that the airway obstruction is both an inspiratory and expiratory events.[11] Bijaoui *et al*. calculated the resistance over both inspiration and expiration and found an increase in the expiratory lung resistance during obstructed breathing in stage two and slow wave sleep, compared with wakefulness and arousal values.[12] The above-mentioned increasing expiratory resistance was supposed to exacerbate the combined asthma. Besides, the high negative intrathoracic pressure caused by airway closure acts on the airway mucosa increases its sensitivity and results in more asthma attacks.

Intermittent hypoxia

In OSA, the episodes of partial or complete obstruction of the upper airway during sleep lead to the intermittent hypoxia. Repetitive hypoxia and reoxygenation increase the reactive oxygen species, followed by complex oxidative stress cascade downstream and inflammation, which can involve the airway and aggravate asthma. Another plausible explanation is the insulin resistance (IR), which is not only significantly associated with progression of sleep disordered intermittent hypoxia[13] but also acts as a main bridge to metabolic syndrome. The metabolic syndrome carries a condition of systemic inflammation that could potentially explain the influence on asthma onset and severity.[14] On the contrary, the weakened pulmonary function caused by asthma to some extent aggravates the hypoxia of OSA as well.

Nerve reflex

Recently, growing data have suggested a possible causal neurogenic association between OSA and asthma. One explanation for our finding is the repeated stimulations on neural receptors in the oropharyngeal region of OSA causing potent neural reflex bronchoconstriction.[15] In addition to the mechanical trauma, the increase in vagal tone that occurs during apneic episodes in OSA stimulates muscarinic receptors in the central airway and results in bronchoconstriction and nocturnal asthma symptoms. Some animal studies even found that mild hypoxia can enhance the bronchial responsiveness to methacholine and histamine.[16] In addition, the hypoxia or hypercapnia in OSA excites peripheral chemical receptor in carotid body and increases the airway sensitivity. OSA also influences the respiratory center's regulation on sleep-related bronchomotor tone and decreases the stability of airway. Therefore, the treatment of continuous positive airway pressure (CPAP) could eliminate the chronic stimulation on oropharynx and stabilize the upper airway to decrease vagal tension.

Inflammation

Asthma is a chronic systemic inflammatory disorder, manifested by inflammatory cells infiltration which affects the strength of respiratory muscles. Correspondingly, the presence of both systemic and airway inflammations has also been suggested in OSA patients.[17] Its local airway inflammation mainly results from the mechanical trauma of airway closure and snoring-induced vibration, as well as the local oxidative stress. Aihara *et al*. pointed out that there was an obviously increasing level of interleukin-6 (IL-6), IL-8, tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF) in respiratory secretions of OSA patients, and all the above-mentioned biomarkers

were obviously correlated with OSA severity.[18] The local inflammation played an important role in the progression of the increasing airflow resistance, airway wall thickness, AHR and comorbidities such as asthma and chronic obstructive pulmonary diseases. Conversely, the presence of systemic inflammation in OSA was also demonstrated. It is mainly due to the oxidative stress induced by obesity and repetitive episodes of intermittent hypoxia in OSA. Vgontzas *et al*. firstly reported in 1997 that IL-6 was obviously increased in the circulation.[19] Lately, many researchers have discovered the similar phenomenon about other inflammatory biomarkers such as IL-6,[20] C-reactive protein (CRP),[21] and TNF-α,[22] which demonstrated a systemic inflammatory reaction in patients with OSA. When involving the lower airway, it can predispose to asthma and increase the risk of acute or sudden-inset fatal asthma exacerbations. Besides, there is emerging evidence that asthma is heterogeneous in its inflammatory cellular profiles[23] and up to 60% of asthmatics who suffer from persistent symptoms have a noneosinophilic, neutrophil-rich type of asthma.[24] A recent study done by Teodorescu *et al*. noted a significant association of apnea scale of the sleep disorders questionnaire with the proportion of sputum polymorphonuclear cells in asthmatics,[25] which demonstrated that OSA is associated with a neutrophilic airway inflammation in asthma, suggesting that it may influence the pathogenesis of a neutrophil-rich rather than an eosinophilic type of asthma. Possible mechanisms that may account for the airway neutrophilia in OSA are intermittent hypoxia and upper airway trauma.[26] Karamanl *et al*. provided a 3-month CPAP treatment to 35 moderate-to-severe asthmatics and found that all markers such as CRP, IL-6, and TNF-α in exhaled breath condensate and nitrotyrosine and 8-isoprostane levels in serum were decreased significantly. Therefore, they came to the conclusion that CPAP treatment could significantly decrease the local inflammation of OSA and also, to some extent, help decrease systemic oxidative stress levels in serum.[27] While improvements have been demonstrated in many studies, its certain effect on local and systemic inflammation is still debatable.[28,29]

Leptin

Leptin, which is mainly synthesized and secreted by adipose tissue, has been known to be elevated in OSA patients. It usually results from factors such as obesity and intermittent hypoxia. As the airway epithelial cells express receptors for adipokins leptin and adiponectin, the increasing leptin was proved to be closely correlated with AHR.[30] An animal model research done by Shore *et al*. proved that the administration of leptin to mice could increase both AHR and serum IgE levels.[31] Besides, leptin also has proinflammatory effect as a member of the IL-6 family of cytokines. Possible reason is considered as the alveolar macrophages' unique sensitivity to leptin in overweight and obese asthmatics, which induces significant production of proinflammatory cytokines.

Vascular endothelial growth factor

Some scholars also pointed out the importance of VEGF in the pathogenesis of the two diseases. VEGF is a hypoxia-sensitive glycoprotein, and its expression can be promoted by OSA and asthma.[32] As a glycoprotein that stimulates the endothelial cell proliferation and neoangiogenesis, VEGF may contribute to bronchial inflammation, hyperresponsiveness, and vascular remodeling in those patients. A recent study completed by Simcock *et al*. supported a critical role for VEGF in vascular remodeling in asthma.[33]

Cardiac dysfunction

OSA can provoke or worsen cardiac dysfunction.[34] Usually, in nonrapid eye movement sleep period, the whole cardiovascular system presents a relaxed state. Metabolic rate and sympathetic nerve activity decrease significantly while the vagal activity rises. Since sleep structure is destroyed in OSA, the cardiovascular system loses its normal relaxed condition. Intermittent hypoxia and hypercapnia easily induce endothelial dysfunction, which finally results in cardiac ischemia, cardiac remodeling and thereby aggravates the process of heart failure.[35] In the meanwhile, the enhanced sympathetic activity and negative intrathoracic pressure lead to the intermittent increasing after load of left ventricular, causing or worsening heart failure. Those above-mentioned changes not only decrease lung compliance and increase peripheral airway resistance, but also activate the renin-angiotensin-aldosterone system.[36] The increasing aldosterone leads to liquid accumulation around the neck, increasing airflow resistance, and worsening OSA. Other studies also suggested that heart failure could induce bronchoconstriction and AHR due to the airway's hyperresponsiveness to cholinergic stimuli. Airway resistance was demonstrated to be higher due to mucosa and pulmonary edema, and the bronchial walls were thicken in those patients who are susceptible to asthma.[37]

Others

There are still several other connecting pathways implicated in the relationship of the two diseases. Tamisier *et al*. pointed out that inspiratory and expiratory resistances during the night in OSA are much higher than those in the daytime. The upper airway resistance increases at the end of the expiratory phase before the inspiratory-induced airway collapse.[38] Given those findings and recognition, the asthma characteristic increasing expiratory airflow resistance may potentially contribute to the upper airway collapsibility during inspiration. Another reasonable mechanism is that poor sleep quality caused by severe asthma can lower arousal thresholds, leading to frequent nocturnal arousals and increasing upper airway collapsibility.[39]

Indirect Effects

Glucocorticoids

Glucocorticoids usually constitute first choice treatment in asthma control, and recently it has been proposed as a contributing factor of OSA. Yigla *et al*. selected 22

difficult-to-treat asthmatics who had received long-term or frequent bursts of oral corticosteroids. It finally came out that 21 (95%) of them were diagnosed with OSA. The proportion was much larger than that of the patients receiving intermittent use of corticosteroids, which identified a dose-response relationship between corticosteroid use and OSA.[40] Though the mechanism by which the two conditions are linked is not fully illuminated, possible reasons proposed recently are as follows: Inhaled corticosteroids cause fat deposition in and around the upper airway, narrowing the airway cross-section area; glucocorticoids can induce myopathy of the airway dilator muscles, which influences the airway dilation; glucocorticoids worsen obesity.

Nasal diseases

Nasal cavity acts as the main breathing route during sleep. Nasal inflammation causes mucosa hyperemia, edema, nasal stenosis, and obstruction. Increased nasal resistance results in higher negative oropharyngeal pressure during inspiration and predisposes to airway collapse.[41,42] A study done by Kalpaklioglu *et al*. demonstrated that patients with allergic rhinitis or nonallergic rhinitis have higher apnea-hypopnea index and nasal resistance.[43] In addition, the trauma on the upper airway produced by snoring and cycles of airway closure/reopening in OSA can also trigger or worsen local inflammation of the nasal and pharyngeal mucosa.

A majority of the asthmatics have nasal diseases as rhinitis and nasal polyposis.[44] In this condition, bacterial colonization from infected areas falls into the lower airway, and proinflammatory and bronchoconstrictive cytokines transfers to the systemic circulation, thus provoking and aggravating local or systemic inflammation and airway obstruction. The chronic inflammatory stimulation on the mucosa can lead to reflective bronchospasm through the way innervated by parasympathetic nose-bronchial reflection. Besides, the substitution of the mouth for the obstructive nose to breath resulting in excessive dry air going into the lower airways, easily causing asthma attack.

Smoking

Smoking is a common risk factor in progression of the two conditions. It can worsen asthma and OSA symptoms. The proximal airway inflammation provoked by smoking has been postulated as the likely mechanism, which increases the surface mucus secretion and induces airway edema, thereby increasing the airway resistance and worsening airway obstruction. Another described mechanism is the hazardous ingredients in cigarettes, which can directly irritate the airways, damage mucosa within a short time, and trigger the symptoms of wheezing, cough, and sputum production. Besides, it was documented that smoking increased the production of leukotrienes,[45] one of the most important inflammatory mediators in asthma attack.

Obesity

Obesity is a known major risk factor for OSA.[46] A research showed that males with neck perimeter larger than 40 cm or females larger than 36 cm were at higher risk of OSA compared with those controls.[47] It has been shown that the neck perimeter is more closely correlated to the severity of the syndrome.[48] Reasons focus on the following aspects: Fat deposits in the neck region, narrowing the pharyngeal airway, weakening the pharyngeal muscles' support, and then making the airway easily to collapse. Fat that deposits in the abdomen can also increase the intra-abdominal pressure, which influence the diaphragmatic motion and decreases the compliance of thoracic wall and lung, thereby limiting the dilation of upper airway and lung, attenuating the stiffening effect of tracheal tug on the pharyngeal upper airway segment, and finally causing the airway collapse.[49] Besides, adipose tissues secrete kinds of hormonally active agents and inflammatory cytokines such as leptin, TNF-α, IL-6, etc.[50] On the other hand, OSA can also lead to obesity via a variety of mechanism: Disturbed sleep architecture and intermittent hypoxia lead to neurohormonal abnormalities, such as changes in the proportion of leptin-ghrelin, subsequently increasing the oral intake; deprival of deep sleep reduces the production of growth hormone which can decompose the adipose tissue; reduction of daytime activities aggravates obesity and increases the difficulty to lose weight; IR, caused by the lower sensitivity of insulin and affinity of its receptors in OSA, plays a significant role in the mechanism of metabolic syndrome like obesity.

Obesity is also a significant risk predictor of asthma. Increasing weight causes more frequent or more severe asthma exacerbations and more difficult-to-control symptoms. Obesity can induce or aggravate the restrictive/obstructive ventilation function disturbance and small airway damage by the effect of fat deposition and inflammation.[51]

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is an independent predictor for habitual snoring. Green *et al*. and Valipour *et al*. reported that GERD was comorbidity in 62% and 58% of patients with OSA syndrome, respectively.[52,53] The upper airway occlusion in OSA causes a higher negative intrathoracic pressure and an increasing transdiaphragmatic pressure.[54,55] In the meantime, autonomic nervous system dysfunction, frequent arousals, and swallowing cause transient lower esophageal sphincter relaxation, which can finally lead to GERD. On the contrary, the clearance ability of gastric acid in patients with GERD usually decreases at night. The proximal migration of gastric acid causes pharyngeal spasm and mucosal exudative neurogenic inflammation, which makes the airway more prone to collapse during sleep. Besides, laryngitis and edema caused by reflux can further aggravate the obstructive degree.

In addition, studies found patients with GERD more easily suffered asthma attack.[56] GERD is one of the risk factors of asthma attack.[8] The vagus is activated in GERD by stimulating the acid-sensitive receptors on esophageal mucosa, causing reflex bronchospasm. After microaspiration, the airway mucosa is injured by gastric contents, which can also induce or worsen asthma.[57]

Clinical Manifestations

There are many similar clinical manifestations between OSA and asthma, including airflow obstruction in corresponding segment, obviously sleep quality declining and daytime fatigue. Both diseases often attack during the night or in the early morning. Series of cardiovascular system complications occur if poorly controlled. Therefore, in clinical work, it is difficult to differentiate OSA from nocturnal asthma just based on patient's complaints. Some functional assessments such as bronchial provocation/dilation test or PSG might help. With the growing awareness of the relationship between the two diseases, some scholars defined them as "alternative overlap syndrome" to help us better stratify the therapies.

Diagnosis

At present, most of the diagnostic procedures of OSA rely on PSG.[58] By monitoring overnight brain electrical activity, respiration, thoracic-abdominal motion, finger oxygen saturation, etc., physicians can get information about the distribution of sleeping state, frequency, and duration of apnea and hypoxia. By contrast, the diagnosis of asthma principally relies on symptoms, accompanied by lung function, allergen test, etc. Since OSA is often neglected in clinical work, current asthma guideline has recommended the testing for OSA in those overweight or obese patients with poorly controlled asthma. By inquiring the patient or his/her bed partner, the symptoms of snoring, witnessed apneas, excessive fatigue, or sleepiness during wakefulness, physicians can get a preliminary inspection.[59]

Therapies

CPAP has been accepted as the main nonsurgical treatment for OSA, which was introduced by Sullivan in 1981.[60] It was found to improve asthmatic symptoms in patients combined with OSA as well. Chan *et al*. assessed a 2-week course of CPAP treatment in nine persons and finally found that it could decrease the frequency of asthma attack all day long, reduce bronchodilator use, and improve peak expiratory flow rates pre-/post-bronchodilators. However, the peak expiratory flow rate returned to levels prior to the therapy after the cessation of CPAP.[61] Guilleminault *et al*. studied 10 people and demonstrated that 6–9 months of CPAP treatment can successfully eliminate nocturnal asthma attacks.[62] Ciftci *et al*. reported that 2-month CPAP therapy resulted in a significant improvement in asthma nocturnal symptom score, but no change in lung function as forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC, and forced expiratory flow 25–75%. Consequently, CPAP treatment is definitely associated with lower odds of nocturnal asthma during the therapy but presents no improvement in lung function after the cessation of it.[63]

CPAP treatment can improve the asthma symptom through a variety of pathways. It decreases the airway resistance to avoid peripheral airway collapse by increasing airway average pressure, minute ventilation, FVC, and total lung capacity. Carr and Essex provided the anesthetic dogs with 20 cm H_2O CPAP treatment and noticed that the diameter of the major airway had increased by 33–71%.[64] CPAP treatment can also lower the bronchial smooth muscle's high reactivity to acetylcholine and help the airway dilation. Besides, as it is mentioned above, the local inflammatory effect caused by OSA can be inhibited by the therapy. Also, CPAP can eliminate the hypoxia caused by OSA and lower the levels of leptin and VEGF. In addition, CPAP alleviates GERD by decreasing the thoracic-abdomen pressure gradient and reducing the chance of awakening.

Limitations also do exist. Heater humidifiers are needed to avoid cold and dry air from inducing asthma or sputum scab formation. Humidifiers must be kept clean to prevent microorganism from propagating in the warm and humid environment and going down the airway. Besides, a study done by Martin and Pak showed that CPAP was hard to intolerant for those nonapneic nocturnal asthmatics. Instead, sleep was interrupted for its uncomfortability.[65] That is to say, CPAP treatment is not recommended for those patients.

In summary, OSA and asthma are common conditions. The term of "alternative overlap syndrome" may represent as a condition with important common characteristics of the two diseases. As the dual interaction between them, we should raise our awareness and provide proper therapy timely to relieve the pain of the patients. Traditional CPAP treatment can improve the asthma symptoms in those people. However, there are still some limitations. Further definitive confirmation completed by large randomized controlled trials, as well as an evaluation to analyze the lower airway structure and function in the two conditions, are still necessary.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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