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Review

Role of lung volume and airway inflammation in obstructive sleep apnea

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ABSTRACT

Obstructive sleep apnea (OSA) is a prevalent disorder that affects not only the upper airways but also the intrathoracic airways. In this review, we summarize the results of studies on lung function and airway inflammation. We provide evidence that the alterations in intrathoracic airways observed in OSA are not purely consequences of mechanical trauma and oxidative stress during apneic events but have a causal role in the structural changes associated with OSA and increasing severity of this disorder.

Contents

Abbreviations: AHI, apnea/hypopnea index; BALF, bronchoalveolar lavage fluid; BMI, body mass index; CIH, chronic intermittent hypoxia; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; EBC, exhaled breath condensate; FENO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICAM, intercellular adhesion molecule; IL, interleukin; ILD, interstitial lung disease; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; OSA, obstructive sleep apnoea; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

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1. Introduction

Obstructive sleep apnea (OSA) is a common disorder that is characterized by repetitive episodes of total or partial collapse of the upper airways during sleep. If OSA is accompanied by symptoms of excessive daytime sleepiness, tiredness, or fatigue, the term obstructive sleep apnea syndrome is used. According to the latest edition of International Classification of Sleep Disorders issued by the American Academy of Sleep Medicine in 2014 [1], OSA is defined as either the presence of daily symptoms/disturbed breathing during sleep/comorbidities together with more than 5 obstructive respiratory events or more than 15 obstructive respiratory events, irrespective of symptoms or comorbidities. Because of the diversity of the diagnostic methods and criteria, the exact prevalence of OSA is not known, but it ranges between 10% and 30% in the general adult population [2]. Obesity, male sex, age, and craniofacial anatomy are the major determinants of OSA susceptibility [2]. Therefore, sociodemographic variations may contribute to diverse epidemiological results as well.

Decreased pharyngeal diameters and an increased possibility of upper airway collapse are important but not the only components of the OSA pathophysiology. Local and central nervous control and systemic inflammation are also frequently recognized factors. However, there has been little attention on the role of intrathoracic airways even though the lungs are under massive oxidative burden caused by chronic intermittent hypoxia (CIH). It seems that the lower airways do not just passively participate in OSA but may contribute to the complex pathophysiology of the disease as well.

This article aims to summarize the current knowledge on the role of lung volume and airway inflammation in OSA.

2. Lung volumes

It has been recognized that reduced lung volumes are related to increased OSA severity, regardless of whether the patients have airway or parenchymal lung disease. This relationship has been confirmed both by body plethysmography [3–6] and spirometry [7,8]. In particular, negative relationships were reported between the severity of OSA, determined using the apnea/hypopnea index (AHI) or respiratory disturbance index, and expiratory reserve volume [3–6], functional residual capacity [4,5], forced expiratory volume in one second (FEV_1) [7,8], and forced vital capacity (FVC) [7]. In line with this, a significant association between lung function loss and all-cause mortality was reported in patients with OSA [9]. However, the contribution of lung volume loss to mortality was lower in patients with sleep disordered breathing than in control subjects (6% vs. 11%, for every 200 mL decrease in FEV_1) [10].

The relationship between reduced lung volume and OSA severity needs to be interpreted carefully because BMI is a strong covariate for this association [7]. Obesity reduces the functional residual capacity, especially in the supine position [11], and is strongly associated with OSA severity [11]. However, there are arguments that the association between lung volume and OSA severity is independent of obesity. First, the lung volume was reduced when patients with OSA were compared with BMI-matched controls [6,8]; the AHI and expiratory reserve volume were found to be related after correction for body mass index (BMI) [4]. Second, OSA is highly prevalent in non-obese patients with restrictive lung disease [12]. Third, reduced lung volume leads to upper airway collapse not only in patients with OSA but also in patients with chronic obstructive pulmonary disease (COPD) [13] and in healthy controls [14,15].

The association between lung volumes and upper airway collapsibility can be explained by mechanical [16] and chemical [17] factors [18]. A higher lung volume causes the mediastinal structures to be pulled caudally, leading to pharyngeal airway dilation [16]. Furthermore, increased lung volume is associated with the storage of more O_2 and CO_2, thus buffering blood gases from changes in ventilation [17]. Some patients with OSA are particularly prone to intermittent hypercapnic episodes, developing respiratory disturbances due to high loop gain [18].

Recently, we described an evening-to-morning increase in FEV_1 in OSA without any change in FVC. This very mild bronchodilation may be caused by sympathetic bursts during apneic periods [7], but the exact reason needs to be investigated in detail. Of note, this increase was observed only in obese patients with OSA; there were no changes in non-obese subjects with OSA or obese control volunteers [7]. Tidal volumes tend to decrease at sleep onset in non-OSA patients of normal weight [19], as well as in non-OSA obese patients [11] and patients with OSA [20].

Continuous positive airway pressure (CPAP) treatment increases the vital capacity and functional residual capacity in non-OSA patients [21]. In addition, increases in lung volume are associated with lower pressures, required to maintain upper airway patency [14]. Thus, it seems that CPAP treatment prevents apneic episodes not only at the level of the upper airways but also by influencing the lower airway volumes. Of note, one study reported that long-term CPAP treatment is associated with worsening lung function, especially in terms of markers of small-airway obstruction [22].

Only one randomized controlled trial investigated if increasing the airway caliber with salmeterol has any effect on AHI in OSA; however, the effect of salmeterol compared to that of the placebo was insignificant [23].

3. Airway inflammation

Both chronic intermittent hypoxia and vibration trauma during snoring may induce inflammatory changes in the upper airways [24]. These include neutrophilia in the nasal

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