Monaldi Arch Chest Dis
2006; 65: 2, 102-105

Airway inflammation in patients affected by obstructive sleep apnea

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ABSTRACT: ***Airway inflammation in patients affected by obstructive sleep apnea. R. Sabato, P. Guido, F.G. Salerno, O. Resta, A. Spanevello, M.P. Foschino Barbaro.***

Obstructive sleep apnea (OSA) is characterised by repetitive episodes of upper airway occlusion during sleep. OSA has been shown to be associated with a variable degree of nasal inflammation, uvula mucosal congestion and airway hyperreactivity. The upper airway inflammation, whose clinical importance is uncertain, is characterised by leukocytes infiltration and interstitial oedema. In addition, recent data has shown the presence of neutrophilic inflammation in the lower airways. The current opinion is that airway inflammation is caused by the local, repeated mechanical trauma related to the intermittent airway occlusion typical of the disease. Another potential mechanism involves the intermittent nocturnal hypoxemia that through the phenomenon of the ischemia-reperfusion injury may induce the production of oxygen free radicals and therefore cause local and systemic inflammation. Finally, a state of low-grade systemic inflammation may be related to obesity *per se* with the pro-inflammatory mediators synthesised in the visceral adipose cells. Several authors stress the role of circulating and local inflammatory mediators, such as pro-inflammatory cytokines, exhaled nitric oxide, pentane and 8-isoprostane as the determinants of inflammation in OSA.

Monaldi Arch Chest Dis 2006; 65: 2, 102-105.

Key words: OSA, airway inflammation, obesity.

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Obstructive sleep apnea (OSA) is characterised by repetitive episodes of upper airway occlusion during sleep. Nasal inflammation, uvula mucosal congestion, airway inflammation and airway hyperreactivity have been shown to be associated with OSA [1, 2, 3]. These alterations, together with a described low grade systemic inflammation, may play a role in the clinical manifestation and in the complications of OSA patients. In addition, airway inflammation may contribute to the pathogenesis of the disease by further decreasing airway caliber.

Airway inflammation in OSA

Several studies have demonstrated the presence of mucosal oedema and structural mucosal changes in the upper airway of patients with OSA. Rubinstein *et al* [1] have described the presence of nasal inflammation in OSA and have suggested that this abnormality may further aggravate the upper airway obstruction. In this study, a local mucosal increase in both polymorphonuclear leukocytes and flogosis mediators such as bradykinin and vasoactive intestinal peptide (VIP) were shown. Sekosan *et al* [2] and Zakkar *et al* [4] have shown inflammation in the soft palate of OSA patients, in the form of increased thickness of uvula mucosa, interstitial oedema and higher number of leukocytes in the lamina propria of these districts. The authors have suggested that upper airway soft tissues inflammation plays a critical role in the pathogenesis of upper airway narrowing during sleep in OSA patients.

Several studies have demonstrated the presence of airway inflammation mediators in OSA. A significant decrease of neutral endopeptidase, a mediator that inactivates pro-inflammatory peptides eliciting interstitial edema, has been described [4]; on the other hand, increased local levels of inflammatory mediators have been demonstrated in obese OSA patients, suggesting the development of inflammation in the airways during sleep. The non-invasive evaluation in the exhaled air of OSA patients, of airway inflammation and oxidative stress markers as pentane and exhaled nitric oxide (eNO) performed by Olopade *et al* [5], have suggested the development of airway inflam-

mation during sleep in this type of patients. Recently, Carpagnano *et al* [6] measured high levels of two markers of inflammation and oxidative stress, IL-6 and 8-isoprostane, in the exhaled breath condensate of obese patients with OSA.

A recent study [7] demonstrated the presence of lower airway inflammation in OSA using the analysis of induced sputum, a valid and widely used technique to investigate the bronchial inflammatory profile, characterised by a variable degree of neutrophilic airway inflammation. In this study, none of the patients were smokers, nor did they have a history of acute or chronic respiratory disease. The clinical role of this abnormality is currently under investigation.

Potential mechanisms of inflammation in OSA

It is not completely known why there is airway inflammation in OSA. There are several possible explanations for the presence of inflammation in the airways of OSA patients. The upper airways and in particular the nasal inflammation are believed to be the consequence of the mechanical stress associated to the obstruction of the air passage, typical of the disease. The repeated mechanical trauma on the airways related to snoring, together with the airway vibration and the forceful suction collapse during apnoeas, likely triggers an inflammatory response locally [8, 9]. Regarding the lower airways, the mechanical stress exerted on the mucosa of the respiratory system by the snoring and the apneas, may also be responsible for bronchial inflammation. In fact, a strong inspiratory effort against a closed airway passage creates a negative pressure which is transmitted to all the respiratory system. The "pressure trauma" may not be the exclusive mechanism involved. A link between airway inflammation and sleep apnea is present in asthma, an inflammatory disease often associated to OSA. Snoring and apnoea, in fact, occur in patients with bronchial asthma more frequently in respect to the general population [10], probably because of the occurrence of rhinitis and nasal poliposis that induce increased nasal resistance and negative pressure in the upper airways during inspiration. The airway collapse and the air turbulence may predispose to the worsening of the bronchoconstriction and to the appearance of OSA [11]. Furthermore, nocturnal hypoxemia itself can induce reflex bronchoconstriction through stimulation of carotid bodies [12]. In addition upper airway reactivity measured using transient reflex laryngeal closure, is increased in OSA patients. This effect is likely to be secondary to the inflammation of the epithelium lining of the upper airway following the repeated airway obstruction, allowing the passage of inhaled irritant to the sub-epithelial receptors [13].

OSAS may induce lung function abnormalities. In so far as intermittent upper airway obstruction is the most important feature of OSA, Bijaoui *et al* [14] in a recent study tested the hypothesis that the repetitive apnoea episodes are accompanied by modifications in the respiratory system. Indeed, upper airway obstruction in OSA predispose to alterations in lung and airway functions. Bijaoui proposes that the observed increase in lung elastance and lung resistance, during obstructed breathing, may lead to nocturnal transient abnormalities in the recruitment of lung units and in the gas exchanging capacity of the lungs.

A state of low-grade systemic inflammation seems to be present in obese adults with OSA, and to some extent in obese adults without OSAS. Airway inflammation may be, at least in part, the epiphenomena of this systemic inflammation. Entzian *et al* [15] suggested the critical role of circulating cytokines in the pathogenesis of OSA; Vgontzas *et al* [16, 17] found that the concentrations of circulating Il-6 and TNF-α were higher in obese subjects affected by sleep apnoea compared to non apnoeic obese subjects; however, the high levels of pro-inflammatory cytokines correlated with nocturnal hypoxemia, diurnal hypersomnia and daytime fatigue measured in healthy subjects with poor refreshing sleep. Elevated levels of inflammatory markers, IL-6, TNF-α, and CRP have been demonstrated in OSA patients but not in control obese subjects without OSA. Moreover, CRP levels were correlated with the severity of OSA, BMI and nocturnal hypoxemia [16, 18, 19]. These findings, taken together, suggest the presence of systemic inflammation in OSA subject, that may also be involved in the elevated prevalence of cardiovascular and coronary artery diseases described respect to general population. Apneas and arousal events, induce an increase of heart rate and blood pressure values related to both a raise in gradient intrathoracic pressure, to nocturnal hypoxia and to inflammatory response [20, 21, 22].

Some authors have hypothesised the importance of the body fat distribution in the obese patients, particularly emphasising the importance of the amount of omental adipose tissue in the synthesis of systemic cytokines, a condition, however, not necessary correlated with sleep apnoea [23].

Recently, some authors have supported the role, as a pro-inflammatory mechanism in OSA patients, of the intermittent nocturnal hypoxemia and the relative ischemia-reperfusion injury. Similar to the ischemia/reperfusion injury seen in coronary artery disease and stroke, sleep apnea is accompanied by cyclical alterations of arterial oxygen saturation, with oxygen desaturations in response to apneas followed by resumption of oxygen saturation during hyperventilation. The consequent excessive oxygen free radicals production ("oxidative stress") would result in local and systemic inflammation [8, 16, 24], likely contributing to the development of cardiovascular disease [25]. Indeed, reactive plasmatic oxygen species (ROS) are associated with OSA with activation of inflammatory cells [26] and increased cytokines levels. The inflammatory cells activated by systemic mediators such as TNF-α, IL-1, Il-6 and IFN-γ may express adhesion molecules which in turn may result in increased endothelial cells/leucocytes interactions that may trigger the atherogenic processes [27, 28]. No conclusive data exists on the potential

role of local airway production of ROS on airway inflammation, their influence on inflammatory exhaled markers, and bronchial inflammatory cells pattern. However, an involvement in the genesis of airway inflammation is likely.

At the moment, no data demonstrates a clear correlation between airway inflammation markers and obesity in OSA patients. Recently Carpagnano *et al* [6] measuring the levels of markers of airway inflammation and oxidative stress in the exhaled breath condensate in OSA, found a significant positive correlation between those markers and neck circumference, or the severity of sleep apnea.

A further mechanism by which airway inflammation may be present in OSA is through the presence of asthma, that is prevalent in obesity [29]. Obesity, in fact, by altering the chest wall mechanics, determines a shift of the elastic equilibrium between lung and chest wall recoil towards a lower functional residual capacity. In so far as there is mechanical interdependence between the lung parenchyma and the intraparenchymal airways, a lower lung volume decreases the tethering of the lung parenchyma on the airways, diminishing the mechanical load opposing the airway narrowing and therefore facilitating airway hyperresponsiveness and asthma (30).

CPAP and airway inflammation in OSA

Nasal continuous positive airway pressure (nCPAP) is a common treatment for OSA. nCPAP improves diurnal and nocturnal symptoms, in addition to the snoring and the often co-existing bronchial asthma. Indeed, nCPAP, by reducing airway obstruction and the desaturation events, may decrease the neural reflex of bronchoconstriction [31, 32]. The effectiveness of nCPAP in reversing airway inflammation and airway hyperreactivity is less compelling. In the study of Nandwani *et al* [33], a 3-month treatment of OSA patients with nCPAP reversed upper airway reactivity likely secondary to the inflammation of the epithelium lining of the airways. Wenzel [34], in his study, supports the concept that in OSA patients with bronchial hyperreactivity the benefits of CPAP excel the potential adverse effects. On the contrary, when bronchial provocation tests are performed before and after two days of treatment with nCPAP, a worsening of the bronchial hyperreactivity has been shown [35]. Nonetheless no conclusive data is available on this regard. CPAP may represent, because of the high mean airway pressure, a mechanical stimulus on the airways theoretically able to determine an inflammatory response.

Conclusion

In conclusion, patients affected by OSA, display upper and lower airway inflammation. Airway inflammation may be the result of the mechanical stress on the mucosa caused by intermittent airway obstruction, the consequence of nocturnal hypoxia, or a systemic inflammation. Further studies are necessary in order to assess the clinical importance of inflammation in OSA, and the effectiveness of the anti-inflammatory therapy on reducing the OSA-induced airway inflammation and in modifying the natural history of the disease. It is possible that in addition to CPAP therapy, surgery and weight reduction, patients affected by OSA may benefit also from treatment aimed at reducing local and systemic inflammation.

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