Inflammation accelerates atherosclerotic processes in obstructive sleep apnea syndrome (OSAS)

QUERCIOLI, Alessandra, MACH, François, MONTECUCCO, Fabrizio

Abstract

Obstructive sleep apnea syndrome (OSAS) is an often underestimated sleep disorder that has been associated with cardiovascular disease. OSAS is characterized by cycles of apnea and/or hypopnea during sleep caused by the collapse of the upper airways. Intermittent hypoxia deriving from the cycles of apnea/arousals (to retrieve the ventilation) plays a pivotal role in the pathogenesis of the disease. Obesity is the most frequent predisposing condition of OSAS. Recent evidence suggests that OSAS could be considered as a pro-atherosclerotic disease, independently of visceral fat amount. Oxidative stress, cardiovascular inflammation, endothelial dysfunction, and metabolic abnormalities in OSAS could accelerate atherogenesis. The present review is focused on the possible pathophysiological mediators which could favor atherosclerosis in OSAS.

Reference


DOI : 10.1007/s11325-010-0338-3
PMID : 20198512

Available at:
http://archive-ouverte.unige.ch/unige:21241

Disclaimer: layout of this document may differ from the published version.
Inflammation accelerates atherosclerotic processes in obstructive sleep apnea syndrome (OSAS)

Alessandra Quercioli · François Mach · Fabrizio Montecucco

Abstract Obstructive sleep apnea syndrome (OSAS) is an often underestimated sleep disorder that has been associated with cardiovascular disease. OSAS is characterized by cycles of apnea and/or hypopnea during sleep caused by the collapse of the upper airways. Intermittent hypoxia deriving from the cycles of apnea/arousals (to retrieve the ventilation) plays a pivotal role in the pathogenesis of the disease. Obesity is the most frequent predisposing condition of OSAS. Recent evidence suggests that OSAS could be considered as a pro-atherosclerotic disease, independently of visceral fat amount. Oxidative stress, cardiovascular inflammation, endothelial dysfunction, and metabolic abnormalities in OSAS could accelerate atherogenesis. The present review is focused on the possible pathophysiological mediators which could favor atherosclerosis in OSAS.

Keywords Obstructive sleep apnea syndrome · Inflammation · Oxidative stress · Atherosclerosis

Introduction

Sleep apnea is an underdiagnosed syndrome, characterized by periods of breathing apnea and/or a marked reduction of the tidal volume (hypopnea) occurring during sleep. Obstructive sleep apnea syndrome (OSAS) is caused by the collapse of the upper airways. OSAS patients manifest excessive daytime sleepiness related to the fragmentation of the sleep by frequent arousal, which might favor the development of cognitive dysfunction and memory loss because of cerebral hypoxemia [1, 2]. Although it is still considered as a local and upper airway disorder, OSAS is now deemed a systemic disease that could involve not only the respiratory but also central nervous and cardiovascular systems. Intermittent hypoxemia (IH, intermittent periods of oxygen saturation below 90%) can increase oxidative stress, pro-inflammatory cytokine production, platelet aggregation, and metabolic dysregulation [1, 3–5]. Importantly, sleep-related IH was independently associated with all-cause mortality in 6,441 men and women participating in the Sleep Heart Health Study [6]. Several studies have demonstrated the association of OSAS with arterial hypertension [7, 8], stroke [9–12], coronary artery disease (CAD) [13–16], or pulmonary hypertension [17]. Sleep-disordered breathing was also significantly associated with coronary artery disease-related mortality [6]. The high mortality risk in untreated sleep-disordered breathing has been shown as independent of age, sex, and body mass index (BMI) [18]. Thus, recent evidence showed that OSAS should be considered as a condition predisposing cardiovascular disease [2, 15, 19–21]. Nevertheless, the elevated incidence of OSAS in the adult population (4% men and 2% women between 30 and 60 years of age manifest the severe form of the disorder, while these percentages go up to 5–15% considering all stages of the disease) [22–24] and the risk of
severe systemic complications confer to the diagnosis and treatment of OSAS a remarkable social importance.

OSAS-associated cardiovascular inflammation and its clinical relevance will be discussed in the present article.

Clinical relevance of OSAS

OSAS represents a systemic worldwide disease, mainly affecting obese subjects (up to 70% of OSAS patients are obese). This association renders difficult to define OSAS impact as an independent factor of risk [25, 26].

Subjects with OSAS have an increased comorbidity (CAD, stroke, arterial hypertension) and mortality, while continuous positive airway pressure (CPAP) treatment seems to improve survival [27, 28]. Marshall and co-workers recently showed that moderate to severe OSAS is independently associated with an increased risk of all-cause mortality in 397 residents of Busselton town (Western Australia) after up to a 14-year follow-up [29]. Doherty and co-workers observed that deaths for cardiovascular disease were more common in the untreated group of patients than in the CPAP-treated one during follow-up (14.8% vs. 1.9%, respectively) [30]. Cross-sectional associations from the Sleep Heart Health Study cohort (6,424 subjects) demonstrated that OSAS induces only modest to moderate effects on cardiovascular disease [15]. On the other hand, OSAS has high incidence among persons with known CAD (30–58%) [31, 32]. The relative risk for myocardial infarction in OSAS subjects for the upper quartile of the apnea index has been shown to be 23.3 compared with the lowest quartile, indicating a strong association between OSAS and the acute coronary syndrome. These studies suggest that OSAS is an independent risk factor for CAD [14]. Subjects with coexistent OSAS and CAD have higher mortality (38% vs. 9%), increased rate of restenose after percutaneous coronary intervention (24% vs. 5%), and increased rate of major adverse cardiac events (37% vs. 15%) as compared to CAD patients without OSAS [33]. Recent studies have shown early atherosclerotic lesions in OSAS subjects (such as the increase of intima–media thickness [IMT]), which can be reduced by CPAP treatment [34–36]. Furthermore, IMT is significantly correlated to levels of C-reactive protein (CRP), interleukin (IL)-6, and severity of OSAS [35]. OSAS is also associated with other signs of early atherosclerosis, such as increased arterial stiffness and heart remodeling (increased left atrial diameter, interventricular septal thickness, and left ventricle mass index), independently of other confounding factors [34, 37].

In the last decades, increasing evidence showed that OSAS is also associated with arterial hypertension [8, 38–40]. Large clinical studies have demonstrated that OSAS is an independent risk factor for hypertension [7, 20, 41] with an adjusted odds ratio for baseline hypertension, non-modifiable risk factors, obesity, and smoke of 2.9 [20]. Several studies have also demonstrated that CPAP treatment not only reduces nocturnal blood pressure [42] but also decreases daytime diastolic blood pressure [43–45]. On the other hand, some authors failed to find any beneficial effect on blood pressure when investigating hypertensive OSAS patients [46].

OSAS has been also related to an increased risk of stroke. The Sleep Heart Health Study showed a small but significant increase in stroke prevalence among OSAS subjects [15]. Yaggi and co-workers showed that OSAS subjects have a 2-fold increased risk of stroke as compared with non-OSAS subjects in a 3.5-year follow-up [12]. Moreover, OSAS is associated with a more serious prognosis after stroke [11, 47].

Other known cardiovascular complications are different types of arrhythmias (brady- and tachyarrhythmias) [48, 49], pulmonary hypertension [50–52], and congestive heart failure [53, 54].

The nasal CPAP is the gold-standard treatment; it significantly improves oxygen saturation and general symptoms. In spite of the existing debate, some studies have shown that CPAP reduces the levels of systemic inflammatory markers such as TNF-α, IL-6, CRP, and IL-8 [55–58].

Several pathogenetic mechanisms have been proposed to explain the possible association between OSAS and cardiovascular disease.

Cardiovascular inflammation in OSAS

Oxidative stress

IH is a key element in the pathophysiology of OSAS and its complications. It consists of cycles of short periods of oxygen desaturation followed by retrieval of the ventilation with normalized oxygenation. It has been postulated that IH is a harmful mechanism analogous to ischemia–reperfusion injury. In ischemia–reperfusion injury, the damage occurs when the blood flow to an ischemic or hypoxic tissue is restored [1, 3, 5, 59, 60] and overproduction of reactive oxygen species (ROS) is induced. The same mechanism might be implicated in intermittent hypoxia during sleep. During reperfusion, ROS are generated through the xanthine oxidase pathway, the NADPH oxidase pathway, and the incomplete oxidative phosphorylation in the mitochondria [22, 61–63]. Accordingly, several oxidative stress markers are increased in OSAS [62, 64–68] and are reduced after CPAP treatment [69, 70]. An increased level of ROS, such as superoxide anion (O$_2^-$), hydroxyl radical (OH$^-$), and peroxynitrite (ONOO$^-$), provides cell membrane damage by lipid peroxidation, protein oxidation, depletion of
intracellular adenosine triphosphate, alteration in calcium homeostasis, cellular apoptosis, and oxidative DNA damage. These events finally could increase endothelial dysfunction and inflammation [60, 62, 71].

ROS production is associated with the upregulation of different genes regulated by the pro-inflammatory nuclear factor kappa B (NF-κB) pathway [3, 72, 73]. NF-κB mediates the production of inducible NO synthase (iNOS) [74] and cyclooxygenase (COX)-2. NF-κB also activates the overexpression of adhesion molecules involved in leukocyte recruitment and migration to the inflammatory site, i.e., intercellular adhesion molecule-1 (ICAM-1), E-selectin, and vascular cell adhesion molecule-1 (VCAM-1) [73, 75, 76]. Accordingly, NF-κB is highly activated in OSAS patients as compared to healthy controls. Furthermore, CPAP treatment strongly reduces NF-κB activation [77]. Interestingly, IH does not seem to activate protective hypoxia-inducible factor-1 (HIF-1), a key regulator of the adaptive pathway to chronic hypoxia [72, 78]. The short duration of hypoxia in IH does not allow the stabilization of HIF-1 and the cyclic re-oxygenation induces mitochondria dysfunction. Thus, it results in the activation of the NF-κB pathway alone [78, 79]. These results are controversial and need further confirmations. Indeed, it is well known that HIF-1 downstream proteins, such as the vascular endothelial growth factor (VEGF, which regulates the oxygen homeostasis), iNOS, and endothelin-1 (a potent vasoconstrictor), are increased in OSAS, suggesting a possible activation of HIF-1 pathway [80–87].

Systemic inflammatory mediators

Several evidences suggest that OSAS might be considered as a systemic inflammatory disease (Table 1). The levels of the pro-inflammatory cytokine TNF-α are correlated with the severity of OSAS. TNF-α modulates physiological sleep [88].

Table 1 Clinical studies investigating the association between inflammatory cardiovascular risk markers and OSAS

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Marker</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vgontzas et al.</td>
<td>2000</td>
<td>14 OSAS; 11 obese; 12 controls</td>
<td>TNF-α and IL-6</td>
<td>Increased TNF-α and IL-6 in OSAS vs. controls</td>
</tr>
<tr>
<td>Minoguchi et al.</td>
<td>2004</td>
<td>24 OSAS; 15 obese; 12 controls</td>
<td>TNF-α</td>
<td>Increased TNF-α serum levels in severe OSAS vs. controls and vs. mild OSAS</td>
</tr>
<tr>
<td>Ryan et al.</td>
<td>2006</td>
<td>67 OSAS male; 30 controls male</td>
<td>TNF-α and IL-8</td>
<td>Increased TNF-α and IL-8 in OSAS vs. controls</td>
</tr>
<tr>
<td>Yokoe et al.</td>
<td>2003</td>
<td>30 OSAS; 14 obese</td>
<td>IL-6</td>
<td>Increased IL-6 in OSAS vs. obese</td>
</tr>
<tr>
<td>Al Lawati et al.</td>
<td>2009</td>
<td>176 OSAS (80.1% AHI≥5 events/h and 25% AHI≥30 events/h)</td>
<td>IL-6</td>
<td>No correlation between IL-6 and OSAS severity</td>
</tr>
<tr>
<td>Minoguchi et al.</td>
<td>2005</td>
<td>36 OSAS; 16 obese</td>
<td>IL-6 and CRP</td>
<td>Increase IL-6 and CRP in OSAS vs. obese</td>
</tr>
<tr>
<td>Can et al.</td>
<td>2006</td>
<td>62 OSAS male (30 subjects with AHI&gt;5 [group 1] and 32 subjects with AHI&lt;5 [group 2]; 30 controls</td>
<td>CRP and homocysteine</td>
<td>Increased CRP and homocysteine in OSAS group 1 vs. group 2. Increased CRP and homocysteine in OSAS groups vs. control</td>
</tr>
<tr>
<td>Taheri et al.</td>
<td>2007</td>
<td>907 OSAS (68.7% AHI&lt;5; 19.1%≤ AHI&lt;15; 12.2%≥ AHI≥15)</td>
<td>CRP</td>
<td>Positive association between CRP and the AHI (AHI 5–15, AHI≥15). No significant association after adjustment for age, sex, and BMI</td>
</tr>
<tr>
<td>Kapsimalis et al.</td>
<td>2008</td>
<td>52 OSAS (26 severe; 26 mild–moderate; 15 non-OSAS</td>
<td>CRP and leptin</td>
<td>Increased CRP in severe OSAS vs. non-OSAS. Increased leptin in severe OSAS and moderate OSAS vs. non-OSAS</td>
</tr>
<tr>
<td>Hayashi et al.</td>
<td>2006</td>
<td>60 OSAS; 30 controls</td>
<td>CRP and MCP-1</td>
<td>Increased CRP and MCP-1 in OSAS vs. control</td>
</tr>
<tr>
<td>Ohga et al.</td>
<td>2003</td>
<td>20 OSAS male; 10 control male</td>
<td>MCP-1</td>
<td>Increased MCP-1 in OSAS vs. controls</td>
</tr>
<tr>
<td>Ip et al.</td>
<td>2000</td>
<td>30 OSAS; 30 non-OSAS matched for BMI, age, sex, and menopausal status</td>
<td>Leptin</td>
<td>Increased leptin in OSAS subjects vs. controls</td>
</tr>
<tr>
<td>Phillips et al.</td>
<td>2000</td>
<td>32 OSAS vs. 32 obese</td>
<td>Leptin</td>
<td>Increased leptin in OSAS vs. controls</td>
</tr>
<tr>
<td>Schafer et al.</td>
<td>2002</td>
<td>55 OSAS (8 patients with 10AHI15; 4 patients with 15AHI20; 22 patients with 20AHI40; 21 patients with AHI&gt;40); 26 controls</td>
<td>Leptin</td>
<td>Leptin levels correlate with AHI (r=0.39, p&lt;0.0003). No significant correlation (r=0.25) after adjustment for body fat content</td>
</tr>
<tr>
<td>Kuramoto et al.</td>
<td>2008</td>
<td>35 patients with 20 ≤ AHI40, 46 patients with AHI&gt;40, 35 non-OSAS (AHI&lt;20).</td>
<td>SAA</td>
<td>Increased SAA in AHI&gt;40 group vs. AHI&lt;20 group</td>
</tr>
<tr>
<td>Tazaki et al.</td>
<td>2004</td>
<td>44 OSAS; 18 controls</td>
<td>MMP-9</td>
<td>Increased MMP-9 in OSAS vs. controls</td>
</tr>
</tbody>
</table>

TNF-α tumor necrosis factor-alpha, AHI apnea–hypopnea index, CRP C-reactive protein, MCP-1 monocyte chemoattractant protein-1, BMI body mass index, SAA serum amyloid A, MMP-9 matrix metalloproteinase-9
and is produced by monocytes and T cells through a transcriptional pathway involving NF-κB and up-regulates VCAM-1, E- and L-selectin, and ICAM-1 expression. TNF-α is involved in the increase of NREM sleep [89] and induces somnolence and fatigue [90]. Accordingly, its levels are significantly higher in OSAS patients as compared to healthy controls and lower after treatment with CPAP, independently of obesity [56, 57, 90–92]. Moreover, in OSAS subjects, the nocturnal peak of secretion of TNF-α is replaced by an abnormal daytime peak, thus altering the secretion rhythm of TNF-α [93]. As these alterations persist after a 3-month treatment with CPAP, it is likely that they require much more time to regress. TNF-α might cause the apneic events by promoting the dysfunction of the upper airway muscles [59]. On the other hand, interleukin (IL)-6 is also produced by the adipose tissue and circulating monocytes through the NF-κB pathway during nocturnal hypoxia [58, 94]. IL-6 represents a major stimulant of CRP production in the liver [95] and might modulate inflammatory processes in sleep disorders. Differently from TNF-α, IL-6 circadian rhythm is not altered in OSAS [93]. Although elevated levels of IL-6 has been shown in OSAS subjects as compared to healthy controls and a significant improvement after CPAP treatment [35, 58, 90, 91, 96], other studies did not confirm the potential role of this cytokine (mainly after covariate analysis and adjustment for BMI) probably because of a less severe OSAS included in the studies (mean apnea–hypopnea index, AHI=22.8/h) [57, 97–99]. Nevertheless, Zhang and co-workers have recently showed that genetic variants of the IL-6 gene confer different susceptibility to develop OSAS, thus suggesting a potential approach to assess the risk for OSAS [100].

The alteration of CRP levels in OSAS obese patients remains controversial, mainly because of the relationship between CRP and BMI [101]. Nevertheless, studies showed that in OSAS subjects, CRP levels are independently associated with the severity of the disease [35, 55, 58, 69, 102–108]. Importantly, 1-month treatment with CPAP significantly reduces CRP levels. More recently, increased levels of CRP were associated with OSAS in obese men independently of adiposity [109]. CRP levels also correlate with the degree of nocturnal hypoxemia independently of obesity [110]. Larkin and co-workers recently showed that an AHI ≥5 is associated with increased CRP serum levels in adolescents without known cardiovascular diseases. The relationship between CRP and sleep-disordered breathing was also confirmed after adjustment of important covariates (including BMI, hypertension, waist-to-hip ratio, and lipid profile) [104]. Conversely, these interesting associations were not confirmed by other studies [96, 111–116]. Larger and controlled studies are needed to better understand the role of CRP-mediated effects in the OSAS pathophysiology.

Elevated levels of IL-8 and monocytes chemoattractant protein (MCP)-1 have been shown in patients with OSAS [57, 76, 114, 117]. IL-8 is also reduced by 6-week treatment with CPAP [57]. Chemokines might play a pivotal role in the pathogenesis of the cardiovascular complications of OSAS through their crucial activation of neutrophils and monocytes [118, 119]. In particular, increased serum levels of leukocyte proteases (such as matrix metalloproteinase [MMP]-9) have been found in OSAS [120].

A relationship between the acute phase reactant serum amyloid A (SAA) and the degree of OSAS has been also shown. Furthermore, SAA levels have been reduced by CPAP treatment [121].

Leptin is the product of the obese gene in the adipocytes and mediates several functions such as the regulation of food intake, the energy balance, and the regulation of lipid and glucose metabolism [122, 123]. In obesity (a condition known as leptin resistance), leptin levels are increased [124, 125]. Leptin activates inflammation and mediates cellular damage synergistically with IH in a rabbit model of OSAS [78]. Although the major inducing factor for leptin production is visceral obesity [112], hypoxia might increase leptin production [126–128]. Furthermore, leptin correlates with OSAS independently of obesity [129–133]. Kapsimalis and co-workers confirmed that nocturnal hypoxemia is associated with leptin independently of obesity [112]. Conversely, other studies did not show a significant association between leptin levels and OSAS after adjustment for obesity [134–137].

Homocysteine is a product of the metabolism of the aminoacid methionine and increases the risk of arterial occlusive disease [138] causing endothelial dysfunction [3, 139–141]. Controversial data have been reported on homocysteine levels in OSAS. Some studies indicate that homocysteine is increased in OSAS subjects with cardiovascular disease (CAD) in comparison with OSAS subjects without CAD and with healthy controls [102, 142]. Accordingly, CPAP treatment reduces homocysteine concentrations [143]. Conversely, other studies did not confirm this association [62, 144]. Finally, studies on insulin [110, 145–147] and adiponectin [132, 147–150] also showed controversial results. Further studies are needed to better address the role of these inflammatory cardiovascular risk markers in OSAS.

Endothelial dysfunction

Endothelium regulates the vascular tone and maintains the pro-/anti-inflammatory equilibrium in the vessel wall. Alterations of the normal homeostasis of the vascular wall represent early signs of cardiovascular diseases [151]. Recent studies have demonstrated that OSAS significantly affects the endothelial function. Indeed, endothelium-
Dependent vasodilation in response to acetylcholine is reduced in OSAS patients in comparison with age- and BMI-matched healthy subjects [152, 153]. Flow-mediated vasodilation is impaired in OSAS with a direct correlation with the severity of the hypoxemia [154]. The normal function of the endothelium depends on the bioavailability of NO. In OSAS, reduced levels of circulating NO [155, 156] and elevated concentrations of endothelial NO synthase inhibitor have been shown, as compared to healthy controls [157].

The mechanisms by which OSAS might affect the endothelial function are dependent on IH and sleep fragmentation [158]. As mentioned above, IH causes a reduction of NO production by affecting the transcriptional and post-transcriptional pathways and by increasing the production of ROS. ROS could react with NO, further reducing its availability and enhance the oxidative stress. Moreover, IH up-regulates cyclooxygenase-2 (COX-2), VEGF, endothelin-1, and iNOS, which might further alter the functional integrity of the endothelium [80–87]. Sleep fragmentation is associated with 50% reduction of the flow-mediated vasodilation [159]. Several studies show increased inflammation, activation of the sympathetic tone, and hypercoagulability during repetitive arousals from sleep during OSAS [160–162]. Accordingly, treatment with CPAP reverses endothelial dysfunction [163].

Endothelial dysfunction could be a key element in atheroprosession in OSAS. Further efforts should be done in order to better understand and possibly prevent endothelial dysfunction in OSAS.

Conclusions

Despite its underestimation, OSAS should be considered a serious disease involving not only the respiratory system but also having cardiovascular and cerebral implications. The promotion of atherogenesis through oxidative stress, inflammation, and endothelial dysfunction is still a matter of debate. Intermittent hypoxia is the distinctive element of OSAS and could play a pivotal role in triggering cardiovascular inflammation. The treatment with CPAP represents a very promising therapeutic strategy to clinically improve OSAS and reduce the associated oxidative stress, cardiovascular inflammation, and endothelial dysfunction. Larger randomized clinical studies are still needed to identify more selective cardiovascular risk markers in OSAS.

Acknowledgments  François Mach and Fabrizio Montecucco equally contributed as last authors to this work. This work was funded by EU FP7, Grant Number 201668, AtheroRemo and supported by a grant from the Swiss National Science Foundation to Dr. F. Mach (#310030-118245).

References


125. Cinaz P, Bideci A, Camurdan MO, Güven A, Gönen S (2005) Morning serum C-reactive protein (CRP) and sleep duration or sleep disordered breathing. Sleep 30:991–996


