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Obstructive Sleep Apnea Syndrome, Vascular Pathology, Endothelial Function and Endothelial Cells and Circulating Microparticles

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Accelerated atherosclerosis and increased cardiovascular risk are frequently reported in patients with obstructive sleep apnea (OSA) syndrome. In this article the authors attempt a review of the current understanding of the relationship between vascular risk and OSA syndrome based on large cohort studies that related the disease to several cardiovascular risk factors and vascular pathologies. We also discuss the pathophysiological mechanisms that may be involved in this relationship, starting with endothelial dysfunction and its mediators. These include an increased oxidative stress and inflammation as well as several disorders of coagulation and lipid metabolism. Moreover, circulating microparticles from activated leukocytes (CD62L_MPs) are higher in patients with OSA and there is a positive correlation between circulating levels of CD62L_MPs and nocturnal hypoxemia severity. Finally, circulating level of endothelial microparticles and circulating endothelial cells seem to be increased in patients with OSA. Also, endothelial progenitor cells are reduced and plasma levels of the vascular endothelial growth factor are increased.

Key Words: Obstructive sleep apnea syndrome, Endothelial dysfunction, Vascular risk, Endothelial cells, Progenitor endothelial cells.

Obstructive Sleep Apnea Syndrome, Hypertension and Vascular Pathologies

Obstructive sleep apnea (OSA) syndrome is a respiratory disorder characterized by the presence of apneas-hypopneas during sleep that lead to episodes of intermittent hypoxia. Clinical manifestations are characterized by snoring, asphyxia waking or daytime sleepiness and fatigue, with 2–4% of the adult population being affected (1). A study conducted in the general population has found that 15% of women and 19% of men had an apnea-hypopnea index (AHI) >10. In addition, this study found that the AHI was associated with blood pressure values after adjusting for other confounding factors (2). Other studies including a population study with 6,132 subjects (3) and another with a prospective design and follow-up of 4 years (4) have shown after adjustment for confounding factors that arterial hypertension (AH) is common in OSA patients, and OSA has therefore been proposed as a cause of secondary hypertension (5). This hypothesis has been confirmed in recent intervention studies, which have shown that treatment of OSA syndrome with continuous positive airway pressure (CPAP) significantly decreases blood pressure (6). The association between OSA and hypertension has important connotations and, as stated above, is based on studies that seem to demonstrate a causal relationship between the two. Furthermore, OSA also appears to be associated with other forms of cardiovascular disorders such as ischemic heart disease and stroke. The independent nature of this relationship has not yet been reliably demonstrated, despite being investigated in large population studies (7). It has recently been shown that the heightened vascular risk observed in patients with OSA syndrome

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decreases after treatment with CPAP (8). Moreover, two studies based on the longitudinal cohort of the Sleep Heart Health Study have shown a relationship between OSA syndrome, stroke, coronary artery disease and heart failure (9,10). There are also studies relating OSA syndrome to atrial fibrillation (11) and other studies relating OSA with left ventricular hypertrophy, hypertensive cardiomyopathy, tachycardia-induced cardiomyopathy, myocardial fibrosis and left ventricular systolic and diastolic dysfunction (12,13). Finally, in addition to the previously mentioned observational study (8), two recent longitudinal studies of large population cohorts (Sleep Heart Health Study and Wisconsin) have demonstrated a relationship between OSA and mortality, independent of confounding factors (14,15). The mechanisms explaining the development of hypertension in OSA syndrome patients are not well understood. It has been suggested that sympathetic nervous system activity increases as a result of nocturnal hypoxic episodes (16) and that OSA syndrome is related to obesity, metabolic syndrome and insulin resistance (17). None of these mechanisms has been proven, however, and it has even been reported that the association of glucose intolerance with OSA is independent of body mass index (BMI) or hypertension (HT) (18).

Recent data from the Sleep Heart Health Study (19) have shown that OSA syndrome is associated with hypertension only in the population aged <60 years. In the same population (20), the presence of other vascular risk markers such as increased waist-hip ratio, diabetes and dyslipidemia were previously found to be more prevalent among young patients. It could therefore be concluded that there are two populations within OSA patients: those with high vascular risk who are the youngest, and others with lower cardiovascular risk, who are often the oldest. The age differences may be attributable to the fact that the former group of patients seeks health care more often for hypertension or manifestations of vascular risk; thus, they are diagnosed earlier. It has also been speculated that elderly patients with OSA could be ''survivors'' with high resistance to vascular risk factors. In any case, the reason for which some, but not all, of the patients with OSA syndrome present greater vascular risk remains unknown.

Finally, during 2012 two studies were published in the same issue of the same journal with opposite results. In agreement with previous studies, Marin et al. (21) conducted a prospective cohort study of 1889 participants without hypertension who were referred to a sleep center in Zaragoza, Spain for nocturnal polysomnography. The investigators observed that the presence of OSA was associated with increased adjusted risk of incident hypertension. Moreover, compared with controls, the adjusted HRs for incident hypertension were greater among patients with OSA ineligible for CPAP therapy, among those who declined CPAP therapy, and among those nonadherent to CPAP therapy, whereas the HR was lower in patients with OSA who were treated with CPAP therapy. Simultaneously, Barbé et al. (22) designed a multicenter, parallel-group, randomized controlled trial in 14 teaching hospitals, also in Spain, where patients were allocated to receive CPAP treatment or no active intervention. They observed that in patients with OSA without daytime sleepiness, the prescription of CPAP compared with usual care did not result in a statistically significant reduction in the incidence of hypertension or cardiovascular events. Therefore, larger randomized controlled trials are required to clarify the effect of CPAP treatment on vascular damage and subsequent cardiovascular morbidity and mortality in patients with OSA.

Endothelial Dysfunction and Sleep Apnea Syndrome

Several studies have suggested that patients with OSA syndrome have an endothelial dysfunction (23,24). The origin of the endothelial injury is unclear but may be associated with intermittent hypoxemia, characteristic of the syndrome, and the consequent generation of reactive oxygen species (ROS) and pro-inflammatory molecules. Endothelial damage would cause an alteration in the balance of different endothelium-derived substances responsible for maintaining vascular tone (25). The resulting vasoconstriction, proliferation of vascular smooth muscle and hypercoagulability may lead to hypertension and more frequent vascular pathology in these patients (26,27). Treatment of OSA with continuous positive pressure airway (CPAP) seems to improve endothelial function (28). In regard to methods for assessing *in vivo* endothelial function, some studies used flow-mediated dilatation (FMD) complemented by high-definition ultrasonography (29), whereas others have used plethysmography (28,30). The following are some of the mechanisms involved in endothelial dysfunction observed in these patients (Figure 1).

Oxidative Stress, Inflammation and Adhesion Molecules

Many authors consider that OSA is a condition that causes a pro-oxidative state (31). In this respect, it seems that the production of free radicals by neutrophils and monocytes is increased in patients with OSA syndrome but decreases after treatment with CPAP (32,33). Furthermore, their lipid peroxidation is greater, resulting in an increased production of ROS (34), which can upregulate the production of adhesion molecules, thereby decreasing the activity of nitric oxide synthase and promoting a reduction in nitric oxide bioavailability (35).

Circulating levels of intracellular adhesion molecule-1 (ICAM-1), the vascular cell adhesion molecule-1 (VCAM-1) and E-selectin are elevated in patients with OSA (36,37). Another inflammatory cytokine, interleukin 6 (IL-6), is known to play a key role in atherogenesis (38). A recent study showed increased levels of soluble IL-6 receptor in patients with OSA (39). Moreover, C-reactive protein