CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN SLEEP MEDICINE

Obstructive Sleep Apnea

An Emerging Risk Factor for Atherosclerosis

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Obstructive sleep apnea (OSA) is independently associated with death from cardiovascular diseases, including myocardial infarction and stroke. Myocardial infarction and stroke are complications of atherosclerosis; therefore, over the last decade investigators have tried to unravel relationships between OSA and atherosclerosis. OSA may accelerate atherosclerosis by exacerbating key atherogenic risk factors. For instance, OSA is a recognized secondary cause of hypertension and may contribute to insulin resistance, diabetes, and dyslipidemia. In addition, clinical data and experimental evidence in animal models suggest that OSA can have direct proatherogenic effects inducing systemic inflammation, oxidative stress, vascular smooth cell activation, increased adhesion molecule expression, monocyte/lymphocyte activation, increased lipid loading in macrophages, lipid peroxidation, and endothelial dysfunction. Several cross-sectional studies have shown consistently that OSA is independently associated with surrogate markers of premature atherosclerosis, most of them in the carotid bed. Moreover, OSA treatment with continuous positive airway pressure may attenuate carotid atherosclerosis, as has been shown in a randomized clinical trial. This review provides an update on the role of OSA in atherogenesis and highlights future perspectives in this important research area. ***CHEST 2011; 140(2):534–542***

Abbreviations: CPAP = continuous positive airway pressure; IH = intermittent hypoxia; LDL = low-density lipoprotein; LpL = lipoprotein lipase; NFκB = nuclear factor κ B; OSA = obstructive sleep apnea; VLDL = very low-density lipoprotein

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of complete or partial collapse of the upper airway during sleep, resulting in apneas or hypopneas, respectively. The futile efforts to breath during obstructed events result in increased negative intrathoracic pressure, intermittent asphyxia, and arousals from sleep. The prevalence of OSA syndrome defined as an apnea-hypopnea index >5 events/h plus symptoms of excessive daytime sleepiness in middle-aged women and men in the Wisconsin cohort was 2% and 4%, respectively.[1] When sleepiness was not included in the definition, the prevalence of OSA was approximately five times higher (9% and 24%, respectively).[1] Several cohort studies have shown recently that severe OSA is independently associated with increased risk of future myocardial infarction, stroke, and death from cardiovascular disease.[2-6] Although the reasons for cardiovascular death have not been investigated in epidemiologic studies, myocardial infarction and stroke are typical clinical manifestations of severe atherosclerotic disease. Furthermore, the accelerated progression of atherosclerosis may explain the link between OSA and cardiovascular

Manuscript received August 26, 2010; revision accepted January 11, 2011.

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Funding/Support: This study was funded by the National Institutes of Health [Grants R01 HL80105, 5P50HL084945]; Fundação Zerbini; Fundação de Amparo à Pesquisa do Estado de São Paulo [Research Fellowship Grant 2010/11681-0]; and the American Heart Association [Grant-in-Aid 10GRNT3360001].

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DOI: 10.1378/chest.10-2223

disease. In this review, we first briefly discuss the fundamental concepts of atherosclerosis. The cascade of intermediate mechanisms linking OSA and atherosclerosis derived from animal studies are reviewed next. Finally, human studies and future directions are discussed.

Atherosclerosis: Fundamental Concepts

In the past, atherosclerosis was considered a lipid storage disease. The current view is that atherosclerosis is a complex phenomenon involving chronic inflammation of the vascular wall.[7] According to the American Heart Association, there are six identified histologic categories of atherosclerotic lesions.[8] Atherosclerotic lesions begin with the fatty streaks composed of macrophages engulfing lipids (foam cells), T lymphocytes, and smooth muscle cells. Further accumulation of lipids results in apoptosis of foam cells and smooth muscle cells and inflammation with fibrosis. As a result, mature fibrous plaques develop. However, in some cases, necrosis and apoptosis predominate over fibrosis, leading to formation of the complicated lesion or unstable plaque, which may result in rupture and thrombosis. All these progressive alterations at the vascular level are generally asymptomatic. Clinical manifestations of the rupture are myocardial infarction, stroke, and peripheral vascular thrombosis, depending on the location of the plaque.

There are several well established risk factors for atherosclerosis that include genetic predisposition, aging, hypertension, diabetes, hyperlipidemia, obesity, physical inactivity, depression, and smoking. In addition to these traditional risk factors, there is evidence that "novel risk factors," including markers of systemic inflammation, homocysteine, fibrinogen, D-dimers, lipoprotein (a), and tissue plasminogen activator, play a role in atherosclerosis progression.[9] These multiple risk factors for atherosclerosis frequently coexist in patients with OSA. Therefore, elucidating a causal relationship between OSA and atherosclerosis is a complex task.

Mechanisms Linking OSA to Atherosclerosis

The mechanisms by which OSA may contribute to atherosclerosis progression comprise a cascade of multiple, interrelated, and not completely known mechanisms that are under investigation. Therefore, any attempt to simplify this entangled cascade of mediators may be misleading. Having this potential limitation in mind, Figure 1 summarizes several key mechanisms involved in the atherogenesis induced by OSA. The primary mechanisms that may link OSA to atherosclerosis are consequences of recurrent

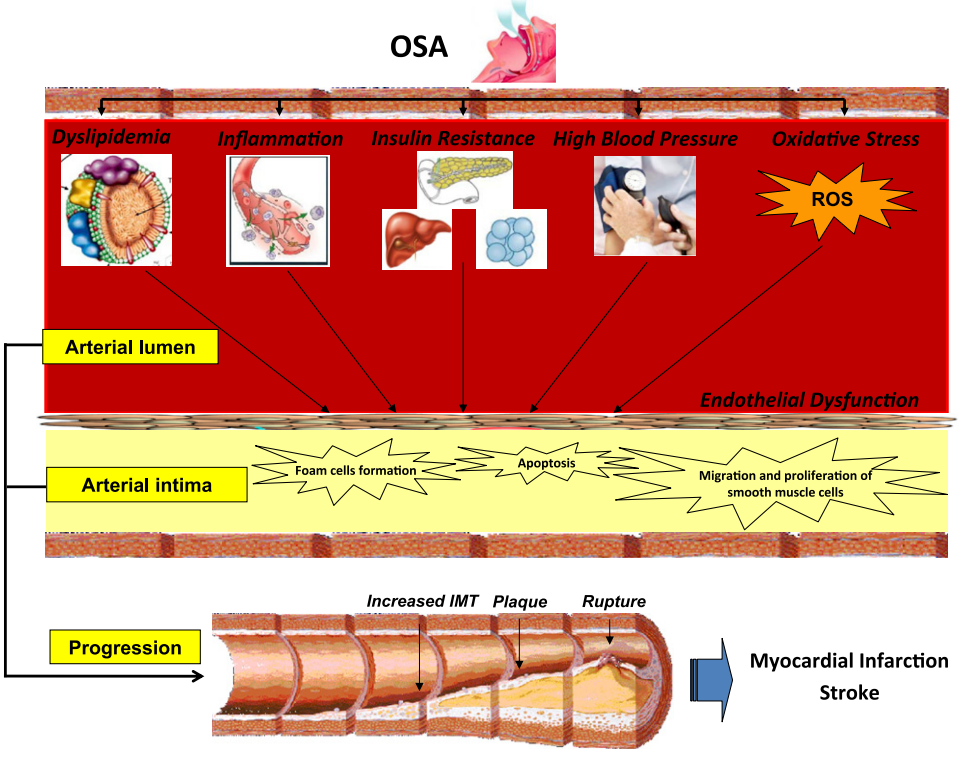

Figure 1. Proposed pathways through which OSA may contribute to the development of atherosclerosis. IMT = intima-media thickness; OSA = obstructive sleep apnea; ROS = reactive oxygen species.

asphyxia and arousals from sleep. There is also evidence that the vibration associated with snoring may contribute to carotid atherosclerosis (see "Snoring" section). OSA also contributes to atherosclerosis progression through indirect mechanisms. For instance, OSA is a recognized secondary cause of hypertension[10] and may contribute to insulin resistance, diabetes, and dyslipidemia,[11,12] which are, in turn, well established risk factors for atherosclerosis. In addition, OSA can trigger intermediate mechanisms that may contribute directly to atherosclerosis progression and are the main focus of this review. The most important insights are derived from animal studies, but a growing number of human studies support the experimental data.

Intermittent hypoxia (IH) is thought to be the main component linking OSA to cardiovascular disease. The mouse model of IH mimics the oxyhemoglobin profile in patients with OSA and has provided important insights into the mechanisms linking IH and atherosclerosis. There are several models of IH that vary in both frequency and severity of the hypoxic stimulus. In one of these models used by one of the authors, the IH is delivered during the 12-h light phase when rodent sleep predominantly occurs. The mice are exposed to alternating air, oxygen, and nitrogen, which results in changes of F_{IO_2} in the chamber from 21% to 6.5% and corresponding fluctuation of arterial oxygen saturation from 95% to 98% to ~70% 60 times/h.[13] This regimen of IH resulted in the following: (1) formation of fatty streaks and small mature plaques in the aortic arch and descending aorta of wild-type male C57BL/6J mice on a high-cholesterol diet; in contrast, atherosclerosis did not develop in mice on a regular chow diet that were exposed to IH or in mice on a high-cholesterol diet that were not exposed to IH[14]; (2) acceleration of the progression of the disease in apolipoprotein E-deficient mice, which are prone to developing atherosclerosis; IH doubled the size of atherosclerotic plaques after only 4 weeks of exposure (Fig 2).[13] These observations in the animal model suggests that the harmful effects of IH on the vascular bed are potentiated when other risk factors for atherosclerosis are also present. This scenario parallels, to some extent, the clinical situation, because multiple risk factors for atherosclerosis frequently coexist in the same patient. In the following discussion, we review the effects of IH on different factors of atherogenesis. In addition, clinical studies are quoted when appropriate.

Dyslipidemia

In the mouse model, IH invariably induces hyperlipidemia by increasing levels of triglyceride-rich lipoproteins (very low-density lipoprotein [VLDL]).[15,16]

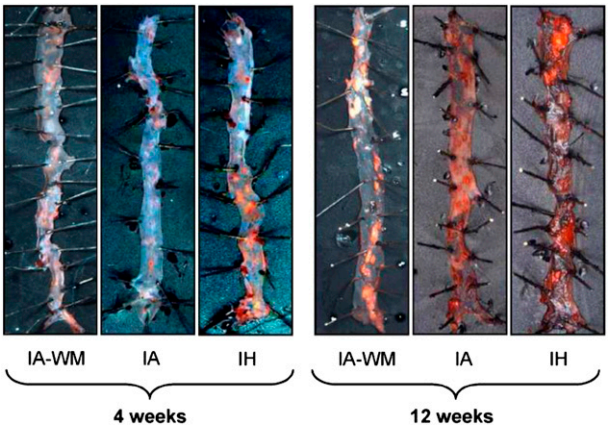

FIGURE 2. En face lesions of the descending aorta in apolipoprotein E-deficient mice exposed to IA, IA-WM, or IH after 4 weeks and 12 weeks on a high-cholesterol diet. Because IH causes weight loss, an IA-WM group was included. Either at 4 weeks or at 12 weeks, IH promoted a significant progression of atherosclerosis lesions in the aorta compared with the other groups. Mice weight matched to the IH group had decreased atherosclerosis, suggesting that IH mediates its proatherogenic effects in a weight-independent manner. IA = intermittent air control; IA-WM = intermittent air control with weight matching; IH = intermittent hypoxia. (Reprinted with permission from Jun et al.[13])

Two major mechanisms of VLDL hyperlipidemia, increased lipoprotein secretion by the liver and decreased lipoprotein clearance, may be induced by IH. First, there is evidence suggesting that IH increases lipoprotein secretion.[17] The increase in VLDL secretion during IH has been attributed to the upregulation of a key hepatic enzyme of lipid biosynthesis, stearoyl coenzyme A desaturase 1.[14,16-18] Notably, hepatic expression of stearoyl coenzyme A desaturase 1 and serum VLDL levels are increased in patients with OSA in direct proportion to the severity of nocturnal hypoxia.[16] Second, there are recent data suggesting that decreased lipoprotein clearance is a complementary mechanism of dyslipidemia during IH.[19] Liver-synthesized VLDL and dietary chylomicrons are cleared from the circulation via a multistep process, which begins with lipoprotein lipase (LpL), a key enzyme in plasma lipoprotein metabolism. LpL is preferentially expressed in adipose tissue, skeletal muscle, and the heart.[20] There is evidence that IH inhibits adipose tissue LpL, probably because of the activation of angiopoietin-like protein 4.[19] One study in humans reported decreased plasma LpL activity in direct proportion to the severity of OSA that was reversed by continuous positive airway pressure (CPAP) treatment of 3 months.[21]

Despite the experimental data and emerging human studies, two recent reviews[22,23] indicated that there is no consistent evidence supporting the relationship between OSA and dyslipidemia in humans. These reviews pointed out that although several cross-sectional studies suggested that OSA is independently

associated with increased levels of total cholesterol, low-density lipoprotein (LDL), triglycerides, and decreased high-density lipoprotein, other studies failed to show such a relationship. In addition, some studies showed that OSA treatment with CPAP may have a beneficial effect on lipid profile (these references are not cited here because of space limitation, see Reference 22). However, most of the studies were not specifically designed to evaluate the lipid profile and ignored important confounding factors such as diet, physical activity, and body composition. Therefore, in contrast to the findings in animal models, the effect of OSA on dyslipidemia and lipid metabolism in humans remains to be fully established.

Oxidative Stress

It is well established that atherogenesis is linked to oxidative stress and lipid peroxidation.[24] The oxidation of polyunsaturated fatty acids by reactive oxygen species leads to the formation of aldehydes that modify lysine residues in apolipoprotein B-100, resulting in oxidized LDL.[24] Oxidized LDL are taken up by macrophages more readily via scavenger receptors A and CD36, leading to macrophage foaming and progression of atherosclerosis.[25] IH increases the generation of reactive oxygen species in the vascular wall,[16] and induces lipid peroxidation[26] and formation of oxidized LDL, creating a substrate for the atherosclerotic plaque.[16] Indeed, IH enhances lipid uptake by human macrophages in vitro.[27] Activation of nicotinamide adenine dinucleotide phosphate oxidase has been identified as a mechanism of oxidative stress during IH in different cell types,[27,28] but the contribution of nicotinamide adenine dinucleotide phosphate oxidase to enhanced production of oxidized LDL is not known. Most studies in humans have shown that OSA leads to increased lipid peroxidation in the serum[29] and elevated levels of oxidized LDL.[30] Nevertheless, the role of oxidative stress in the progression of atherosclerosis is equivocal. Several clinical studies showed no beneficial effect of antioxidant therapy on coronary and cerebrovascular disease.[31,32] In fact, oxidative stress could be a consequence of vascular inflammation rather than a cause of atherosclerosis.[24]

Endothelial Dysfunction and Inflammation

Endothelial dysfunction is another pivotal mechanism of atherosclerosis.[33] There is good evidence, both in the animal model of IH[33,34] and in humans,[35] that OSA is associated with endothelial dysfunction that can be reversed by CPAP.[36] IH may trigger endothelial dysfunction via multiple pathways that are discussed briefly. OSA-induced dyslipidemia and oxidative stress, as well as hypertension and insulin resistance,[33,36,37] can all lead to endothelial dysfunction. In addition, recent studies have shown that patients with OSA have elevated serum levels of tumor necrosis factor-α, IL-6, IL-8, C-reactive protein, and adhesion molecules (intercellular adhesion molecule-1, vascular cell adhesion molecule-1, L-selectin, soluble E-selectin, P-selectin),[38-41] which are markers of systemic inflammation with proatherogenic properties. Experiments in rodents demonstrated that IH increases levels of endothelin-1, activates endothelin-1 signaling,[42] and upregulates the sympathetic nervous system and the renin-angiotensin system,[43] which can induce endothelial dysfunction directly or indirectly via hypertension.

A number of recent studies explored novel pathways of atherogenesis in patients with OSA. Ryan et al[44] have shown in vitro in HeLa (derived from cervical cancer) and bovine endothelial cells that IH activates a transcription factor nuclear factor κ B(NFκB), which regulates multiple proinflammatory genes linked to atherosclerosis.[45] Supporting the experimental data, circulating tumor necrosis factor-α levels were higher in OSA patients than in control subjects, but were normalized with CPAP treatment.[44] Polotsky et al[46] have recently exposed human aortic endothelial cells to IH and have shown that IH upregulates the expression and secretion of a proinflammatory and proatherogenic cytokine IL-8. Jelic et al[47] studied freshly harvested endothelial cells in patients with OSA. They showed that OSA is associated with increased levels of NFκB and oxidative stress, whereas expression and activity of endothelial NO synthase was decreased, and that these endothelial abnormalities were reversed by CPAP treatment. In summary, endothelial dysfunction, a key mechanism involved in the genesis of atherosclerosis, can be triggered by virtually all factors described in this review. The inflammatory response induced by IH/OSA is linked to the NFκB activation in the endothelial cells.

Snoring

Recently, it has been postulated that snoring is an atherogenic factor.[48] The rationale is that the vibration of snoring is transmitted though the surrounding tissues to the carotid artery wall, triggering an inflammatory cascade, which leads to atherosclerosis. The effects of vibration on the vascular bed have also been observed in a rabbit model.[49] The observation that patients with primary snoring present signs of atherosclerosis only in the carotid artery and not in other vascular beds supports the hypothesis of an independent role of snoring.[48] However, the aforementioned studies point to an association rather than definitive cause-effect relationships between snoring and atherosclerosis.[50] Moreover, snoring alone was not

associated with an increased risk of future cardiovascular or cerebrovascular events in the Spanish cohort.[2] Future studies are needed to clarify the contribution of snoring in the pathogenesis of carotid atherosclerosis.

Markers of Atherosclerosis in Patients With OSA

Performing a search in PubMed (search terms were "apnea," "obstructive sleep apnea," "sleep apnea syndromes," "atherosclerosis," "arteriosclerosis," "intima-media thickness," "plaque," "catheterization," "ultrasound," "intravascular ultrasound," and "coronary artery calcium") for articles that evaluated atherosclerosis in patients with OSA (excluding studies that evaluated only endothelial function, arterial stiffness, and coronary flow), we found 36 studies from 1998 (the year of the first report of atherosclerosis in patients with OSA) to December 2010.[51-86] The consistency of the data can be verified by the fact that 33 of the 36 studies found a positive association between markers of atherosclerosis (most in the carotid bed) and OSA. A major drawback of these numerous studies was that in a majority of research subjects, multiple proatherogenic factors coexisted with OSA. Therefore, the role of OSA in atherogenesis could not be established unequivocally. To avoid confounding factors associated with OSA, Drager et al[60] examined a select group of young (< 55 years) male OSA patients who were free of comorbidities and were on no medications. Compared with proper matched control subjects without OSA, patients with OSA had increased arterial stiffness and early signs of atherosclerosis, including increased carotid intima-media thickness. Moreover, the severity of all vascular abnormalities in patients with OSA correlated with the severity of OSA expressed by the apnea-hypopnea index and minimal nocturnal oxygen saturation. One limitation of this study is that these relatively young patients with OSA may not represent the typical patient with OSA. For instance, among patients with OSA, approximately 50% have hypertension, a well known risk factor for atherosclerosis.[75] In addition, many patients with OSA present with masked hypertension, defined as normal clinical BP values (< 140/90 mm Hg) but abnormal diurnal ambulatory BP monitoring (≥ 135 or ≥ 85 mm Hg).[87,88] A subsequent study found that patients with OSA had similar signs of atherosclerosis to those with hypertension, and that patients with both conditions (ie, OSA and hypertension) showed additive effects on validated markers of atherosclerosis (Fig 3).[75] More recently, Drager et al[82] studied consecutive patients with metabolic syndrome, all of whom had risk factors for atherosclerosis. Interestingly, OSA was present in 63% and was independently associated with markers of atherosclerosis. Of note, all studied markers of atherosclerosis were similar in OSA patients with or without daytime sleepiness, suggesting that the harmful effects of OSA are not confined to individuals with hypersomnolence.[82] Together, these results indicate that the atherosclerotic burden of OSA affects patients with and without comorbidities.

Cross-sectional studies can provide helpful hints, but cannot determine cause-effect relationships between OSA and atherosclerosis. To further evaluate the hypothesis that OSA is an independent risk factor for atherosclerosis, Drager et al[69] performed a randomized study evaluating the effects of 4 months of CPAP therapy on early markers of atherosclerosis, arterial stiffness, 24-h BP monitoring, plasma C-reactive protein, and catecholamines in patients with severe OSA. To control for possible secondary effects of CPAP on atherosclerosis by improving BP or glucose control, the investigators recruited only relatively young patients without significant comorbidities and on no medications. Four months of effective treatment with CPAP significantly improved validated markers of atherosclerosis in these patients (Fig 4). The improvement was associated with reductions in markers of inflammation and sympathetic activity, as evaluated by plasma C-reactive protein and catecholamines, respectively, without concurrent changes in weight or lipids. Patients assigned to CPAP therapy showed decreases in the carotid intima-media thickness to values that were similar to the previously reported healthy control subjects.[60,69] Taken together,

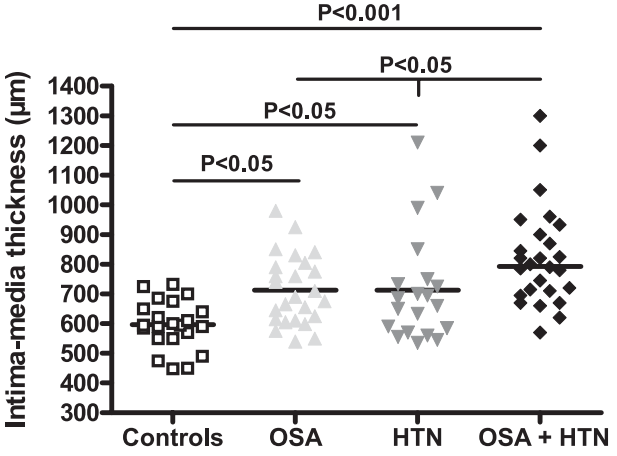

Figure 3. Carotid IMT in control subjects, patients with OSA, patients with HTN without OSA, and patients with OSA and HTN. Compared with the control group, carotid intima-media and carotid diameter were 19.4% and 8.2% greater in the OSA group, 19.5% and 9.4% in the HTN group, and 40.3% and 20.6% in the OSA + HTN group, respectively. HTN = hypertension. See Figure 1 for expansion of other abbreviations. (Adapted with permission from Drager et al.[75])

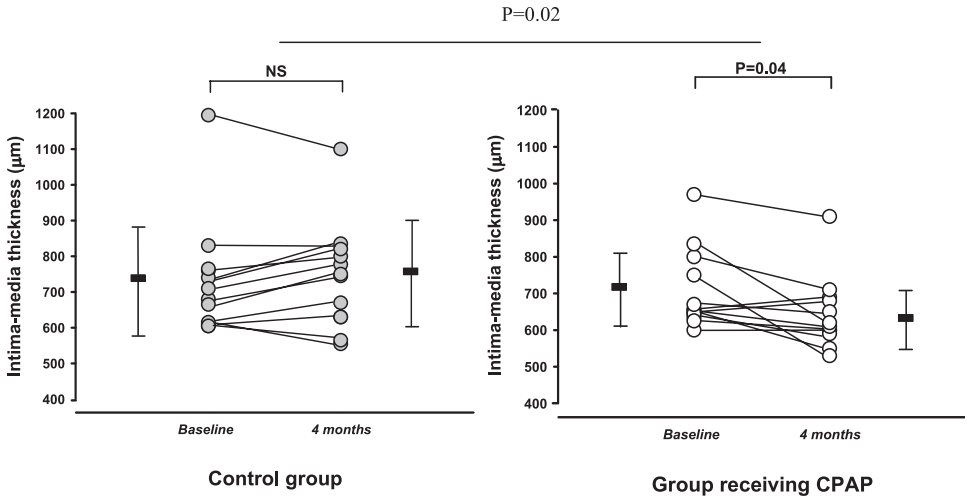

FIGURE 4. Individual values for the IMT at study entry and after 4 months of no treatment (control) or CPAP in patients with severe obstructive sleep apnea. In the control group, IMT did not change during the study period. In contrast, IMT significantly decreased in the group randomized to CPAP therapy. Short horizontal lines and bars are mean ± SD. NS = not significant. CPAP = continuous positive airway pressure. See Figure 1 for expansion of the other abbreviation. (Reproduced with permission from Drager et al.[69])

the results from this study strongly suggest that OSA is an independent risk factor for atherosclerosis. The clinical implication of such a finding is that treatment of OSA may significantly alter the natural course of cardiovascular disease.

Future Directions

As suggested by Figure 1, OSA can induce atherosclerosis via multiple mechanisms. As discussed in this review, there is a growing body of evidence from clinical studies and animal models suggesting that OSA contributes to the progression of atherosclerosis. However, the majority of human data is based on cross-sectional studies focused on the carotid bed. It must be stressed that increased markers of atherosclerosis were observed mainly in patients with moderate and severe OSA. These findings are in line with those of epidemiologic studies. For instance, the Sleep Heart Health Study found that only severe OSA was associated with increased future cardiovascular events. This association was stronger for stroke than for coronary artery disease.[5]

Several issues must be clarified, and definitive evidence linking OSA to atherosclerosis progression is still lacking. There is a strong need to systematically explore the impact of OSA treatment on the progression or regression of atherosclerosis. Future mechanistic research should be focused on the relative role of OSA on several atherogenic pathways, including high BP, insulin resistance, dyslipidemia/lipid metabolism, inflammatory/immunologic regulation, and angiogenesis. Potential effects of OSA on circadian variability sleep structure, sleep fragmentation, and sleep deprivation have received little attention and also deserve future investigation. A recent report found that a surrogate marker of sleep duration, reduced activity on wrist actigraphy, was inversely associated with coronary artery calcification.[89] However, the investigators did not perform sleep studies, and the potential contribution of OSA was not explored. Finally, one cohort study has shown an association between OSA treatment with CPAP and reduced cardiovascular mortality.[2] Large prospective, randomized studies are necessary to fully establish whether the treatment of OSA can forestall or even reverse atherosclerosis progression and ultimately decrease cardiovascular events.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

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