REVIEW ARTICLE

OSA and atherosclerosis

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ABSTRACT Untreated obstructive sleep apnea (OSA) is increasingly recognized as a risk factor contributing to cardiovascular morbidity and mortality. Research in recent decades has uncovered many components of the complex pathological events leading to the atherosclerotic vascular diseases in OSA, which involve heightened oxidative stress as a result of intermittent hypoxia, vascular inflammation, activation of platelet and coagulation cascades, endothelial dysfunction and ultimately the formation of atherosclerotic plagues. The close association of OSA and conventional cardiovascular risk factors including hypertension, diabetes mellitus, dyslipidemia and obesity adds to the adverse cardiovascular sequelae. Further studies are required to clarify further on the pathophysiological processes, and the effect size of OSA therapy, and other potential preventive strategies.

KEY WORDS Obstructive sleep apnea; atherosclerosis; intemittent hypoxia; inflammation; oxidative stress; endothelial dysfunction; coronary; artery disease; cerebrovascular accident

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Introduction

Obstructive sleep apnea (OSA) is a common sleep related breathing disorder characterized by repetitive upper airway collapse during sleep resulting in intermittent hypoxia and sympathetic over-activity. The condition affects all age groups and is prevalent across different populations globally. According to a study undertaken in Fuzhou, China, the estimated prevalence of obstructive sleep apnea hypopnea syndrome (OSAS) in adults aged over 20 years, defined by apnea-hypopnea index (AHI)≥5/hour and Epworth sleepiness scale≥9, was 4.78% (1). Another study including more than 1,000 primary snorers from Jiangsu found mild (AHI 5-20), moderate (AHI>20-40), and severe OSA (AHI>40) in 21.7%, 16.5% and 37.7% of subjects respectively (2). Such figures are similar to estimated prevalence rates of OSAS reported from epidemiologic studies involving diverse ethnic populations of Caucasians and Asians, which range from 1.2% to 7.5%, while asymptomatic OSA affected as many as one in five middle-aged adults (3). A previous community-based study of middle-aged Chinese subjects between 30-60 year old in Hong Kong reported the prevalence of OSAS (AHI≥5/hour plus presence of excessive sleepiness) to be 4.1% in men and 2.1% in women (4,5). A similar scale of problem is seen in children. A recent study recruiting community-dwelling students, aged 6-12 years, from 13 primary schools in Hong Kong found that OSAS, based on the International Criteria of Sleep Disorders version II, affected 5.8% and 3.8% of boys and girls respectively (6).

Obesity, in particular central obesity, is the most well-established risk factor of OSA (7). Obesity is increasingly prevalent in western countries since the last century, and the pandemic is sweeping across the oceans to Asia (8). With the rapid socioeconomic development occurring in many parts of China, many local customs including lifestyle and dietary habits have been gradually changing, which would result in a shift of disease pattern similar to developed countries in the west. According to several cross-sectional studies undertaken in the recent two decades, it is estimated that up to one-third of adults in China are overweight or obese, and 10-20% of all adults are affected by metabolic syndrome (9). The prevalence of overweight and obesity among Chinese children and adolescents has also been increasing steadily from 1991 to 2006, and those from urban areas and high income families are particularly affected (10).

Undeniably, OSA is strongly linked to obesity and other obesity-related medical conditions such as hypertension, impaired glucose metabolism, cardiovascular diseases, or the metabolic syndrome (11,12). In western countries, atherosclerotic diseases and its associated morbidity and mortality lead to tremendous economic loss (13). Data

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from the China Health and Nutrition Survey revealed a dramatic increment in blood pressure levels and prevalence of hypertension among Chinese children and adolescents from 1991 to 2004, after exclusion of confounding factors (14). The prevalence of diabetes mellitus is also expected to escalate in parallel with the sweeping epidemic of obesity (15). According to the report of WHO Disease Control Priorities Project, cerebrovascular disease and ischemic heart disease, diseases predominantly due to atherosclerosis, were the first and third leading causes of mortality in China and accounted for 18% and 8% of total mortality in 2001. With the emerging evidence illustrating potential independent contribution of OSA to various cardiometabolic diseases, the clustering of these diseases pose a significant healthcare burden.

Pathogenesis of atherosclerosis

Atherosclerosis is a chronic inflammatory process involving the vascular walls which takes years to evolve. The mechanisms leading to the formation of atherosclerotic plagues involve a complex interplay of dysfunctional endothelium and systemic inflammatory and hemostatic mechanisms including platelets and coagulation pathways. The vascular endothelium is believed to be important in regulating vascular tone, modulating platelet activation and cellular adhesion, in face of a variety of circulatory signals and vascular stressors (16). A healthy endothelium could also promote ongoing repair mechanisms to maintain its integrity in response to various insults. Endothelial dysfunction precedes the development of atherosclerosis.

Shear stress triggers endothelial injury, which allows the entry of serum lipoproteins and circulatory factors into the vascular intima, leading to activation of macrophages and T-lymphocytes locally. Such intrusion of vascular integrity results in the release of many cytokines and chemokines from damaged endothelial cells and macrophages, and increased expression of endothelial cell-adhesion molecules, all of which further encourage influx of circulatory inflammatory cells and adhesion of platelets. Systemic oxidative stress and reactive oxygen species released from activated leukocytes promote oxidation of lipoproteins and various macromolecules, perpetuating inflammation and further tissue injury. Along with the systemic pro-inflammatory phenotypes of many cardiovascular risk factors, a self-perpetuating cascade of inflammation is formed inside the plague, leading to its progression and even rupture. Rupture of atherosclerotic plague would expose underlying tissue factors and switch on the coagulation cascade, resulting in rapid progression of vascular occlusion and clinical cardiovascular syndromes including myocardial infarction and ischemic cerebrovascular events.

Detection of subclinical atherosclerosis

Several non-invasive tools are being used in clinical care and research for the detection of subclinical atherosclerosis or atherosclerotic burden, which could facilitate early initiation or intensification of therapy. Carotid intima-media thickness (CIMT) is a measurement of the thickness of the intima and media layers of the carotid artery with the use of ultrasound. Previously, concerns were raised about its reliability and reproducibility, but with the availability of more sophisticated technology wares and increasing experience with the technique, the measurement has been shown to be highly reproducible (17). Increased CIMT has been shown to be associated with atherosclerosis, and predicts future cardiovascular events including myocardial infarction and stroke. It has also been shown to correlate well with traditional cardiovascular risk factors, such as aging, hypertension, diabetes mellitus, hyperlipidemia and smoking, and treatment of those modifiable factors would improve CIMT (17).

Arterial stiffness reflects arterial properties including compliance and distensibility, and can be assessed by analysis of the arterial waveform or measurement of pulse-wave velocity (PWV). Increased PWV correlates well with the presence and extent of atherosclerosis, and traditional cardiovascular risk factors (18). In later stages of development of atherosclerosis, calcium deposits occur within the fibrous plaques and assessment of coronary artery calcification by means of computed tomography is shown to predict obstructive coronary artery disease and future coronary events (19).

The intact endothelium maintains a homeostatic balance of vasodilating and vasoconstricting substances which mediate optimal response of arterial walls in the face of various stimuli, and impairment of endothelial function antedates the development of atherosclerosis and predicts related cardiovascular diseases (20). Vascular responses on provocation by pharmacolgoic or mechanical stimuli serve as an indicator of vascular function mediated by either endothelium dependent or independent mechanisms (20). Endothelium-dependent vasodilatation can be assessed by measuring blood flow response to pharmacologic or physical stimuli with the use of invasive angiography or noninvasive imaging techniques such as doppler echocardiography. Reactive hyperemic response of forearm arteries after a brief period of occlusion, indicating endothelial nitric oxide dependent vasodilation, is a commonly used surrogate measure of the endothelial function, and has been shown to correlate with coronary endothelial dysfunction (21). Such hyperemic response can be assessed with the measurement of flow-mediated dilatation (FMD) of brachial artery by doppler ultrasound (22), or lately with another non-invasive device assessing peripheral artery tonometry which await further validating outcomes data (23,24). Numerous circulating

substances, such as C-reactive protein (CRP), fibrinogen, adipokines and cytokines, have been found to be biomarkers of atherosclerosis (25). CRP level is increasingly important as a prognostic biomarker of adverse cardiovascular events in established cardiovascular diseases (26), though its exact role and application in primary prevention of such events is not conclusive (27,28).

OSA and atherosclerosis - epidemiolgic and clinical studies

OSA has been shown to be closely linked to various cardiovascular diseases (CVD), most of which are pathologically related to atherosclerosis, including hypertension, coronary heart diseases, cerebrovascular accidents, arrhythmias and cardiac dysfunction (12). The Sleep Heart Health Study, which included more than 6,400 community-dwelling individuals, has demonstrated a clear association between OSA and coronary artery disease or stroke, with respective odds ratio being 1.27 (95% CI 0.99-1.62) and 1.58 (95% CI 1.02-2.46) comparing those with OSA (AHI>11) and those without OSA (AHI<1.3) (29). A longitudinal study of subjects free of cardiovascular diseases and diabetes mellitus at baseline, followed up for 7 years, showed that OSA at baseline was a significant predictor of future incident CVD (odds ratio 4.9; 95% CI 1.8-13.6) and effective treatment with CPAP reduced such excess risk (30). Subsequently, a large-scale prospective cohort study which followed up more than 1500 subjects for a mean duration of 10 years, found that untreated severe OSAS significantly increased the risk of fatal (odds ratio 2.87, 95% CI 1.17-7.51) and non-fatal (3.17, 1.12-7.51) cardiovascular events compared with non-OSA controls, and such risks were attenuated significantly with CPAP treatment (31). Another observational study reported a dose-dependent relationship between the severity of OSA and the risk of stroke or death, after adjustment for known confounders (32). With the emergence of these longitudinal data, though observational, a causal relationship between OSA and atherosclerotic vascular disease is highly suggested.

Apart from epidemiologic studies, numerous clinical studies have focused on direct measurement of atherosclerosis or its surrogate markers in subjects with different degrees of OSA. The assessment of an independent association between OSA and atherosclerosis is potentially affected by a number of confounders, which would need vigilant exclusion or statistical adjustments. Carotid intima-media thickness was found to be elevated in OSA subjects, compared to non-OSA subjects in several case-control studies (33,34) and cross-sectional studies (35). Of note, the severity of OSA, as indicated by apnea-hypopnea index or oxygen desaturation parameters, was positively correlated with measures of early atherosclerosis including PWV and CIMT (35-37). In line with these findings, the formation of atherosclerotic plagues and extracranial stenosis were more pronounced in OSA individuals (36,38). These associations were also found in Asian subjects. In a Japanese study, brachial-ankle PWV was higher in the OSA groups compared to the non-OSA counterparts independent of other risk factors (39). Two subsequent Chinese studies have demonstrated a higher brachial-ankle PWV (40) and CIMT (41) in OSA group compared to non-OSA group, though CIMT did not change after CPAP therapy for 3 months in the latter non-randomized study (41). On the contrary, a Brazilian randomized control trial has shown a reduction in CIMT and PWV, as well as circulating CRP and catecholamine levels after 4 months of CPAP treatment (42). The presence of OSA in addition to hypertension (43) and metabolic syndrome (44) was found to have additive provoking effects on early markers of atherosclerosis including CIMT, carotid distensibility and carotid-femoral PWV. A recent randomised controlled cross-over study from India reported a significant improvement in lipid profile, glycated hemoglobin, blood pressure as well as lowering of frequency of metabolic syndrome in the CPAP treated group compared with the sham-CPAP group, but significant improvement of CIMT was only seen in the CPAP adherant subgroup (45).

Mechanistic links between OSA and atherosclerosis

Intermittent hypoxia and oxidative stress

The episodic complete or incomplete cessation of breathing in OSA is coupled with intermittent hypoxia and reoxygenation to body tissues and organs. Atherosclerosis is believed to represent a state of heightened oxidative stress, which is the result of an imbalance in production of reactive oxygen species (ROS) and intrinsic antioxidant activity that prevent tissue damage from oxidation (46). Repeated sequential hypoxia-reoxygenation in OSA may lead to overproduction of ROS and resultant oxidative stress (46). Many studies have provided supportive evidence for the presence of oxidative stress in OSA, with the use of different biomarkers, although the findings are not entirely consistent (46). Lipid peroxidation is a marker of systemic oxidative stress. OSA patients have been found to be more susceptible to lipid peroxidation and this was mitigated by CPAP treatment (47). Data from our group also demonstrated elevated levels of plasma 8-isoprostane, an oxidative stress biomarker produced *in vivo* by the free radical-catalyzed peroxidation of arachidonic acid, in OSA subjects, and which was associated with dysfunctional high density lipoprotein and increased oxidation of low density lipoprotein (48). Other oxidative stress biomarkers, thiobarbituric reactive substances (TBARS) and peroxides (PD), were found to be higher in OSA subjects with or

without CVD, compared to controls, and antioxidant protective enzyme paraxonase-1 were lower in those with OSA and CVD (49). Studies have also shown increased ROS production from inflammatory leukocytes such as neutrophils and monocytes in OSA patients, which were reversed with effective CPAP treatment (50,51). Notwithstanding, such evidence for increased oxidative stress in OSA was not reproducible in some other studies (52-54). In order to demonstrate an association between OSA and increased oxidative stress conclusively, multiple confounders including obesity, comorbid conditions, smoking and even dietary influence must be properly addressed. The choice and adequacy of measured sleep parameters for reflecting the severity of intermittent hypoxia may also contribute to heterogeneity of findings.

Several studies have approached the question from another angle by demonstrating a lower level of anti-oxidant activity in OSA, which could be partially reversed by CPAP treatment (55,56). Subsequently, another study has found impaired serum albumin antioxidant properties in OSA patients (57). The beneficial effect of intravenous vitamin C supplementation, a dietary antioxidant, on endothelial function in OSA supported the role of anti-oxidant imbalance in vascular pathogenesis in OSA (58). Lately, a study focusing on in-situ red-ox kinetics occurring in the microcirculation nicely demonstrated increased oxidant production (microcirculatory peroxynitrite deposit) and reduced anti-oxidant mechanisms (transcription of endothelial nitric oxide synthase and superoxide dismutase 1) in the microcirculation in OSA individuals (59).

Advanced glycation endproducts (AGE), products of non-enzymatic glycation and oxidation of proteins and lipids, are highly associated with angiopathy in the setting of diabetes mellitus and aging (60). In our previous study, serum levels of AGE of non-diabetic OSA patients were not as elevated as that in diabetic subjects, but higher than control non-diabetic subjects recruited from a general poupulation, and the AGE levels were associated with severity of OSA and levels of 8-isoprostane (61). Our latest study in healthy subjects with or without OSA confirmed the association between elevated levels of AGEs and OSA, though this association was independent of insulin sensitivity (62).

Inflammatory cascade

It is now well-established that inflammation is involved in the initiation, progression and acute rupture of atherosclerotic plagues. Inflammatory markers, in particular C-reactive protein (CRP), the assay for which is widely available in clinical laboratories, have become important prognostic indicators for cardiovascular morbidity and mortality.

Intermittent hypoxia/reoxygenation cycles and the resultant oxidative stress in OSA may activate pro-inflammatory signaling pathways involving nuclear factor kappa B (NF-KB), and this was shown to be the case in OSA subjects (63,64). NF-KB is a transcription factor mediating inflammatory and immune responses by regulating inflammatory gene expression, including the genes for cytokines, chemokines, growth factors and cell adhesion molecules. Activated monocytes and neutrophils are further sources of ROS resulting in self-perpetuating vicious cycle of inflammation. Cell adhesion molecules (intercellular adhesion molecule-1), enzymes (inducible nitric oxide synthase, cycloxygenase-2), cytokines (interleukin-6, tumour necrosis factor-alpha) and chemokines (monocyte chemoattractant protein-1, interleukin-8), have been shown to be upregulated in OSA subjects (65,66). Of note, these positive results were not entirely consistent (67), particularly after taking into account the effect of obesity and concomitant inflammatory diseases.

Leptin and adiponectin are hormones secreted from adipose tissue, and they modulate a number of metabolic processes. Both have been shown to play a role in suppressing insulin resistance and its consequences including diabetes mellitus and atherosclerosis (68). Many observational studies have found an elevated level of leptin in OSA or sleep-deprived subject independent of obesity though results were inconsistent (69-73). Leptin may also contribute to coexisting hypertension in OSA (74). Adiponectin was found to be reduced in OSA in several cross sectional studies (75-77), but not in others (78). Furthermore, positive effects from CPAP treatment on reversing these abnormal adipokine levels have not been demonstrated convincingly by any randomized controlled study. Thus, the relationship between these adipokines and OSA is still highly controversial.

CRP, which is an acute phase reactant released from the liver in response to stimulation from TNF-alpha, IL-6 and IL-8, and a biomarker for CVD risks, has been extensively studied in the setting of OSA. Despite a few negative studies, most of the cross-sectional studies demonstrated that OSA was independently associated with higher levels of CRP, supporting heightened systemic inflammation in OSA (65). Our group has also investigated such association in a group of healthy Chinese adults free of cardio-metabolic diseases and found that CRP was correlated with indices of severity of OSA after adjustment of known confounders including visceral adiposity (79). However, the effect of CPAP treatment on CRP level in OSA is much less consistent, with some studies failing to show any beneficial effect. A lack of response may be related to the relatively short duration of treatment period in some studies, or the inflammatory process in established atherosclerosis may not be fully reversible (65). Another acute phase reactant, serum amyloid A, was also found to be related to the severity of OSA (80), and the level was reduced with CPAP treatment (81). Caroid intima media thickness was demonstrated to be significantly correlated with CRP, IL-6, IL-18, duration of hypoxia and severity of OSA, and the primary factor predicting CIMT was duration of hypoxia

during sleep (34). Taken in summary, these findings suggest that systemic inflammation in OSA may be associated with the development or progression of atherosclerosis.

Endothelial dysfunction

The endothelium is a crucial regulator of vascular homeostasis, which exerts a number of vasoprotective effects, such as vasodilation in response to ischemia or tissue injury, and inhibition of inflammatory responses. Endothelial dysfunction precedes the development of atherosclerosis (82).

The increased oxidative stress observed in OSA may suppress nitric oxide synthase activity (83,84), which results in dysregulation of vasomotor tone and endothelial dysfunction. Our group has demonstrated that flow mediated dilatation of brachial artery was significantly lower in men with OSA free of comorbidities compared to non-OSA counterparts, and such impairment was reversible with CPAP treatment (85).

In addition to intermittent hypoxia, sleep deprivation and fragmentation in OSA provide another potential pathway linking to endothelial dysfunction. Sleep deprivation for 4 weeks was associated with reduced FMD in a group of healthy young men (86). A number of studies have shown that elevated inflammatory markers, sympathetic over-activity and hypercoagulability occur in sleep-deprived subjects (87,88), which could all contribute to vascular atherogenesis.

Recently, circulating cell-derived microparticles, a relatively novel marker of endothelial dysfunction, was found to be elevated in minimially symptomatic OSA, and the correlation between elevated circulating microparticles and OSA severity was also demonstrated in children (89,90). Circulating endothelial progenitor cell levels, which reflect the repair capacity of endothelium in response to stress and injury, have also been found to be lower in those with OSA in several small-scale studies, but the results were not repeatable in others (84).

Platelet activation and coagulation abnormalities

Platelets exert a spectrum of pro-atherogenic properties by adhering to diseased endothelium and secreting a series of atherogenic mediators such as cytokines, chemokines, growth factors, adhesion molecules and coagulation factors. Such expressions would promote further leukocytes activation, proliferation, adhesion, and migration into the atherosclerotic plagues (91). Multiple studies have shown that platelets are activated and more prone to aggregate in OSA subjects (92-94) and may be alleviated by CPAP treatment (92,95,96). In a recent study, greater degree of platelet activation was associated with more severe oxygen desaturation during sleep (97). OSA and sleep disruption have also been linked to an imbalance in circulatory thrombotic and anti-thrombotic activity, resulting in a switch of the coagulation profiles to a pro-thrombotic states (98-100).

Mechanical and hemodynamic factors

Atherosclerosis is a common pathology in blood vessels in hypertension. Abundant evidence support that untreated OSA could predispose to systemic hypertension (12). The exact pathophysiologic etiology of hypertension in OSA is not definitely clear, but it is believed that sympathetic over-activity as a result of intermittent hypoxia and repeated arousals and a series of neuro-hormonal alterations account for the surges in blood pressure (12). The heightening of sympathetic tone and elevated nocturnal endothelin release lead to systemic vasoconstriction, and thus higher systemic blood pressure (101), and the renin-angiotensin-aldosterone system is also activated resulting in sodium and fluid retention (102). Systemic hypertension is linked to increased shear stress to vascular endothelium, vascular remodeling, endothelial dysfunction and atherogenesis (103).

Snoring is extremely common in subjects with OSA. The process of snoring involves vibrations of soft tissues surrounding the pharynx which can be transmitted to the carotid arteries (104). A study using rat tail blood vessels found that vibration at 60 Hz for 4 hours per day caused vasoconstriction, injury to endothelial cells and endothelial denudation (105). Recently, another study examined the effect of vibration simulating snoring in a ventilated rabbit model. The vibrated carotid artery showed decreased vasodilatation to acetylcholine compared with control arteries, demonstrating a direct effect of vibrations on endothelial function independent of hypoxia or apnea (106). Indeed, independent of nocturnal hypoxia and OSA severity, snoring was demonstrated to be associated with carotid atherosclerosis but not femoral atherosclerosis (107). These findings support the hypothesis of snoring vibration-induced endothelial injury contributing to subsequent carotid atherosclerosis, providing a mechanical route in addition to metabolic pathways by which subjects with OSA may be at increased risk of carotid atherosclerosis.

Cardiovascular risk factors

Metabolic factors are established risk factors for atherosclerosis and related cardiovascular diseases. The metabolic syndrome, representing a cluster of metabolic phenotypic characteristics comprising of central obesity, hypertension, insulin resistance and dyslipidemia, is a classical risk factor for atherosclerotic CVD and diabetes mellitus which itself is an important cause of atherosclerosis. Given the common risk factor of obesity, it is not surprising that OSA is strongly associated with the metabolic

syndrome (108). But in addition, an association independent of obesity has been repeatedly demonstrated between OSA and various metabolic diseases which could aggravate atherosclerosis (11,109). Animal and cellular experiments using intermittent hypoxia as a model of OSA have also demonstrated many adverse metabolic effects including promotion of dyslipidemia and insulin resistance, and induction of relevant cellular or molecular signaling pathways (110-112). Lipoproteins are directly involved in the pathogenesis of atherosclerosis. Similarly, insulin resistance and diabetes mellitus are also major pathogenetic factors for atherosclerosis. Clinical evidence regarding the independent association between OSA and dyslipidemia is conflicting with some studies showing an increased LDL, increased triglycerides or reduced HDL levels in OSA (113). The impact of OSA on glucose metabolism is a hot topic under research, with many observational studies supporting a deleterious effect (11,114). However, the effects of CPAP treatment on metabolic profiles have been conflicting. A recently published randomized controlled study has nicely demonstrated beneficial effects of CPAP treatment on metabolic parameters in OSA subjects (45). Although it is an intuitively logical hypothesis that OSA may lead to atherosclerosis through these metabolic pathways, much remains to be understood regarding the complex interactions of multiple risk factors in the pathogenesis of atherosclerosis and clinical vascular disease in OSA.

Conclusions

Clinically, OSA is connected to a network of cardiovascular risk factors, while mechanistically, OSA may lead to oxidative stress, heightened inflammation and endothelial dysfunction which are pathological processes underlying atherosclerosis. However, much remains to be delineated regarding vascular pathogenesis in OSA. The demonstrated benefits of CPAP treatment of OSA on some of these parameters are encouraging, since they imply that potential adverse sequelae on the vasculature could be halted with early detection and timely treatment of OSA. Further evidence from large-scale randomized controlled trials with comprehensive clinical outcomes as endpoints are necessary to address many important clinical questions, including the optimal threshold for treatment of OSA, effect size, interactions of OSA with other cardiometabolic risk factors, and potential differences in the vasculature at different sites.

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