Obstructive sleep apnoea syndrome: a new paradigm by chronic nocturnal intermittent hypoxia and sleep disruption

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SUMMARY

Obstructive sleep apnoea syndrome (OSAS) is associated with severe cerebro-cardiovascular morbidity and mortality. It is an independent risk factor for atherosclerosis, arterial thrombosis and metabolic syndrome, and recently has been associated with an increased incidence of cancer and death. A causal link between OSAS and atherosclerosis has been partially established. Recent research on atherosclerosis in OSAS has focused on thrombotic tendency and blood viscosity, providing new insight into disease mechanisms. Hypoxia is a critical pathophysiological element in OSAS that leads to intensive sympathetic activity, in association with inflammation, oxidative stress and pro-coagulant activity. Hypoxia and the induction of oxidative stress can simultaneously represent an underlying mechanism in the pathogenesis of cancer development and progression. This mini-review will discuss the latest findings on the association and potential relationship between OSA and pathological vascular sequelae.

KEY WORDS: Atherosclerosis • Cancer • Chronic intermittent hypoxia • Obstructive sleep apnoea • Sleep disruption

Introduction

Increased atherosclerosis with cardiovascular morbidity and mortality is associated with obstructive sleep apnoea syndrome (OSAS); the association persists after controlling for diabetes, hypertension, smoking and dyslipidaemia. OSAS is characterised by recurrent episodes of complete or partial collapse of the upper airways during sleep, and can induce apnoea or hypopnoea, respectively, with recurrent episodes of intermittent hypoxia and higher carbon dioxide levels, leading to possible frequent interruption of sleep. The association between OSAS, cardiovascular disease and coagulation abnormalities was suspected for many years and is supported by large scale epidemiological and prospective studies. The mechanisms that mediate this association are not completely understood. The prognostic factors have not been determined, and studies to identify which patients are at higher risk have given controversial and disappointing results. Moreover, OSAS has been emerged as independently and strongly associated with cancer incidence and mortality. Current data suggest that inflammatory processes leading to endothelial dysfunction play a central pathogenic role in OSAS-related complica-
tions. Chronic intermittent hypoxia (CIH) and sleep disruption are considered important causes of cerebro-cardio-vascular diseases in OSAS patients. Oxidative stress induced by CIH is an important physiological mechanism of the disease. Increased blood clotting, caused by changes in the rheological properties (flow properties) of blood and plasma, seems to be an important factor linking OSAS to cardiovascular complications (CV). CIH may be responsible for increased blood hypercoagulability (platelet activation and decreased fibrinolytic activity) which predisposes patients to thrombotic events. In addition, it is well known that chronic hypoxia plays an important role in regulating various stages of cancer formation and progression. This review provides a critical analysis of the current evidence of an association between OSAS and haemostatic alterations, vascular remodelling/atherosclerosis and cancer. The aim is to discuss the contributing factors and potential mechanisms that may be responsible for this association.

Effects of chronic nocturnal intermittent hypoxia/sleep fragmentation: mechanisms of vascular remodelling in atherosclerosis

OSAS, via the chronic intermittent hypoxia and sleep disruption, can trigger the development of systemic inflammation, oxidative stress, endothelial dysfunction, and metabolic syndrome. Atherosclerosis is a chronic inflammatory disease that maintains a silent course for several decades before reaching clinical significance. The majority of studies have demonstrated a considerable mortality rate in OSAS, which is associated with the severity of atherosclerosis. The incidence of CV events, i.e. stroke, myocardial infarction, or CV death, is very high, with an odds ratio (OR) of CV events or mortality varying in magnitude from 2 to 7 for moderate to severe OSAS. This finding was confirmed by a subsequent study on 202 consecutive patients who were investigated with electron-beam computer tomography. Patients were asymptomatic in terms of their coronary artery disease (CAD) and were investigated by an overnight-sleep study, with a prevalence of OSAS of 76%. Coronary artery calcification (CAC) was found in 67% of OSAS patients and in 31% of non-OSAS patients (p ≤ 0.001). The median CAC score was 9 in OSAS patients and 0 in non-OSAS patients (p ≤ 0.001), strongly supporting the theory that OSAS is an independent risk factor for CAD.

CIH and sleep disruption leads to systemic hypertension due to the activation of the sympathetic system in patients on a high-cholesterol diet. The sympathetic hyperactivity determines haemodynamic alteration and high blood pressure, as well as cardiovascular inflammation (increased cell adhesion molecules, endothelial cell dysfunction, prothrombotic factor activation) and vascular remodelling. OSAS is also associated with insulin resistance and glucose intolerance, which are known risk factors for atherosclerosis. CIH can lead to insulin resistance and glucose intolerance in obese patients with dyslipidaemia. The intermittent hypoxia is a major stimulus for oxidative stress with the production of reactive oxygen species (ROS) that contributes to the generation of systemic inflammation characterised by inflammatory cell proliferation and cytokine/chemokine production. Moreover, CIH may trigger the activation of pro-inflammatory transcription factors including hypoxic inducible factor (HIF)-1α and nuclear factor (NF)-κB, which also share some gene products, such as inducible nitric oxide synthase. However, the role of HIF-1α is still controversial in OSAS studies. The transcriptional reprogramming induced by CIH includes the induction of cell adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and selectins, cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), chemokines, such as IL-8, and C-reactive protein (CRP). Other researchers have reported that CIH increases lipid peroxidation in the myocardial tissue of rats, and activates inflammatory pathways in vitro. Recently, it has been demonstrated that CIH significantly increased sizes of atherosclerotic lesions, and the mRNA levels of both cyclooxygenase (COX)-1 and thromboxane synthase (TXBS). Lesion size was correlated with levels of COX-1 and TXBS mRNA, and treatment with the selective COX-1 inhibitor SC-560 reduced lesion progression in intermittent hypoxia mice. This study has demonstrated, for the first time, that the activation of the COX-1 pathway in response to CIH is associated with increased atherosclerotic lesions in mice. In addition, in OSAS patients with cardiovascular risk factors an increase in urinary excretion of 11-dehydro-thromboxane B2 (11-dTXB2) was observed, supporting the emerging role for COX-1 in CIH-induced vascular changes.

Detailed analysis of hypercoagulability in OSAS

Some studies have demonstrated considerable changes in haemostatic system components in OSAS patients, including platelet activation and increased plasma levels of tissue factor, von Willebrand factor (vWF) and fibrinogen. CIH and sleep disruption are a critical pathophysiological issue triggering greater sympathetic nervous system activity in association with the levels of markers of inflammation, such as oxidative stress and procoagulant activity. Hypercoagulability has been shown to be a risk factor for cardiovascular morbidity and mortality in OSAS patients. One possible explanation for the increase in blood coagulability is that during apnoea, desaturation triggers inflammatory factors, catecholamine and increased plasma levels of tissue factor as well as platelet aggregation, which alter capillary blood flow due to an increased sympathetic activity and a broader micro-endothelial damage, resulting in blood coagulability. Recently, one study has demonstrated increased pulmonary artery hypertension (PAH) in OSAS patients, which could be correlated with a genotypic heterogeneity with the plasminogen activator inhibitor-1 (PAI-1).
5G/5G polymorphism, possibly in relation with the severity of hypoxaemia and apnoea. vWF, a glycoprotein that plays an important role in stopping the escape of blood from vessels (haemostasis) following vascular injury, works by mediating the adherence of platelets to one another and to sites of vascular damage, preventing factor-VIII degradation. At present, the relation between OSAS and vWF is controversial, with some data showing an increase of vWF in patients with OSAS, and other data showing no significant differences between controls and patients. Increased levels of clotting factors XIa (FXIa) and VIIa (FVIIa), thrombin and antithrombin (TAT) has been shown in patients with OSAS. TAT is marker of thrombin turnover and indicates a tendency to blood coagulation disorders. TAT increased in patients with severe nocturnal desaturation, and FVIIa was found to be reduced in patients who practiced continuous positive airway pressure (CPAP) therapy.

Both FVIIa and FXIa have been associated with increased mortality from CV diseases. The observed increase in the clotting factors in OSAS suggest that CIH may predispose to hypercoagulability. Robinson et al. have found that serum levels of these clotting factors were not improved after one month of treatment with optimal CPAP therapy. A possible explanation may be that the short-term treatment with CPAP therapy was not able to facilitate the improvement of sympathetic activity and CIH. Since there are no long-term studies, the role of CPAP therapy remains unclear. Although not consistently, some studies have found a correlation between platelet activation and OSAS. The cause of the increased platelet activation in OSAS patients remains unclear, but the severity of OSAS seems to influence platelet aggregation as a function of nocturnal hypoxic time. A possible interpretation is the release/activation of catecholamines during oxygen desaturation, triggering more intense platelet activation. OSAS patients have indeed increased levels of urinary adrenaline/noradrenaline that correlate with the degree of oxygen desaturation and apnoea index during sleep. The therapeutic use of CPAP treatment on platelet aggregation is controversial. CPAP therapy decreases urinary adrenaline/noradrenaline by enhancing its elimination from the blood. The study by Hui et al. found that platelet aggregation decreases after one day for up to three months of treatment with CPAP therapy in patients with severe OSAS, without changes in the control group. Oga et al. found that one month of treatment with CPAP is insufficient and only after 90 days of treatment with CPAP can a reduction in platelet activation be demonstrated. Therefore, data from the literature indicate that treatment with CPAP improves platelet aggregation, but the duration of therapy remains uncertain. Platelet activation results in the shedding of sub-microscopic membrane vesicles, known as platelet-derived microparticles (PDMPs), which are less than 1.5 µm in diameter and enriched in pro-coagulant platelet proteins. The membrane of PDMPs embraces all the properties of the activated platelet membrane, including the ability to bind to the components of pro-coagulant complexes, such as factor V (Va) and VIII (VIIa). Plasma PDMPs have been shown to be amplified in patients with acute coronary syndrome, suggesting that PDMPs may play a role in the pathogenesis of arterial thrombosis in OSAS patients. Increased levels of the pro-coagulation factors soluble CD40 ligand (sCD40L) and soluble P-selectin (sP-selectin) have been demonstrated in OSAS patients in correlation with the degree of nocturnal desaturation. CPAP therapy reduces their plasma levels. sCD40L and sP-selectin appear in plasma during the early stages of blood coagulation and are well-known indicators of thrombogenic conditions, such as disseminated intravascular coagulation (DIC). Furthermore, levels of sCD40L and s-P-selectin are increased in patients with hypertension, hyperlipidaemia and diabetes mellitus.

Blood viscosity is defined as the internal resistance of the blood to shear forces. Blood viscosity is determined by plasma viscosity, haematocrit (volume fraction of erythrocytes, which constitutes 99.9% of the cellular elements) and the mechanical behaviour of erythrocytes. Increased blood clotting caused by changes in the rheological properties of blood and plasma seems to be an important factor linking OSAS and cardiovascular complications. Hyperviscosity is a potential mechanism for increased coagulability in OSAS, but the studies on this issue are limited by the small sample size and the absence of well-matched controls.

PAI-1, a member of the serine protease inhibitor family, inhibits fibrinolytic activity by binding to tissue type plasminogen activator (tPA). It was demonstrated that higher apnoea-hypopnoea index (AHI)/hs and Nadir SaO₂% were both associated with a higher concentration of circulating PAI-1 in a group of OSAS patients. Increased concentrations of PAI-1 in OSAS predicted the occurrence of acute myocardial infarction in middle-aged men and women with a high prevalence of coronary heart disease. However, many uncertainties still remain as to the independent effects of OSAS on increased blood coagulability, largely due to the common co-existence of other CV risk factors and the incomplete normalisation of coagulation after CPAP treatment.

Venous thromboembolism and OSAS

There are limited data in the literature that have shown a relationship between venous thromboembolism (VTE) and pulmonary embolism (PE) in association with a coagulation-related clinical problem. The above studies are not extensive nor do they have a control group. These data suggest a high prevalence of OSAS in patients with PE. A retrospective study showed a percentage higher than in the general population, accounting for 15.5% of OSAS in patients with VTE. The study is, however, limited due to incomplete instrumental diagnostics, since data on polysomnography is missing. A review of the current considerable evidence demonstrates that OSAS is associated with a pro-coagulant state, although the relationship between OSAS and individual clotting factors are uncertain. More clinical
studies are needed in order to better control for confounding factors such as cardiovascular morbidity and mortality, demonstrating that a hypercoagulability state is induced by OSAS before the onset of cardiovascular disorders

**CHI and cancer: future perspectives for research**

CHI and sleep disruption are known to trigger pathophysiological pathways leading to systemic disease. In fact, OSAS has been associated with diseases with a high inflammatory potential, such as psoriasis and other autoimmune disorders. The potential mechanisms involved in hypoxia-driven cancer development and progression have been previously investigated. Moreover, it has been shown that nocturnal intermittent hypoxia can regulate different stages of cell differentiation and proliferation. Cellular hypoxia (also present in cancer) and the adaptive response is related to a family of transcription factors, the most significant being HIF-1, which activates the transcription of genes that play a fundamental role in angiogenesis and genetic modification, with the formation of cancer-related stem cells. The HIF-1 pathway has been associated with a considerable increase in ROS generation during periods of hypoxia/reoxygenation, which may play an important role in modifying gene expression by regulating the activity of some redox-sensitive transcription factors. These include activator protein (AP)-1, which may play a key role in carcinogenesis through the induction of apoptotic inhibitory factors, matrix metalloproteases and pro-angiogenic factors including vascular endothelial growth factor (VEGF).

A recent animal model study has spurred an emerging pathophysiological hypothesis linking OSAS to cancer. The authors have demonstrated that when mice are exposed to intermittent hypoxia mimicking OSAS, the frequency of melanoma was twice high as in normal controls. These promising results in experimental animals have encouraged studies on humans with the aim of evaluating the potential link between OSAS and cancer. Two independent large-scale clinical studies have recently investigated this possible relation. The first assessed the association between OSAS and cancer in a cohort of patients from Wisconsin (USA) (1,522 subjects), and showed a significant increase in the likelihood of cancer death in patients with severe OSAS. Another database, called the Spanish Sleep Network, involved 5,000 patients with a median 5-year follow-up and found that OSA is associated with increased incidence of cancer. These two studies reported an increased cancer incidence and mortality in OSAS patients compared with those who do not have OSAS, also after adjustment for important confounders (age, sex, smoking, alcohol consumption and body mass index). In this context, it can be hypothesised that nocturnal intermittent hypoxia and consequent sleep disruption may play a key role in cancer development. It would be important to determine whether the OSAS-cancer combination gives rise to a specific histological type of tumour, since different types of malignant cells have different adaptive responses to intermittent hypoxia. The identification of confounding factors will

![Fig. 1. Potential biological pathways mediating the development of atherosclerosis and cancer in sleep apnoea.](image-url)
also be significant. A key issue that deserves further study is the potential role of CPAP therapy in cancer risk associated with OSA, and to investigate whether the effect of anti-cancer drugs is changed following treatment of CPAP.

Conclusions and future guidelines

The available data highlight that patients with OSAS experience a pro-coagulant condition that may represent a contributing factor in the development and progression of vascular diseases. The potential for anticoagulant and anti-platelet drugs to decrease morbidity/mortality is worth further investigation. Broad randomised studies will be necessary to provide greater statistic power in order to determine whether the treatment of OSAS with CPAP/drugs can stop or even reverse vascular remodelling, atherosclerosis progression and, ultimately, reduce the rate of cardiovascular disease. The possible relationship between OSAS and cancer is a good gateway for further research and an opportunity to perform international clinical studies that can answer the many open questions still remaining.

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