Review Article


Cardiovascular consequences of obstructive sleep apnoea

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Obstructive sleep apnoea (OSA) is a form of sleep disordered breathing with a high prevalence rate and is often underdiagnosed. OSA is associated with hypertension, coronary artery disease, stroke, peripheral vascular disease, heart failure, and arrhythmias. The presence of OSA may be a strong predictor of fatal cardiovascular events in patients with cardiovascular disease (CVD). Increased sympathetic drive, activation of metabolic and inflammatory markers, and impaired vascular function are some of the proposed mechanisms that could explain the association between OSA and cardiovascular diseases. Understanding these mechanisms is important for identifying treatment strategies. The presence of OSA should be considered in clinical practice, especially in patients with CVD. Randomized intervention studies are needed to establish whether early identification and treatment of OSA patients reduces cardiovascular morbidity.

Key words Cardiac arrhythmias - cardiovascular risk - CPAP - ischaemia - myocardial infarction - OSA

Introduction

Obstructive sleep apnoea (OSA) is characterized by repetitive interruption of ventilation during sleep due to collapse of the pharyngeal airway. The inspiratory airflow can be either reduced (hypopnoea) or completely absent (apnoea), and an apnoea that lasts 10 sec or longer, associated with ongoing ventilatory effort, characterizes a patient with OSA. To establish a definitive diagnosis, a full polysomnography is required. The diagnosis of OSA is confirmed when a person has an apnoea-hypopnoea index (AHI; number of apnoeas and hypopnoeas per hour of sleep) > 5 events/h associated with symptoms of excessive daytime sleepiness.

OSA is a public health issue due to its high prevalence in North American, European and Asian nations. Epidemiologic data in the US population show that approximately 20 per cent of adults have at least mild OSA (AHI > 5 events/h) and about 7 per cent of adults have moderate to severe OSA (AHI > 15 events/h), affecting preferentially the male gender. Home sleep studies suggest that 7.5 per cent of urban middle-aged Indian men have OSA. Longitudinal data have confirmed that obesity and ageing increase the risk of OSA. It has also been suggested that the nocturnal pathophysiologic mechanisms activated in OSA patients might lead to cardiovascular diseases (Fig. 1). This review will provide insights into mechanisms that might link OSA to cardiovascular diseases, and outline evidence of the association between OSA and cardiovascular conditions.
Pathophysiological mechanisms linking OSA with cardiovascular risk

OSA patients experience intermittent hypoxaemia and CO₂ retention that modify the autonomic and haemodynamic responses to sleep⁸. Although there is no consistent evidence of the causal role of OSA, the frequent nocturnal cardiovascular stressors experienced by these patients over the years might contribute to the development of chronic cardiovascular diseases. Acute hypoxaemia activates pathophysiological responses that might also lead to acute nocturnal cardiac events⁸–¹¹.

(i) Sympathetic activation and cardiovascular variability

In OSA patients, recurrent nocturnal apnoeas are followed by sympathetic activation. Interestingly, higher sympathetic drive persists during daytime wakefulness even in normoxic conditions⁹ (Fig. 2). Heightened muscle sympathetic activity to peripheral blood vessels in OSA patients appears to be independent of obesity¹². OSA patients also have faster heart rates during resting wakefulness, suggesting that there is also an increased cardiac sympathetic drive¹³.

(ii) Inflammation

Hypoxaemic stress may also play a role in the activation of systemic inflammatory pathways¹⁴. In fact, OSA patients (who also have a combination of repetitive episodes of hypoxaemia and sleep deprivation) have increased levels of plasma cytokines, adhesion molecules¹⁵,¹⁶, serum amyloid-A¹⁷, and C-reactive protein (CRP)¹⁶,¹⁸–²⁰. Increased CRP levels in OSA patients appear to be independent of adiposity²⁰.

Obstructive sleep apnoeic patients also have enhanced leukocyte activation²¹,²². In vitro experiments showed that monocytes from OSA patients bind more actively to endothelial cells than do monocytes from control subjects, and this can be attenuated by treatment with continuous positive airway pressure (CPAP)²¹.

Insights from cell culture studies also provide evidence that intermittent hypoxia may promote different reactions when compared with sustained hypoxia, and might help to explain the association between OSA and the development of cardiovascular diseases. Intermittent hypoxia followed by complete reoxygenation selectively activates the pro-inflammatory transcription factor NFkB, and increases circulating tumour necrosis factor

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Fig. 1. Schematic outlining proposed pathophysiologic components of OSA, activation of cardiovascular disease mechanisms, with consequent development of established cardiovascular disease. [Reprinted with permission from Wolters Kluwer Health (Circulation 2008; 118: 1080-111)].

Fig. 2. Recordings of sympathetic activity, respiration and intra-arterial blood pressure in a patient with sleep apnoea on no medications and free of other diseases. Measurements were obtained during wakefulness (top left), during obstructive sleep apnoea (OSA) in rapid eye movement (REM) sleep (bottom), and during REM sleep after treatment of OSA with continuous positive airway pressure (CPAP). During wakefulness, sympathetic activity was high and blood pressure was approximately 130/60 mmHg. During REM sleep, repetitive apnoea resulted in hypoxia and chemoreflex stimulation with consequent sympathetic activation. The vasoconstriction resulting from sympathetic activation causes marked surges in blood pressure to levels as high as 250/110 mmHg at the end of apnoea, because of increases in cardiac output at termination of apnoea. Treatment of sleep apnoea and elimination of apnoeic episodes by CPAP resulted in stabilization and lower levels of both blood pressure and sympathetic activity during REM sleep. [Reprinted with permission from The American Society for Clinical Investigation (J Clin Invest 1995; 96: 1897-904)].
(TNF)-alpha in OSA patients. These effects can be reduced by the use of CPAP therapy\textsuperscript{23}.

\textbf{(iii) Endothelial dysfunction}

Increased oxidative stress and systemic inflammation together with reduced nitric oxide (NO) availability and cell apoptosis might contribute to the endothelial dysfunction observed in patients with OSA\textsuperscript{24,25}. Although there are conflicting results regarding the presence of endothelial dysfunction in OSA patients\textsuperscript{26-28}, recent data showed reduced endothelial nitric oxide synthase (eNOS) and phosphorylated e-NOS (P-eNOS) expression in OSA, suggestive of endothelial dysfunction\textsuperscript{29}. These changes are reversed after 4 wk of CPAP therapy. Moreover, this study showed an inverse relationship between eNOS and P-eNOS in venous endothelial cells and OSA severity\textsuperscript{29}. Oxygen tension might play an important role in NO production\textsuperscript{30}; in fact, it has been proposed that conduit vessel endothelial dysfunction in OSA patients is proportional to the nocturnal hypoxaemia\textsuperscript{31}.

Experimental data suggest that hypoxaemia induces endothelin-1 release in cultured human endothelium\textsuperscript{32}. Phillips and colleagues\textsuperscript{33} have shown that several hours of untreated severe sleep apnoea results in increased endothelin-1 levels, which correlated with the changes in blood pressure. Recent data support a role for endothelin-1 in raising blood pressure in OSA patients\textsuperscript{34}.

\textbf{(iv) Intra-thoracic pressure changes}

In patients with OSA, the abrupt and repetitive inspiratory effort against a closed upper airway during the apnoeic episodes generate changes in negative intra-thoracic pressure that increase transmural gradients across the atria, ventricles and aorta\textsuperscript{35,36} and may disrupt ventricular function\textsuperscript{37}, leading to autonomic and haemodynamic instability\textsuperscript{37}. Moderate to severe OSA is associated with impaired right and left ventricular function, increased left atrial volume, wall stress, and afterload\textsuperscript{38,39}, and impaired diastolic function\textsuperscript{38,40}. These cardiac changes may contribute to the development of atrial fibrillation and heart failure in OSA patients. Furthermore, Sampol and colleagues\textsuperscript{41} suggest that the increased aortic transmural pressure may impose an additional risk of aortic dissection in OSA patients.

\textbf{The Association between OSA and cardiovascular diseases}

\textbf{Myocardial ischaemia}

Experimental data have shown that chronic intermittent hypoxia induces atherosclerosis in the presence of a high cholesterol diet\textsuperscript{42}. Indeed OSA patients who were free of co-morbidities presented early signs of atherosclerosis\textsuperscript{43}. In a more recent study, Turmel et al\textsuperscript{44} showed a strong correlation between AHI and atherosclerotic plaque volume measured by intravascular ultrasound imaging. Chronic effects of OSA that might contribute to atherogenesis include systemic inflammation, oxidative stress, vascular smooth cell activation, lymphocyte activation, increased lipid lowering in macrophages, lipid peroxidation, high-density lipoprotein dysfunction, and endothelial dysfunction\textsuperscript{45}.

On the other hand acute effects of OSA that could potentially be a trigger for plaque rupture with consequent cardiac ischaemia include severe intermittent hypoxaemia, acidosis, increased blood pressure and sympathetic vasoconstriction, in conjunction with simultaneous changes in intra-thoracic and cardiac transmural pressures\textsuperscript{6}. Nocturnal angina and ST depression have been described in OSA patients, and may be diminished after treatment with CPAP\textsuperscript{46,47}. However, a later study\textsuperscript{48} did not find evidence of nocturnal myocardial injury detectable by measurements of cardiac troponin T in patients with established coronary artery disease and moderate/severe OSA, before and after a single night’s sleep.

Recent evidence shows that patients with OSA have an altered diurnal variation in the occurrence of myocardial infarction (MI). In the general population, the greatest likelihood of onset of MI is between 06:00 and 11:00 h. In striking contrast, almost half of patients with OSA had their onset of MI during the sleep hours, between 22:00 and 06:00 h (10:00 PM to 6:00 AM) (Fig. 3)\textsuperscript{11}. This observation suggests that OSA may

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Day-night pattern of MI based on three eight-hour time intervals in OSA (64) and non-OSA (28) patients. [Reprinted with permission from Elsevier (\textit{J Am Coll Cardiol} 2008; 52 : 343-6)].}
\end{figure}
precipitate nocturnal MI and that nocturnal MI may contribute to the increased likelihood of nocturnal sudden cardiac death observed in OSA patients.

Treatment of OSA was associated with a decrease in the occurrence of new cardiovascular events in patients with combined OSA and coronary artery disease. Doherty et al. observed that total cardiovascular deaths were less common in CPAP-treated patients compared to CPAP intolerant patients.

Even though there is evidence of an association between sleep apnoea and coronary artery disease, there is still no proof of causality.

Heart failure

There is a high likelihood of OSA in patients with systolic heart failure and diastolic dysfunction. About 10 per cent of systolic heart failure patients are thought to have OSA. The association between these two conditions is reinforced by the observation that both systolic and diastolic functions improve with adequate treatment of the sleep disorder of breathing. While CPAP therapy seems to improve ejection fraction, there is as yet no evidence that treating OSA can reduce mortality in heart failure patients.

Obstructive events, which may occur hundreds of times over the course of the night, and induce abrupt increases in left ventricle transmural pressure, could play an important role in the development of myocardial ischaemia, contractile dysfunction, and ventricular dilation. The sympathetic surges and blood pressure increases may also be expected to worsen heart failure in patients with co-existent OSA.

Heart failure may directly exacerbate OSA by oedema formation in the soft tissues of the neck. Reduction in the intravascular volume and attenuated venous congestion resulting from heart failure treatment could potentially reduce OSA severity.

Systemic hypertension

There is evidence that OSA and hypertension are causally related, with OSA often undiagnosed. An apnoea-hypopnoea index of 15 events/h or more was independently associated with a 3-fold increased risk of developing hypertension in the Wisconsin cohort study. OSA patients tend to lack the sleep related nocturnal decrease in blood pressure (non-dippers). The attenuation of nocturnal blood pressure reduction is an independent risk factor for cardiovascular morbidity.

Intermittent hypoxaemia, chemoreceptor stimulation, sympathetic activation, and the renin-angiotensin system are possible mechanisms by which OSA might lead to hypertension.

Sleep disordered breathing and endothelial dysfunction are more likely to occur in patients with pre-eclamptic toxaemia. The concept that pregnancy may exacerbate sleep apnea is supported by evidence that the severity of sleep apnoea and the associated blood pressure responses as measured in the third trimester, improve significantly (P=0.03) after parturition.

Treatment of OSA may help decrease daytime blood pressure, especially in patients with resistant hypertension (defined as a clinic BP of > 140/90 mmHg while taking a combination of three or more antihypertensive drugs, titrated to maximally recommended doses) and in patients with relatively mild hypertension.

Pulmonary hypertension

The prevalence of pulmonary hypertension (PH) in OSA patients ranges from 17 to 53 per cent. The reason for this wide range may be due to methodological problems, such as selection bias. Even though OSA patients experience frequent episodes of increased pulmonary artery pressure during sleep, the pulmonary hypertension is generally milder than in primary PH. Patients with OSA in conjunction with PH tend to have higher BMI, left heart disease, parenchymal lung disease, and greater nocturnal oxygen desaturations. Hypoxic vasoconstriction with consequent vascular remodeling is thought to be the likely primary mechanism for any OSA-related pulmonary arterial hypertension.

Pulmonary arterial pressure and pulmonary vascular reactivity to hypoxia is reduced with continuous positive airway pressure (CPAP) therapy.

Stroke

Stroke has been linked to OSA in both cross-sectional and case-controlled studies, and sleep apnoea is highly prevalent in patients with stroke. Patients at risk for OSA and at risk for stroke share common demographic features.

The fluctuations in blood pressure, reduction in cerebral blood flow, altered cerebral autoregulation, endothelial dysfunction, accelerated atherogenesis, and pro-thrombotic and pro-inflammatory states are some of the mechanisms that have been implicated in increased risk of stroke in OSA patients.
OSA in post-stroke patients may be associated with reduced motivation, cognitive impairment, increased risk of recurrent stroke, and death. A significant relation is also evident between AHI and the degree of metabolic impairment in cerebral white matter. These alterations may be associated with neuropsychological and cognitive dysfunction in OSA patients.

The potential for rehabilitation post-stroke may be improved with positive airway pressure treatment among stroke patients. CPAP treatment in acute stroke can be started in about 50 per cent of patients with sleep-disordered breathing but can be chronically maintained in only a minority of patients. On the other hand, the percentage of continued CPAP usage among stroke patients with OSA was higher in another study. It is still unclear whether OSA by itself, independent of other factors, is a significant cause of stroke.

**Arrhythmias**

OSA is associated with different types of cardiac arrhythmias. Their prevalence and complexity increase with the severity of the OSA and the associated hypoxaemia.

Bradyarrhythmias are sometimes seen in OSA, in conjunction with obstructive apnoeas. Vagally mediated sinus bradycardia occurs as a physiological response to apnoea and hypoxaemia. Various forms of nodal heart block are common and may occur even in the absence of any disease of the cardiac conduction system. Treatment of underlying OSA usually eliminates these arrhythmias.

Atrial fibrillation is also common in people with OSA. The mechanisms that predispose to the development of atrial fibrillation in OSA patients are hypoxaemia, sympathetic activation, blood pressure surges, transmural pressure changes and systemic inflammation. Gami et al. showed an increased risk of incident atrial fibrillation in younger patients with OSA. Kanagala et al. in a prospective study, observed that patients cardioverted for atrial fibrillation in the setting of untreated OSA had a high likelihood of recurrence of the atrial fibrillation compared to OSA patients treated with CPAP.

Ventricular arrhythmias varying from benign premature ventricular contractions (seen in up to two-thirds of patients with OSA) to fatal ventricular tachycardia have been reported in patients with OSA. A significant link between sleep apnoea and nocturnal ventricular ectopy was evident in the Sleep Heart Health Study. Nocturnal arrhythmias in OSA patients are often attenuated by effective treatment of the disordered breathing.

**Management of OSA patients**

**Continuous positive airway pressure (CPAP)**

CPAP consists of an air-pressure source that keeps a constant positive pressure in the airway through the respiratory cycle. The airflow is delivered through a nasal or oronasal interface, and maintains patency of the upper airway. The optimal pressure level is determined during a sleep study and is intended to eliminate the respiratory events in all sleep stages and all sleeping positions. CPAP continues to be the primary therapy for patients with OSA. Besides improvement in daytime sleepiness, and neurocognitive function, there is also evidence that therapy might reduce cardiovascular risk in OSA patients. Reduction in sympathetic activity, blood pressure and arterial stiffness and improvement in baroreflex sensitivity and endothelial dysfunction are some of the proposed mechanisms by which CPAP therapy might reduce cardiovascular risk.

Bi-level positive airway pressure (BiPAP) is also an option that maintains a constant positive pressure in the airway, but provides two pressure levels, with a lower expiratory pressure, which reduces work of breathing and might increase acceptance and compliance. This might be a better choice in patients with OSA associated with chronic obstructive pulmonary disease.

**Positional therapy**

This refers to the use of sleep posture that might have a positive impact on breathing pattern during sleep. Since apnoea is often worse in the supine posture, avoidance of this posture during sleep can be achieved through a variety of means including body belts, an uncomfortable object sewn into the back of the nightshirt, positional alarms and specially designed pillows. Cervical extension might be helpful since this position is associated with an increase in upper airway cross-sectional size and reduced airway resistance.

**Oral appliances**

Mandibular advancement devices (MADs) are the most common oral appliance used for treatment of OSA. These devices increase the antero-posterior dimensions of the oropharynx through mechanical advancement of the mandible. While some studies have shown reduced AHI and snoring, improvement in sleep architecture,
oxidative stress and endothelial dysfunction\textsuperscript{114}, there is
as yet no evidence of reduced cardiovascular risk after
treatment with oral appliances\textsuperscript{115}. However, MADs
could be considered when patients cannot tolerate, or
are not complaint with CPAP therapy.

\textbf{Weight loss}

Obesity plays a major role in the pathogenesis of sleep apnoea and probably also in the associated cardiovascular risk\textsuperscript{116}. A prospective cohort study of mildly overweight individuals showed that a 10 per cent weight loss predicted a 26 per cent decrease in sleep apnoea severity\textsuperscript{4}. The exact mechanism of improvement is not completely understood, but might be related to improvement in airway structure, neurophysiologic regulation of respiration, and chemoreflex function\textsuperscript{117}.

\textbf{Surgery}

The goal of surgical treatment in OSA patients is to increase airway size and reduce airway resistance\textsuperscript{118}. Uvulopalatopharyngoplasty (UPPP) is the most common surgery for OSA, and is used to enlarge the retropalatal airway. The procedure is complex, and involves some amount of risk and discomfort, and long term efficacy needs to be better understood. Tracheostomy can be considered in patients with life-threatening OSA who fail or do not accept non-surgical treatment\textsuperscript{119}. There is a lack of studies comparing the efficacy of CPAP versus surgery in cardiovascular risk reduction.

\textbf{Conclusion}

There is a high and rising prevalence of OSA due to the rising incidence of obesity. Therefore, the presence of OSA should be considered in clinical practice, especially in obese patients with co-morbid cardiovascular disease. Whether treating OSA will reduce cardiovascular risk and improve outcomes is still controversial. Therefore randomized controlled trials are needed to assess the efficacy of OSA treatment in reducing cardiovascular morbidity and mortality.

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\textbf{References}


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