Review Article

Obstructive Sleep Apnoea and Cardiovascular Disease

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Abstract

Obstructive sleep apnea (OSA) is a common disorder associated with an increased risk of cardiovascular disease and stroke. As it is strongly associated with known cardiovascular risk factors, including obesity, insulin resistance, and dyslipidemia, OSA is an independent risk factor for hypertension and has also been implicated in the pathogenesis of congestive cardiac failure, pulmonary hypertension, arrhythmias, and atherosclerosis. Inflammation and oxidative stress has been recently proposed in the pathophysiology of cardiovascular disease related to sleep apnea.The current standard treatment for OSA-nasal continuous positive airway pressure (CPAP)-eliminates apnea and the ensuing acute hemodynamic changes during sleep. Long-term CPAP treatment studies have shown a reduction in nocturnal cardiac ischemic episodes and improvements in daytime blood pressure levels and left ventricular function. Despite the availability of effective therapy, OSA remains an under diagnosed and undertreated condition. A lack of physician awareness is one of the primary reasons for this deficit in diagnosis and treatment.

Key words: Sleep apnea, Inflammation, CPAP.

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Cardiovascular Diseases and OSA

Hypertension

Moderate to severe OSA presenting with an apnoea-hypopnoea index (AHI >15/hr) (apnoeas and hypopnoeas per hour of sleep) affects 4% of women and 9% of men in their middle age[1]. The prevalence of hypertension in OSA patients may be as high as 50% and in hypertensive patients, OSA can be diagnosed in up to 30%. With moderate to severe OSA, hypertension was 2.89 times more likely to occur in a 5-years period. Treatment of OSA may help decrease daytime blood pressure (BP), 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.

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 ischemia, contractile dysfunction, and ventricular dilation (see fig.1). 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 edema 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.

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[2]. Even though OSA patients experience frequent episodes of increased pulmonary artery pressure during sleep, the pulmonary hypertension is generally milder than in primary PH[3]. 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[4].

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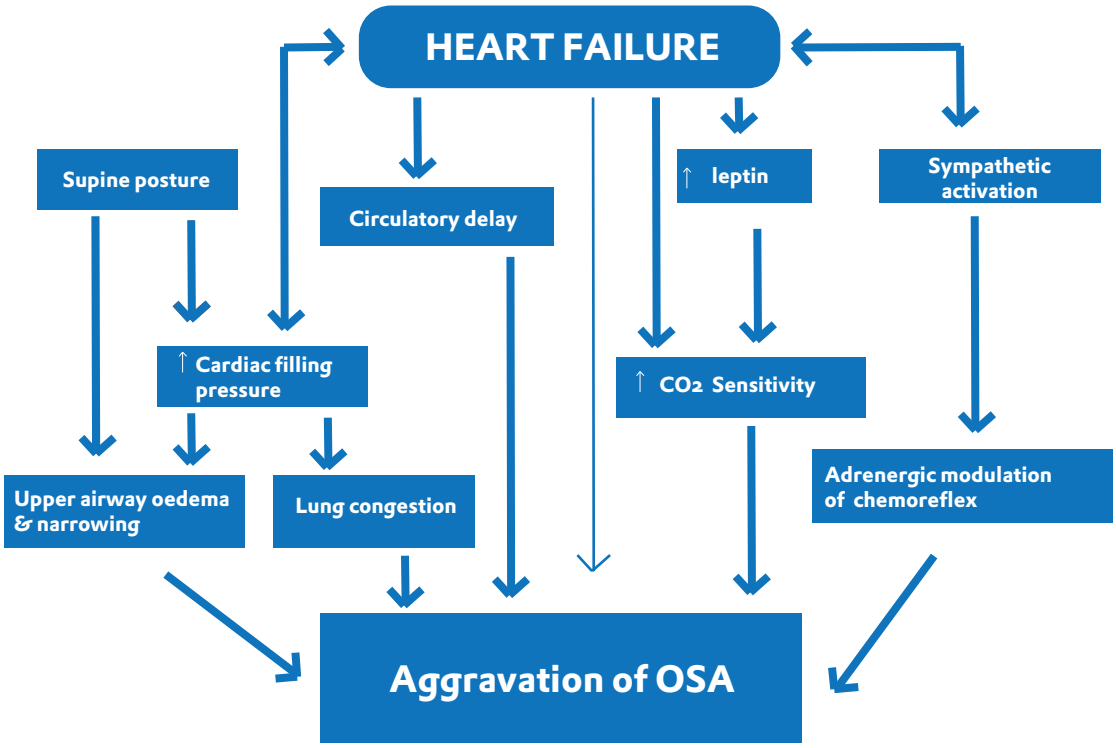

Fig 2. Schematic outlining possible mechanisms underlying development of OSA and the possible feedback from OSA resulting in exacerbation of heart failure.

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 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 hypoxemia. Brady arrhythmias are sometimes seen in OSA, in conjunction with obstructive apnoeas. Vagally mediated sinus bradycardia occurs as a physiological response to apnoea and hypoxemia. 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. CPAP ventilation has been shown to reduce the incidence of atrial fibrillation. 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. Nocturnal arrhythmias in OSA patients are often attenuated by effective treatment of the disordered breathing.

Molecular Basis

More recently[5], oxidative stress and consequently vascular inflammation resulting from the nocturnal hypoxia/reoxygenation cycles have been proposed to mediate the effects of sleep apnoea on the cardiovascular system.

Sleep apnoea patients have increased production of oxygen reactive species in granulocytes and monocytes. This leads to increased expression of adhesion molecules and proinflammatory cytokines, which results in increased avidity of monocytes and lymphocytes and increased cytotoxicity of lymphocytes against endothelial cells[5-6]. Circulating levels of several markers of inflammation like tumor necrosis factor alpha (TNF-alpha) and interleukin 6 (IL-6), chemokines such as IL-8, and C-reactive protein (CRP) have been implemented in the pathophysiology of sleep apnoea. The increased adhesion and cytotoxicity of sleep apnoea patients' monocytes and lymphocytes to endothelial cells in culture could be blocked by employing antibodies against selectins and tumor necrosis factor-, suggesting the active involvement of adhesion molecules and inflammatory cytokines in endothelial cell injury and dysfunction. Reports on increased plasma lipid peroxidation, C-reactive protein and serum amyloid-A, and decreased levels of plasma nitric oxide[7-10] in sleep apnoea, confirmed the existence of increased oxidative stress, vascular inflammation, and endothelial cell injury, all implicated in atherogenic sequelae. These observations are complemented by the demonstration that

cardiovascular disease-free sleep apnea patients display endothelial dysfunction as determined by assessment of endothelium-dependent vasodilation[11]. Endothelial dysfunction is considered to be the earliest manifestation of atherosclerosis and to predict cardiovascular events[12]. Finally, sleep apnea has been shown to be associated with classical markers of atherosclerosis such as increased carotid wall thickness[13] and the prevalence of calcified carotid artery atheromas[14].

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