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Advances in the Study of the Inflammatory Association Between Obstructive Sleep Apnea and Coronary Heart Disease

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Abstract: This study examines the inflammatory association between obstructive sleep apnea (OSA) and coronary artery disease (CAD), highlighting the central role of the inflammatory response. Apnea and hypoxemia during sleep in patients with OSA activate inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, promoting vascular endothelial damage and plaque formation. Metabolic dysfunction induced by intermittent hypoxia, particularly insulin resistance and abnormal lipid metabolism, enhances the development of coronary atherosclerosis. Furthermore, OSA-induced sympathetic hyperactivation elevates the blood pressure and accelerates the heart rate, further exacerbating the risk of CAD. Therefore, controlling the inflammatory response in patients with OSA is essential for alleviating the risk of coronary heart disease.

Keywords: Obstructive Sleep Apnea; Coronary artery disease; Inflammatory response

1. Introduction

Obstructive sleep apnea (OSA) is a prevalent disorder characterized by recurrent upper airway collapse during sleep. Polysomnography, which measures the severity of the condition by recording the apnea–hypnea index (AHI), is the gold standard for diagnosing OSA. This condition can be categorized into three grades based on the AHI values: mild (5 episodes/h ≤ AHI < 15 beats/h), moderate (15 beats/h ≤ AHI ≤ 30 beats/h), and severe (AHI > 30 beats/h) [1]. According to current medical research findings, OSA is an independent risk factor for cardiovascular diseases such as coronary heart disease. The link between OSA and coronary heart disease involves a complex inflammatory mechanism. Repeated apnea experienced by patients with OSA during sleep leads to intermittent hypoxia, fragmentation of sleep structures, and hyperactivation of the sympathetic nervous system. These factors are critical links in the pathogenesis of coronary artery disease (CAD), thus revealing the close association between OSA and CAD. Therefore, timely diagnosis and treatment of OSA are pertinent to alleviate the risk of cardiovascular disease.

2. OSA and the inflammatory response

Respiratory interruptions caused by OSA reduces oxygen intake and carbon dioxide excretion, leading to intermittent hypercapnia and hypoxia. OSA-induced chronic intermittent hypoxia (CIH) can contribute to the progression of OSA by activating various inflammatory pathways. Inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-33, IL-17, IL-10, IL-1β, IL-6, and IL-8, etc., are involved in the inflammatory process of OSA[2–4]. Studies have confirmed that the levels of IL-17, IL-1β, IL-6, and IL-8 are increased in patients with OSA and that they interact with each other. For example, IL-33 stimulates the production of TNF-α, IL-1 and IL-6, IL-5, and IL-13, and these associations collectively form an action network that influences the disease process in OSA[5, 6]. Moreover, inflammatory markers such as IL-6 and C-reactive protein (CRP) were significantly higher in patients with OSA combined with CAD, confirming the involvement of chronic inflammation in the pathologic process of progression to combined CAD in patients with OSA.

3. Coronary heart disease and the inflammatory response

Inflammation is a critical driver of all stages of atherothrombosis. Initially, lipids—predominantly low-density lipoprotein (LDL) choles-

terol particles—penetrate the subendothelial layer of the arterial wall. Subsequently, LDL cholesterol is oxidized, triggering an inflammatory response. Moreover, adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1, are upregulated. This upregulation facilitates the binding, rolling, and infiltration of inflammatory cells, including monocytes and T cells, to the sites of early plaque initiation[7]. Infiltrating monocytes differentiate into resident macrophages within the subendothelial space, where they phagocytose oxidized LDL particles and transform into foam cells, thereby exacerbating the inflammatory response. Over time, numerous foam cells aggregate to form a lipid core.

Thickening of the subendothelium results in the formation of a fibrous cap of varying thickness that covers the surface of the lipid core. Inflammation influences the formation and stability of collagen within the fibrous cap, thereby determining the structural stability of atherosclerotic plaques[8]. Cytokines released by foam cells, T cells, and other cellular components promote the migration of vascular smooth muscle cells into the intima, producing interstitial collagen, which constitutes the extracellular matrix surrounding the lipid core. Concurrently, the vasa vasorum in the adventitial layer facilitates the formation of new blood vessels within the plaque by extending through the media into the growing plaque. In addition, a distinct inflammatory response occurs in the fibrous cap, where metalloproteinases—enzymes that degrade the fibrous cap—preferentially accumulate at the shoulder of the plaque. This accumulation compromises the integrity of the protective fibrous cap surrounding the lipid core and further increases plaque instability. This aggravates the risk of rupture and thrombosis, ultimately resulting in myocardial ischemia and acute coronary syndrome[9].

In summary, atherosclerosis is a chronic inflammatory response, with inflammatory factors being the key indicators. These factors are not only directly involved in the occurrence of atherosclerotic plaque rupture but also closely related to the occurrence and development of coronary heart disease.

4. Mechanisms of Inflammatory Response Between OSA and Coronary Heart Disease

4.1 Mechanisms of endothelial dysfunction

The link between OSA and coronary heart disease is largely mediated through inflammatory responses and oxidative stress. The intermittent hypoxia and sleep fragmentation experienced by patients with OSA increase oxidative stress. Oxidative stress disrupts the balance between the body's antioxidant defense system and free radical production, resulting in an excessive accumulation of free radicals and exert toxic effects on the cells. This toxic effect damages important intracellular components, including lipids, proteins, carbohydrates, and nucleic acids, thereby altering the normal physiologic function of the cells. Endothelial dysfunction induces an inflammatory response in the vascular wall that involves the activation of leukocytes and releases a range of pro-inflammatory cytokines, such as TNF-α, IL-6, and CRP. These inflammatory factors are involved in the systemic inflammatory responses and may damage coronary artery endothelial cells, thereby contributing to atherosclerosis formation and progression. For example, in a rat model, OSA has been shown to contribute to atherosclerosis formation by increasing the circulating levels of endothelin-1 (ET-1) and expressing vascular wall intercellular adhesion molecule-1 (ICAM-1) to a degree comparable to that of diabetes mellitus and hyperlipidemia, with increasing severity of OSA[10]. In addition, intermittent hypoxia can directly damage endothelial cells to initiate the NF-κB inflammatory pathway, the activation of which can also activate neutrophils via intermittent hypoxia before further acting on vascular endothelial cells[11].

4.2 Mechanisms of sympathetic nervous system hyperactivation

OSA causes recurrent apnea and hypoxemia, triggering increased sympathetic activity. When the airway is obstructed, oxygen concentration in the body decreases, and carbon dioxide concentration increases, which in turn stimulates the central nervous system and prompts sympathetic arousal. Sustained high sympathetic activity leads to cardiac remodeling, promotes atherosclerosis, and increases the risk of myocardial ischemia and arrhythmia. Furthermore, sympathetic nerves stimulate inflammatory cells, such as macrophages and lymphocytes, by releasing mediators such as norepinephrine. These mediators promote the production of proinflammatory factors (TNF-α and IL-6). The increase in proinflammatory factors, in turn, aggravates endothelial cell dysfunction and augments endothelial adhesion to monocytes and lymphocytes. This adhesion causes leukocytes to migrate to the vessel wall and transform into foam cells. These are a key cell type in atherosclerotic plaque formation, and their accumulation leads to lipid deposition and production of atherosclerotic plaques. Moreover, proinflammatory factors protect plaques by regulating the proliferation and migration of smooth muscle cells, contributing to the enhanced synthesis of extracellular matrix and the formation of a fibrous cap. Nonetheless, under a sustained inflammatory environment, the stability of plaques decreases and makes them more prone to rupture, exacerbating the development of atherosclerosis. In addition, the activation of sympathetic nerves induces oxidative stress, exacerbating the inflammatory response and creating a vicious circle.

A large body of data supports the idea that CIH alters sympathetic excitation and the vascular system. For instance, in rodent models of intermittent hypoxia, the density of noradrenergic endings increases in the medulla oblongata and pontine regions[12]. These changes augment

sympathetic activation and adrenal catecholamine release in response to hypoxia by modifying the neural substrates. Furthermore, CIH may activate microglia directly or indirectly via peripheral proinflammatory cytokines.

OSA is often accompanied by metabolic syndromes such as obesity, hypertension, and diabetes mellitus, which strengthens the link between OSA and coronary heart disease via the action of sympathetic nerves. Enhanced sympathetic nerve activity can affect insulin resistance and worsen poor glycemic control, which not only affects the body's glucose utilization but also increases dyslipidemia, promoting the development of atherosclerosis.

4.3 Mechanisms of metabolic abnormalities

Metabolic function plays a critical role in the association between OSA and CAD. This relationship is primarily manifested via insulin resistance and abnormal blood lipid metabolism. In patients with OSA, increases in inflammatory factors, coupled with the effects of hypoxia, reduce cell sensitivity to insulin. This process involves multiple signaling pathways, including alterations in pathways such as PI3K/Akt and AMPK. This alteration is supported by animal experiments demonstrating that CIH exacerbates fasting hyperglycemia, glucose tolerance abnormalities, and insulin resistance in mice with diet-induced obesity and genetic obesity [13]. Moreover, human experiments have supported the adverse effects of hypoxia. Insulin resistance and impaired β-cell function were observed in a study of healthy volunteers exposed to intermittent hypoxia[14].

In terms of lipid metabolism, abnormal function of high-density lipoproteins (HDL) in patients with OSA creates favorable conditions for the development of CAD. The composition of HDL changes during the acute phase, resulting in the loss of several of its anti-atherosclerotic properties, and may even become pro-oxidant and proinflammatory [15]. Even outside the acute phase, HDL may remain pro-inflammatory [16]. In addition, the inflammatory response triggered by OSA promotes inflammation in the adipose tissue and enhances fatty acid release, further exacerbating abnormal lipid metabolism.

4.4 Mechanisms of macrophage polarization

Macrophages are key cells in the immune system, and they can polarize into two main phenotypes based on signals from the microenvironment: type M1 (proinflammatory) and type M2 (anti-inflammatory)[17]. In patients with OSA, oxidative stress increases owing to the cyclical occurrence of intermittent hypoxia and reoxygenation. This state causes macrophage polarization toward the M1 type, which secretes large amounts of proinflammatory cytokines such as TNF-α and IL-6, directly damaging the vascular endothelium and promoting the development of atherosclerosis[18]. In addition, M1-type macrophages promote the recruitment and activation of inflammatory cells, exacerbating the inflammatory response and tissue damage[19]. In contrast, M2-type macrophages play an essential role in homeostasis and repair processes by secreting anti-inflammatory cytokines, such as IL-10 and TGF-β, which help attenuate the inflammatory response and promote tissue repair and vascular stability[20]. In the early stages of atherosclerosis, M2-type macrophages may aid in eliminating lipids and cellular debris and prevent plaque formation. Nevertheless, in advanced stages of atherosclerosis, M2-type macrophages may adversely affect disease progression by promoting neovascularization and increasing plaque instability[21]. Thus, the polarization status of macrophages is critical in the immunoinflammatory association of OSA with coronary heart disease. By regulating the direction of macrophage polarization, it may provide new strategies for treating OSA-associated coronary heart disease[22].

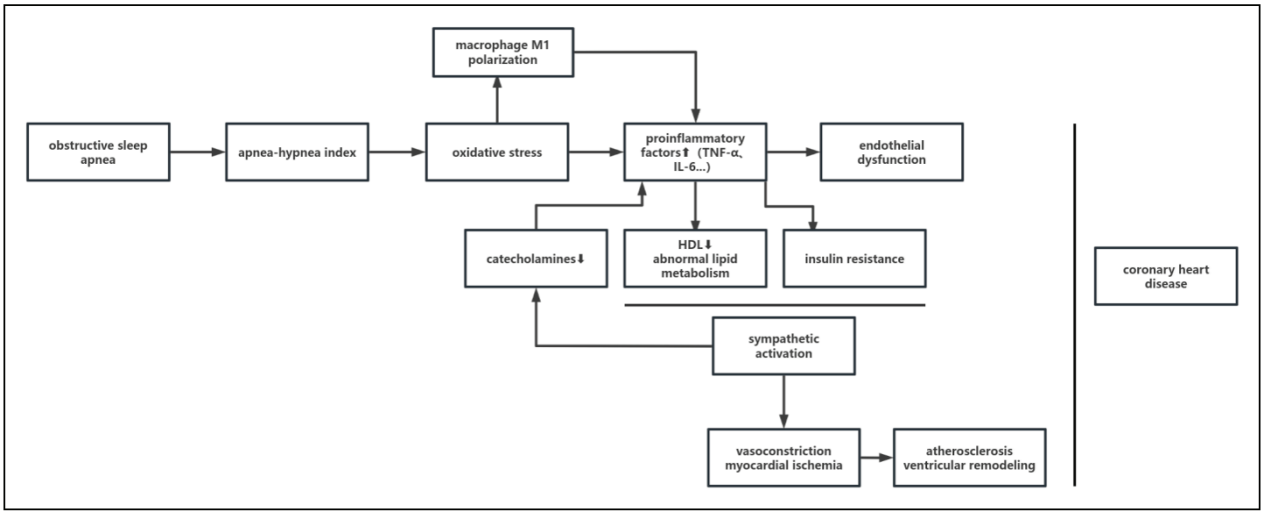

Figure 1. The potential mechanism of inflammatory response between OSA and Coronary Heart Disease

In conclusion, OSA is strongly associated with the development of coronary heart disease by triggering intermittent hypoxia and inflammatory cell activation. The hypoxemia and intermittent hypoxia caused by OSA damage the vascular endothelium, activate the inflammatory pathways, and induce insulin resistance and dyslipidemia, particularly reducing the protective effect of HDL.

5. Conclusions

OSA enhances sympathetic nerve activity, causing an increase in blood pressure and heart rate, further exacerbating the risk of coronary heart disease. CPAP ventilation for OSA decreases the incidence of coronary heart disease. However, its long-term effects on reducing cardiovascular and cerebrovascular events require further investigations. Early identification and intervention of OSA is important for preventing coronary heart disease.

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