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REVIEW

Chronic Intermittent Hypoxia and Hypertension: A Review of Systemic Inflammation and Chinese Medicine*

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ABSTRACT Obstructive sleep apnea syndrome (OSAS) and hypertension commonly coexist. Clinical studies indicate that OSAS plays a key role in increasing the risk of prevalent hypertension. Chronic intermittent hypoxia (CIH) is the core pathological mechanism of OSAS, and has a close relationship with systemic inflammation. Growing evidence shows that CIH and hypertension are strongly related, involving markers or pathways indicative of systemic inflammation, such as high-sensitivity C-reactive protein (hs-CRP), interleukin-6, nuclear factor-kappa B, tumor necrosis factor-α, interleukin-8 and p38 mitogen-activated protein kinase (MAPK)-dependent pathways. Oxidative stress also plays an important role in this process, including in the activation of polymorphonuclear neutrophils. However, the pathophysiological and clinical significance of systemic inflammation in CIH and hypertension is not proven. This review article highlights the relationship between CIH and hypertension through systemic inflammation and the current interventions available in Chinese medicine, to offer a background for the future treatment of OSAS-related hypertension with integrative medicine.

KEYWORDS chronic intermittent hypoxia, obstructive sleep apnea syndrome, hypertension, systemic inflammation, Chinese medicine

Obstructive sleep apnea syndrome (OSAS) is a common disease, affecting about 2%–4% of the general population and characterized by repetitive upper airway collapse, frequent arousals and sleep disruption.[1] Data convincingly show a high correlation between OSAS and cardiovascular disorders such as hypertension, coronary artery disease, arrhythmia and stroke.[2] Great strides have been made in establishing OSAS as an independent risk factor for hypertension.[3] The high correlation between OSAS and hypertension was first discovered in the 1970s; scholars reported an improvement in blood pressure (BP) after surgical intervention for a variety of sleep disorder-related breathing problems.[4-6] In the past several decades, a number of studies have found a relationship between OSAS and hypertension. Additionally, hypertension has been observed in 40% of OSAS patients. Meanwhile, OSAS is found in 30%–40% of patients with hypertension. These results indicate that OSAS and hypertension are intimately related.[7] However, the mechanism of OSAS-related hypertension remains unclear. Because of upper airway obstruction, disordered breathing events lead to the intermittent occurrence of hypoxia throughout the sleep period. This phenomenon is called chronic intermittent hypoxia (CIH).[8] CIH is different from continuous hypoxia. The former is distinguished by periods of low oxygen between periods of normal oxygen. However, both of them independently lead to inflammation. While the underlying mechanisms of OSAS-related hypertension are poorly understood, systemic inflammation may play a key role in the process.

Indeed, the circulating levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-8 are elevated in patients with OSAS,[9-12] suggesting that CIH may be pivotal in systemic inflammation. Inflammation has been receiving a fair amount of attention as the etiology for the initiation and progression of hypertension. In brief, endothelial dysfunction develops at an early stage in response to the afore-mentioned inflammatory cytokines. This process leads to the up-regulation

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of intercellular adhesion molecules, which promote leukocyte adherence to and extravasation into the endothelium.[13] This is a potential mechanism leading to hypertension.

Few studies have evaluated the potential interactions among OSAS, hypertension and systemic inflammation in the development of these disorders. The objectives of this paper are, first, to review the correlation between systemic inflammation caused by CIH and the pathogenesis of hypertension, including biochemical/molecular mechanisms; and second, to review the progress of interventions with Chinese medicine in treating OSAS-hypertension. CM interventions could provide a useful alternative treatment to prevent cardiovascular complications after hypertension.

CIH and Inflammatory Activation Pathways

CIH and Nuclear Factor-Kappa B

Recent studies exploring the relationship between hypertension and OSAS have focused on the role of the transcription factor nuclear factor-kappa B (NF-κB). Many studies have revealed the complex regulation by NF-κB of genes involved in cell growth, survival, and division, as well as in apoptosis, stress, hypoxia, and the immune system.[14-16] CIH increases the expression of NF-κB, which then up-regulates the expression of inflammatory factors, including chemokines, adhesion molecules, cytokines, nitric oxide synthase, tissue factor and blood coagulation factor Ⅷ.[17] Ryan, et al[18] found higher NF-κB expression in intermittent hypoxia (IH) mice, in accordance with recent studies showing NF-κB activation in cardiovascular tissue from hypoxic mice[17] and in cells cultured under IH.[19] IH-induced NF-kB activation could underlie the inflammatory alterations in OSAS patients.

IH-induced activation of NF-κB could also improve the survival rate of polymorphonuclear neutrophils (PMNs).[20] The long-term presence of a growing number of PMNs may lead to hypertension by causing endothelial dysfunction. After apoptosis, PMNs are unresponsive to inflammatory stimuli. Simultaneously, apoptosis improves the clearance of PMNs from the blood.[21,22] Apoptosis is thus considered a fundamental mechanism for halting inflammation.

NF-κB can provide a strong anti-apoptotic signal in PMNs.[23] The up-regulation of NF-κB under CIH, which suppresses PMN apoptosis, was confirmed by using the NF-κB inhibitors-gliotoxin[24] and parthenolid.[25,26] Interestingly, parthenolid has been shown to increase apoptosis only in PMNs exposed to CIH and it did not affect the apoptosis of PMNs under normoxia.[27] NF-κB is clearly implicated in the survival of PMNs under CIH conditions.

Expression of the downstream survival gene-IL-8, induced by NF-κB, may activate the inflammatory pathways.[20] CIH induces the activation of NF-κB p65, after which levels of Bcl-2 and IL-8 are elevated, and PMN apoptosis is suppressed. IL-8, one of the most important survival cytokines,[28,29] has been shown to increase PMN survival.[30,31] IL-8 transduces its signals through interactions with chemokine receptors (CXCR) 1 and 2.[32] The expression of CXCR2 is down-regulated during PMN apoptosis, and up-regulation of CXCR2 during activation protects PMNs from apoptosis.[30,33] CIH-induced expression of IL-8 thus parallels the up-regulation of CXCR2 expression and increased PMN survival.

CIH and p38 Mitogen-activated Protein Kinase

P38 mitogen-activated protein kinase (MAPK) belongs to a serine/threonine kinase family that is involved in a variety of cellular stress responses.[34] P38 MAPK was reported to increase the number of PMNs[35] and to improve PMN survival under continuous hypoxi.[36] Furthermore, a study by Dyugovskaya[37] found that the anti-PMN-apoptosis role of p38 MAPK signaling pathways is more significant under IH than under normoxia. The question arises whether p38 MAPK and NF-κB result in the same ongoing inflammatory response. Therefore, the possibility of p38 MAPK elevating the number of PMNs through interactions with NF-κB and TNF-α is discussed follow.

Further connecting p38 MAPK and NF-κB, p38 MAPK plays an important role in the IH-induced activation of NF-κB. The p38 MAPK inhibitor SB203580 increased apoptosis and decreased NF-κB expression, and using siRNA to degrade p38 MAPK can significantly attenuate the IH-induced activation of NF-κB.[38]

Furthermore, important interactions occur between p38 MAPK and TNF-α in the development

of inflammation. TNF-α-stimulated PMN survival is entirely IL-8-dependent,[29] but the expression of IL-8 requires p38 MAPK.[21] Exposure of PMNs to TNF-α results in phosphorylation of IκBα, which leads to the activation of NF-κB. It is widely accepted that two main TNF-α receptors are involved in PMN apoptosis: TNF receptor 1 (TNFR1) and TNFR2. Both independently mediate the activation of NF-κB, thereby promoting PMN survival.[39,40] Together, these results suggest that CIH, and therefore TNF-α, suppress PMN apoptosis.[41]

CIH and Oxidative Stress

Oxidative stress and inflammation have a close relationship; each appears capable of triggering the other. Under normal conditions, oxidizing agents and endogenous anti-oxidants maintain a balanced state. Once this homeostasis is disrupted, cell damage and inflammatory responses follow because of an increasingly oxidative environment.[42,43]

Is there an increased incidence of oxidative stress in CIH? Though scholars have demonstrated that inflammation can be activated by oxidative stress, the molecular events upstream of the oxidative stress biomarkers remain unknown. The only mechanism discovered so far is that reactive oxygen species (ROS) are produced by a protein enzyme called xanthine oxidase.[44] Studies have shown that CIH contributes to an increase in oxidative stress markers, providing strong reasons to explore the activation of oxidative stress combined with CIH in the pathophysiology of OSAS. Discussions of clinical trials, animal experiments and treatments affecting oxidative stress follow.

Currently, small-scale clinical studies have proved that systemic oxidative stress is enhanced in OSAS patients.[45-47] Oxidative stress biomarkers, such as advanced oxidation protein products, ferric reducing antioxidant power, superoxide radicals, serum nitrate and nitrite levels, are significantly different between OSAS patients and matched controls.[48] Serious OSAS patients even appear to have decreased resistance to oxidation.[46]

Sleep-disordered breathing is related to many other factors, such as obesity, awakening stimuli and sympathetic nervous system problems, all of which promote oxidative stress.[49] If CIH really plays a key role in the oxidative stress response, increases in oxidative stress markers would also be expected among animal models of hypoxia. Xu, et al[50] found increased levels of protein oxidation, lipid peroxidation and nucleic acid oxidation in hypoxic mouse brain cortex. Liu, et al and Nair, et al exposed mice to an IH environment, and observed a significant elevation in superoxide dehydrogenase activity and nicotinamide adenine dinucleotide phosphate oxidase.[51,52]

Many studies have shown that continuous positive airway pressure (CPAP) treatment, for either a long or a short time, can relieve oxidative stress;[53-55] the production of oxidative stress markers, including asymmetrical dimethylarginine, lipid peroxide, superoxide dismutase and thiobarbituric acid reactive substances,[56] is inhibited by this OSAS treatment. Del, et al[57] observed 138 OSAS patients and found that oxidative stress markers were reversed after CPAP treatment for 6 months. Together, these findings suggest an important inhibitory role of CPAP in oxidative stress caused by CIH.

Chinese Medicine Interventions: Clinical and Experimental Evidence

The Chinese medicines (CM) ligustrazine, rauwolfia and kudzu vine have been shown to reverse hypertension and improve related symptoms.[58] There is evidence of CM reversing endothelial injury. Repairing endothelial damage also has antihypertensive effects.[59] This has led to investigations designed to clarify whether CM interventions can protect endothelial function and reduce BP by blocking the activation of proinflammatory pathways. Is it possible for CM to make an impact on inflammatory processes? Could this propensity of inflammatory mediators to induce endothelial injury and hypertension be decreased by CM treatment? Some clinical trials found that the production and migration of inflammatory mediators, including NF-κB, TNF-α, high-sensitive (hs)-CRP and IL-6, are favorably modified by treatment with herbal preparations.[60,61]

NF-κB is a central activating factor of the inflammatory cascade. Thus, research has been undertaken to investigate whether CM antihypertensive agents reduce NF-κB levels. Zhang, et al[62] used different concentrations of astragalus polysaccharide (APS) to affect the lipopolysaccharide (LPS)-induced activation of NF-κB in human umbilical

venous endothelial cells. LPS-induced I-κ Ba mRNA degradation was significantly inhibited by APS, leading to inhibition of NF-κ B in a dose-dependent manner. Sun, et al[60] explored the effects of puerarin on NF-κ B expression in kidneys of spontaneously hypertensive rats (SHR) by dividing 24 SHR into three groups: control group, puerarin group and benazepril group. Results showed that NF-κ B was expressed by SHR, and NF-κ B expression decreased remarkably in the benazepril group and puerarin group compared with the control group. Puerarin significantly inhibited NF-κ B.

A common inflammatory marker, high-sensitivity hs-CRP, has been considered one of the risk factors for cardiovascular disease in recent years by the European hypertension guidelines.[63] A variety of CM preparations can reduce hs-CRP, including Xuezhikang Capsule,[61] Qingxuan Tiaoya Recipe (清眩调压方),[64] and calming Liver and restraining Yang formula.[65] These treatments showed favorable effects in depressing blood pressure and decreasing the hs-CRP levels in patients.

The level of hs-CRP has been reported to be increased significantly in cases of excess syndrome combined with deficiency syndrome compared with cases of deficiency syndrome.[66] The hs-CRP level was statistically higher in yin deficiency and overwhelming yang patients than in yin and yang deficiency or overwhelming liver fire patients.[67,68] Furthermore, a small-scale randomized clinical trial showed that Jiangya Capsule (降压胶囊, a CM preparations having the efficacy of calming Liver yang) could improve the blood pressure and control the increase in serum hs-CRP in hypertensive patients.[69]

As noted above, CM interventions reversed hypertension and inflammation, but the mechanism by which they act is unclear. However, an excess accumulation of blood stasis or a hyperactivity of yang and phlegm may indicate a higher risk of hypertension and other cardiovascular events.[70] Phlegm and stasis was positively correlated with IL-6 and hs-CRP levels.[71] These findings imply that CM solved the pathological factors and the corresponding inflammatory factors were also suppressed. Wang, et al[72] divided 60 hypertension patients into excessive accumulation of phlegm dampness type cases and non-excessive accumulation of phlegm dampness type cases. The former patients received Tanreqing Injection (痰热清注射液) plus telmisartan and the latter cases received telmisartan only. Six weeks later, compared with control patients, the levels of hs-CRP, TNF-α and IL-6 were significantly increased in hypertensive patients. After treatment, levels of the three inflammatory factors aforementioned were significantly reduced in the excessive accumulation of phlegm dampness group.

Overall, the data indicate that CM reduced BP and inhibited NF-κ B, TNF-α and IL-6. These findings imply that CM interventions are more effective than Western medicine in improving the inflammatory response in patients with hypertension. CM treatment against hypertension was also shown to improve the apnea hypopnea index (AHI) of OSAS patients.[73] Together, these results strengthen the need for early CM intervention in apneic individuals at risk for hypertension, and suggest new therapeutic options for these patients.

Conclusions and Perspectives

Despite the high correlation between OSAS and hypertension, little evidence is available regarding their pathophysiological and clinical outcomes. Most information involves cross-sectional analyses of selected clinical cohorts and there are no long-term follow-up studies. Future research into the relationship between CIH and hypertension needs to include matched control subjects, more consistent definitions and stricter criteria for outcomes. The finding that CIH-induced hypertension mainly involves systemic inflammation needs to be confirmed.

Although there is evidence in CIH and hypertension of overlapping mechanisms involving inflammation, oxidative stress and leukocyte dysfunction, there may be differences in the magnitude and consequences of these responses. Furthermore, the role of inflammatory markers in predicting hypertension in OSAS is unclear and lacks long-term prospective studies. If systemic inflammation is important in CIH and hypertension, studies in overlapping patients should provide insights regarding the nature and significance of these responses. These findings are clinically relevant because systemic inflammation may contribute to the pathogenesis of hypertension, and the molecular pathways involved are similar in OSAS. Studies of patients with OSAS and hypertension should provide insights into the mechanisms of systemic inflammation and help to

develop new therapies. Great strides have been made in establishing obstructive sleep apnea as a target for therapy in hypertensive patients. Additionally, CM interventions have shown some advantages in controlling OSAS-related hypertension. In the future, based on the relationship between CIH, inflammation and hypertension, further clinical and animal experimental studies of integrative medicine will be needed to offer high quality evidence for the prevention and control of OSAS-related hypertension.

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