Editorial Comment

Hypoxia-Induced Cardiac Remodeling in Sleep Apnea Syndrome: Involvement of the Renin-Angiotensin-Aldosterone System

Yoshikazu MIWA[1] and Toshiyuki SASAGURI[1]

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Sleep apnea syndrome (SAS) has become a focus of public attention as one of the major causes of traffic accidents by commercial vehicle drivers, since this disorder induces daytime somnolence. However, the harm caused by SAS is not limited to traffic accidents. SAS is often found in patients with hypertension (*1–3*) and is closely associated with cardiovascular diseases such as ischemic heart disease (*4*, *5*), pulmonary hypertension (*6*), cardiac arrhythmias (*7*), and stroke (*8*). Most cases of SAS consist of obstructive SAS (OSAS) caused by upper airway obstruction. OSAS is often induced by obesity, and thus is becoming a serious health problem in Japan as the Japanese lifestyle becomes increasingly westernized. Therefore, it will be important to investigate the mechanisms by which OSAS affects the heart and blood vessels in order to prevent cardiovascular diseases.

Recent studies have reported the occurrence of cardiac remodeling in OSAS patients. In one such study, the left ventricular (LV) mass index as determined by echocardiography was significantly higher in male patients with OSAS than in control subjects (*9*). Other investigators have also reported that OSAS patients frequently showed LV hypertrophy (*10*, *11*). However, the pathogenesis of LV remodeling in patients with OSAS remains poorly elucidated. Until recently, acute hemodynamic changes and sympathetic hyperactivity caused by airway obstruction and apnea had been suggested to cause LV dysfunction. Upper airway obstruction in patients with OSAS reduces intrathoracic pressure, which increases LV afterload (*12*) and reduces LV systolic function (*13*, *14*). Recurrent apnea stimulates sympathetic nerve activity and thereby induces peripheral vasoconstriction, resulting in a sustained elevation of systemic blood pressure. The efficacy of continuous positive airway pressure (CPAP) treatment for OSAS (*15–17*) supports this hypothesis, because CPAP reduces LV afterload and suppresses sympathetic nerve activity (*18*). CPAP has been reported to improve LV systolic function (*19*) and to reverse LV hypertrophy (*20*) in OSAS patients.

On the other hand, recent evidence has suggested the involvement of the renin-angiotensin-aldosterone system (RAAS) in the pathogenesis of cardiovascular disorders in OSAS patients. In one study, OSAS patients showed higher plasma levels of angiotensin II (Ang II) and aldosterone than healthy control subjects (*21*). In others, the levels of inflammation markers, such as C-reactive protein (*22*) and tumor necrosis factor-α (*23*, *24*), and the production of reactive oxygen species (*25*) were increased in patients with OSAS. It has been established that Ang II induces cardiac remodeling by producing reactive oxygen species, inducing inflammatory reaction, and activating extracellular matrix proteinases (*26*). Ang II activates NADPH oxidase through the Ang II type 1 (AT_1) receptor and induces sympathetic hyperactivity in chronic heart failure (*27*, *28*). Independently of its antihypertensive effect, the Ang II receptor blocker olmesartan has been shown to improve hypertensive diastolic heart failure, attenuating macrophage infiltration with decreased gene expression of pro-inflammatory cytokines such as transform-

From the [1]Department of Clinical Pharmacology, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan.

Address for Reprints: Toshiyuki Sasaguri, M.D., Ph.D., Department of Clinical Pharmacology, Faculty of Medical Sciences, Kyushu University, 3–1–1 Maidashi, Higashi-ku, Fukuoka 812–8582, Japan. E-mail: sasaguri@med.kyushu-u.ac.jp

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ing growth factor-β1 and monocyte chemoattractant protein-1 (*29*). Moreover, recent studies using mineralocorticoid receptor antagonists have indicated that aldosterone is involved in the development of cardiac fibrosis. Mineralocorticoid receptor antagonists inhibited Ang II–induced inflammatory reactions (*30*) and oxidative stress (*31*), and also suppressed cardiac remodeling without changing blood pressure. Together, these findings suggest that RAAS is likely to be involved in the hypoxia-induced cardiac remodeling found in OSAS patients.

In this issue of *Hypertension Research*, Yamashita *et al*. (*32*) reported that chronic hypoxia induced cardiomyocyte hypertrophy and interstitial fibrosis in the LV myocardium in apolipoprotein E (ApoE) knockout mice without changing LV systolic pressure. In ApoE knockout mice, hypoxia increased oxidative stress, nuclear binding of nuclear factor κB (NFκB), and the activity of matrix metalloproteinase-9. However, the treatment with olmesartan, a selective AT_1 receptor blocker, suppressed these changes. Taking into account that hypoxia has been reported to enhance expression of the cardiac AT_1 receptor (*33*), the AT_1 receptor may play a significant role in hypoxia-induced LV remodeling, probably by inducing inflammation and oxidative stress. Interestingly, hypoxia did not induce LV remodeling in wild type mice, which was in agreement with a previous study using normal rats (*34*). This suggests that some unidentified mechanisms associated with the lack of ApoE are also involved in the process of hypoxia-induced LV remodeling. The role of ApoE in sleep apnea and hypoxia-induced LV dysfunction remains unclear, although an association between the ApoE genotype and SAS has been reported (*35*, *36*). The most probable explanation may be the excessive production of lipid peroxides due to high levels of serum lipids in ApoE knockout mice, since oxidized lipids can induce inflammatory responses. However, further studies will be needed to clarify this point.

The prevalence of OSAS in Japanese is around 2% (*37*), not very different from that in Caucasians (*38*). However, the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004) do not mention OSAS as a major cause of hypertension, whereas SAS is described as the primary cause of secondary hypertension in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (*39*). In Japan as well as in Western countries, it seems likely that OSAS will soon be recognized as a major cause of hypertension and cardiovascular diseases. Even if nocturnal CPAP is the most effective procedure for the treatment of OSAS, we need to identify antihypertensive agents that can prevent cardiovascular complications in hypertensive patients with OSAS. Adrenergic receptor antagonists have been assumed to benefit the patients because they inhibit sympathetic nerve hyperactivity. However, satisfactory results have not been obtained so far, probably because of their metabolic side effects. Further study of the involvement of the RAAS in OSAS may lead to new insights for the effective pharmacological treatment of OSAS.

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