Editorial Comment

The Role of Adrenomedullin in Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) is associated with increased cardiovascular morbidity and mortality (1). Although cardiovascular morbidity in patients who have OSA is not only due to atherosclerosis, atherosclerosis may play important roles in OSA-associated cardiovascular mortality because deaths from cardiovascular diseases in patients with untreated sleep apnea are due mainly to acute myocardial infarction and stroke (2). Recent studies suggest that ongoing inflammatory responses are involved in the pathogenesis of atherosclerosis. Several inflammatory markers, including high sensitivity C-reactive protein (CRP), tumor necrosis factor- α , interleukin-6, and matrix metalloproteinase-9, are reportedly elevated in patients with OSA (3–5). Moreover, carotid intima-media thickness and the percentage of silent brain infarction are also increased in patients with OSA (6, 7). These findings suggest that OSA may increase the risks of atherosclerosis and cardiovascular diseases.

OSA is characterized by repetitive periods of upper airway collapse and results in cyclic periods of hypoxia/reoxygenation that cause the increased generation of oxygen species by oxidative stress (8). In fact, production of oxygen species from neutrophils and monocytes obtained from patients with OSA has been shown to be enhanced, and treatment with nasal continuous positive airway pressure (nCPAP) significantly decreased the production of oxygen species from these cells (9). Because repeated apnea-related hypoxia is present in patients with OSA, oxidative stress may promote both oxidative stress and inflammation (10). Therefore, oxidative stress may contribute to the cardiovascular risk profile in patients with OSA.

Adrenomedullin (AM) can be produced by a variety of cell

types, including endothelial cells and vascular smooth muscle cells (11, 12). AM acts as a potent vasodilator. Several stimuli, such as hypoxia, shear stress, and inflammatory cytokines, can induce AM production. Because these stimuli are increased in patients with OSA, a few investigators have tried to measure the circulating levels of AM in patients with OSA and to evaluate the effect of nCPAP on the levels of AM. However, the results of these reports have been inconsistent (13, 14). In this issue of *Hypertension Research*, Yamamoto and colleagues provide the further important observation that circulating levels of AM were elevated and were associated with the magnitude of oxyhemoglobin desaturation in highly selected patients with OSA by excluding several comorbid conditions that may have influence on the levels of AM (15). Furthermore, they also demonstrated that oxidative stress as measured by reactive oxygen species (ROS) production by leukocytes was associated with the levels of AM. Moreover, treatment with nCPAP reduced all these parameters in patients with OSA. Therefore, in addition to hypoxia, shear stress, and inflammatory cytokines, ROS may induce the production of AM.

The upregulation of AM presented in this study constitutes an adaptive counteractive mechanism to protect against cardiovascular diseases in patients with OSA. Further studies are necessary to elucidate the precise role of circulating AM on hypertension as well as atherosclerosis in patients with OSA.

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