Breaking barriers in obstructive sleep apnea. Focus on “Intermittent hypoxia-induced endothelial barrier dysfunction requires ROS-dependent MAP kinase activation”

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ONE OF THE MORE COMMON HEALTH issues affecting our society is obstructive sleep apnea (OSA), which affects at least 10% of the general population, primarily overweight or obese men (12). OSA, defined as the cessation of breathing caused by the repetitive, episodic collapse of the pharyngeal airway due to an airway obstruction or increased airway resistance during sleep, is a well-known public health problem due to its prevalence and the severe consequences of this disorder. The most common symptoms of OSA are morning fatigue, increased daytime sleepiness, arousals with nocturnal diuresis, and frequent snoring, yet many patients present with minimal or absent symptoms by compensating with lifestyle modifications. OSA is diagnosed following a sleep evaluation with polysomnography, which involves simultaneous recording of sleep, air flow, respiratory effort, oxygen saturation, and brain activity. The consequences of OSA include neurocognitive impairment and cardiovascular morbidities including hypertension, stroke, coronary artery disease, and heart failure (7). Additionally, several studies have shown OSA to be associated with pulmonary edema (4) and pulmonary hypertension (10). A substantial number of patients with cardiac disorders and concomitant OSA do not report excessive daytime sleepiness and are therefore not considered for diagnostic sleep evaluation and treatment for OSA. It is well understood that untreated OSA can lead to the progression of cardiovascular disease and increased mortality.

Recurrent apneas result in chronic intermittent hypoxia (CIH), a hallmark of OSA. Exposure of rats and mice to CIH for 3 to 5 weeks is sufficient to induce pathological changes similar to those seen in OSA patients, such as endothelial dysfunction, atherosclerosis, systemic hypertension, pulmonary hypertension, and heart failure (3). It has been suggested that the carotid bodies constitute the frontline defense system for detecting systemic hypoxia associated with apneas (2). The two major effects exerted by CIH on the carotid body are augmented response to acute hypoxia and long-lasting activation of the carotid body, which persist for several hours after termination of CIH (9). It has been proposed that the pathological effects of CIH-induced augmented carotid body responses are due to increased reactive oxygen species (ROS) (8). CIH results in increased ROS by both upregulation of pro-oxidants and downregulation of anti-oxidants (6). ROS are a group of highly unstable molecules generated during normal cellular metabolism or during incomplete reduction of molecular oxygen. These species are involved in the regulation of fundamental cellular activities such as growth and differentiation, however, overproduction of ROS results in oxidative stress and causes significant injury (11). Mice and rats exposed to CIH display elevated ROS in the carotid body, adrenal medulla, and central nervous system resulting in increased

Fig. 1. Intermittent hypoxia induces reactive oxygen species (ROS)-dependent activation of MAP kinases leading to endothelial barrier dysfunction. Exposure to intermittent hypoxia results in an increase in ROS, which leads to activation of ERK1/2 and JNK. MAP kinase-mediated phosphorylation of junctional proteins results in reorganization of the cytoskeleton and formation of stress fibers, leading to endothelial barrier dysfunction. Disruption of the endothelial barrier results in increased permeability to fluid, leukocytes, and proteins.
plasma catecholamine levels and increased blood pressure. The effects of CIH on catecholamine secretion, blood pressure elevation, and long-term activation of the carotid body can all be blocked by coadministration of a superoxide scavenger (9). These studies demonstrate the critical role of ROS in the development of cardiovascular morbidities associated with CIH. There is a substantial amount of evidence that increased ROS and oxidative stress increase endothelial permeability to fluids and macromolecules. While the exact mechanisms underlying endothelial barrier dysfunction following exposure to ROS have not been completely deciphered, numerous studies suggest that endothelial cells respond to oxidative stress by remodeling the actin filament network.

In this issue of American Journal of Physiology-Cell Physiology, Makarenko and colleagues (5) identify the role of ROS-dependent MAP kinase activation in intermittent hypoxia (IH)-induced pulmonary endothelial barrier dysfunction. The authors show that IH-induced pulmonary endothelial barrier dysfunction, as indicated by decreased trans-endothelial electrical resistance, is mediated by increased ROS production and can be prevented by pretreatment with a ROS scavenger. Furthermore, Makarenko and colleagues demonstrate reorganization of the cytoskeleton and junctional proteins as well as stress fiber formation in lung microvascular endothelial cells following exposure to IH, which could also be prevented by pretreatment with a ROS scavenger. Finally, the authors determined that activation of the MAP kinases ERK1/2 and JNK by IH-induced ROS leads to cytoskeletal reorganization, stress fiber formation, and alteration in endothelial barrier function. Pretreatment with inhibitors of ERK1/2 and JNK blocked the cytoskeletal reorganization and restored endothelial barrier function. These results presented in this study suggest that IH-induced endothelial barrier dysfunction is mediated by cytoskeletal reorganization initiated by ROS-dependent activation of MAP kinases (Fig. 1).

This study is one of the first to describe ROS-mediated endothelial barrier dysfunction in the setting of CIH. Maintenance of barrier function requires the structural and functional integrity of the endothelium, and if either is compromised excess plasma fluid and inflammatory cells may leak through the monolayer (1). Increased ROS are considered potent activators of inflammatory pathways, resulting in increased expression of proinflammatory cytokines and cell adhesion molecules, which facilitates the recruitment of leukocytes and platelets to the endothelium. Indeed, OSA is associated with systemic inflammation. Circulating levels of inflammatory markers, which are classically associated with atherosclerosis, including interleukin-6, interleukin-8, tumor necrosis factor-α, and cell adhesion molecules, have been reported to be increased in OSA patients. There is increasing evidence that inflammation plays a central role in the cardiovascular pathophysiology of OSA. The current most effective treatment for OSA is continuous positive airway pressure (CPAP), which has been shown to decrease cardiovascular morbidity and mortality. There is some evidence that CPAP therapy decreases circulating levels of inflammatory markers in OSA patients. This study by Makarenko and colleagues highlights the role of ROS-mediated activation of MAP kinases in IH-induced endothelial barrier dysfunction and suggests that the use of antioxidants or a MAP kinase inhibitor in combination with CPAP may have additional benefits for OSA patients. More studies are needed to determine the therapeutic benefit of targeting MAP kinases and ROS to prevent endothelial barrier dysfunction in OSA.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
K.A.S. prepared figures; K.A.S. drafted manuscript; K.A.S. and J.X.-J.Y. edited and revised manuscript; K.A.S. and J.X.-J.Y. approved final version of manuscript.

REFERENCES