VASCULAR CONSEQUENCES OF INTERMITTENT HYPOXIA

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Abstract: In patients with obstructive sleep apnea (OSA), nocturnal exposure to intermittent hypoxia causes elevations in arterial pressure that persist throughout the day. Animal models have shown that this hypertensive effect requires an intact sympathetic nervous system and an intact carotid chemoreceptor reflex. The renin-angiotensin system contributes importantly to hypertension in this model, because renal nerve denervation, angiotensin II receptor blockade, and suppression of the renin-angiotensin system by high salt diet all prevent the rise in blood pressure. The vascular endothelium is functionally impaired in this model and also in patients with OSA. These individuals demonstrate decreased plasma levels of nitric oxide metabolites, increased production of superoxide by neutrophils, and increased levels of 8-isoprostan e in breath condensate. Increased levels of pro-inflammatory cytokines are also present. Thus, oxidant stress and inflammation are potential mediators of intermittent hypoxia-induced vascular dysfunction. Once the mechanisms of intermittent hypoxia-induced alterations in vascular structure and function are understood, strategies can be developed to reverse or prevent them. Such research has relevance not only to hypertension, but also to atherosclerosis and other important cardiovascular sequelae of OSA.

Key Words: sleep apnea, sympathetic nervous system, chemoreceptor reflex, vascular reactivity

INTRODUCTION

Obstructive sleep apnea (OSA) is associated with hypertension and other forms of cardiovascular morbidity. OSA-related hypertension is characterized by sympathetic nervous system overactivity, impaired endothelial function, and vascular remodeling. Episodes of OSA impose multiple insults; however, intermittent hypoxia, rather than hypercapnia, sleep disruptions, or intrathoracic pressure oscillations, is thought to be the most important pro-hypertensive factor. While much is known about the acute vascular effects of hypoxia, the mechanisms by which acute exposures lead to long-term adaptations in vascular regulation are just beginning to be elucidated.
EFFECTS OF ACUTE HYPOXIC EXPOSURE ON VASCULAR REGULATION

The caliber of arterioles, the resistance vessels in the systemic circulation, is determined by the net effect of multiple constrictor and dilator influences (Figure 1), many of which are altered by hypoxia. Acute exposure to hypoxia produces a generalized, dose-dependent increase in sympathetic vasoconstrictor outflow caused primarily by engagement of the carotid chemoreceptor reflex (2; 13; 88). Evidence for this effect in humans is a brisk, hypoxia-induced increase in muscle sympathetic nerve activity (80; 81). Hypoxia is largely responsible for the dramatic rise in sympathetic outflow to skeletal muscle during episodes of OSA and during voluntary breath-holds (56; 62).

Figure 1. Summary of the neural, chemical, and mechanical factors that determine the caliber of resistance arterioles in the skeletal muscle circulation. Constrictor influences (shown in black) are opposed by dilator influences (shown in gray). Ang II, angiotensin II; AVP, arginine vasopressin; Epi, epinephrine; ATP, adenosine triphosphate; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; NE, norepinephrine, NPY, neuropeptide Y; TXA2, thromboxane; ET-I, endothelin-I; O2•−, superoxide; NO, nitric oxide; PGI2, prostacyclin; PGE2, prostaglandin E2; EET, eicosatrienoic acid, CO, carbon monoxide; H2O2, hydrogen peroxide; AM, adrenomedullin.

Acute hypoxic exposure also alters blood-borne regulators of resistance vessel tone. Circulating levels of the constrictor substances angiotensin II (Ang II) and endothelin-I are increased by hypoxic exposure (33; 95). Plasma from hypoxia-exposed rats caused