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Review

Hypertension and Sleep Apnea

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ABSTRACT

Obstructive sleep apnea is more prevalent in patients with hypertension than in the general population and many with obstructive sleep apnea also have hypertension. Obstructive sleep apnea increases the risk of hypertension-related morbidities such as stroke, heart failure, and premature death. Are such associations coincidental or causal and if the latter, what are their implications for clinical practice? Despite compelling epidemiological and mechanistic links between obstructive sleep apnea and hypertension, the effect in clinical trials of the treatment of obstructive sleep apnea on blood pressure has been modest and variable. The purpose of this review is to summarize our present understanding of: (1) the relevant epidemiology and mechanisms that might be responsible for the bidirectional relationship between obstructive sleep apnea and hypertension; and (2) available evidence regarding the effect of treating obstructive sleep apnea on blood pressure.

RÉSUMÉ

L'apnée obstructive du sommeil est plus répandue chez les patients souffrant d'hypertension que dans la population générale. De plus, beaucoup de patients souffrant d'apnée obstructive du sommeil souffrent également d'hypertension. L'apnée obstructive du sommeil augmente le risque de maladies liées à l'hypertension telles que l'accident vasculaire cérébral, l'insuffisance cardiaque et la mort prématurée. Ces associations sont-elles fortuites ou causales? Et si elles étaient causales, quelles sont ses conséquences sur la pratique clinique? En dépit des liens épidémiologiques et mécanistiques irréfutables entre l'apnée obstructive du sommeil et l'hypertension, les essais cliniques ont démontré que l'effet du traitement de l'apnée obstructive du sommeil sur la pression artérielle était modeste et variable. Le but de cette revue est de résumer notre compréhension actuelle de : 1) l'épidémiologie et des mécanismes pertinents qui seraient responsables de la relation bidirectionnelle entre l'apnée obstructive du sommeil et l'hypertension; 2) des données probantes disponibles concernant l'effet du traitement de l'apnée obstructive du sommeil sur la pression artérielle.

Moderate or severe obstructive sleep apnea (OSA) can be detected in a third or more of patients with primary hypertension and in up to 80% of individuals with drug-resistant hypertension. Is this a coincidence or a manifestation of causal mechanisms? The intent of this brief review is to summarize: the epidemiology of OSA and its relation to blood pressure and cardiovascular risk; mechanisms by which OSA could promote the development or progression of hypertension; and the effect of treating OSA on blood pressure.

Sleep and Circadian Hemodynamic Rhythms

Blood pressure and heart rate exhibit circadian rhythms of principally neurogenic origin. During nonrapid eye movement sleep, central sympathetic outflow diminishes and cardiac vagal tone is augmented.[1-3] As a result, blood pressure and heart rate decrease by approximately 25% from average waking values and increase by a corresponding amount upon awakening.[4,5] In most patients with hypertension but without sleep-related breathing disorders, blood pressure decreases to normotensive levels during sleep.[5]

This circadian hemodynamic rhythm, with corresponding reductions in myocardial load and oxygen demand, is critical for cardiovascular health, because cardiac metabolic gene expression exhibits a similar rhythm. Diurnal variations in myocardial workload are anticipated and substrate availability is synchronized accordingly. Temporal misalignment of gene expression and myocardial demand promotes left ventricular hypertrophy and insulin resistance and exacerbates a number of pathological processes, such as ischemia-reperfusion injury and adverse remodelling after experimental infarction.[6-10] In humans, nighttime systolic and diastolic blood pressures are more potent predictors of subsequent cardiovascular morbidity and mortality than corresponding office, average 24-hour, or average daytime ambulatory blood pressure readings,[11,12] particularly in women[13] and in patients with diabetes.[14]

OSA

OSA, resulting from complete or partial collapse of the pharynx during sleep, is the most potent expression in human

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biology of a chronic circadian misalignment between hemodynamic and metabolic demands and these rhythms of myocardial and vascular gene expression. Obstructive apneas or hypopneas (Table 1) will occur if muscle dilator nerves fail to maintain normal upper airway patency and airflow throughout sleep. Some are genetically at risk for OSA. Some are predisposed to develop OSA because of altered craniofacial structure, a small upper airway lumen or low lung volume, poor upper airway muscle function, respiratory instability, visceral or neck obesity, advancing age, a low arousal threshold, nasal congestion, or peripheral edema.[16-18]

Each episode of airway occlusion initiates a train of adverse hemodynamic, chemical, and autonomic events (Fig. 1).[19] First is the abrupt generation of negative intrathoracic pressure, to as low as −60 mm Hg. This cardiac afterload, which is undetected by any conventional blood pressure measurement device, acutely increases ventricular and atrial wall tension and myocardial oxygen demand. Over time this can stimulate ventricular hypertrophy and atrial remodelling. Apnea disengages pulmonary stretch receptors, and releases their inhibitory reflex constraint on sympathetic outflow. The partial pressure of oxygen decreases, disturbing the myocardial oxygen supply/demand ratio. The partial pressure of carbon dioxide increases. Hypoxia and hypercapnia are potent, chemoreceptor reflex-mediated stimuli to efferent sympathetic discharge and neuronal norepinephrine release. The sleeper is spared asphyxia by a brief arousal, but the adverse consequences of this event include sleep fragmentation, further adrenergic activation coupled with vagal inhibition, surges in blood pressure and heart rate, and a burst of oxidative stress. Breathing instability recurs with the resumption of sleep. The cycle of apnea and hyperpnea repeats itself, minute after minute, over the course of the night (Fig. 2).

The apnea-hypopnea index (AHI), quantified by polysomnography, is a measure of the frequency of apneas and hypopneas detected during each hour of sleep (Table 1). There is a dose-response relationship between the AHI and the risk of premature death,[21-23] cardiovascular death, and events such as stroke.[23-27] Men with an OSA > 30% are 58% more likely to develop heart failure.[28] Other indices of OSA severity, such as the frequency and depth of oxygen desaturation,[27] or the frequency of arousal from sleep, or of accompanying periodic leg movement also have prognostic implications.[15,16,29]

In the first systematic study of the prevalence of sleep-disordered breathing in a general sample of the American population aged between 30 and 60 years, 24% of Wisconsin men and 9% of its women were identified as having an AHI $\geq$ 5 events per hour and 9% of men and 4% of women with an AHI $\geq$ 15 events per hour.[30] Two decades later, present estimates of the prevalence of moderate or severe OSA in adult Americans of all ages are much higher.[31]

Only a minority of individuals with cardiovascular disease and OSA will complain of excessive daytime sleepiness.[17,32] Its absence might be a consequence of chronic activation, by OSA, of central adrenergic alerting mechanisms: in heart failure patients with OSA subjective daytime sleepiness relates inversely and significantly with efferent sympathetic discharge to skeletal muscle.[33] Daytime sleepiness commonly draws patients to medical attention; its absence has important implications. Patients with untreated OSA remain at greater risk of developing a range of cardiovascular morbidities. Reliance on symptoms as an entry criterion for clinical research is an important cause of selection bias in the present literature; many age-matched 'control' subjects might in fact have significant but unrecognized OSA.

Table 1. Definitions

Term	Definition
Polysomnography	Multi-channel recording during sleep of electroencephalographic, electro-oculographic, electromyographic, electrocardiographic, and respiratory activity
Apnea	Cessation of airflow for more than 10 seconds
Hypopnea	Reduction in, but not complete cessation of, airflow to < 50% of normal, usually in association with a reduction in oxyhemoglobin saturation
AHI	The frequency of apneas and hypopneas per hour of sleep
Obstructive sleep apnea and hypopnea	Apnea or hypopnea due to complete or partial collapse, respectively, of the pharynx during sleep
Mild OSA	OSA with an AHI of 5-15 events per hour
Moderate OSA	OSA with an AHI of 15-30 events per hour
Severe OSA	OSA with an AHI > 30 events per hour
Central sleep apnea and hypopnea	Apnea or hypopnea due to complete or partial withdrawal or central respiratory drive, respectively, to the muscles of respiration during sleep
Oxygen desaturation	Reduction in oxyhemoglobin saturation, usually as a result of an apnea or hypopnea
Sleep apnea syndrome	At least 10 to 15 apneas and hypopneas per hour of sleep associated with symptoms of sleep apnea including loud snoring, restless sleep, nocturnal dyspnea, morning headaches, and excessive daytime sleepiness
Arousal	Transient awakening from sleep lasting less than 10 seconds

AHI, apnea-hypopnea index; CSA, central sleep apnea; OSA, obstructive sleep apnea.

Adapted from Bradley and Floras[15] with permission of the American Heart Association.

Mechanisms That Link OSA and Blood Pressure

OSA is characterized by oscillations, entrained to the apnea cycle, in vasoconstrictor muscle sympathetic nerve activity (MSNA), blood pressure, and heart rate (Fig. 2). Blood pressure by the end of each apnea might exceed that recorded during wakefulness.[20] OSA often evokes a 'nondipping' ambulatory blood pressure phenotype and nocturnal hypertension.[20,34-36] Is this sufficient to cause chronic daytime hypertension?

A sustained aftereffect of OSA on MSNA has been documented during wakefulness in subjects with normal and impaired left ventricular systolic function. In the latter, MSNA is increased on average by 11 bursts per 100 cardiac cycles and decreases equally if OSA is abolished with the use of continuous positive airway pressure (CPAP) therapy,[37-39] a finding consistent with the concept that OSA and heart failure interact through a process of additive summation to increase central sympathetic outflow.[40] Summation of the independent excitatory effects of OSA and heart failure might occur via sensitization of chemoreceptor reflexes, which elicits increased sympathetic nerve discharge,[40] or by sleep apnea, which engages a cortical autonomic network.[41]