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Chemoreflexes, Sleep Apnea, and Sympathetic Dysregulation

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Abstract

Obstructive sleep apnea (OSA) and hypertension are closely linked conditions. Disordered breathing events in OSA are characterized by increasing efforts against an occluded airway whilst asleep, resulting in a marked sympathetic response. This is predominantly due to hypoxemia activating the chemoreflexes, resulting in reflex increases in sympathetic neural outflow. In addition, apnea, and the consequent lack of inhibition of the sympathetic system that occurs with lung inflation during normal breathing, potentiates central sympathetic outflow. Sympathetic activation persists into the daytime, and is thought to contribute to hypertension and other adverse cardiovascular outcomes. This review discusses chemoreflex physiology and sympathetic modulation during normal sleep, as well as the sympathetic dysregulation seen in OSA, its extension into wakefulness, and changes after treatment. Evidence supporting the role of the peripheral chemoreflex in the sympathetic dysregulation seen in OSA, including in the context of co-morbid obesity, metabolic syndrome and systemic hypertension is reviewed. Finally,

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COMPLIANCE WITH ETHICS GUIDELINES

Human and Animal Rights and Informed Consent

The manuscript does not contain any studies with human or animal data.

Conflicts of interest

Meghna P. Mansukhani has no conflicts to disclose.

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alterations in cardiovascular variability and other potential mechanisms that might play a role in the autonomic imbalance seen in OSA are also discussed.

Keywords

sleep disordered breathing; obstructive sleep apnea; hypoxia; hypercapnia; carotid body; peripheral chemoreceptors; autonomic imbalance; autonomic dysfunction; autonomic control; sympathetic activation; sympathetic activity; sympathetic response; sympatho-excitation; cardiovascular variability; heart rate variability; mechanisms; systemic hypertension; obesity; metabolic syndrome; renin angiotensin system; baroreflex; vascular factors; sleep deprivation

INTRODUCTION

Obstructive sleep apnea (OSA) is a common condition. Recent community studies estimate that 10–17% of males and 3–9% of females aged 30–70 years have moderate to severe sleep apnea [1]. There has been a significant increase in the prevalence in the last two decades [1]. OSA is characterized by upper airway collapse, occurring in a repetitive fashion throughout sleep, leading to sleep disruption, daytime sleepiness and increased risk of work place and motor vehicle accidents. OSA has also been associated with a number of adverse cardiovascular consequences including hypertension, coronary artery disease, stroke, both systolic and diastolic heart failure, and arrhythmias [2–9]. Of these, the link between OSA and systemic hypertension is the most well defined, with several population-based studies demonstrating an increased incidence of baseline and future hypertension in subjects with OSA [10–13]. This is an important issue for clinicians treating patients with hypertension, as approximately 50% of these patients have co-morbid OSA [14], which is a readily treatable condition [15], and there is a dose-response relationship between severity of untreated OSA and the incidence of hypertension [12, 16]. In addition, OSA appears to be the most common secondary cause of elevated blood pressure (BP) in those with resistant hypertension [14].

Currently, the mechanisms underlying the increased risk of hypertension and other adverse cardiovascular effects in OSA are not fully understood. The relative contribution of obesity versus OSA to the overall increased risk is especially unclear [17, 18]. There is a growing body of evidence to suggest that autonomic dysfunction, specifically altered chemoreflex control of sympathetic activity, may play a prominent role in this relationship [19–21].

In this review, we discuss normal chemoreflex control of sympathetic activity and how this is altered in the setting of OSA, both in sleep and wakefulness, as well as in the treated OSA patient. The relationship between the resulting sympathetic dysregulation in OSA and disorders of obesity, metabolic syndrome, and especially hypertension are discussed. Other possible mechanisms contributing to sympathetic dysregulation in the setting of OSA are also described. The term sleep apnea in this review refers to OSA. Autonomic dysfunction pertaining to central sleep apnea (CSA), seen frequently in patients with heart failure, is beyond the scope of this review. Discussion is limited to studies involving adult subjects.

The chemoreflexes

The chemoreflexes include central chemoreceptors in the brain stem, and peripheral chemoreceptors in the carotid bodies that are located near the internal carotid arteries. The central chemoreceptors respond mainly to hypercapnia, whereas the peripheral chemoreceptors mostly respond to hypoxia. There have been recent advances in the understanding of the molecular mechanisms involved in the functioning of the peripheral carotid chemoreceptors [22–25]. Hypoxic and/or hypercapnic chemoreflex activation elicits increases in central sympathetic outflow, but also stimulates hyperventilation, which inhibits sympathetic activity [26–28]. The peripheral chemoreceptors, responding to hypoxia, appear to be more influenced by this inhibition. Perhaps this is due to the thoracic afferents and afferents from peripheral chemoreceptors synapsing close to the nucleus tractus solitarius in the brainstem [29, 30].

The chemoreflexes play an important role in the control of ventilation and activation of the chemoreflex causes hyperventilation. They also play a significant role in cardiovascular control with activation resulting in increased BP due to sympathetic activation [31–33]. Control of breathing and cardiovascular systems by the chemoreflexes are closely linked, such that when there is an increase in ventilation, chemoreflex mediated cardiovascular responses are attenuated due to stretch of the thoracic afferents [26, 27, 34]. There is also a negative feedback mechanism operating within the cardiovascular system, in that chemoreflex induced activation of the cardiovascular system results in increased BP that activates the arterial baroreceptors, which in turn serves to attenuate the chemoreflex response [28, 32, 35]. This mechanism is more prominent for responses mediated by hypoxia rather than hypercapnia [28].

When an apnea occurs, hypoxia and/or hypercapnia without accompanying increase in ventilation activate the peripheral chemoreflex, which results in marked sympathetic activation of blood vessels in the musculature causing vasoconstriction. In other words, sympatho-excitation is unopposed in the face of lack of inhibition from normal ventilation. The peripheral chemoreflex also simultaneously increases vagal activity to the heart. Thus, the so-called “diving reflex” is activated, whereby apnea and hypoxia result in peripheral vasoconstriction and bradycardia [36–38]. These responses may explain the mechanisms mediating increased risk of hypertension and other adverse cardiovascular consequences in OSA patients.

Sympathetic activity in normal sleep

NREM sleep—Alterations in ventilation, heart rate (HR) and BP occur in normal sleep that are predominantly sleep stage dependent [39, 40]. These changes are mediated by modifications in autonomic control [40]. There is a progressive reduction in central respiratory drive, minute ventilation, and PaO₂ accompanied by a rise in PaCO₂ in non-rapid eye movement (NREM) sleep stages 1 through 3. There is a simultaneous increase in parasympathetic tone and decrease in sympathetic activity, such that HR, BP, stroke volume and systemic vascular resistance all show a decline [40, 41].

Arousals—Arousals from sleep are associated with abrupt increases in both respiratory and cardiovascular activity [42, 43]. Augmentation of ventilatory drive occurs and is above what would be expected for the given PaCO₂ level [43]. At the same time, there is an increase in sympathetic activity and a decrease in cardiac vagal activity exceeding normal wakefulness levels, causing significant surges in HR and BP [42]. One study suggested the presence of long-lasting sympathetic activation in normal subjects exposed to repetitive arousals from sleep [44]. This could potentially predispose to the future development of hypertension. Also, an increased number of arousals are seen in the context of recurrent respiratory events in patients with OSA.

REM sleep—The chemoreflexes appear to play a less important role in rapid eye movement (REM) sleep [39, 45]. Atonia of the respiratory muscles excluding the diaphragm and reduction in chemosensitivity occur in REM [39]. A combination of these two factors results in an increase in PaCO₂ and decrease in ventilation to levels lower than that seen in NREM sleep. In contrast, HR, BP and sympathetic nerve activity increase to reach levels similar to wakefulness [40].

Sympathetic activity in OSA

During sleep—In patients with OSA, sympathetic activity and cardiovascular parameters during sleep depend on the severity and duration of the apnea rather than sleep stage. Repetitive episodes of apnea and hypoxia in sleep result in activation of the chemoreceptor reflex, and increase sympathetic activation [34]. Once breathing resumes, venous return and cardiac output increase, but the increased cardiac output is delivered into a highly constricted peripheral vasculature, resulting in surges in BP as high as 250/110 mm Hg at the end of an apnea [34, 46, 47]. It is thought that the phenomenon of “non-dipping” of BP at night in many individuals, linked to increased risk of adverse cardiovascular consequences [48], may in fact arise as a result of undiagnosed sleep apnea causing these BP surges [49, 50]. Prevalence of sleep apnea in hypertensive patients with absence of blood pressure reduction during the night is frequent and therefore the “non-dipping” phenomenon could be considered as a simple indirect clinical marker of increased risk of the presence of sleep apnea.

During wakefulness—Subjects with OSA have increased sympathetic activity even during wakefulness when they are breathing normally. Studies of sympathetic nerve activity have been made easier by the advent of microneurography, which permits direct intra-neural measurement of sympathetic nerve traffic. Studies in humans have shown increased muscle sympathetic nerve activity (MSNA) under hypoxic conditions at simulated altitude [51]. This increased sympathetic nerve activity has been known to persist even after removal from acute short-term exposure to intermittent hypoxia [52–57].

Sympathetic nerve activity and mean arterial BP have been found to be increased not just with acute intermittent hypoxia but with chronic intermittent hypoxia as well, in animal [58–60] and human studies [61]. Both acute and chronic intermittent hypoxia appear to be more potent in inducing this sympatho-excitatory response than sustained hypoxia, at least in rodent studies [62].

Intermittent hypoxia has been noted to increase circulating catecholamines [63, 64] and sympathetic nerve activity in rats [56], which appears to be mediated by enhanced acute hypoxia sensing via formation of reactive oxygen species [65, 66]. This effect appears to be independent of respiratory drive [57], and correlates with increased expiratory activity [60] in rats. Caution needs to be exercised before extrapolating these results to human subjects.

Studies in humans have also revealed increased urinary noradrenaline levels during the day [67–69] and increased sympathetic nerve activity in subjects exposed to intermittent hypoxia under experimental conditions [70]. A handful of studies have revealed increased sympathetic activity in human subjects with OSA during wakefulness under conditions of normoxia; this was true whether subjects were on antihypertensive therapy or not [34, 71, 72]. One study demonstrated that hyperoxia reduced HR, BP and MSNA in human subjects with OSA but not in controls [73] and similar findings have been noted by other researchers as well [74]. Together, these studies reflect increased sympathetic activity in the setting of intermittent hypoxia in animals and humans. The sympatho-excitatory response appears to be more sensitive to hypoxia as the stimulus as opposed to hypercapnia [54, 75], although apnea and hypercapnia may contribute to, and in fact, act synergistically to elicit the overall response [26, 71, 76, 77].

In one recent study of healthy human subjects, increased MSNA was shown to be independently associated with pulse wave velocity, a powerful predictor of cardiovascular morbidity and mortality [78]. Further research is needed to confirm these findings in patients with OSA.

In summary, patients with OSA tend to have acute and chronic intermittent hypoxia during sleep. Sustained hypoxia or hypercapnia in the setting of OSA without co-morbid respiratory or neuromuscular conditions and/or obesity hypoventilation syndrome are rare. Both acute and chronic intermittent hypoxia are powerful stimuli for the sympathetic activation seen during sleep and wakefulness in subjects with OSA.

Sympathetic activity in treated OSA patients—Treatment of OSA with tracheostomy has been shown to reduce nighttime urinary catecholamine and daytime MSNA (Fletcher 1987). Continuous positive airway pressure (CPAP), the most commonly used therapy for OSA, has been noted to result in decreased sympathetic activity and attenuated BP surges in sleep (Somers 1995). In addition, CPAP has been shown to lower MSNA after 6 months and 1 year of treatment in treated OSA compared to untreated OSA patients [79, 80], and this effect is greatest in those with the highest number of hours of CPAP usage [81, 82]. Reduction in sympathetic activity with CPAP, measured by urinary noradrenaline levels, appears to be more prominent in patients with severe OSA [83] and in those with diabetes mellitus [84].

Long term CPAP treatment has also been shown to decrease BP, particularly 24 hour BP, in pre-hypertensive [85, 86] and hypertensive OSA patients [84, 87–91]. A similar decline in 24 hour mean BP has been noted with oral appliance treatment for OSA as well [92]. However, several meta-analyses show only very modest blood pressure lowering effects, of

around 2 mmHg [89, 91]. Interestingly, CPAP has been noted to possibly decrease the risk of incident new hypertension by some investigators [12] but not by others [93].

A recent study performed in a cohort of subjects with resistant hypertension demonstrated significant reductions in 24 hour mean and diastolic BP after 12 weeks in those who received CPAP treatment compared to those who did not receive CPAP. The percentage of patients displaying a nocturnal “dipping” pattern was higher in the CPAP versus the no-CPAP group [94].

There appears to be an interaction between sleepiness and BP response to CPAP treatment in OSA patients. Some studies have shown no significant BP reduction after CPAP in the absence of sleepiness [93, 95, 96] or an enhanced response in patients who are sleepy [88].

Role of the chemoreflex in sympathetic dysegregation seen in OSA

It is clear that OSA is associated with a state of sympathetic dysregulation. Mechanisms leading to this dysregulation have been the focus of attention in a number of studies. The chemoreflex is thought to play an important role [20, 26, 27, 97–101], although other mechanisms may contribute, as described below. Animal studies have indicated that the peripheral chemoreceptors located in the carotid body play a pivotal role in the response to hypoxia seen in OSA [102–109]. More recent analyses have demonstrated differential expressions of the various Hypoxia Inducible Factor (HIF) subtypes in the carotid body associated with local inflammation [110–112]. In the future, functional neuroanatomic imaging studies of the carotid bodies could potentially provide more insight into the exact pathologic processes involved [113].

Several studies have determined that increased peripheral chemoreflex sensitivity [97, 103, 114–116], and tonic activation [29, 54, 72, 117] of the peripheral chemoreceptors even during normoxia are mechanisms that could explain the observed increased sympathetic activity seen during wakefulness in OSA.

It is not entirely clear whether healthy human subjects experience sympathetic dysregulation in response to intermittent hypoxia. One study revealed increased pressor and cerebrovascular resistance responses in healthy subjects exposed to intermittent hypoxia [118]. Another study showed increased MSNA with voluntary apnea in trained divers but not in controls [119], while other studies have noted no significant differences in autonomic measures between trained healthy divers and controls at rest, suggesting that sympathetic dysregulation in response to hypoxia is seen in OSA, but generally not with voluntary apnea training in healthy subjects [120, 121]. Nevertheless, it is evident that the chemoreflex induced sympathetic response to hypoxia in OSA is exaggerated compared to subjects without OSA who are exposed to hypoxia. There appears to be a blunting of this effect with recurrent apneas, at least in animal studies [122], leading one to infer that the exaggerated chemoreflex is a pathophysiologic characteristic rather than consequence of OSA.

Relationship with obesity—Whether obesity plays an intermediary or supplementary role in the relationship between OSA and autonomic imbalance is not fully known. Sympatho-excitation has been observed in OSA patients as a response to apnea with

associated hypoxia, and is more marked than in weight-matched controls without OSA experiencing a similar level of induced hypoxia [71, 73]. Similarly, increased MSNA has been detected in subjects with OSA compared to obese and normal weight non-OSA subjects, both of the latter two demonstrating fairly similar levels of sympathetic activity [73]. These results indicate that the enhanced sympathetic drive, and any underlying chemoreflex mechanism, in OSA is likely not related to obesity per se.

Relationship with metabolic syndrome—OSA and metabolic syndrome are frequently co-morbid conditions. It appears that OSA may worsen the sympathetic dysregulation already present in patients with metabolic syndrome. One study showed higher MSNA in subjects with metabolic syndrome and OSA compared to metabolic syndrome without OSA and healthy controls. In the metabolic syndrome patients overall, MSNA was significantly associated with severity of OSA, assessed by the apnea-hypopnea index (AHI), after accounting for confounders [123]. Another study showed that baseline MSNA was higher in subjects with OSA plus metabolic syndrome compared to those with OSA minus metabolic syndrome, which in turn was higher than that observed in healthy controls. Increased MSNA in response to isocapnic hypoxia was also greater in those with OSA plus metabolic syndrome compared to the other two groups. OSA in this study was defined as an AHI of equal to or greater than 15 per hour [124].

Relationship with hypertension—OSA is tightly linked to hypertension and the chemoreflex has been implicated as a possible major contributor. Canine studies have shown a sustained increase in daytime BP related to repeated airway occlusion, but not if there were repeated awakenings without airway manipulation [125]. Several studies in rodents have demonstrated increased arterial BP in response to intermittent hypoxia [22, 100, 115, 126], but not with hypercapnia. In one study of human subjects with OSA, the sympathetic response to hypoxia was found to be related to AHI and nocturnal urinary adrenaline levels, and was independently associated with increased diurnal and nocturnal mean BP [117]. Taken together, these results suggest a possible mediating role of peripheral chemosensitivity in the relationship between OSA and hypertension.

Interestingly, the increased peripheral chemoreflex response to hypoxia that occurs in normotensive sleep apneics [72] is seen in patients with mild hypertension as well [127]. Thus, there appear to be some similarities in the sympatho-excitatory response between normotensive subjects with OSA and those with early mild hypertension [18, 29, 62]. Previous studies have demonstrated increased MSNA in subjects with mild hypertension [128–130], related to nighttime and daytime HR but not to the morning surge in BP [131]. Autopsy studies in hypertensive humans have also shown morphologic abnormalities in the carotid bodies [132–134].

In summary, there seems to be an association between abnormalities in the carotid body, sympathetic dysregulation and hypertension; however, it is not completely clear whether these changes precede or occur as a result of hypertension. In one study of rats, exposure to chronic intermittent hypoxia produced a shift in the HR variability power spectrum reflecting a predominance of sympathetic modulation at 14 days, but arterial BP did not increase until day 21 of exposure [135]. These data suggest that changes in autonomic

balance may precede the development of hypertension induced by chronic intermittent hypoxia, but further studies are required to corroborate these findings in human subjects with OSA.

Cardiovascular variability

OSA patients not only have evidence of increased sympathetic activity during wakefulness, they also demonstrate abnormalities of cardiovascular variability when awake, another reflection of the autonomic dysfunction occurring in this group [136]. Abnormalities in cardiovascular variability include highly increased BP variability and decreased R-R variability occurring in a dose-response fashion with the severity of OSA, even in the absence of hypertension [136–138]. Treatment with CPAP has been shown to normalize HR variability indices acutely and chronically [139, 140]

A recent study showed changes in HR variability suggesting reduction in cardiac vagal modulation in subjects with asymptomatic OSA when compared to obese controls [141]. Hence, there is a decrease in parasympathetic activity and increase in sympathetic activity in OSA patients, opposite to that noted in normal sleep. These changes have been linked to adverse cardiovascular effects [142–145] and may explain later development of hypertension in normotensive OSA patients [29]. These metrics provide a potential avenue for the screening of asymptomatic individuals with OSA for the development of hypertension as well as other adverse cardiovascular consequences, and then possibly target these individuals for treatment of OSA. It is worthwhile noting that when utilizing HR variability techniques to assess autonomic function, respiratory measures should be obtained simultaneously, since both normal and abnormal respiratory function can influence HR variability, especially frequency domain measures, and thus confound the results [29, 146].

Other mechanisms contributing to sympathetic dysregulation in OSA

Baroreflex dysfunction—The baroreflexes are also thought to play a role, although less important than the chemoreflex, in the sympathetic dysregulation seen in OSA [72, 147–151]. Patients with OSA have been noted to have decreased baroreceptor sensitivity [40, 147]. Stretch of the carotid sinus and aortic arch baroreceptors increase cardiac vagal activity and decrease sympathetic activity, but since HR and BP both peak in OSA, the baroreceptors probably do not play a major role in mediating the autonomic response [146], although they likely contribute to the post apnea reduction in MSNA [34]. Furthermore, chronic repetitive surges in blood pressure may lead to “resetting” of baroreceptors at a higher baseline blood pressure level. Such dysfunction of the baroreflex feedback system further contributes to chronic sympathetic activation with subsequent chronic increase of blood pressure and heart rate. There may also be an indirect effect, as input from baroreceptors (in addition to that from the chemoreceptors) influences the amount of parasympathetic and sympathetic tonic activity upon which breathing can exert its influence [152]. In this context, the effects of baroreceptor stimulation on respiration [153] and the short and long term effects on BP [20, 154, 155] have recently been described in greater detail. The role of low pressure baroreceptors in onset and progression of hypertension in OSA patients remains unclear.

Central control—Changes in central neural control may also play a role in the sympathetic response to OSA [156, 157]. Increase in the central response to chronic intermittent hypoxia may partly explain the sensitization to acute hypoxia [30, 158]. A recent study in rats showed increase in pro-inflammatory cytokines TNF α , and IL β 1 as well as an increase in c fos positive neurons in the nucleus tractus solitarius [100]. Another study showed changes in delta fosB in central autonomic nuclei, thought to contribute to the maladaptive changes causing chronically elevated sympathetic nerve activity in OSA [159, 160]. Furthermore, circulating catecholamines as well as circulating angiotensin II, levels of which are elevated as a consequence of OSA mediated increases in sympathetic activation, may directly cross the hematoencephalic barrier and thus directly stimulate sympathetic nuclei located in the hypothalamus and brainstem as well [161]. This positive feedback mechanism can substantially contribute to central elevation of sympathetic tone with all of its important hemodynamic, neurohumoral and metabolic consequences [161, 162].

Local reflexes in the heart—Normal inspiration results in increased HR and venous return that stimulates receptors in atria as well as caval and pulmonary veins, which then reduces cardiac vagal efferent activity. The effects on sympathetic activity, on the other hand, are less clear. In animal studies, increased sympathetic cardiac efferent outflow has been noted [163, 164] but in humans, decreased MSNA, reduced forearm vascular resistance and absence of tachycardia have been described [165, 166]. A recent study showed blunted forearm resistance in response to voluntary apnea under experimental conditions in young healthy women but not in healthy postmenopausal women or men, implying that female sex hormones may dampen the effects of apnea induced sympathetic vaso-constriction [167]. These early data could potentially explain why OSA is seen more frequently and tends to be more severe in men than in women, but further research is warranted to substantiate these findings.

Vascular factors—More recent studies have focused on the role of vascular factors in the sympatho-excitatory response to OSA [161, 168], such as nocturnal endothelin release [169], endothelial cell dysfunction [170, 171] and apoptosis [172]. These adverse vascular effects may in fact be reversible with CPAP treatment [172, 173]. One study demonstrated that atorvastatin prevented vascular endothelial dysfunction, oxidative stress and hypertension in response to intermittent hypoxia in rats [174]. Thus, statins could provide a potentially useful adjunctive treatment strategy in OSA patients to help lower BP if efficacy is proven in future trials in humans.

Renin angiotensin system—The renin angiotensin system is increasingly being implicated in the relationship between OSA and hypertension [175–177]. Up-regulation of angiotensin 1 receptors in the carotid body and oxidative stress have been shown to play a role in the increased sympathetic activity resulting from intermittent hypoxia in rats [111, 178]. Also important is the link between the renin angiotensin and sympathetic nervous systems. Sympathetic activation is the major factor stimulating release of renin from the juxtaglomerular system of the kidney. Subsequently created angiotensin II increases sympathetic tone by several different mechanisms at both central and peripheral levels.

Tissue specific production of catecholamines and angiotensin II induced by OSA mediated hypoxia seems to be of clinical relevance also, but its description is out of the scope of this article.

Other factors—Sleep deprivation or short sleep duration [179, 180] and impaired exercise tolerance [181, 182] seen in the context of OSA may also contribute to the excess cardiovascular risk seen in OSA patients. Additional studies are required to clarify the exact mechanisms through which these factors could exert their influence.

CONCLUSIONS

The chemoreflexes play an important part in regulation of ventilatory and cardiovascular responses. Sympathetic activity is sleep stage dependent in normal sleep but is proportional to the duration and severity of apnea and hypoxia in OSA. In addition, repeated arousals associated with respiratory events may result in sympathetic surges. Ultimately, sympathetic activity and pressor responses to hypoxia are increased in patients with OSA, not just in sleep but during wakefulness as well. Treatment of OSA appears to ameliorate this effect. The peripheral chemoreflex acting via the carotid bodies is thought to play a prominent role in this response, although other mechanisms involving the baroreflex, vascular factors and/or the renin angiotensin system may contribute. OSA patients appear to have increased peripheral chemosensitivity and tonic activation of the chemoreceptors, which is not seen in weight-matched healthy controls. The response to hypoxia in OSA is exaggerated compared to non-OSA subjects exposed to hypoxia and is similar to that observed in early hypertension. The chemoreflex and altered sympathetic activity may explain the link between OSA and hypertension and other adverse cardiovascular consequences, but needs further study, particularly in human subjects. There are some data suggesting that autonomic dysfunction may precede and lead to the development of hypertension. Methods to measure the chemoreflex contribution to sleep apnea could provide exciting new ways to potentially predict the onset of hypertension and other cardiovascular outcomes in asymptomatic patients and target them for individualized treatment.

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