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Cardiovascular Regulation in Obstructive Sleep Apnea

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Abstract

The majority of patients with obstructive sleep apnea (OSA) suffer from hypertension as a complication of both the metabolic syndrome and OSA. In animal studies, intermittent hypoxia that simulates changes seen in OSA leads to chemoreceptor and chromaffin cell stimulation of sympathetic nerve activity, endothelial damage and impaired blood pressure modulation. Human studies reveal activation of sympathetic nerves, endothelial damage and exaggerated pressor responses to sympathetic neurotransmitters and endothelin. Although treatment of the OSA normalizes sympathetic nerve responses, it only lowers blood pressure modestly. Agents that block the consequences of sympathetic over activity, such as β 1 blockers and angiotensin antagonists have effectively lowered blood pressure. Diuretics have been less successful. Treatment of hypertensive patients with OSA usually requires consideration of both increased sympathetic nerve activity and the metabolic syndrome.

Introduction

Obstructive sleep apnea (OSA) causes obstruction in the upper airway leading to hypoxia. The frequency of these hypoxic episodes ranges from 5 per hour for mild OSA to more than one a minute. A hypoxic episode typically terminates with arousal, compensatory hyperventilation and a surge of blood pressure driven by sympathetic nervous activation. Patients with OSA are frequently hypertensive and have increased cardiovascular mortality (1). There is reason to believe that OSA causes the hypertension since arousals from apneas cause nocturnal blood pressure surges and intermittent hypoxia can raise blood pressure. Indeed, many (2) but not all (3) large studies find OSA associated with increased hypertension after correction for other causes of hypertension, such as obesity. Since OSA is most common in elderly obese men, it occurs in a population with a high incidence of hypertension. The hypertension of OSA is frequently severe and responds differently to drug therapy. So what makes the hypertension of OSA different? As we discuss below and in the summary Figure, the hypertension found in OSA is greatly influenced by intermittent hypoxia and comorbid metabolic syndrome.

Intermittent hypoxia

Patients with OSA have intermittent, 10-30 s long obstructions of the upper airway during sleep. As a result they are exposed to both chronic intermittent hypoxia and chronic intermittent hypercapnia. Chronic continuous moderate hypoxia leads to a benign physiological adaptation. However, chronic intermittent hypoxia is associated with

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hypertension, stroke, myocardial infarction (4) and elevated sympathetic tone (5). Although OSA is a seemingly simple disorder of intermittent obstruction of the upper airway during sleep, patients with OSA and hypertension have a complex physiology usually including the metabolic syndrome (6) and vascular pathology. Animal models have the advantage of isolating individual components of OSA for study but they fail to replicate the complex physiology found in a hypertensive patient with OSA. (7). OSA is associated with increased level of oxidative stress and reactive oxygen species (ROS). Intermittent hypoxia elevates transcriptional factor HIF-1 (hypoxia-inducible factor 1) (5) which in turn induces increased release of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). Apneic episodes begin with negative intrathoracic pressure which increases venous return to the heart and lungs, causing atrial stretch and increased release of ANP and BNP [8]. Subsequent hypoxia and hypercapnea lead to an arousal that limits the extent of slow wave sleep and disturbs REM sleep. The arousal is accompanied by a brief period of hyperventilation, a spike in sympathetic nerve activity and a brief increase in blood pressure. Most animal models replicate only the episodic hypoxia of OSA. Surprisingly, they also replicate the hypertension and some of the endothelial dysfunction of OSA.

The chemoreflex

The arterial chemoreflex regulates respiration. Arterial hypoxemia stimulates peripheral chemoreceptors increasing input to the central pattern generator in the brainstem, ultimately leading to a compensatory increase in ventilation, sympathetic nerve activity and elevated blood pressure (8). Exposure of rats or mice to intermittent hypoxia during sleep increases nerve activity in cervical, splanchnic, thoracic and lumbar sympathetic chains (9). The prolonged sympathetic activation parallels the sympathetic activation seen in human OSA (10). Hypoxia induced pressor responses are exaggerated in OSA patients both at night and in the daytime (11). Intermittent hypoxia exaggerates arterial chemoreflex responses in cats and mice, enhances sympathetic nerve activity and raises blood pressure. The carotid bodies are the major oxygen sensors modulating respiration and their denervation prevents hypertension from intermittent hypoxia. After rats were exposed to chronic intermittent hypoxia, direct recordings of carotid body nerve output showed an exaggerated response to acute hypoxia. The longer the exposure to intermittent hypoxia, the greater was the baseline activity of the carotid bodies. This phenomenon appears to be a characteristic of the carotid bodies themselves, since it was induced in surgically removed carotid bodies (6). In animal models intermittent hypoxia sensitizes the carotid bodies hypoxic response causing unstable breathing and worsening of apneas. It also induces a long lasting increase in the carotid bodies baseline activity named sensory long-term facilitation (sLTF) (12, 13) leading to sympathetic over activity and increased blood pressure (14). There is some evidence that sensitization to hypoxia is a consequence of oxidative stress caused by an imbalance between pro-oxidant and anti-oxidant activity resulting in increased production of reactive oxygen species (5). Treatment of rats with a scavenger of reactive oxygen species during intermittent hypoxia prevented the increase in carotid body signaling activity (15). The response was partially mediated by up regulation of endothelin-1 and its ET_A receptor and also by serotonin. Thus far, many of the animal models of intermittent hypoxia are consistent with the human responses in OSA of sympathetic activation and hypertension. The animal models predicted the sensitization of OSA patients' respiratory responses to acute hypoxia. It is possible that up regulation of carotid body baseline activity is also responsible for the chronic increase in sympathetic nerve activity seen in patients with OSA. Patients with OSA who are treated with continuous positive airway pressure (CPAP) correct both their intermittent hypoxia and their excess sympathetic nerve activity (16).

The baroreflex in OSA

There is a bidirectional interaction between chemoreflex and baroreflex in normal humans. The activated baroreflex inhibits peripheral chemoreflex responses (17) while an activated peripheral chemoreflex inhibits baroreflex responses (18). The chemoreflex can increase sympathetic nerve activity in response to hypoxia. The baroreflex can decrease sympathetic nerve activity when high blood pressure stretches the baroreceptors. The human cardiovascular baroreflex decreases with both increasing age and increasing blood pressure, due in part to rigidity of large arteries, preventing stretch of the baroreceptors (19). Local neurotransmitters and central nervous system modulation also affect the baroreflex (9). Several studies report attenuated vascular and cardiac responses to activation of the baroreceptors in patients with OSA. Since OSA patients are predominantly elderly and hypertensive, the relative role of OSA in impairment of baroreflex function is uncertain. Animal studies support an effect of intermittent hypoxia. Rats exposed to several days of intermittent hypoxia had impaired blood pressure modulation (20). Studies suggest a blunting of sympathetic nervous withdrawal in response to induced hypertension following intermittent hypoxia (10) or a selective loss of sympathetic neuronal activation in response to hypotension in patients with sleep apnea (21). Neither of those studies showed a daytime baroreflex defect but nighttime baroreflex parasympathetic control is diminished in OSA patients (22). One study in OSA patients found reduced baroreflex sensitivity and increased baroreflex operating point in the mornings that may actually promote hypertension (23).

Several studies have attempted to document selective baroreflex deficits in patients with OSA compared with carefully matched controls. However, most patients with OSA are elderly, obese and have high blood pressure. Those factors lead to impaired sympathetic and parasympathetic baroreflex responses. OSA probably introduces further baroreflex defects, but they may be difficult to detect when starting from a baseline level of diminished baroreflex sensitivity due to age and hypertension. This loss of baroreflex buffering of blood pressure can have important clinical consequences. Apneic episodes are typically followed by a spike in blood pressure during arousal. One would expect that blood pressure spike to be larger and last longer if the baroreflex is diminished.

Intermittent hypoxia up regulates the chemoreceptor, increasing blood pressure. It may also down regulate baroreflex modulation of that elevated blood pressure. In addition, studies on adrenal chromaffin cells from rats exposed to intermittent hypoxia showed facilitated catecholamine release due to up regulation of T-type calcium channels (24). Catecholamines released by this three pronged mechanism can raise blood pressure directly and also through activation of the renin angiotensin system. Patients with OSA and rats exposed to intermittent hypoxia have a hypotensive response to angiotensin AT1 receptor antagonists (25). The pressor effects of catecholamines and angiotensin II are greater in subjects with endothelial dysfunction. Patients with OSA have elevated endothelin levels (26) and an exaggerated pressor response to endothelin (27). Although endothelin antagonists are not practical human antihypertensive drugs, rats with intermittent hypoxia induced hypertension have their blood pressure normalized by endothelin antagonists.

The above studies suggest a mechanistic pathway for blood pressure elevation in OSA. Intermittent hypoxia augments catecholamine release because of neuronal activation mediated by the chemoreceptor and facilitation at catecholamine releasing nerve and adrenal cells. The hypoxia and metabolic syndrome damage vascular endothelium, leading to exaggerated pressor responses to catecholamines, angiotensin II and endothelin. The baroreflex should buffer this pressor response, as should endothelial release of nitric oxide (NO). However, both the baroreflex and endothelium are damaged in patients with OSA and

the metabolic syndrome. The consequence of inadequate blood pressure buffering is a prolonged pressor stimulus.

Intermittent hypoxia raises blood pressure in rats, mice and man. Nevertheless, the complex pathophysiology of OSA patients makes it difficult to state that intermittent hypoxia is a major cause of hypertension in human OSA. One large study failed to find that OSA raised blood pressure when adjusting for the effects of obesity (3). Patients with OSA also have sleep disruption, decreased REM and slow wave sleep and usually have the metabolic syndrome (6). An ongoing study of a large cohort of normotensive elderly men with OSA finds that lack of slow wave sleep, not sleep apnea, predicts the development of hypertension (Fung, M. personal communication). Treatment with CPAP can nearly eliminate apneas, yet CPAP therapy has had a disappointingly small effect on blood pressure of patients with OSA (2). These considerations cast doubt on the primacy of hypoxia as a cause of hypertension in OSA, yet hypertension is a problem for a majority of patients with OSA. Unlike animal models that separate out the causes of hypertension, human experience combines overeating, lack of exercise, consumption of saturated fats and OSA into a frequently lethal pathology wherein OSA itself may double mortality (1).

Fluid balance and OSA

In edematous states such as congestive heart failure fluid accumulation appears to predispose to OSA and diuretic therapy may decrease the number of apneas (28). Excess fluid retained in the legs can shift toward the neck during recumbence and this may contribute to OSA in patients with resistant hypertension, obesity or mild renal insufficiency (29). The 5 to 10% of patients with hypertension resistant to therapy often have both hyperaldosteronism and OSA (30). Nitric oxide (NO) participates in the regulation of sodium and water excretion (31) and inhibition of endothelial nitric oxide synthase (32) decreases salt and volume excretion. These fluid retaining states can predispose toward both OSA and hypertension. However, patients with OSA who do not have a primary cause for fluid retention may instead experience a spontaneous diuresis. Inspiratory effort due to upper airway obstruction in OSA increases venous return into the heart, stretching the right atrium and causing release of BNP. Children with OSA had high levels of BNP (32) as did adults with OSA (33). Most patients with mild to moderate OSA and hypertension have normal aldosterone levels (34). Since OSA increases nighttime blood pressure, it would be expected to cause a nocturnal pressure diuresis, which we have observed in a series of patients with OSA. This may be behind the observation that diuretics are not very effective antihypertensive drugs in patients with OSA and hypertension uncomplicated by fluid retention (35). In addition, diuretic therapy can increase sympathetic nervous activity, which is already elevated in OSA. In sum, diuretic therapy is beneficial for patients with OSA who have fluid retention but may not be helpful for the many OSA patients who have elevated nighttime BNP levels and a nocturnal diuresis.

The blood pressure response to drugs

The blood pressure response to antihypertensive drugs of OSA patients can reveal important cardiovascular characteristics. Rats exposed to intermittent hypoxia develop hypertension, which can be prevented by a scavenger of reactive oxygen species; no similar treatment has been tried in man. However, humans with OSA have been treated with CPAP to eliminate the source of intermittent hypoxia and the blood pressure lowering effect of CPAP has been small, about one-fourth that of many antihypertensive drugs. Patients with OSA have increased sympathetic nerve activity both night and day. The hypotensive effect of drugs that act on sympathetic nerves has been little studied in OSA. Clonidine decreases REM sleep, the period with the greatest density of apneas, and moderately diminishes apneas,

shortens sleep latency and increases total sleep time. However, the effect of clonidine on blood pressure in OSA patients has not been systematically studied, but the effect of adrenergic receptor blockers suggests that sympathetic nervous activation drives some of the hypertension of OSA. The β_1 specific antagonist atenolol was the most effective agent tested in two comparative studies (33, 35). The β_1 specific antagonist nebivolol was also an effective antihypertensive in patients with OSA (25). The α_1 antagonist doxazosin diminished arterial constriction following apneas, but failed to lower nighttime blood pressure any more than enalapril. Since doxazosin does not lower blood pressure very well in recumbent subjects, its small effect on nighttime blood pressure may reflect a postural effect. In sum, although drugs that decrease sympathetic nerve activity have not been adequately studied in the hypertension of OSA, drugs that block sympathetic stimulation of β_1 adrenergic receptors have been among the most effective antihypertensive agents.

Renin release is stimulated by β_1 receptors and renin catalyzes the formation of angiotensin II, a potent pressor. Renin and angiotensin II levels are normal or slightly increased in OSA. The ACE inhibitors block the formation of angiotensin II and lowered BP effectively, but not dramatically in two studies of OSA hypertension (37, 38). The angiotensin II receptor antagonist valsartan had a similar antihypertensive effect (25). Angiotensin II causes vasoconstriction and stimulates the release of aldosterone. Aldosterone levels are generally normal in OSA except in patients with treatment resistant hypertension or severe OSA (30, 39). The aldosterone antagonist spironolactone has been remarkably effective in treating resistant hypertension (40) and a recent preliminary report suggests that it can also decrease the severity of OSA (41). The renin-angiotensin-aldosterone axis is stimulated by the sympathetic nervous system and angiotensin II and aldosterone may be elevated in severe OSA. Treatment responses support the role of angiotensin II and aldosterone in the hypertension of severe OSA.

In summary, animal and human models of OSA using intermittent hypoxia develop many of the sympathetic neuronal, cardiovascular and blood pressure abnormalities seen in OSA patients. This begins with a direct effect of intermittent hypoxia on the chemoreceptor, which leads to chronic activation of sympathetic nerve output. The consequent blood pressure elevation would ordinarily be countered by the baroreflex and by endothelial NO release, but both are impaired by intermittent hypoxia. Unfortunately, this blood pressure elevation typically occurs in patients with the metabolic syndrome, which is also associated with impaired baroreflex and endothelial function. Treatment of the OSA typically has only a modest effect on hypertension, since it can ameliorate the intermittent hypoxia, but not the metabolic syndrome. Severe OSA has been associated with increased angiotensin and aldosterone; moderate OSA was usually associated with normal levels of these agonists. Accordingly, ACE inhibitors, angiotensin II receptor blockers and aldosterone antagonists had a moderate antihypertensive effect in moderate OSA. In severe OSA, aldosterone antagonists may be even more effective. Thiazide diuretics have not been very effective antihypertensive agents in OSA patients without fluid retention and this may reflect a spontaneous diuresis in OSA driven by natriuretic peptides and a nocturnal pressure diuresis. The sympathetic neuronal activation of OSA suggests that sympatholytic drugs should be effective antihypertensives and this has held true for β_1 antagonists, although other sympatholytics have had little study. These observations lead to common sense guidelines for therapy of patients with OSA and hypertension. They should be treated with CPAP to lower their excess sympathetic tone. Those non compliant with therapies directed toward the OSA should have a drug regimen to block sympathetic stimulation and they often benefit from an antagonist of the renin – angiotensin – aldosterone pathway. Thiazide diuretics may have only a modest effect on blood pressure and should be monitored closely for side effects such as increased blood glucose. However, the diuretic spironolactone has been efficacious in severe OSA. Adjunctive treatment with diet, exercise, aspirin and cholesterol lowering

agents is frequently called for to diminish the cardiovascular risk (1) of patients with both OSA and the metabolic syndrome.

OSA, hypertension and the metabolic syndrome

We have discussed OSA in hypertensive patients with the metabolic syndrome. However, these are distinct entities and their individual influences on blood pressure are important. Unfortunately, most studies cannot separate the influences of OSA from those of the metabolic syndrome on blood pressure. This may be because obesity can cause OSA and OSA may predispose to the metabolic syndrome (42). The common coexistence of these two syndromes among hypertensives creates important considerations for antihypertensive therapy. Perhaps the most defining characteristic of the metabolic syndrome is insulin resistance. The beta adrenergic blockers effectively lower blood pressure in OSA, but some have been associated with worsening insulin resistance. Since the ACE inhibitors and angiotensin receptor blockers have been associated with improved insulin sensitivity, they may be first line therapy for many with the metabolic syndrome. Non-specific beta blockers should be avoided in OSA, since they might worsen airway obstruction and insulin sensitivity. The beta blockers carvedilol and nebivolol are claimed to not worsen insulin resistance and one of them has been quite successful in lowering blood pressure of patients with OSA (25). On the other hand, the thiazide diuretics have not been as effective at lowering blood pressure in patients with OSA and also worsen insulin resistance. These considerations guide initial antihypertensive therapy in OSA and the metabolic syndrome. Unfortunately, many of these patients have difficulty to treat hypertension that requires multiple drugs to return blood pressure to normal. There is no guidance in the literature as to the best second or third drug for hypertensive OSA patients, but both basic research and clinical studies suggest that a sympatholytic agent should be one component of therapy.

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Most patients with obstructive sleep apnea (OSA) and hypertension also have multiple aspects of the metabolic syndrome such as insulin resistance, obesity and hyperlipidemia, which lead to atherosclerosis. Pathways leading to hypertension from the intermittent hypoxia of OSA are shown in the upper part of the figure. Pathways leading to hypertension from the metabolic syndrome are shown ascending from the bottom. Both OSA and the metabolic syndrome are associated with endothelial damage. The + signs indicate an exaggerated pressor response to endothelin and to sympathetic agonists in OSA. Excess activation of the renin-angiotensin-aldosterone pathway has been documented in severe human OSA, but not in mild to moderate OSA. Chromaffin cell activation has been demonstrated in animal models of OSA, but not in human subjects. Animal models demonstrate the effects of intermittent hypoxia for most of the descending pathways in the figure. However, the metabolic syndrome is so prevalent in hypertensive humans with OSA that the effects of OSA in humans have not been clearly separated from the effects of the metabolic syndrome.