Sympathetic Over Activity in the Etiology of Hypertension of Obstructive Sleep Apnea

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This will be the last in this series addressing previously published articles in SLEEP and the progress in that scientific area since their publication. For reasons of space, we have elected not to publish this original article. However, the reference is: Fletcher EC, Miller J, Schaaf JW, Fletcher JG: Urinary catecholamines before and after tracheostomy in patients with obstructive sleep apnea and hypertension. SLEEP 1987;10:35-44. This reference can be easily found on the Journal Website.

BACKGROUND

PUBLISHING NEARLY SIMULTANEIOUSLY IN 1985, FOUR GROUPS DESCRIBED AN ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNEA AND SYSTEMIC HYPERTENSION.1-4 Over the next 15 years, researchers argued the etiologic association between these two disorders. This argument centered around co- morbidity factors such as obesity, male sex, and advanced age as probable causes of hypertension in sleep apnea patients rather than apnea itself. Recently, evidence from extensive epidemiological studies, case control studies, and experiments with obstructive apnea and intermittent hypoxia in animals strongly point to the fact that obstructive sleep apnea is an independent risk factor for systemic hypertension.5-8

For reasons which follow, over activity of the sympathetic nervous system remains a viable theory as to the mechanism leading to systemic hypertension in obstructive apnea patients. This hinges on several observations: 1) elevated catecholamines and direct measurement of muscle sympathetic nerve activity in obstructive sleep apnea subjects during apneas as well as awake; 2) observation of differing vascular reactivity between obstructive sleep apnea subjects and controls, 3) changes in sympathetic (humeral, muscle sympathetic nerve activity) and vascular reactivity with treatment of the obstructive sleep apnea, and 4) confirmation of these observations in animals subjected to intermittent hypoxia or apnea. What role sympathetic nervous system over activity plays in “essential” hypertension in general is important to understand how it might affect blood pressure in obstructive sleep apnea patients.

Classic theory holds that sympathetic over activity may be important in initiating “essential” hypertension, but it’s role in sustaining chronic blood pressure elevation is questionable.9 This theory was popular 20 years ago because of the observation of high cardiac output and high sympathetic activity in young patients with systemic hypertension. It was proposed that long-term vascular adaptation occurred in response to high cardiac output and that structural changes in the vasculature must sustain the hypertension, since cardiac output returns to normal levels later in the disease process. While this theory fit young hypertensives, the onset of most hypertension is after the age of 60 years. Evidence to support the role of sympathetic nervous system over activity in the early phase of hypertension included increase in norepinephrine levels in blood and various organs, increased total body norepinephrine spillover, and increased muscle sympathetic nerve activity measured directly. Later, in established hypertension, normal levels of norepinephrine are observed but this is believed to be abnormal (high) since normal catecholamine levels in the face of hypertension is inappropriate.

Current evidence suggests that sympathetic nervous system over activity still contributes to the later stages of systemic hypertension. First, normalization of blood pressure with alpha-blockers in hypertensive patients causes plasma norepinephrine to double. It appears that sympathetic over activity is being suppressed by the chronically increased blood pressure and is “unmasked” by lowering it. Secondly, organ specific radiotracer spillover studies show markedly elevated cardiac and renal sympathetic nerve activity in essential hypertension. Thirdly, nor-epinephrine and angiotensin II demonstrate growth promoting influences on vascular smooth muscle. These hormones could contribute to chronic changes in contractile force by creating vascular hypertrophy and resetting blood pressure to a higher threshold.

Sympathetic Nerve Activity in Human Obstructive Sleep Apnea

Strong epidemiological data linking obstructive sleep apnea and systemic hypertension were lacking in the mid 1980’s. A mechanistic link was sought to explain this relationship. It was logical to examine parameters of sympathetic activity in sleep apnea patients, partly because sympathetic over activity was espoused as a cause of human “essential” hypertension and partly because hypoxic chemoreflex activation (as seen in apnea) in animals (e.g. spontaneously hypertensive rats) resulted in increased sympathetic traffic and blood pressure.10 A theoretical mechanism follows.

Acute hypoxia and negative pressure effort against a closed airway lead to chemoreceptor activation and increased sympathetic activity (peripheral, adrenal and renal). Baroreceptor resetting may also occur, contributing to increased basal blood pressure. Circulating and tissue hormones such as angiotensin II, catecholamines, endothelin-1, thromboxane A2, prostacyclin and renin may play a role but their activity is difficult to prove in a chronic setting. Down regulation of vasodilators such as nitric oxide (NO), through generation of superoxide anions or nitric oxide synthase activity might also occur. The end result of these is increase in resting vascular tone (see below). This has been demonstrated in apnea patients by blunted vasodilator and vasoconstrictor dose response curves. Over the long term, there may be vascular remodeling, with changes in the wall to lumen ratio of small resistance vessels. Norepinephrine and angiotensin II, both of which are released by increased peripheral sympathetic tone, are parallel growth-promoting or trophic...
factors on the heart and vasculature. These two hormones can contribute to long term changes in vessel wall and ventricular compliance through hypertrophy of smooth muscle and myocardium.

A unique opportunity presented itself to us in the mid 1980’s. Eight subjects with severe, symptomatic obstructive sleep apnea were about to undergo elective tracheostomy (this was the pre-CPAP era). We collected urinary catecholamines before and within 2 weeks after tracheostomy. Eight hour aliquots of urine were collected during daytime, evening and overnight hours in these hypertensive apnea patients and in five obese hypertensive, non-apneic controls. While urinary epinephrine and metanephrine levels were not above control, norepinephrine and its metabolite normetanephrine (reflecting peripheral sympathetic synapse activity) were significantly elevated (Figure 1). Following tracheostomy, catecholamines in these 8 patients returned to control levels in each aliquot. More or less similar data have since been published by Jenin12 (plasma catecholamines), Lipinsky13 (plasma and urinary catecholamines), Maroni14 (plasma catecholamines) and Demsdale.15 More recently, catecholamine levels were examined in 38 patients with obstructive sleep apnea who were prospectively treated with either nasal CPAP or placebo CPAP.16 Both plasma and urinary catecholamine levels fell by nearly 50% in the actively treated patients while remaining at baseline in placebo patients.

Insertion of a tungsten microelectrode into the peroneal nerve allows measurement of muscle sympathetic nerve activity (MSNA) directly. Hedner published a study measuring MSNA in obstructive sleep apnea subjects in 1988.17 These authors clearly demonstrated that the hypoxia and hypercapnia of acute apnea were associated with increased MSNA, returning to baseline following the event. Subsequent publications corroborated this work and in addition showed that the use of nasal CPAP to eliminate apneas predictably eliminated the cyclic increase of sympathetic nerve activity.18 Of great significance was the demonstration that sympathetic traffic was elevated (Figure 2) during daytime normoxic wakefulness in obstructive sleep apnea patients and that these differences correlated with arterial plasma norepinephrine levels in subjects versus controls.19 This elevated activity persisted in both normotensive and hypertensive apneic patients. Somers et al. showed through the use of MSNA that normal autonomic mechanisms are disrupted by obstructive sleep apnea.20 Instead of the normal decrement in blood pressure, heart rate, and sympathetic nerve activity (which accounts for the nocturnal “dip” in blood pressure), sympathetic activity varies solely as a function of recurrent apneic events.

Importantly, follow-up in obstructive sleep apnea patients with nasal CPAP treatment has demonstrated marked lowering in MSNA after long-term treatment (Figure 3).21 Eleven obstructive sleep apnea patients and nine “controls” (non-compliant with CPAP therapy) were followed for one year by repeat measures of MSNA at baseline, one and six months, and one year after beginning therapy. Patients compliant with nasal CPAP showed a striking diminution in MSNA at one year, but “controls” showed no change in MSNA activity (Figure 4).

These data suggest that recurrent hypoxia and hypercapnia acutely stimulate chemo-receptors, invoking cyclic sympathetic over activity hour after hour throughout the night. But how would this translate into sustained, daytime non-hypoxic sympathetic over activity, elevating diurnal systemic blood pressure? The answer to this is suggested by work from Xie et al.22 These authors administered a hypercapnic hypoxic gas mixture intermittently (20s on, 40s normoxia) to 7 healthy patients for 20 minutes. SaO2 was cyclically reduced to between 79-85% and CO2 to an end title level 5 mmHg above baseline. MSNA was measured throughout the cyclic asphyxia, progressively increasing to 175% of baseline in the final 5 min of intermittent hypoxia. However, unlike minute ventilation, which returned to baseline 2 minutes after terminating the asphyxia, MSNA activity remained elevated out to the end of the experiment (20 minutes longer). MSNA followed a cyclic crescendo decrescendo pattern of asphyxia, but with each successive 40s inter-asphyxic (normoxic) period, MSNA became progressively elevated, not returning to baseline (Figure 5). By the end of the 20 minute cyclic asphyxia-normoxia period, sympathetic activity during the resting normoxic phase was equal to sympathetic activity during the asphyxic phase. The authors attribute this phenomenon to facilitation of central nervous system sympathetic memory, either by enhanced synaptic efficacy or by persistent increase in excitatory central nervous system neuro-transmitters.

A study by Greenberg et al23,24 suggests how central nervous system sympathetic facilitation may occur following recurrent bouts of apnea or

![Figure 1](https://academic.oup.com/sleep/article-abstract/26/1/15/2696657/6030644)

![Figure 2](https://academic.oup.com/sleep/article-abstract/26/1/15/2696657/6030644)
hypoxia. These researchers exposed rats to 30 days of intermittent hypoxia. They found increased c-fos labeling in the nucleus tractus solitarius, medullary reticular formation, midline raphé, and other brainstem regions involved in regulation of tonic and reflex control of sympathetic neural discharge and integration of peripheral afferent input. The authors suggested that c-fos changes after chronic intermittent hypoxia might indicate neuronal genetic transcription modulating central nervous system sympathetic output. With repetitive hypoxic exposure, facilitation of the central nervous system sympathetic centers could lead to increase sympathetic output even after the stimulus is terminated.

**Vascular Reactivity in Human Obstructive Sleep Apnea**

The mechanism of hypertension in obstructive sleep apnea patients is almost certainly multi-factorial. Increase in resting vascular tone and reactivity, partially through sympathetic over activity and/or changes in vascular neurohumoral/neurotransmitter agents would account for sustained blood pressure elevation. Alteration of the vascular structure could also affect vascular resistance and reactivity. Several studies have emerged addressing changes in vascular tone in patients with obstructive sleep apnea.

Carlson et al. examined forearm blood flow and vascular resistance in eight normotensive and eight hypertensive obstructive sleep apnea subjects subjected to graded acetylcholine and sodium nitroprusside infusion. Both groups of obstructive sleep apnea subjects showed diminished responsiveness to the vasodilator effect of acetylcholine (nitric oxide dependent) compared to matched controls, suggesting impaired nitric oxide release. The hypertensive obstructive apnea subjects also showed diminished vascular reactivity to sodium nitroprusside (nitric oxide independent) suggesting vascular structural changes not evident in the other groups.

The same group later addressed vasoconstrictor responses to infused angiotensin II in 10 normotensive apnea males. Following angiotensin II infusion, conductance was 40% lower in the sleep apnea subjects compared to matched healthy controls. This increased vasoconstrictor activity is compatible with 1) early structural alterations of the arteriolar wall 2) increased sensitivity of the vascular wall to angiotensin II, or 3) reduced co-activity of endothelial nitric oxide. In the third manuscript of this series, the same authors examined norepinephrine, phenolamine (alpha-blocker) and isoproterenol (beta-II blocker) vascular reactivity in 10 normotensive controls and obstructive sleep apnea subjects. They found that norepinephrine vasoconstriction (but not phenolamine) and isoproterenol vasodilation were diminished in the apnea group. This suggested functional down regulation of both α and β adrenergic vascular receptors, either because of decreased sensitivity or reduced numbers of receptors, compatible with chronically elevated sympathetic stimulation.

Conclusions that can be drawn from these studies are limited because they are "point in time" studies. Longitudinal studies could examine sympathetic over activity in treated patients, thus furthering our knowledge. Such studies have been done. For example, forearm vasodilation dose response curves were performed in 12 normotensive obstructive sleep apnea patients versus 12 non-apnea controls using either bradykinin (endothelium NO dependent pathway) or nitroglycerin (NO independent). The authors found that the bradykinin curve was depressed (lower nitric-oxide dependent vasodilatation) when compared to the controls. More importantly, after two months of treatment with nasal CPAP, there was a return of the curves to control levels. The degree of abnormality appeared to be related to the severity of hypoxemia during sleep.

Another longitudinal study produced similar results. Imadojemu et al. examined reactive hyperemic blood flow, blood pressure and MSNA in obstructive sleep apnea patients (N=8) before and after (N=7) between one and 24 months of nasal CPAP therapy. The obstructive sleep apnea subjects had markedly reduced reactive hyperemic blood flow and forearm vascular conductance at baseline compared to nine, non-apneic controls (Table 1). MSNA in treated apnea subjects decreased after therapy by about 40 percent from baseline. Both reactive hyperemic blood flow and conductance increased by about 25 percent. These results are extremely important because they demonstrate that chronic therapy with nasal CPAP leads to recovery of vascular responsiveness.

**Animal Models of Sympathetic Over Activity**

It is helpful when findings in humans can be correlated with information from animal models proposed to mimic the disease process. The development of animal models to simulate the various cardiovascular effects of recurrent apnea and hypoxia have increased our ability to define the mechanisms leading to hypertension in apnea patients. The dog and rat have been used to study chronically elevated blood pressure in the setting of repetitive intermittent hypoxia or apnea.
Brooks et al. have developed a dog model of sleep apnea with repetitive, intermittent occlusion of a tracheostomy using telemetry and real time EEG sleep staging. These authors have shown that intermittent occlusion of the airway daily from one to three months produces a 16 mmHg increase in mean resting arterial blood pressure, which reverses several weeks after discontinuation of apnea. Recurrent arousal administered in a frequency and pattern similar to the apnea did not result in sustained elevation of daytime blood pressure.

Indirect evidence of sympathetic over activity and changes in vascular reactivity have also been described in intermittent hypoxia rats. Rats are exposed to rapid swings in ambient oxygen creating changes in SaO₂ similar to that seen in humans with obstructive apnea, but without the apnea. In this model, rats are individually housed in cylindrical Plexiglas chambers. Using a timed solenoid valve, nitrogen followed by a compressed air flush reduces the ambient fractional concentration of oxygen (FiO₂) to 3-5% for approximately 3-6 seconds. The rat is then returned to normoxia and the cycle repeated, twice per minute during the day for six to eight hours on consecutive days. Serial arterial blood samples during episodic hypoxia have shown the average nadir level of SaO₂ in this system is 60 to 80%, similar to that in human apnea patients.

Studies with this model over the past 12 years have demonstrated that recurrent, intermittent hypoxia (up to 800 episodes per day) for 35 days can cause increase in mean arterial blood pressure of 10-20 mmHg above baseline in unrestrained rats. The hypertension lasts 1-3 weeks after cessation of episodic hypoxia. Hypertension resulting from intermittent hypoxia in this model is blocked by section of the carotid sinus nerve, compromising peripheral chemoreceptor function and ultimately sympathetic activation.

Supporting sympathetic nervous system activity as a chronic process in this model is the fact that ablation of the peripheral sympathetic nervous system using intra-peritoneal injections of a sympathetic nerve toxin (6 OH-dopamine) blocks the increase in blood pressure. Also, bilateral renal artery denervation (ablation of renal sympathetic) and bilateral adrenal medullectomy eliminate the chronic diurnal blood pressure increase. This suggests that recurrent acute sympathetic nervous system activity works through the kidney to bring about diurnal elevation of blood pressure. The fact that adrenal medullectomy with intact renal nerves also blocked the hypertension suggests that circulating epinephrine may also play a role in regulating blood pressure in the setting of hypoxic stress. Epinephrine is known to enhance presynaptic norepinephrine release and facilitates neurogenic vasosconstriction. Epinephrine may also enhance renin-angiotensin activity through renal artery sympathetic activity. Post chronic intermittent hypoxia levels of plasma epinephrine, norepinephrine, renin-angiotensin system activity, and tissue catecholamines (heart, kidneys) are roughly two to three times those of respective control animals. Angiotensin II is involved, as demonstrated by increased renin-angiotensin system activity and the fact that an angiotensin II receptor blocker, Losartan, prevents the chronic blood pressure response to episodic hypoxia.

Similar to the human data on vascular dose response curves, data in rats suggests diminished vascular reactivity changes following chronic administration of intermittent hypoxia. Tahawi et al examined vascular dose response curves in rats subjected to episodic hypoxia for 35 days compared to non-exposed controls. Those rats exposed to intermittent hypoxia increased resting blood pressure from a mean baseline of 93 mm/Hg to 108 mm/Hg. Vascular reactivity was measured in a cremaster muscle preparation (arterioles < 50 microns observed under videomicroscopy) from the hypoxia and control rats. There was no difference in vascular reactivity to norepinephrine or endothelin, but acetylcholine vasodilatation was attenuated in the intermittent hypoxia exposed rats, similar to the findings of Carlson and Duchna. Furthermore, at the end of the experiment, vasoconstriction was induced via administering L-NAME which blocks nitric oxide synthase and enhances vasosconstriction. The rats that were subjected to intermittent hypoxia showed less vasconstrictor response than the control rats. This implied less baseline nitric oxide activity maintaining vasodilator tone.

**SUMMARY**

Beginning with modest clinical observations in 1984, a picture has evolved suggesting that sympathetic nervous system activity over activity may be responsible in part for the elevated blood pressure seen in obstructive sleep apnea patients. Early studies of urinary and plasma catecholamines indirectly suggested sympathetic over activity carried to daytime, non-apneic conditions. Later intra-neuronal recordings of muscle sympathetic nerve activity directly demonstrated both acute and diurnal (non-apneic) sympathetic over activity. Most importantly, diurnal sympathetic over activity has been shown to diminish with adequate treatment of apnea using nasal CPAP. Norepinephrine and angiotensin II are both released with increased peripheral sympathetic activity and are parallel vascular growth-promoting factors. Thus, one would expect alterations in vascular structure and function in a state of chronic sympathetic over activity. While changes in peripheral vascular structure have not been demonstrated in hypertension of sleep apnea, changes in peripheral vascular responsiveness have. There is reduced response to acetylcholine and isoproterenol vasodilation, and to norepinephrine and angiotensin vasoconstriction in humans with sleep apnea. Some of these vascular reactivity changes are shown to reversed with chronic nasal CPAP treatment. Finally, complimentary to the above evidence in humans, there is indirect evidence of sympathetic over activity as well as differences in vascular reactivity in intermittent hypoxia challenged rats.

We have made significant strides in the past 15-20 years towards understanding systemic hypertension related to sleep apnea, especially the role of the sympathetic nervous system. Future research will need to look at exact mechanisms of sympathetic nervous system over activity, particularly how central nervous system pathways may undergo facilitation, leading to daytime over activity. Furthermore, the mechanisms of...
sustained hypertension in sleep apnea patients is almost certainly of multiple etiologies. There is no marker for separating sleep apnea patients with hypertension derived solely from intermittent hypoxia from other secondary causes. Perhaps endothelial cell molecular markers could help to identify patients at risk for cardiovascular change associated with snoring and apnea, as well to guide treatment. Finally, studies demonstrating microvascular changes in blood vessels are extremely difficult to do, but promise to yield important knowledge about cellular mechanisms and results of long term treatment of sleep apnea on cardiovascular disease.

REFERENCES