Hypertension and CPAP Treatment of Sleep Apnea
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There is abundant evidence that obstructive sleep apnea is associated with the development of hypertension and that hypertension has grave consequences for cardiovascular disease. Effective treatment of sleep apnea could impact the treatment of hypertension and thereby have immense consequences for public health. This article will describe evidence that the gold standard treatment for sleep apnea has substantial value in the treatment of hypertension.

**CPAP effectively treats the symptoms of sleep apnea**

Continuous positive airway pressure (CPAP) treatment eliminates the principal physiological abnormality in obstructive sleep apnea—the collapse of the pharynx during sleep, which results in repetitive upper airway obstruction. A randomized controlled trial demonstrated the effectiveness of CPAP in the treatment of sleep apnea, reducing excessive daytime sleepiness and improving daytime functioning. Men with obstructive sleep apnea were randomly assigned to receive CPAP or subtherapeutic treatment in which the machine was adjusted to deliver too little pressure to be effective in preventing pharyngeal collapse (one tenth of the effective pressure). After four weeks the patients were assessed for daytime sleepiness and self-reported health status. For two measures of daytime sleepiness, therapeutic CPAP users had large improvements that were significantly greater than seen with the subtherapeutic controls. A similar result was seen with the ability of the patients to maintain wakefulness which, for the therapeutic group, was similar to the scores of healthy people. Self-reported health status also showed a large improvement compared to the subtherapeutic control. These improvements demonstrate that CPAP effectively treats the symptoms of sleep apnea.

**Effects of sleep apnea on hypertension and sympathetic nervous activity are attenuated by CPAP**

Does treating sleep apnea work to treat hypertension? Because the sympathetic nervous system activates the body’s fight or flight response, including raising blood pressure, a small study of patients referred for evaluation of sleep apnea measured blood pressure, heart rate, and sympathetic nervous activity during sleep and wakefulness. It further examined the effects of treatment with CPAP. Of eighteen patients referred, two did not have sleep apnea and six could not be studied because it was impossible to obtain stable nerve recordings of sympathetic nervous activity using microneurography, in which a fine tungsten electrode is inserted into the peroneal nerve of one leg. For the remaining ten subjects, age and sex matched volunteers, free of sleep apnea and from whom successful nerve recordings could be obtained, were used as controls. Five obese subjects who were free of sleep apnea were also recruited as controls. Sympathetic burst frequency when awake was much higher in sleep apnea patients (fifty-nine bursts/minute) than in age and sex matched controls (thirty-four bursts per minute) or obese controls (twenty-four bursts per minute). Overnight recordings of sympathetic nervous activity, sleep apneas, and blood pressure showed large oscillations in blood pressure and sympathetic nervous activity in synchrony with apneas. Sympathetic nervous activity ceased abruptly at the end of apneic events, and blood pressure went as high as 240/130 mm Hg in some subjects. Despite being much higher

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than in normal subjects during wakefulness, sympathetic nervous activity in sleep apnea patients increased to still higher levels during sleep. With sleep apnea patients, blood pressure did not fall during sleep, as it would in healthy individuals, and peak blood pressure was higher than wakefulness for all sleep stages. Blood pressure, heart rate, and sympathetic activity were also recorded during sleep for three of the normal controls. As expected, and in contrast to what was seen with the sleep apnea patients, blood pressure and sympathetic nervous activity decreased during sleep. Four patients with moderate to severe sleep apnea were awakened after several hours of sleep and were treated with CPAP that same night. After treatment with CPAP, blood pressure increases during sleep were not significantly different from wakefulness, and sympathetic nervous activity decreased during sleep, as was the case with the controls. Thus, the normal cycles of sympathetic nervous activity and blood pressure changes are disrupted in sleep apnea patients, but these disruptions are greatly attenuated by even brief treatment with CPAP.

One way in which obstructive sleep apnea is thought to cause hypertension is to increase the activity of the sympathetic nervous system, creating an autonomic nervous system imbalance. A double-blind, randomized controlled trial was done to see if treatment with CPAP improves this imbalance3. Trial subjects were males with moderate to severe sleep apnea recruited from patients referred to a sleep center because of excessive daytime sleepiness. After randomization, patients were assigned to either therapeutic CPAP or subtherapeutic CPAP, in which the pressure of the machine was set too low to keep the pharynx open. Patients were assessed at baseline and after four weeks of treatment for urinary catecholamine excretion, baroreflex sensitivity, arterial stiffness, and twenty-four-hour ambulatory blood pressure. Fifty patients completed the therapeutic trial and forty-nine completed the subtherapeutic trial. Therapeutic CPAP treatment reduced twenty-four-hour excretion of the catecholamine normetanephrin, the metabolite of the neurotransmitter released by sympathetic nervous system neurons that act to increase the rate of heart contractions, by a statistically significant average of 26 percent. Baroreflex sensitivity, an established index of cardiac parasympathetic responsiveness, increased by a significant average of 24 percent following therapeutic CPAP treatment, which means that the ability to relax the heart to normal blood pressure following a stress increased toward normal values. Arterial stiffness decreased significantly (5.4 percent) following therapeutic CPAP. Twenty-four-hour mean ambulatory blood pressure fell 2.6 mm Hg4. Thus, compared to subtherapeutic CPAP, four weeks of therapeutic CPAP led to significant improvement in baroreflex sensitivity and arterial stiffness, and a significant reduction in sympathetic nervous activity and twenty-four-hour mean ambulatory blood pressure. The authors conclude that treatment of symptomatic obstructive sleep apnea patients with CPAP reduces a number of well-established risk factors for cardiovascular disease, including hypertension, and may thus improve patients’ survival.

Adherence to CPAP treatment rapidly reduces blood pressure and makes drug treatment more effective

Can treatment with CPAP modify hypertension? A randomized trial compared therapeutic and sham CPAP treatment in 118 men between thirty and seventy-five years of age with sleep apnea of more than ten events per hour5. Diagnosis of hypertension at entry was not a factor in choosing trial subjects. An automatic device recorded twenty-four-hour ambulatory blood pressure every thirty minutes. Daytime sleepiness was assessed by questionnaire and by an objective test.

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4 This blood pressure data was also included in another study discussed in this article; see note 5, infra.

Patients were then randomly assigned to either therapeutic CPAP or subtherapeutic CPAP, in which the pressure was set too low to hold the pharynx open. A second twenty-four-hour ambulatory blood pressure measurement was made after four weeks of treatment, and the mean nightly use of CPAP was determined from the meters on the machines. Average twenty-four-hour mean arterial pressure was significantly reduced in the therapeutic CPAP group—a decrease of 2.5 mm Hg compared to an increase of 0.8 in the subtherapeutic CPAP group. The decrease was 1.1 mm Hg in those with less severe sleep apnea and 5.1 mm in those with more severe sleep apnea. Those patients who used therapeutic CPAP more than the median five hours per night had a drop of 4.9 mm Hg compared to no change in those who used less than the median five hours per night. Eleven patients in each group were taking drugs to treat hypertension. Those in the subtherapeutic group on antihypertensives showed a small decrease of 1.2 mm Hg while those in the therapeutic group taking antihypertensives showed a drop of 7.9 mm Hg. This unexpected benefit could indicate that untreated sleep apnea antagonizes the effectiveness of antihypertensives. As to how significant are the reductions in hypertension seen in this study, the authors note that large prospective studies have established that a decrease of 3.3 mm Hg would be expected to be associated with a 20 percent reduction of risk for stroke and a 15 percent reduction of risk for coronary heart disease.

A similar study done a few years later obtained similar results. The principal difference was that therapeutic or subtherapeutic CPAP was continued for twelve weeks instead of four weeks before the second measurement of twenty-four-hour ambulatory blood pressure was made. In this case the subjects were 100 consecutive respiratory clinic patients newly diagnosed with sleep apnea on the basis of overnight polysomnography showing five or more events per hour plus daytime sleepiness or similar symptoms. After recording baseline twenty-four-hour ambulatory blood pressure, the fifty-six patients who agreed to participate were randomized into two groups receiving either therapeutic or subtherapeutic CPAP treatment. Twenty-three patients in each group completed the three-month study. There were no significant changes in any of the blood pressure parameters in the subtherapeutic group. In the therapeutic group there were significant decreases in twenty-four-hour diastolic and mean blood pressure and sleep time systolic and mean blood pressure.

A third randomized placebo-controlled trial used a crossover after six weeks of treatment. The initial goal of the study was to determine the effects of CPAP on the metabolic syndrome and its components (in addition to raised blood pressure, increases in fasting glucose and lipid levels and insulin resistance). The subjects were patients with a confirmed diagnosis of sleep apnea (greater than fifteen events per hour, i.e., moderate to severe sleep apnea) recruited from a sleep clinic and not known to suffer from other medical conditions or to be receiving medications. Patients with waking blood pressure of 180/110 or greater were excluded, but patients with abnormal glucose or lipid levels in the absence of diabetes were not excluded. Patients were predominantly obese and sleepy during the day. After baseline measurements of body composition and metabolic variables, patients were randomized to receive either therapeutic CPAP or sham CPAP with pressure set too low to provide effective therapy. After six weeks, the patients were assessed and the therapeutic group was switched to sham treatment and vice versa, followed by an additional six weeks with a final assessment. Compliance with CPAP use was automatically recorded and defined as use of 3.5 hours per night or more. Thirty-four patients completed the study (seventeen

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in each group). After six weeks of CPAP therapy, subjective sleepiness, systolic, diastolic, and mean arterial blood pressure were all significantly lower compared to the results of the same individuals after six weeks of sham treatment. No significant changes were observed in any metabolic variable. The decreases observed in blood pressure in this blinded placebo-controlled study show that changes in an important cardiovascular variable can occur relatively rapidly and independently of changes in metabolic outcomes.

**Effectiveness of CPAP in reducing blood pressure increases with severity of sleep apnea, compliance in using CPAP, and severity of hypertension**

A meta-analysis of twelve randomized controlled trials of the effect of CPAP treatment of patients with obstructive sleep apnea on twenty-four-hour ambulatory mean blood pressure was done to quantify the size of the effect of CPAP, and identify the characteristics associated with the greatest blood pressure reductions\(^8\). The pooled estimate of the effect of CPAP intervention was a drop in twenty-four-hour mean ambulatory blood pressure of 1.69 mm Hg, a small but significant decrease. The authors make the point that in hypertensive patients, even reductions of 1-2 mm Hg are associated with reduced odds of stroke, major cardiovascular events, and heart failure. Statistical analysis of these trials showed that greater reduction was obtained with more severe sleep apnea and with higher use per night of the CPAP apparatus.

Comparing the effects of long-term treatment of sleep apnea in patients with different degrees of hypertension showed the greatest benefit in patients with the most severe hypertensive disease\(^9\). This was a retrospective study in which the medical records of all patients who had had a polysomnography with CPAP treatment at two medical centers in Oklahoma were reviewed. Patients included were diagnosed with obstructive sleep apnea, had a history of hypertension drug therapy, and had three or more daytime blood pressure measurements at various times during one year of CPAP therapy. Resistant hypertension was defined as a daytime blood pressure of at least 140/90 despite stable use of a combination of three or more antihypertensive medications. Two groups of patients were identified at baseline: patients with controlled hypertension on two or fewer drugs, and patients with resistant hypertension. From 764 patients screened, fifty-six were found for the controlled hypertension group and forty-two for the resistant hypertension group. Patients with resistant hypertension showed a statistically significant decrease in median mean arterial pressure (5.6 mm Hg) and systolic blood pressure by twelve months. However, there were no significant changes by three months. There were no significant changes in the controlled hypertension group, even by twelve months. Further, CPAP therapy permitted decreasing the antihypertensive drug therapy in a significant proportion of the resistant hypertension patients.

**Conclusion:** Continuous positive airway pressure (CPAP) effectively treats the symptoms of obstructive sleep apnea, attenuates the abnormal nighttime sympathetic nervous activity associated with sleep apnea, and lowers blood pressure. Treating sleep apnea has a greater effect in lowering blood pressure with longer duration of treatment, more hours of use each night, more severe sleep apnea, and more severe (drug resistant) hypertension.

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