Cardiovascular Disease and CPAP Treatment of Sleep Apnea
James B. Lewis, PhD

Because cardiovascular diseases are the leading cause of death worldwide, because of the strong association between sleep apnea and cardiovascular disease, and because continuous positive airway pressure (CPAP) is the gold standard for treating sleep apnea, a number of studies have looked at the effect of CPAP treatment of sleep apnea upon cardiovascular disease risk factors and incidence. Those studies that have specifically looked at treatment of hypertension alone as one component of cardiovascular disease are considered in a separate article.

An article published in 2007\(^1\) cited the then already extensive evidence of an independent association between obstructive sleep apnea and cardiovascular disease, particularly with hypertension, but also with ischemic heart disease, cardiac arrhythmias, and stroke. The study reviewed the cardiovascular outcomes of CPAP therapy, which was already well-documented to completely control obstructive sleep apnea and greatly improve daytime measures impacted by sleep apnea. The article cited studies demonstrating effectiveness of CPAP therapy with respect to hypertension, coronary artery disease, cardiac arrhythmias, and (with some limitations) stroke. The ways in which sleep apnea contributes to cardiovascular disease were briefly reviewed, including sympathetic nervous system overactivity, inflammation, endothelial dysfunction, insulin resistance, and disordered lipid metabolism.

**Effects upon disease incidence and survival**

In a prospective study\(^2\), 182 middle-aged men with a history of snoring, but no known cardiovascular disease, were divided into two groups according to the presence (sixty men) or absence (122 men) of sleep apnea at the beginning of the study, and followed study subjects for seven years. The results demonstrate that subjects with sleep apnea at the beginning of the study had an almost five-fold increased risk of developing cardiovascular disease over the course of seven years. Those diagnosed with sleep apnea were offered treatment using CPAP, surgery, or an oral appliance. Of the sixty men who had sleep apnea at the beginning of the study, fifteen complied with treatment and were found to be treated efficiently for sleep apnea. Among the fifteen, only one experienced cardiovascular disease over the seven years—the same rate as those without sleep apnea at the beginning of the study.

To assess obstructive sleep apnea as a risk factor for cardiovascular disease and to assess the protective effect of CPAP treatment, groups of men with or without sleep apnea, treated or untreated, were followed for an average of 10.1 years to determine the incidence of new fatal and non-fatal cardiovascular events\(^3\). The study included 264 healthy men, 377 who snored but did not have sleep apnea, 403 with untreated mild to moderate sleep apnea, 235 with untreated severe disease (or mild to moderate disease plus severe daytime sleepiness), and 372 with sleep apnea treated with CPAP. An observational study, rather than a randomized controlled trial, was done because the available evidence for the effectiveness of CPAP in controlling symptoms makes it unethical to withhold treatment for the length of time needed for the study. Therefore, the untreated group consisted of men with severe sleep apnea who were initially offered CPAP.

---


©Copyright, 2013. Doctor Alliance Group™. All rights reserved.
Cannot be copied or duplicated without express written consent from DAG™.
treatment, but who refused it. These untreated patients were offered conservative advice, such as losing weight, avoiding sleep deprivation, etc. The healthy men were chosen from a pool who did not have sleep apnea or excessive daytime sleepiness, who did not snore, and who were similar in age and body mass index to each of the men in the untreated severe sleep apnea group. A full polysomnography was done for each participant at the beginning of the study. Blood pressure and cardiovascular disease events were recorded yearly during follow-up. A fatal event was death from myocardial infarction or stroke; a non-fatal event was a non-fatal myocardial infarction, a non-fatal stroke, coronary bypass surgery, or angiography. Simple snorers and patients with sleep apnea attended the clinic at least once a year. CPAP compliance was assessed yearly as mean daily use of more than four hours per day. Non-compliant patients were not included in the final statistical analysis. The number of non-fatal cardiovascular events per 100 person-years was 0.45 for healthy men, 0.58 for simple snorers, 0.89 for untreated mild to moderate sleep apnea, 2.13 for untreated severe sleep apnea, and 0.64 for those treated with CPAP. The number of deaths per 100 person-years was 0.30 for healthy men, 0.34 for simple snorers, 0.55 for untreated mild to moderate sleep apnea patients, 1.06 for untreated severe sleep apnea patients, and 0.35 for those treated with CPAP. Thus, patients with severe, untreated sleep apnea had the worst outcomes, while simple snorers and patients treated with CPAP (for at least four hours per night) had outcomes comparable to those of healthy participants. Patients with mild to moderate untreated sleep apnea had intermediate outcomes.

To clarify the extent to which CPAP treatment of sleep apnea reduces the incidence of fatal and non-fatal cardiovascular events, a randomized controlled trial would be desirable. However, as previously stated, given the efficacy of CPAP treatment at improving the quality of life of sleep apnea patients with respect to daytime sleepiness, accident frequency, etc., it is unethical to withhold treatment from sleep apnea patients experiencing daytime sleepiness. Consequently, a randomized study was done with a cohort of non-sleepy sleep apnea patients. Participants were chosen from among patients referred to hospital sleep units for snoring or apneas observed by bed partners. Chosen participants had moderate to severe sleep apnea as determined by an overnight sleep study, no daytime excessive sleepiness, and no history of previous cardiovascular events, or chronic disease. At the beginning of the study 50 percent of the patients had hypertension. Patients were randomized to receive CPAP or no active intervention. Clinical personnel assessing cardiovascular events and blood pressure were blinded to patient treatment. Participants were followed for an average of four years to determine participants who had normal blood pressure at the beginning of the study who then became hypertensive during the study, and to determine cardiovascular events among all participants. The CPAP treatment group had 357 patients (313 male) and the control group 366 (306 male). New hypertension occurred in 147 patients and fifty-nine cardiovascular events occurred. The incident rate per 100 person-years for cardiovascular events or new hypertension was 11.02 for the CPAP treatment group and 9.20 in the control group. At the end of the study, 36 percent of the CPAP-treated participants had a mean CPAP adherence of less than four hours per night (median 1.0 h/night); 64 percent had a mean adherence of four or more hours per night (median 5.96 h/night). The latter good-compliance group had significantly fewer incidents than the former poor-compliance group (a ratio compared to the control group of 1.13 for the poor-compliance group and 0.72 for the good-compliance group). A protective effect of CPAP was thus seen in the good-compliance group even though that group was more obese and had a higher prevalence of hypertension at the beginning of the study. One reason for the lesser benefit of CPAP treatment in this study may be that CPAP is less effective in non-sleepy patients. Results may also have been skewed because patients presenting

---

with hypertension were included. In summary, this study adds to the total evidence that CPAP treatment used at least four hours per night has a beneficial effect upon cardiovascular disease incidence, but it also illustrates the difficulty of doing a completely controlled, randomized trial given the ethical issues surrounding withholding CPAP treatment.

Studies of the link between sleep apnea and cardiovascular events, and of the protective effect of CPAP treatment, have been done predominantly or exclusively in men. To clarify whether obstructive sleep apnea is also a risk factor for cardiovascular death in women, and whether CPAP treatment modifies that risk, all women consecutively referred to two sleep clinics over a nine-year period (1116) were studied for a median follow-up of seventy-two months. Each woman had a diagnostic sleep study and was classified as either a control, mild to moderate obstructive sleep apnea, or severe obstructive sleep apnea. CPAP treatment was offered to every patient in the severe category and to those in the mild to moderate category who also had daytime sleepiness. Adherence to CPAP was determined by reading the time counter on the device. Participants were considered treated if average cumulative adherence was four or more hours per day (the median adherence of patients in this group was six hours per day), and untreated if the patient declined or could not use the device or averaged less than four hours per day. The end point of the study was cardiovascular death (death from stroke, myocardial infarction, heart failure, or arrhythmia). Statistical analysis compared the number of cardiac deaths divided by the number of person years accumulated during follow-up (cardiovascular mortality rate) for each of the five groups: no sleep apnea controls (0.28 cardiovascular deaths per 100 person-years), CPAP treated with mild to moderate sleep apnea (0.10), CPAP treated with severe sleep apnea (0.31), untreated with mild to moderate (0.94), and untreated with severe sleep apnea (3.71). After adjusting for age, body mass index, hypertension, diabetes, and previous cardiovascular events, untreated severe sleep apnea was an independent predictor of cardiovascular mortality, with an adjusted hazard ratio of 3.5. The CPAP-treated severe sleep apnea, CPAP-treated mild to moderate, and untreated mild to moderate groups did not differ significantly from the control group without sleep apnea. Despite the inherent limitations of a study that cannot ethically be randomized, this study provides strong evidence that untreated, severe sleep apnea is an independent cause of cardiovascular deaths in women, that CPAP treatment eliminates the increased risk due to severe sleep apnea, and that four hours per night is a relevant minimum for effective treatment.

**Effects on disease parameters**

Because sleep apnea may contribute to the progression of heart failure, the effect of treatment of sleep apnea on disease parameters was tested in a group of twenty-four patients who were being treated for mild to moderate heart failure. The subjects underwent overnight sleep studies in a hospital sleep laboratory. After awakening they were measured for blood pressure and by echocardiography to determine left ventricular end-diastolic and end-systolic dimensions and ejection fraction. Patients were randomly assigned to either a control group that continued to receive optimal drug therapy for heart failure, or a treatment group that received CPAP in addition to optimal drug therapy for one month. No significant changes were seen within the control group. In the treated group, obstructive sleep apnea was markedly reduced, from severe to little or no obstructive apnea. The treated group also had significant reductions in daytime

---


©Copyright, 2013. Doctor Alliance Group™. All rights reserved. Cannot be copied or duplicated without express written consent from DAG™.
systolic blood pressure (by ten mm Hg) and heart rate (by four beats per minute). The treated group also showed significant improvements in heart failure parameters: the left ventricular end-systolic dimension was reduced from 54.4 to 51.7 mm and the ejection fraction was increased from 25 percent to 33.8 percent. The patients in the trial were evenly divided between ischemic and non-ischemic causes of heart failure, and comparable improvements were seen with both causes. Compliance with CPAP use in the treated group was excellent (six hours per night on average) despite the absence of daytime sleepiness before treatment, indicating that daytime sleepiness is not necessary to derive cardiovascular benefits from CPAP. Although the patients were obviously not blinded to their treatment group, the persons measuring cardiovascular outcome were blinded to the treatment group. The authors conclude that “…there needs to be greater awareness among physicians that obstructive sleep apnea may have an adverse pathophysiological role in heart failure that can be addressed by targeted therapy.”

Because established serum markers of cardiovascular morbidity are known to be elevated in patients with obstructive sleep apnea, the effect upon these markers of treatment of sleep apnea was studied, with special attention to the effect of treatment compliance, that is, the number of hours per night that CPAP was used. To assess the effect of CPAP compliance on the lipid profile and pro-inflammatory status of obese but otherwise healthy sleep apnea patients, patients with newly diagnosed moderate to severe sleep apnea were recruited from a sleep hospital unit to which they had been referred because of sleep-related breathing problems. CPAP therapy was prescribed for all patients, and they were assessed by polysomnography and by blood tests for C-reactive protein, homocysteine, total cholesterol, triglycerides, and several lipoprotein markers. Patients were reexamined after one, three, and six months. Patients were evaluated for sleepiness and compliance with therapy, and those with greater than 5 percent change in BMI or significant changes in health habits or with new disease diagnosis or medications were excluded from the study. Polysomnography and blood tests were repeated after six months. Patients were classified according to compliance: twenty patients had used CPAP four or more hours per night, nineteen patients had used CPAP less than four hours per night, and fourteen had refused CPAP therapy. The good-compliance group had significantly decreased daytime sleepiness and significant decreases in C-reactive protein, homocysteine, total cholesterol, and two other lipoprotein markers indicative of cardiovascular disease. Triglycerides were unchanged. The poor-compliance group had significantly decreased daytime sleepiness and decrease in homocysteine that was less than in the first group, but still significant. They had no significant changes in other markers. The group who had refused CPAP therapy had no change in either daytime sleepiness or in serum markers. Thus good compliance to CPAP treatment improves metabolic and inflammatory serum markers in sleep apnea patients, indicating a reduction in cardiovascular risk.

Because sleep apnea is associated with myocardial infarction and stroke, because atherosclerosis is a key mechanism for these events, and because studies indicate the presence of early signs of atherosclerosis in patients free of co-morbidities, a study was done to determine the effect of CPAP treatment. From a sleep clinic, twenty-four male patients with severe sleep apnea were recruited who were free of hypertension, diabetes, heart failure, coronary artery disease, stroke, smoking, or chronic use of medications. Patients older than sixty and with severe obesity were also excluded. Because of rigorous exclusion of patients with co-morbidities, 400 were screened to select twenty-four participants. Patients were randomized to receive either CPAP or no

---

treatment for four months (twelve in each group). At the beginning of the study and after four months, participants were assessed for arterial stiffness, the thickness of the innermost two layers of the carotid arterial walls, carotid diameter, blood pressure, cholesterol, catecholamines (hormones produced by the sympathetic nervous system), and C-reactive protein (an indicator of inflammation). Vascular properties were determined by personnel blinded to the randomization. At the end of the study all patients randomized to the control group were treated with CPAP. Sleep apnea was virtually eliminated in the treated group. The thickness of carotid arterial walls, arterial stiffness, C-reactive protein, and catecholamines all decreased significantly in the treated group, but were unchanged in the controls. None of the other parameters assayed were significantly affected by CPAP treatment. Thus "... [four] months of effective treatment with CPAP significantly improves validated markers of atherosclerosis in normotensive middle-aged men with severe OSA." Further, these improvements correlated with decreased inflammation and decreased sympathetic nervous system activation. Consequently early detection and treatment of sleep apnea can alter the course of cardiovascular disease.

**Conclusion:** Over six-to-ten-year study periods, the occurrence of both non-fatal and fatal cardiovascular events among patients with severe sleep apnea who refused treatment was more than three times greater than among comparable patients treated with continuous positive airway pressure (CPAP). Heart failure patients treated with CPAP showed improvement in left ventricular parameters of heart failure. Sleep apnea patients who used CPAP treatment four or more hours per night showed substantial improvements in serum markers of cardiovascular disease. Early detection and treatment of sleep apnea can alter the course of cardiovascular disease.