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# The effect of obstructive sleep apnea on chronic medical disorders

## ■ ABSTRACT

Evidence is mounting that obstructive sleep apnea causes or contributes to many chronic medical diseases, and that treatment with continuous positive airway pressure (CPAP) often improves concomitant diseases. The author reviews the association of obstructive sleep apnea with arterial hypertension, pulmonary hypertension, stroke, coronary artery disease, heart failure, sudden death, gastroesophageal reflux disease, and diabetes mellitus.

## ■ KEY POINTS

A clear link exists between obstructive sleep apnea and hypertension, as an estimated 70% of sleep apnea patients are hypertensive.

CPAP therapy lowers blood pressure in hypertensive patients who have obstructive sleep apnea by about as much as any single antihypertensive medication.

The association between stroke and sleep apnea is very strong, perhaps as strong as the association between cigarette smoking and stroke. However, CPAP treatment is difficult in stroke patients.

Severe untreated sleep apnea appears to cause an increased risk of sudden death and cardiovascular death.

The data suggest that treatment of obstructive sleep apnea can improve pulmonary hypertension.

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**M**ANY PATIENTS with common medical problems seen in everyday practice, such as hypertension, coronary artery disease, and diabetes mellitus, also have obstructive sleep apnea—and vice versa.

We have learned much in recent years about obstructive sleep apnea and how it affects other medical disorders, and there is evidence that it actually causes or contributes to many of these other diseases.

In this paper, I review the basic pathophysiology of obstructive sleep apnea and its association with a number of disorders: hypertension, coronary heart disease, stroke, pulmonary hypertension, diabetes, and gastroesophageal reflux disease (GERD). I will also look at some of the literature regarding the effect of treating sleep apnea with continuous positive airway pressure (CPAP) on these disorders. I hope that my presentation will make you think about sleep apnea in some of your patients in whom you might not otherwise consider it.

## ■ WHAT HAPPENS DURING OBSTRUCTIVE SLEEP APNEA?

Patients with obstructive sleep apnea experience repetitive episodes of obstruction of the upper airway during sleep, lasting as long as 30 to 60 seconds. With no air flowing into the lungs, arterial oxygen levels drop and carbon dioxide rises. As the patient struggles to inhale against an obstructed airway, the thorax has increasingly negative pressure swings. Blood pressure initially drops and then drifts upward during the episode. Finally, the patient awakens with a surge of sympathetic nervous system activity and resumes breathing. Blood pressure shoots up during the arousal (sometimes by as much as 80 mm Hg systolic).

The number of these episodes per hour of sleep, as measured in a polysomnographic sleep study, is called the *apnea-hypopnea index*. Some patients have 50 or more episodes per hour; the upper limit of normal is probably 5 to 10.

The immediate consequence is that sleep is fragmented, and the patient feels tired and sleepy during the day. Long-term consequences include an increased risk of cardiovascular diseases via several intermediate mechanisms: sympathetic activation, endothelial dysfunction, vascular oxidative stress, inflammation, increased coagulation, and metabolic dysregulation.

### ■ APNEA CAUSES HYPERTENSION

A clear link exists between obstructive sleep apnea and hypertension, as an estimated 70% of sleep apnea patients are hypertensive.

A cause-and-effect relationship between obstructive sleep apnea and hypertension has been shown in experiments in animals.<sup>1</sup>

Furthermore, many patients who have isolated diastolic hypertension and who are “nondippers” have obstructive sleep apnea. “Dipping” is the normal physiologic decline in blood pressure and heart rate that occurs at night during sleep. Patients with sleep apnea lose this dipping pattern.<sup>2</sup> Nondippers have higher rates of stroke and end-organ damage and an overall worse prognosis than patients who are regular dippers.

Prospective studies suggest that obstructive sleep apnea precedes the onset of hypertension. For example, researchers began keeping data on employees of the state of Wisconsin in the late 1980s in an ongoing prospective study called the Wisconsin Sleep Cohort.<sup>3</sup> The mean age at study entry was 46 years. Data are collected every year, and every 4 years the participants undergo overnight polysomnography in the sleep laboratory. At the time of its first report that looked specifically at hypertension, 709 of the participants had had their first 4-year visit and 184 had come back for their second 4-year visit.

In this latter group, the higher the apnea-hypopnea index, the greater the chance that the participant would have hypertension at a follow-up visit. The association persisted after adjustment for body mass index, sex, waist circumference, neck circumference, and alcohol

and cigarette use. Participants with an apnea-hypopnea index of 15 or higher had almost a three times higher risk of developing hypertension than participants with an apnea-hypopnea index of 0.

It is speculated that many patients with refractory hypertension have obstructive sleep apnea. Logan et al<sup>4</sup> performed sleep studies in 41 patients with refractory hypertension, which they defined as blood pressure greater than 140/90 mm Hg despite taking at least three antihypertensive medications. They excluded patients who had secondary hypertension or who did not comply well with taking medication. They found a prevalence of sleep apnea of 83%, including 95% of the men (only one of the men did not have obstructive sleep apnea) and 65% of the women.

### Can treatment of obstructive sleep apnea with CPAP improve hypertension?

One study<sup>5</sup> did not include hypertensive patients, and it did not show an effect on mean 24-hour blood pressure although nocturnal blood pressure did improve. Two other studies,<sup>6,7</sup> however, did show an effect. In a study by Becker et al,<sup>7</sup> almost 50% of the patients were on antihypertensive medications, and their mean arterial pressure decreased by almost 10 mm Hg ( $P = .01$ ), which is approximately the same as the effect of one antihypertensive medication.

Treatment of sleep apnea helps refractory hypertension. Logan et al<sup>8</sup> started CPAP therapy in 11 patients with refractory hypertension. These patients had severe apnea: their mean apnea-hypopnea index was 45. They were compliant with CPAP, using the device an average of 4 hours per night. After 2 months of therapy, their mean 24-hour blood pressure had decreased significantly by 10 mm Hg systolic and 6 mm Hg diastolic.

The most recent report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure lists sleep apnea first as an identifiable cause of hypertension.<sup>9</sup>

### Comment

We should consider obstructive sleep apnea in any patient with hypertension, especially if the hypertension is difficult to control.

**Think about sleep apnea in patients with hypertension that is difficult to treat**

### ■ APNEA CAUSES MILD PULMONARY HYPERTENSION

Pulmonary pressure also rises during obstructive episodes, due to hypoxic vasoconstriction of the pulmonary arteries. The increase is proportional to the duration and degree of oxygen desaturation and shows an upward trend across the course of the night as the patient has repetitive oxygen desaturations.<sup>10</sup>

Despite interest in this topic, only about 500 patients have been studied, of whom only about 10% were women. The prevalence of pulmonary hypertension in patients with sleep apnea appears to be between 15% and 53%, with most researchers estimating it at about 20%. Only 12 studies have looked at the prevalence and not all of them used right heart catheterization for diagnosis; some used echocardiography, which is not quite as good. The definition of pulmonary hypertension varied from paper to paper as well.

The pulmonary hypertension that is associated with sleep apnea appears to be relatively mild, with mean pulmonary artery pressures of 25 to 30 mm Hg. Therefore, if a patient has moderate or severe pulmonary hypertension and sleep apnea, the sleep apnea is probably playing a role but is not the sole cause of the pulmonary hypertension.

### Does treatment of sleep apnea affect pulmonary artery pressures?

Sajkov et al<sup>11</sup> and Alchanatis et al<sup>12</sup> monitored pulmonary pressures in patients with severe obstructive sleep apnea (but not necessarily pulmonary hypertension) to see what happens after treatment with CPAP. Pulmonary artery pressures decreased in the subgroups with pulmonary hypertension at baseline.

Arias et al<sup>13</sup> conducted a randomized crossover trial in 23 sleep apnea patients and 10 healthy controls who received CPAP or sham CPAP for 3 months. (During sham CPAP, the pressure was set to only 2 cm H<sub>2</sub>O, rather than at a therapeutic level). Sleep apnea patients had a higher systolic pulmonary pressure at baseline than the controls did, and 10 of the 23 had a systolic pulmonary pressure of greater than 30 mm Hg. CPAP reduced the mean pulmonary systolic pressure

from 29 to 24 mm Hg ( $P < .0001$ ), with the biggest decrease in patients with pulmonary hypertension or left ventricular diastolic dysfunction at baseline.

### Comment

The data suggest that treatment of obstructive sleep apnea can improve pulmonary hypertension.

### ■ STROKE: STRONG ASSOCIATION, BUT TREATMENT IS DIFFICULT

The association between stroke and sleep apnea is very strong, perhaps as strong as the association between cigarette smoking and stroke.

The Sleep Heart Health Study,<sup>14</sup> a prospective study that began in the early 1990s, is monitoring more than 6,000 participants who undergo polysomnography every 4 years. In a cross-sectional analysis that was adjusted for several variables, the log odds ratio of developing or having a stroke increased with the apnea-hypopnea index.<sup>15</sup>

The mechanism by which sleep apnea might increase the risk of stroke might have to do with cerebral hemodynamics. During the apneic episode, oxygen saturation goes down while carbon dioxide goes up, resulting in dilation of the cerebral blood vessels and an increase in cerebral blood flow. In addition, the intermittent hypoxia results in endothelial dysfunction as well as increased vascular oxidative stress. Furthermore, sleep apnea patients have elevated levels of fibrinogen as well as increased platelet activation, putting them in a more thrombosis-prone state.

The prevalence of obstructive sleep apnea in patients with an acute stroke or transient ischemic attack is incredibly high<sup>16–20</sup>—as high as 95% in one study<sup>17</sup> that used an apnea-hypopnea index of 10 or higher as the criterion for obstructive sleep apnea.

One might argue that the stroke might have caused the sleep apnea. However, I think it likely for a number of reasons that the obstructive sleep apnea preceded the stroke. Most (about 90%) of the sleep apnea in stroke patients is obstructive, not central, apnea. The prevalence or type of sleep apnea does not vary on the basis of location of the stroke or whether

**The link between sleep apnea and stroke is as strong as that between smoking and stroke**

the stroke was hemorrhagic or thrombotic. In addition, patients with stroke have about the same prevalence of sleep apnea as patients with transient ischemic attack.

Furthermore, after the stroke, obstructive sleep apnea persists but central sleep apnea tends to go away. Parra et al<sup>20</sup> performed sleep studies in 161 consecutive patients with acute first stroke or transient ischemic attacks. Of the strokes, 112 were ischemic and 10 hemorrhagic; 39 patients had transient ischemic attacks. The investigators repeated the sleep studies in about half of the patients 3 months later. The apnea-hypopnea index did drop a bit at the 3-month interval, but almost all of that drop was explained by resolution of central apneas.

Arzt et al<sup>21</sup> analyzed the relationship between sleep apnea and stroke in the Wisconsin Sleep Cohort. In a cross-sectional analysis, participants with an apnea-hypopnea index of 20 or greater had an odds ratio for stroke of 3.83, even after adjustment for age, sex, body mass index, alcohol consumption, smoking, diabetes, and hypertension. In a cross-sectional analysis the odds ratio was 3.08; however, the *P* value was not significant.

Yaggi et al<sup>22</sup> followed more than 1,000 patients who had undergone sleep studies, about two thirds of whom had obstructive sleep apnea (defined as an apnea-hypopnea index of 5 or higher). The hazard ratio for stroke or death from any cause was 1.97 (95% confidence interval 1.12–3.48; *P* = .02) after adjustment for several variables, including hypertension. The worse the sleep apnea, the higher the risk for stroke.

Stroke patients who have obstructive sleep apnea do not fare as well as stroke patients without apnea. Dyken et al<sup>18</sup> followed 24 patients who underwent a sleep study following the onset of acute stroke. The 4-year mortality rate was 21% in those with obstructive sleep apnea, and all the patients who died had sleep apnea.

Turkington et al<sup>23</sup> followed 120 acute stroke patients for 6 months following polysomnography within 24 hours of stroke onset. The mortality rate in stroke patients with obstructive sleep apnea was 5%, vs 25% in those without sleep apnea, and the patients

with obstructive sleep apnea had a longer hospital stay.

### **CPAP is problematic in stroke patients**

Whether CPAP therapy improves the outcome in stroke patients with sleep apnea is not known at this point. CPAP is problematic in stroke patients for a number of reasons, and studies in this area are somewhat weak.

In a nonrandomized study, Wessendorf et al<sup>24</sup> found that blood pressure decreased in patients with acute stroke who used CPAP for 10 days, but not in patients who did not use CPAP. In a randomized study, Sandberg et al<sup>25</sup> showed that stroke patients who received CPAP had fewer depressive symptoms at 1 week and at 1 month compared with untreated controls.

A more recent study illustrates the difficulty of using CPAP in stroke patients. Palombini and Guilleminault<sup>26</sup> recruited 50 stroke patients, of whom 18 did not meet the initial clinical criteria. Another 11 withdrew after learning more about CPAP. The remaining 21 underwent a sleep study, and 7 more were excluded at this stage because they did not fit the polysomnographic criteria. Two more patients withdrew after the first night of CPAP, leaving 12. Five more dropped out during the first week, leaving 7 who participated for 8 weeks.

### **■ HEART DISEASE, SUDDEN DEATH**

In the Sleep Heart Health Study,<sup>15</sup> sleep apnea was an independent predictor of coronary artery disease. In some studies, the prevalence of sleep apnea in patients with acute coronary syndrome was 40% to 50%.

Granted, sleep apnea and coronary artery disease tend to occur in similar populations, with high prevalences of diabetes, hypertension, and overweight. Nevertheless, patients who have coronary artery disease and also have sleep apnea are at increased risk for nocturnal ischemia from their repetitive episodes of obstructive apnea and hypopnea. On electrocardiography, they show nocturnal ST segment changes, probably because of ischemia associated with oxygen desaturation.

Prevalence studies found that up to 37% of patients with congestive heart failure also have sleep apnea. And we know now that

**Severe untreated sleep apnea is linked to risk of sudden death**

severe untreated sleep apnea appears to cause an increased risk of sudden death and cardiovascular death.

Gami et al<sup>27</sup> retrospectively reviewed the cases of 112 patients who had undergone polysomnography before dying suddenly. Almost half of the patients with sleep apnea died between the hours of midnight and 6 AM, compared with 21% of those without obstructive sleep apnea. A possible explanation is that the patients with sleep apnea died suddenly during periods of apnea.

### CPAP improves heart disease

Marin et al<sup>28</sup> followed 1,651 men for 10 years. Men with severe untreated sleep apnea had a higher incidence of fatal and nonfatal cardiovascular events than men with untreated mild or moderate disease, simple snorers, and treated patients and three times the risk of healthy controls, even after a number of adjustments.

Kaneko et al<sup>29</sup> conducted a study in 24 patients with systolic congestive heart failure (defined by an ejection fraction < 45%) and severe sleep apnea, with apnea-hypopnea indices of 37 to 45. The group was randomized to receive either optimal medical treatment alone or optimal medical treatment plus treatment of their sleep apnea with CPAP for 1 month.

The results were quite impressive. The ejection fraction increased dramatically with CPAP treatment, from 25% at baseline to 34% ( $P < .001$ ), whereas it did not change significantly in the medical therapy group. Systolic blood pressure also went down by 10 mm Hg ( $P = .03$ ) after 1 month of CPAP.

### ■ GASTROESOPHAGEAL REFLUX DISEASE

GERD is extremely common in patients with sleep apnea: between one half and three fourths of patients with sleep apnea have significant GERD. It is more frequent and prolonged in sleep apnea patients than in controls matched for body mass index.

A plausible theory is that sleep apnea increases GERD via the negative intrathoracic pressure that is generated during apneic episodes, which might pull contents from the stomach up into the esophagus. However, there must be more to the story, because only

about half of the GERD episodes are temporally related to the apnea.

### Treatment of sleep apnea helps GERD

Green et al<sup>30</sup> started CPAP treatment in 204 patients who had sleep apnea and GERD, and they found that the patients who were compliant with their therapy had much lower GERD scores (the higher the score, the worse the GERD) than those who were noncompliant.

Interestingly, the higher the CPAP level, the lower the GERD score. How might that work? If you are putting positive pressure in the nose and down into the chest, you are closing the esophagus because of that positive pressure, and that may be why GERD improves more with higher CPAP.

### ■ DIABETES

Epidemiologic studies in Denmark, Sweden, and the United States have shown that habitual snoring is independently associated with glucose intolerance and diabetes. But not everybody who snores has sleep apnea, and these studies were based on self-reported snoring, not on polysomnographic data.

Two studies,<sup>31,32</sup> with 150 and 270 patients, respectively, showed that the apnea-hypopnea index and low oxygen saturations were associated and independently correlated with insulin resistance and glucose intolerance, and this effect was independent of body mass index.

In 2,656 participants in the Sleep Heart Health Study who had undergone in-home polysomnography and fasting and 2-hour glucose tolerance tests,<sup>33,34</sup> Punjabi et al found that, after adjusting for confounding variables, those with an apnea-hypopnea index of 5 or more had twice the risk of having impaired or diabetic glucose tolerance. Furthermore, the impairment in glucose tolerance was related to the severity of oxygen desaturation during the episodes.

In the Wisconsin Sleep Cohort, Reichmuth et al<sup>35</sup> did both a cross-sectional analysis and a longitudinal analysis of 1,387 patients. At baseline, the higher the apnea-hypopnea index, the higher the prevalence of diabetes: if the apnea-hypopnea index was 15 or higher the prevalence of diabetes was 15%, whereas if it was less than 5, fewer than 3% had diabetes.

**Hemoglobin A<sub>1c</sub>  
fell by 0.5%  
with CPAP**



In a longitudinal analysis, after adjustment for age, sex, and body habitus, the odds ratio for developing diabetes within 4 years was 1.62 with an apnea-hypopnea index of 15 or more compared with an index of 5, but the difference was not statistically significant.

By what mechanism might sleep apnea be related to diabetes? Sleep deprivation in itself seems to result in some glucose intolerance, and chronic and acute sleep deprivation result in appetite dysregulation and risk of waking.<sup>36</sup> This appetite dysregulation seems to result in insulin resistance and in susceptible patients, may also increase the risk for type 2 diabetes.

In addition to sleep fragmentation, patients with sleep apnea also have intermittent hypoxemia, which is thought to stimulate the sympathetic system with release of catecholamines. The hypothalamic-pituitary-adrenal axis is also affected, and the increases in cortisol and catecholamines might ultimately result in glucose intolerance, insulin resistance, and diabetes.<sup>36</sup>

### CPAP may improve diabetic control

Thirteen studies to date have examined the effect of treatment of sleep apnea with CPAP on diabetes.<sup>37</sup> Six of the 13 studies showed that CPAP has a beneficial effect on diabetes, but only two of the 13 studies had a control group. The duration of treatment was anywhere from 1 night to 6 months. The most improvement in diabetes seemed to occur in patients who had a lower body mass index, which might make sense intuitively because their diabetes might be less related to their weight and more related to their sleep apnea.

Hassaballa et al<sup>38</sup> performed a retrospective analysis of 38 patients with severe sleep apnea (the mean apnea-hypopnea index was 53) and type 2 diabetes who had been on CPAP therapy for an average of 134 days. Although their medication regimen had not changed, their hemoglobin A<sub>1c</sub> levels fell from 7.8% before therapy to 7.3% ( $P < .001$ ).

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