Sleep Related Breathing Disorders Are Common Contributing Factors to the Production of Essential Hypertension But Are Neglected, Underdiagnosed, and Undertreated

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There is now strong evidence from animal studies and, in humans, from epidemiological studies as well as from retrospective and prospective intervention studies, that obstructive sleep apnea (OSA) can cause persistent hypertension not only during sleep but during waking hours as well. There is also some evidence that habitual snoring alone, even without OSA, can do the same. Many of the hitherto unexplained epidemiological, clinical, biochemical, hematological, and physiological abnormalities seen in essential hypertension (EH) could be explained by the accompanying sleep related breathing disorders (SRBD). Many cases of resistant hypertension are probably due to SRBD. Recent studies show that SRBD are extremely common in EH but that the vast majority of patients with these sleep disorders are being missed by physicians who are treating the accompanying hypertension, even when the patients already have blatant symptoms of OSA. Recent investigations have shown that the probable reason for this underdiagnosis of OSA is lack of physician knowledge about the condition. This lack of knowledge is prevalent not only among family physicians, but among hypertension specialists and researchers in the field of hypertension as well. OSA is a common, easily diagnosed, and eminently treatable condition that is associated not only with disturbed sleep, loud snoring and excessive daytime sleepiness (which greatly increases the risk of traffic accidents), but also with hypertension, especially resistant hypertension, a broad range of cardiovascular problems, decreased sexual functioning, memory deficits, difficulty concentrating, and changes in personality and mood. It deserves much more attention by physicians treating hypertension than it is currently getting. Am J Hypertens 1997; 10:1319–1325 © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Obstructive sleep apnea, sleep related breathing disorders, essential hypertension, snoring, upper airway resistance syndrome.
Obstructive sleep apnea (OSA) is a disorder in which there is repetitive collapse and closing of the pharynx during sleep.\(^1\)–\(^4\) Although there is still not a standard definition of OSA, the most widely accepted definition is the occurrence of an average of at least ten breathing abnormalities (apneas or hypopneas) per sleep hour. There is growing evidence that sleep related breathing disorders (SRBD), including both OSA and habitual snoring without OSA, are important contributing factors to the production of essential hypertension (EH).\(^1\)–\(^4\) Despite this evidence, the relationship between SRBD and hypertension seems to be ignored by a large percentage of physicians, health authorities, and clinical and basic researchers in the field of hypertension, as judged by the following observations:

1) Most patients with OSA are being seen by physicians who are treating these patients’ hypertension while missing the diagnosis of OSA. About 40% of patients with EH have OSA, and these cases account for about half of all OSA cases.\(^1\)–\(^4\) Most people in the community who have hypertension are aware that they are hypertensive,\(^5\) ie, they have at one time or another seen a physician for it. If doctors treating EH had diagnosed all those hypertensives with associated OSA, about 50% of all cases of OSA would be diagnosed today. It appears, however, that less than 10% of OSA cases are being diagnosed.\(^4\)–\(^6\) It is clear, then, that most hypertensive patients with OSA are being seen by physicians for their hypertension but the accompanying OSA is being missed. This situation appears to be even worse for women than for men, ie, a higher percentage of women than men who have OSA are being missed, although women with OSA were recently found to have sleep symptoms (habitual snoring, snorting, apneic episodes, and excessive daytime sleepiness) of similar prevalence and severity to those of men.\(^7\) The situation is even worse in the elderly. In a recent US study of 140 middle aged and elderly hypertensive men\(^8\) 80% were found to have OSA, and in 34% of all the study patients the OSA was severe. Of the group with proven OSA almost 20% had symptoms clearly suggesting the presence of a severe sleep disturbance; however, despite this, only one of the 140 EH patients (0.7%) had been identified previously as having OSA.

2) A recent textbook on hypertension fails to mention OSA as either a cause or contributor to the production of EH.\(^9\)

3) Among the approximately 2600 abstracts submitted to two recent (1996) hypertension meetings, those of the American and the International Society of Hypertension, except for two invited lectures there were only two abstracts about OSA, representing only 0.08% of all the abstracts submitted. This for a condition that is present in about 40% of patients with EH. Simple mathematics shows that research efforts in this field are underrepresented by a factor of 500 to 1.

4) Both obesity and increased sympathetic activity are extremely common in EH\(^10,11\) as well as in OSA\(^12,13\) and OSA could contribute to the hypertension seen in obesity and to the increased sympathetic activity seen in EH. However, a recent review on the pathogenesis of hypertension in obesity\(^10\) and on the pathogenesis of the increased sympathetic activity in EH\(^11\) failed to mention OSA as either a possible cause or possible contributing factor to hypertension.

5) The 1996 guidelines by the expert committee of the World Health Organization on hypertension control in the community fail to mention the role of SRBD in the diagnosis or treatment of the hypertensive patient in the community, although they mention 11 other possible contributors to EH, including fish oil and fiber.\(^14\)

6) Recent reviews on the nonpharmacological therapy of HT fail to mention treatment of OSA.\(^15,16\)

7) A recent major review of causes and treatment of secondary hypertension fails even to consider the role of obstructive sleep apnea.\(^17\)

8) A recent study\(^18\) retrieved every article written on the subject of sleep in six of the major US and British general practice and family medicine journals over the past several years. On the average, less than one article on sleep disorders was written per journal over a period of 2 years, leading us to the conclusion that sleep disorders are rarely covered by these important journals.

9) American medical schools devote, on the average, only about 2 h to teaching sleep medicine during the 4 years of medical education.\(^19\) In 29.4% of the medical schools surveyed, no time at all was allotted to the subject. Similarly, a recent survey of British medical schools showed that absolutely no time was spent in the teaching of sleep medicine in the neurology, general medicine, or geriatric medicine curriculum.\(^20\) In a test of knowledge about OSA among 405 physicians in Canada, a great variance of knowledge about OSA across all specialties was found.\(^21\) In addition the longer the period of time since the physicians completed internship, the less knowledgeable they were on the subject. The most crucial finding, however, was that the more the physicians knew about OSA, the more patients they knew about who had the disease, suggesting that those physicians who are more aware of the entity are more likely to make the diagnosis. The importance of prior physician knowledge about sleep disorders was confirmed in a recent study\(^22\) that recorded the frequency of obtaining sleep histories during encounters with simulated patients by experienced primary care practitioners, noninstructed medical interns, and interns who had had
previous instruction about sleep disorders. Sleep histories were obtained in 0%, 13%, and 81.8% of the three groups, respectively, showing that focused instruction about sleep disorders influences physician ability to identify sleep disorders.

EVIDENCE THAT SLEEP RELATED BREATHING DISORDERS CAN CAUSE HYPERTENSION

Perhaps the neglect of this subject, the contribution of SRBD to the development of EH, is justified. Perhaps physicians view the evidence linking SRBD to EH as so unconvincing that their avoidance of, or lack of interest in, the subject is justified. We, on the contrary, feel that the evidence linking SRBD and EH is compelling:

1) A recent study of OSA induced in dogs by intermittent tracheal occlusion during sleep demonstrated clearly for the first time, in an animal model, a cause and effect relationship between OSA and the development of systemic hypertension. The canine model was similar to the human condition but, unlike studies in humans, there were no confounding variables. In this study, the production of OSA in dogs led to an increase in daytime awake BP (as well as sleeping BP) within a few weeks. Following cessation of OSA the blood pressure returned to normal within 1 to 3 weeks.

2) EH is much more common in persons with OSA than in those without it. Conversely OSA is much more common in patients with EH than in normotensives. We recently recalculated the data from a US study of a random sample of the population in which both nocturnal polysomnographic and 24 h ambulatory BP measurements were performed. This analysis showed that 38.9% of hypertensive men in the community had evidence of OSA compared with only 19.8% of normotensive men. Among women the figures were even more striking: 65.4% of hypertensive women in the community had evidence of OSA, compared with only 5.9% of normotensive women. If those with OSA and those who are just habitual snorers without OSA are added together, 63% of hypertensive men and 100% of hypertensive women in the community have evidence of SRBD. These results are similar to those mentioned earlier in a recent US study, in which 80% of middle-aged and elderly male hypertensives being treated in a medical clinic were found to have OSA.

3) In 25 of 36 observational studies, OSA has been found to be an independent risk factor for EH, even when confounding risk factors such as obesity, age, gender, alcohol intake, and smoking were taken into consideration. Obesity in particular is common in both OSA and EH. What the above studies suggest is that the obese patient with hypertension is likely to have OSA and that, the more severe the OSA, the more severe the hypertension. They also suggest that it is the severity of the OSA and not the severity of the obesity per se that is linked to the presence or absence and degree of severity of the hypertension.

4) Retrospective studies have shown that successful treatment of OSA is associated with a fall in blood pressure (BP) even without a change in weight.

5) Seventeen of 21 prospective studies of OSA have shown that its successful treatment by nasal continuous positive airway pressure (nCPAP), pharyngeal surgery, or avoiding sleeping in the supine position, is associated with a fall not only in the BP during sleep but during the awake hours as well, and that this happens without a change in weight.

6) In patients with OSA who were being successfully treated with nCPAP, stopping this treatment caused an increase in awake BP, and restarting the treatment caused the BP to fall once again.

7) About one-third of patients with EH and about the same percentage of OSA patients have BP that fails to dip normally during sleep (ie, they are nondippers). Those patients with EH who are nondippers have been found to have an increased number of arousals (electroencephalogram evidence of partial wakings) during sleep and to have a high prevalence of OSA or habitual snoring without OSA. These arousals are caused, at least partially, by increases in inspiratory effort during sleep in both OSA and non-OSA snoring patients. This increased work of breathing is caused by episodes of increased upper airway resistance due to partial or complete upper airway collapse during sleep. This suggests that many EH patients who are nondippers actually have OSA as the cause of this nondipping.

8) The two conditions, OSA and EH share identical characteristics. Many of the hematological, biochemical, and physiological abnormalities produced by both OSA and EH are listed in Table 1. Treatment of OSA returns many of these abnormalities to normal. Many of the epidemiological and clinical characteristics seen in both OSA and EH are listed in Table 2. In OSA, many of these clinical conditions improve with successful treatment. The pattern of inheritance of OSA and EH are also very similar. Taken together, these data suggest that EH and the hypertension of OSA may, in many cases, be one and the same disease.

9) In the middle-aged and elderly with EH described earlier, even when matched for age, sex, body mass index (BMI), neck circumference, smoking, and type and dose of medications, those whose BP remained elevated despite antihypertensive treatment had more severe OSA and spent a longer time snoring than did EH patients who were normotensive on treatment. Conversely, others have also found that hyper-
tensive patients with OSA are more resistant to antihypertensive treatment than are those without OSA. This suggests that OSA may be a common and important cause of resistant hypertension. This may be one reason why about two-thirds of treated hypertensives still have an elevated BP, whether it is measured in the doctor’s office or by 24 h ambulatory readings. Perhaps their associated (and untreated) SRBD is making them resistant to treatment.

10) The relatively high rate of occurrence of myocardial infarction and stroke during sleep and during the early waking hours could be due, at least in part, to OSA with its associated nocturnal hypertension, hypoxia, hypercarbia, increased plasma fibrinogen, and increased platelet activation and aggregation. Perhaps the failure of antihypertensive medications to reduce the incidence of myocardial infarction as much as would have been predicted from the correction of EH is due to the associated, unrecognized, and untreated OSA. OSA is associated with an increased prevalence of acute cardiovascular events such as sudden death, congestive heart failure, myocardial infarction, and cerebrovascular accidents.

HABITUAL SNORING WITHOUT OSA AS AN IMPORTANT CONTRIBUTING FACTOR TO THE DEVELOPMENT OF EH

About 40% of people with EH have habitual snoring without OSA. This condition is also a likely causative factor of the hypertension, because of the following:

1) The prevalence of hypertension in habitual snorers without OSA is greater than that in nonsnorers, even when confounding variables have been taken into consideration, and in some studies is equal to the prevalence of hypertension in OSA patients.

2) In a recent study, 20 (74.1%) of 27 patients with EH who were habitual snorers but without OSA were found to have an increased number of arousals during sleep, which (as mentioned previously) reflects, in some cases, episodes of increased upper airway resistance.

3) Compared with nonsnorers, the BP of snorers without OSA increases slightly during sleep as compared to their BP while awake (as it does in OSA patients), whereas the BP of normal nonsnorers decreases.

4) Nonapneic snorers who have an increased number of arousals during sleep may have the so-called upper airway resistance syndrome. Patients with this syndrome who had the highest daytime BP (borderline EH) were also found to have the greatest levels of upper airway resistance during sleep. What this implies is that the nonapneic snorers who develop hypertension are those with the most severe upper airway resistance during sleep. As in most studies of OSA patients, the successful treatment of this condition with nCPAP was associated with a fall in BP not only during sleep but during the awake hours as well.

### TABLE 1. HEMATOLOGICAL, BIOCHEMICAL, AND PHYSIOLOGICAL CHARACTERISTICS SHARED BY ESSENTIAL HYPERTENSION AND OBSTRUCTIVE SLEEP APNEA

<table>
<thead>
<tr>
<th>Hematological and Biochemical Findings</th>
<th>Physiological Responses</th>
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<tbody>
<tr>
<td>Elevated hematocrit</td>
<td>Exaggerated pressor response to hypoxia</td>
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<tr>
<td>Hyperuricemia</td>
<td>Exaggerated ventilation response to hypoxia</td>
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<tr>
<td>Reduced renin levels during sleep</td>
<td>Reduced baroreceptor sensitivity</td>
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<td>Increased sympathetic activity</td>
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<tr>
<td>Elevated atrial natriuretic factor</td>
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<td>Elevated ratio of vasoconstrictor to vasodilator prostaglandins</td>
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<td>Reduced testosterone levels in men</td>
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<td>Reduced endothelium dependent relaxation factor</td>
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<td>Reduced blood fibrinolytic activity</td>
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<td>Increased platelet activation and aggregation</td>
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<td>Increased plasma fibrinogen levels</td>
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<tr>
<td>Increased serum erythropoietin levels</td>
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Derived from Silverberg and Oksenberg.

### TABLE 2. EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS SHARED BY ESSENTIAL HYPERTENSION AND OBSTRUCTIVE SLEEP APNEA

<table>
<thead>
<tr>
<th>Epidemiological Findings</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased prevalence of obesity and central obesity</td>
<td>Improvement with weight loss</td>
</tr>
<tr>
<td>More common in middle-aged men than in women</td>
<td>Increased prevalence of</td>
</tr>
<tr>
<td>More common in older than in younger women</td>
<td>Snoring</td>
</tr>
<tr>
<td>More common in black Americans than in white Americans</td>
<td>Cardiovascular complications</td>
</tr>
<tr>
<td>More common with alcohol abuse</td>
<td>Renal damage</td>
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</tbody>
</table>

Derived from Silverberg and Oksenberg.
POSSIBLE PATHOGENETIC MECHANISMS FOR HYPERTENSION IN OSA AND IN HABITUAL SNORERS

The mechanisms whereby partial or complete airway collapse during sleep contribute to the production of hypertension are still unclear.1–3 In OSA the frequent apneic events are associated with intermittent episodes of hypoxia, hypercapnia, and increased effort of breathing. All these factors, together or separately, can cause frequent arousals during sleep, and all four of these factors can cause frequent bursts of sympathetic activity and consequently an increase in heart rate and in systemic as well as pulmonary blood pressure. Chronic exposure of the blood vessels to the increased sympathetic activity and hypertension may cause vascular alterations that lead to persistent hypertension and organ damage. Other changes that may also result from SRBD and contribute to making the hypertension persistent throughout the day and night include reduced baroreceptor sensitivity (perhaps caused by the effect of hypoxia on the baroreceptor), an increased ratio of vasoconstrictor to vasodilator prostaglandin production, increased endothelin production, reduced endothelium derived relaxation factor, polycythemia (which often occurs in OSA), increased intracranial pressure, and renal damage.1–4,43,44

ESTABLISHING THE ASSOCIATION BETWEEN EH AND SLEEP RELATED BREATHING DISORDERS

The way to demonstrate that increased upper airway resistance during sleep is a common and crucial factor in the development of essential hypertension is:

1) to measure the severity of this upper airway resistance during sleep in patients with EH. Unfortunately polysomnography, as currently performed in most sleep disorders units, although it does measure air flow, chest and abdominal effort, and the presence of arousals (and can therefore diagnose OSA) does not routinely measure upper airway resistance and can therefore miss the diagnosis of upper airway resistance syndrome. This can, however, be diagnosed by measuring intrathoracic pressure by esophageal pressure, either with esophageal balloon manometry or with a water filled catheter connected to a transducer,31,32 or by careful assessment of air flow patterns.45 Such studies have not as yet, to our knowledge, been performed in patients in essential hypertension.

2) If patients with essential hypertension are indeed found to have SRBD (including upper airway resistance syndrome), most should respond to the nonsurgical forms of therapy used for OSA, with a reduction not only in the number of episodes of upper airway obstruction during sleep46 but also with a fall in awake and asleep blood pressure (BP).1–3 Such treatments include weight reduction, nCPAP, oral prosthetic mandibular advancing devices, and, in many cases, simply avoiding sleeping in the supine position.47 In a study of 574 adult OSA patients we found that, in 56% of them, the number of apneic/hypopneic episodes was more than double when they slept in the supine position than when they slept in the lateral position.48 When 13 such positional OSA patients were taught to avoid sleeping in the supine position for 1 month, the 24 h, awake, and sleeping BP (as measured by ambulatory BP measurements) fell significantly, as did the BP load and the BP variability.49 The fall in BP was more pronounced in the six hypertensive than in the seven normotensive patients.

In cases where the above treatments fail, surgical treatment may be necessary.46

It is also possible that OSA plays a role in the production of hypertension in diabetes mellitus, hypothyroidism, excessive alcohol intake, and acromegaly,2 and that OSA may cause renal damage as well.33,44

In light of all the previously mentioned data, is it not time for those involved in the research, diagnosis, and treatment of hypertension to become more interested in the role of SRBD in the development of hypertension? Certainly more research is needed. But if >90% of cases of OSA are being missed,46,50 half of whom are hypertensive,1–4 and if OSA is being missed in >95% of those patients with EH who also have OSA,8 there is clearly a glaring, “yawning,” and unacceptable gap between the prevalence of OSA and its diagnosis that is crying out for improvement—a gap that can be overcome only by more awareness and concern by physicians.21,22,50 How many more animal and epidemiological studies linking SRBD to hypertension have to be done before doctors treating hypertension simply begin asking these patients and their bedroom partners routinely about snoring, gasping, and breathing pauses at night? How many more intervention studies showing that treatment of OSA lowers the blood pressure have to be done before doctors simply start routinely asking their hypertensive patients and their families about excessive daytime sleepiness, or posing questions such as whether they wake up tired and sleepy (and with a dry mouth) in the morning, or whether they doze off or fall asleep during different passive activities such as sitting and reading an interesting book, watching an interesting program on TV, watching an interesting production in a public place such as a theater or a movie, sitting as a passenger in a car, sitting and talking to someone, or, most important of all, while driving a car? A recent study has shown that physicians who inquire routinely about these symptoms in all patients and follow up suspected cases with polysomnography are likely
to increase the number of cases of OSA in their practice by about eightfold. Patients with these symptoms who are also hypertensive have about a 70% chance of having moderate to severe OSA. In a patient with resistant hypertension the physician should routinely think about OSA in the differential diagnosis.

The patient whose SRBD is diagnosed and treated receives so many benefits. Successful treatment not only will improve the snoring and the sleepiness, reduce the hypertension and the risk of acute cardiovascular events, but will also reduce the risk of traffic accidents in these patients, which, because of excessive daytime sleepiness, is increased by up to seven times. In addition, patients with OSA often experience decreased sexual functioning, decreased motor skills, and cognitive deficits including memory loss, decreased vigilance, and impaired judgment. The successful treatment of these sleep related abnormalities not only improves the quality of sleep but improves all of the above disturbances as well, and, as a consequence, has a major positive impact on the quality of life. However, before the patients can be awakened, somebody has to awaken their physicians to the existence and importance of this entity; and, sadly, if the epidemiological statistics mentioned herein are correct, physicians—the crucial actors in this drama—are, more often than not, fast asleep.

REFERENCES

6. Dement WC, Mitler MM: It’s time to wake up to the importance of sleep disorders. JAMA 1993;269:1548–1550.


