Treating Obstructive Sleep Apnea Improves Essential Hypertension and Quality of Life

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About one half of patients who have essential hypertension have obstructive sleep apnea, and about one half of patients who have obstructive sleep apnea have essential hypertension. A growing body of evidence suggests that obstructive sleep apnea is a major contributing factor in the development of essential hypertension. Despite many patients with obstructive sleep apnea having clear symptoms of the disorder, an estimated 80 to 90 percent of cases are undiagnosed. When physicians routinely seek the diagnosis of obstructive sleep apnea by asking patients (especially those with hypertension) three basic sleep-related questions about snoring, excessive daytime sleepiness and reports of witnessed apneic events, the number of cases diagnosed and treated increases by about eightfold. Eliminating snoring and occurrences of apneic-hypopneic episodes will dramatically improve patients' quality of sleep and eliminate excessive daytime sleepiness, which has a detrimental effect on general functioning. Increased alertness will reduce the likelihood that patients will be involved in motor vehicle crashes. In most studies in which blood pressure was measured following treatment for obstructive sleep apnea, daytime and nighttime blood pressure levels were found to decrease significantly. This decrease in blood pressure may also reduce the likelihood of cardiovascular complications. The key to the diagnosis of obstructive sleep apnea is physician knowledge about the disorder. The dramatic improvement in quality of life that occurs when patients are successfully treated for obstructive sleep apnea makes detecting and treating this disorder imperative. (Am Fam Physician 2002;65:229-36. Copyright© 2002 American Academy of Family Physicians.)

O *A patient information handout on snoring, obstructive sleep apnea, and high blood pressure, written by the authors of this article, is provided on the* AFP *Web site.*

Obstructive sleep apnea (OSA), defined as an average of at least 10 apneic and hypopneic episodes per sleep hour, is a common sleep-related breathing disorder that leads to excessive daytime sleepiness because of marked fragmentation of sleep. Patients are frequently not diagnosed despite years of being symptomatic (especially with hypersomnolence), because physicians do not routinely look for the disorder. Additionally, the role of OSA in the production of essential hypertension (EH) is frequently not appreciated.[1-4] The purpose of this article is to demonstrate how commonly OSA occurs, how the quality of patients' lives can improve with successful treatment, and how the disorder is related to EH.

OSA is characterized by a repetitive partial (hypopnea) or complete (apnea) closing of the pharynx during sleep. By definition, apneas or hypopneas that last a minimum of 10 seconds are considered clinically significant, although they usually last from 20 to 30 seconds and can last more than one minute. Most of these episodes end when the patient wakes up slightly, almost always without being aware of it. This "arousal response" causes the airway to reopen. In severe cases, the cycle of opening and closing of the pharynx can recur 400 to 600 times a night.

The apnea-hypopnea index (AHI), also called the respiratory disturbance index, is the average number of apneas and hypopneas that occur per sleep hour. Although different thresholds exist for defining OSA, it is often defined as an AHI of 10 or more. The prevalence of OSA depends on how it is defined. When using the definition of an AHI of 10 or more, about 10 percent of persons 30 to 60 years of age (5 percent of women and 15 percent of men) have OSA.[5] However, if OSA is defined as an AHI of

See editorial on page 182.

Obstructive sleep apnea is a very common sleep disorder with major clinical and social consequences, yet it is often neglected, underdiagnosed and undertreated.

five or more and the primary symptom of hypersomnolence is present, OSA is present in 2 percent of women and 4 percent of men between 30 and 60 years of age.[5] A patient with an AHI of 40 or more is generally considered to have severe OSA.

Diagnosing OSA

The first question to ask patients suspected of having OSA is if they snore and, if so, whether they snore loudly or quietly, frequently or infrequently, and only when lying on their back or when lying on their side. In most cases, patients cannot hear their own snoring. Even if they admit to being told that they snore, patients often have a tendency to underestimate the loudness and frequency of their snoring. Snoring marked by frequent changes in loudness and frequency (as opposed to quiet and steady snoring) is highly suggestive of OSA. A bed partner or person in the household may be needed to give an accurate description of the patient's snoring. If the patient lives alone, a tape recorder can be placed near the bed and used to record hours of sleep to assess snoring.

The second question related to OSA is if patients have excessive daytime sleepiness. Patients may have difficulty describing their sleepiness and may call it "tiredness" or "fatigue." Physicians should ask patients exactly what they mean, and they may have to ask directly, "Do you mean you are sleepy most of the time?" Patients may then volunteer that they wake up feeling sleepy and remain uncontrollably sleepy throughout the day, especially when engaging in passive activities (e.g., reading, watching television, or even driving an automobile).

A patient's spouse or bed partner can usually describe the sleep behavior much better than the patient. It is *crucial*, therefore, that a bed partner be present during the interview. While patients may report being "a little sleepy," persons who live with patients may describe them as being very sleepy. If asked, patients may admit to having had one or more motor vehicle crashes or near crashes because of lack of attentiveness or falling asleep while driving. Patients who have OSA have a significantly greater chance of having a motor vehicle crash when compared with persons who do not have OSA.[6] Excessive daytime sleepiness may also manifest as difficulty concentrating, remembering things, or thinking clearly. Other causes of sleepiness such as sleep deprivation, shift work, depression, hypothyroidism, or use of sleeping pills, sedatives, or excessive alcohol should be eliminated. Other sleep disorders, such as narcolepsy, should be ruled out.

Successful treatment of OSA will eliminate apneic and hypopneic breathing episodes, snoring, and the arousal responses caused by these respiratory events. Patients usually regain restful, uninterrupted sleep, which should dramatically improve their alertness during daytime hours. Also, patients' chances

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of being involved in motor vehicle crashes will be greatly reduced.[6]

The third question to ask (which should be directed to the bed partner, if possible) is whether the patient has episodes during sleep when breathing stops. The bed partner may describe periods of loud snoring by the patient followed by silence or a total absence of breathing lasting a few seconds up to one minute or longer. At the moment patients arouse from the apneic episode and the airway is opened, they usually take several deep, loud, gasping breaths that may be accompanied by gross body movements. The noise and body movements may awaken the bed partner.

Besides asking the three preceding questions, another useful question to ask is if the patient has a dry mouth on waking during the night or in the morning. Most heavy snorers and patients with OSA have a dry mouth because they usually breathe through their mouth when they sleep.

Another factor in the presence of OSA is nocturia, which is present in about one third of patients. Apneic episodes cause an increase in secretion of atrial natriuretic factor, which causes diuresis throughout the night. What may appear to be a prostatic problem may actually be diuresis caused by OSA. The nocturia may disappear with successful treatment of OSA.[7]

Hypertension is another major indicator of the presence of OSA because about one half of patients with EH have OSA, and about one half of all patients with OSA have EH.[1-4] In fact, in the last two years, seven major studies[8-14] have shown that OSA is an independent risk factor for hypertension and, generally, the more severe the OSA, the more prevalent and severe the hypertension. In addition, many studies,[1-4] including four that have been recently published,[15-18] have shown that successful treatment of OSA is associated with a significant reduction in blood pressure levels, although two other studies[19,20] did not report similar findings. A recent long-term study[21] also showed that normotensive patients with OSA are far more likely to develop hypertension over a four-year period than those without OSA.

If ambulatory blood pressure monitoring indicates that a patient is a "nondipper" (i.e., blood pressure during sleep fails to fall, or "dip," by at least 10 percent as it normally does when compared with the mean awake blood pressure level), then the chances that the patient has OSA are increased.[22]

Obesity is a major indicator of the presence of OSA. Many patients with OSA may report a recent weight gain along with an increase in snoring and sleepiness. The risk of OSA is particularly high in patients who are obese and who have a large neck circumference and central obesity (i.e., a large waist-to-hip ratio). Although about 70 percent of patients with OSA are obese, thin people also can have OSA.

OSA can be worsened by sleep deprivation, alcohol intake, smoking, use of central nervous system depressants, and chronic nasal congestion.

Missed Diagnosis

Eighty to 90 percent of patients with OSA are undiagnosed, despite having clear signs and symptoms.[23,24] When patients are finally diagnosed with OSA, they have had obvious symptoms of the disorder for an average of seven years, during which time they report having seen a family physician about 17 times and a subspecialist about nine times.[25] The most likely reason for missed diagnosis is that physicians simply do not suspect sleep apnea. Studies have shown that when physicians are informed about the disorder, their index of suspicion is high and they routinely ask their patients about OSA symptoms,[26] which increases the numbers of patients diagnosed and treated in their practices by about eightfold.[27]

OSA As a Major Contributing Factor in EH

Evidence that OSA can cause elevated blood pressure levels during sleep and during the

day is very strong *(Table 1)*.[1-4,8-23,28-33] Not only are OSA and EH clinically similar but also, as shown in *Table 2*,[1-4] the physiologic, biochemical and hematologic characteristics that contribute to the persistence of hypertension are similar. Therefore, in many cases, OSA and EH appear to be the same condition.[1]

Some evidence suggests that OSA may also be an important contributor in the development of coronary heart disease, stroke, cardiac

TABLE 1

Evidence That OSA Causes Hypertension and Contributes to Essential Hypertension

About 50% (range 30 to 80%) of patients with EH have OSA.
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In patients with OSA, mean blood pressure during sleep often fails to fall as it normally does during sleep, but remains at a level similar to the awake blood pressure. This "non-dipping" is caused by frequent apneic/hypopneic episodes (up to 600 per night) ending with arousals that are associated with marked spikes in blood pressure that last for several seconds.
One third of patients with EH have blood pressure levels during sleep that fail to fall normally (i.e., they are non-dippers). Ninety percent of these patients have been found to have OSA.
Multiple studies have shown that OSA is an independent risk factor for the presence of EH even when considering age, gender, and degree of obesity.
Patients who are normotensive and who have OSA are much more likely to develop EH during the next few years than those without OSA.
The more severe the OSA, the higher the blood pressure levels and the greater the prevalence of EH.
Numerous studies have shown that treatment of OSA by CPAP or position therapy lowers the awake and 24-hour blood pressure levels.
In persons successfully treated with CPAP, cessation of treatment causes blood pressure levels to increase, while restarting treatment causes blood pressure levels to fall again.
The more severe the OSA, the more difficult it becomes to control blood pressure levels with medications.
In animal studies, the production of OSA causes sleeping and awake systemic hypertension to develop within a few weeks, and the cessation of OSA causes blood pressure levels to return to normal within a few weeks.
Some evidence exists that habitual snoring, especially loud frequent snoring, even without OSA is associated with elevated blood pressure levels during the night and day, and that treatment with CPAP can lower blood pressure levels.

OSA = obstructive sleep apnea; EH = essential hypertension; CPAP = continuous positive airway pressure.

Information from references 1 through 4, 8 through 23 and 28 through 33.

TABLE 2

Similarities Between Obstructive Sleep Apnea and Essential Hypertension

Epidemiologic findings
Increased prevalence of obesity and central obesity
More common in middle-aged men than women
More common in older than younger women
More common in blacks than whites
More common in persons who abuse alcohol (Alcohol is an important cause of hypertension and can worsen OSA and snoring.)
Genetic characteristics
A similar hereditary pattern is present in OSA and EH
Clinical findings
Improve with weight loss
Increased prevalence of snoring, cardiovascular complications, renal damage, cognitive dysfunction, headaches, impotence, non-dipping blood pressure levels during sleep, increased blood pressure variability, diabetes and insulin resistance
Hematologic and biochemical findings
Elevated hematocrit
Hyperuricemia
Reduced renin levels during sleep
Increased sympathetic activity
Elevated atrial natriuretic factor
Elevated ratio of vasoconstrictor to vasodilator prostaglandins
Reduced testosterone levels in men
Reduced endothelium dependent relaxation factor (nitric oxide)
Reduced blood fibrinolytic activity
Increased platelet activation and aggregation
Elevated erythropoietin levels
Elevated plasma fibrinogen levels
Elevated endothelin
Elevated leptin levels
Elevated von Willebrand factor
Physiologic responses
Increased chemoreceptor sensitivity as seen by exaggerated pressor response and ventilation response to hypoxia
Reduced baroreceptor sensitivity

Information from references 1 through 4.

arrhythmia, and congestive heart failure,[34] because about one half of all patients with coronary heart disease,[35] stroke,[36] and congestive heart failure[37] have OSA. Additionally, retrospective studies have shown that successful treatment of OSA is associated with a marked reduction in hospitalization[38] and mortality,[39] and prospective studies have shown that successful treatment of OSA improves nocturnal angina,[40] nocturnal cardiac arrythmia,[41] and congestive heart failure.[42]

The Role of OSA in Secondary Hypertension

Some evidence suggests that OSA may also contribute to hypertension associated with hypothyroidism, acromegaly, alcohol abuse, and chronic renal failure.[1]

Diagnostic Evaluation of OSA

Several reviews[43,44] have been published about the diagnosis and physical examination of patients with OSA. The common physical findings in OSA are listed in *Table 3*.[43,44] Because many patients with OSA have an upper airway abnormality, an ear, nose and throat evaluation is essential in the diagnostic workup.

The gold standard for an accurate diagnosis of OSA is a polysomnography evaluation performed in a sleep disorders unit. During this overnight evaluation, the number of apneas and hypopneas can be quantified, their duration measured, their relationship to body position and sleep stages determined, the level of oxygen desaturation measured and the existence of arrhythmic episodes can be quantified. This information determines the severity of the disorder and helps determine the treatment choice. Other tests often performed to objectively evaluate daytime sleepiness include the Multiple Sleep Latency Test and the Maintainence of Wakefulness Test.

Treatment of OSA

Treatment of OSA includes nonsurgical and surgical approaches.[45-54] No successful pharmacologic treatment currently exists for snoring or OSA.

The gold standard for accurate diagnosis of obstructive sleep apnea is a polysomnography examination in a sleep disorders unit.

NONSURGICAL PROCEDURES

Weight Loss. Weight loss should always be strongly encouraged in patients with OSA who are obese (about 70 percent of all patients who have OSA are obese). Weight loss can produce good results and even small reductions in weight can produce major improvements in OSA.[46,47] Because compliance with this treatment is usually poor,[46] physicians should not delay initiating other

TABLE 3
Common Physical Findings in OSA

Obesity
Primarily central obesity as assessed by an increased waist-to-hip ratio
Short neck and increased neck circumference
On oral examination
No clear abnormalities present in some cases
Crowded mouth with low-extending soft palate sometimes present
Large uvula
Generalized erythema and swelling of all tissues including the pharyngeal pillars
Large tonsils and adenoids may be present, especially in children
Large tongue (macroglossia)
High, arched and narrow hard palate (causes a narrow and crowded mouth)
Overbite of upper teeth
Retrognathia or micrognathia
Obstructed nasal passages
Evidence of hypothyroidism and acromegaly

Information from references 43 and 44.

Nasal continuous positive airway pressure is the treatment of choice for most patients with moderate to severe cases of obstructive sleep apnea.

forms of therapy unless patients are making serious attempts to reduce their weight.

Continuous Positive Airway Pressure (CPAP). During sleep, room air is continuously applied by a small, quiet air compressor that delivers positive pressure through a nasal mask. The CPAP system acts as a physical pressure splint to prevent partial or complete collapse of the upper airway during sleep. CPAP is the treatment of choice for patients with moderate to severe OSA, but it is also used to treat patients with mild OSA and those with loud and continuous snoring.

While CPAP is an extremely effective form of therapy, there are two pitfalls in its use. It is not a permanent cure; when patients stop treatment, OSA returns within a few days. Secondly, because patients may be reluctant to attempt CPAP or persist in using it, family physicians should encourage and closely follow patients because the beneficial effects on quality of life can be great.[45,48]

Position Therapy (Avoiding the Supine Position). A large study[49] of patients with OSA who were diagnosed in a sleep disorders unit recently demonstrated that "positional patients" (those who have more than twice as many abnormal breathing episodes when sleeping in the supine position than when sleeping in the lateral position) represent more than one half of patients with OSA. These patients, in most cases, were found to have mild OSA. These results were not surprising because, when lying in the lateral position, patients have significantly fewer breathing abnormalities than when lying in the supine position. In some instances, a total absence of breathing disturbances was observed when patients were lying in the lateral position. For these patients and those who had an AHI of 10 or less while lying in the lateral position, position therapy represented a valuable and effective therapy.

Results from another study[50] showed that patients with OSA who were hypertensive and normotensive and who avoided sleeping in the supine position for one month by using the tennis ball technique, a simple and inexpensive behavioral method, had a significant reduction in 24-hour blood pressure values and blood pressure variability. (In the tennis ball technique, a wide cloth belt with a pocket that a tennis ball is placed into is worn around the chest so that the pocket with the ball is positioned in the middle of the back. When the patient rolls onto his or her back, the pressure of the tennis ball causes the patient to roll onto their side again.) If these preliminary results are confirmed in larger studies, avoiding the supine position during sleep could become a new nonpharmacologic treatment for many hypertensive patients.

Oral Devices. Oral devices placed in the mouth at bedtime to keep the mandible and tongue in a forward position during sleep can prevent upper airway obstruction during sleep. This therapy has been shown to be useful primarily in patients with simple snoring and in patients with mild to moderate OSA.[51]

SURGICAL PROCEDURES

A wide variety of surgical procedures are currently used to treat OSA and, of these, uvulopalatopharyngoplasty is the most common. This procedure can be performed using conventional or laser techniques. Unfortunately, only about 40 to 60 percent of patients who have OSA show an improvement in symptoms following the procedure, and it is impossible to predict which patients will benefit from surgery and which will not. Other surgical procedures include relief of nasal obstruction, tonsillectomy, adenoidectomy, mandibular-maxillary surgery, and, most recently, somnoplasty, in which radiofrequency energy is used to shrink part of the tongue and soft palate.[52-54]

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REFERENCES

1. Silverberg DS, Oksenberg A. Essential and secondary hypertension and sleep disordered breathing: a unifying hypothesis. J Hum Hypertens 1996; 10:353-63.
2. Silverberg DS, Oksenberg A. Essential hypertension and abnormal upper airway resistance during sleep. Sleep 1997;20:794-806.
3. Silverberg DS, Oksenberg A, Iaina A. Sleep related breathing disorders are common contributing factors to the production of essential hypertension but are neglected, underdiagnosed, and undertreated. Am J Hypertens 1997;10:1319-25.
4. Silverberg DS, Oksenberg A, Iaina A. Sleep-related breathing disorders as a major cause of essential hypertension: fact or fiction? Curr Opin Nephrol Hypertens 1998;7:353-61.
5. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. New Engl J Med 1993;328:1230-5.
6. Findley LJ, Suratt PM. Serious motor vehicle crashes: the cost of untreated sleep apnea. Thorax 2001;56:505.
7. Krieger J, Follenius M, Sforza E, Brandenberger G, Peter JD. Effects of treatment with nasal continuous positive airway pressure on atrial natriuretic peptide and arginine vasopressin release during sleep in patients with obstructive sleep apnoea. Clin Sci (Lond) 1991;80:443-9.
8. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 2001;163: 685-9.
9. Grote L, Ploch T, Heitmann J, Knaack L, Penzel T, Peter JH. Sleep-related breathing disorder is an independent risk factor for systemic hypertension. Am J Respir Crit Care Med 1999;160:1875-82.
10. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000;283:1829-36.
11. Davies CWH, Crosby JH, Mullins RL, Barbour C, Davies RJ, Stradling JR. Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects. Thorax 2000;55:736-40.
12. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Leiby BE, Vela-Bueno A, et al. Association of hypertension and sleep-disordered breathing. Arch Intern Med 2000;160:2289-95.
13. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ 2000;320:479-82.
14. Ohayon MM, Guilleminault C, Priest RG, Zulley J, Smirne S. Is sleep-disordered breathing an independent risk factor for hypertension in the general population (13,057 subjects)? J Psychosom Res 2000;48:593-601.
15. Minemura H, Akashiba T, Yamamoto H, Akahoshi T, Kosaka N, Horie T. Acute effects of nasal continuous positive airway pressure on 24-hour blood pressure and catecholamines in patients with obstructive sleep apnea. Intern Med 1998;37:1009-13.
16. Voogel AJ, van Steenwijk RP, Karemaker JM, van Montfrans GA. Effects of treatment of obstructive sleep apnea on circadian hemodynamics. J Auton Nerv Syst 1999;77:177-83.
17. Pankow W, Lies A, Lohmann FW. Sleep-disordered breathing and hypertension. New Engl J Med 2000;343:966-7.
18. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med 2001;163:344-8.
19. Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK. Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. Circulation 1999; 100:2332-5.
20. Dimsdale JE, Loredo JS, Profant J. Effect of continuous positive airway pressure on blood pressure: a placebo trial. Hypertension 2000;35(1 pt 1):144-7.
21. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378-84.
22. Portaluppi F, Provini F, Cortelli P, Plazzi G, Bertozzi N, Manfredini R, et al. Undiagnosed sleep-disordered breathing among male nondippers with essential hypertension. J Hypertens 1997;15:1227-33.
23. Stoohs RA, Gingold J, Cohrs S, Harter H, Finlayson E, Guilleminault C. Sleep-disordered breathing and systemic hypertension in the older male. J Am Geriatr Soc 1996;44:1295-300.
24. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep 1997;20:705-6.
25. Rahaghi F, Basner RC. Delayed diagnosis of obstructive sleep apnea: Don't ask, don't tell. Sleep & Breathing 1999;3:119-24.
26. Haponik EF, Frye AW, Richards B, Wymer A, Hinds A, Pearce K, et al. Sleep history is neglected diagnostic information. Challenges for primary care physicians. J Gen Intern Med 1996;11:759-61.
27. Ball EM, Simon RD Jr., Tall AA, Banks MB, Nino-Murcia G, Dement WC. Diagnosis and treatment of sleep apnea within the community. The Walla Walla Project. Arch Intern Med 1997;157:419-24.
28. Noda A, Okada T, Hayashi H, Yasuma F, Yokota M. 24-hour ambulatory blood pressure variability in obstructive sleep apnea syndrome. Chest 1993; 103:1343-7.
29. Stradling JR, Partlett J, Davies RJ, Siegwart D, Tarassenko L. Effect of short term graded withdrawal of nasal continuous positive airway pressure

on systemic blood pressure in patients with obstructive sleep apnea. Blood Press 1996;5:234-40.
30. Grote L, Hedner J, Peter JH. Sleep-related breathing disorder is an independent risk factor for uncontrolled hypertension. J Hypertens 2000;18: 679-85.
31. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest 1997;99:106-9.
32. Young T, Finn L, Hla KM, Morgan B, Palta M. Snoring as a part of a dose-response relationship between sleep-disordered breathing and blood pressure. Sleep 1996;19(10 suppl):S202-5.
33. Guilleminault C, Stoohs R, Shiomi T, Kushida C, Schnittger I. Upper airway resistance syndrome, nocturnal blood pressure monitoring, and borderline hypertension. Chest 1996;109:901-8.
34. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163:19-25.
35. Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. Lancet 1990;336:261-4.
36. Dyken ME, Somers VK, Yamada T, Ren ZY, Zimmerman MB. Investigating the relationship between stroke and obstructive sleep apnea. Stroke 1996; 27:401-7.
37. Chan J, Sanderson J, Chan W, Lai C, Choy D, Ho A, Keung R. Prevalence of sleep-disordered breathing in diastolic heart failure. Chest 1997;111:1488-93.
38. Bahammam A, Delaive K, Ronald J, Manfreda J, Roos L, Kryger MH. Health care utilization in males with obstructive sleep apnea syndrome two years after diagnosis and treatment. Sleep 1999;22:740-7.
39. Partinen M, Jamieson A, Guilleminault C. Long-term outcome for obstructive sleep apnea syndrome patients. Mortality. Chest 1988;94:1200-4.
40. Franklin KA, Nilsson JB, Sahlin C, Naslund U. Sleep apnoea and nocturnal angina. Lancet 1995;345: 1085-87.
41. Koehler U, Fus E, Grimm W, Pankow W, Schafer H, Stammnitz A, et al. Heart block in patients with obstructive sleep apnoea: pathogenetic factors and effects of treatment. Eur Respir J 1998;11:434-9.
42. Malone S, Liu PP, Holloway R, Rutherford R, Xie A, Bradley TD. Obstructive sleep apnea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. Lancet 1991;338:1480-4.
43. Chervin RD, Guilleminault C. Obstructive sleep apnea and related disorders. Neurol Clin 1996;14: 583-609.
44. Strollo PJ Jr., Rogers RM. Obstructive sleep apnea. New Engl J Med 1996;334:99-104.
45. Hudgel DW. Treatment of obstructive sleep apnea. A review. Chest 1996;109:1346-58.
46. Strobel RJ, Rosen RC. Obesity and weight in obstructive sleep apnea: a critical review. Sleep 1996;19:104-15.
47. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA 2000;284: 3015-21.
48. Davies RJ, Stradling JR. The efficacy of nasal continuous positive airway pressure in the treatment of obstructive sleep apnea syndrome is proven. [Editorial]. Am J Respir Crit Care Med 2000;161: 1775-6.
49. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs non-positional obstructive sleep apnea patients: Anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. Chest 1997:112:629-39.
50. Berger M, Oksenberg A, Silverberg DS, Arons E, Radwan H, Iaina A. Avoiding the supine position during sleep lowers 24 h blood pressure in obstructive sleep apnea (OSA) patients. J Hum Hypertens 1997;11:657-64.
51. Marklund M, Franklin KA, Sahlin C, Lundgren R. The effect of a mandibular advancement device on apneas and sleep in patients with obstructive sleep apnea. Chest 1998;113:707-13.
52. Sher AE. Soft-tissue surgery for obstructive sleep apnea syndrome. Semin Respir Crit Care Med 1998;19:165-73.
53. Troell RJ, Powell NB, Riley RW. Hypopharyngeal airway surgery for obstructive sleep apnea syndrome. Sem Respir Crit Care Med 1998;19: 175-83.
54. Powell NB, Riley RW, Troell RJ, Li K, Blumen MB, Guilleminault C. Radiofrequency volumetric tissue reduction of the palate in subjects with sleep disordered breathing. Chest 1998;113:1163-74.