Obstructive Sleep Apnea and the Kidney1,2

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ABSTRACT
Recent studies of obstructive sleep apnea and its comorbidity with other systemic diseases have stimulated interest in the relationship of apnea to renal disease and hypertension. Polysomnographic sleep studies in patients on dialysis who complain of daytime fatigue or sleepiness reveal significant apnea in up to 73% of those studied. Abnormalities in respiratory controller mechanisms from chronic hypocarbia, metabolic acidosis, and uremic toxins have been blamed for the occurrence of apnea in this setting. Proteinuria and sometimes nephrotic syndrome have been recognized in morbidly obese patients with sleep apnea syndrome. Renal biopsies of such patients have shown glomerulomegaly and focal segmental sclerosis. It is postulated that these lesions may result from increased glomerular filtration and blood flow. Elevated urine output, sodium and chloride excretion, and atrial natriuretic peptide have been well demonstrated in obstructive apnea patients and correct to control levels with treatment of the apnea. Both acute (with each apnea) and chronic daytime blood pressure elevation are frequently observed in sleep apnea patients, and occult sleep apnea is postulated as one possible cause of "primary" hypertension in middle-aged men. In younger patients, such hypertension seems to be more reversible with the elimination of apnea. In older patients, however, the cure of systemic hypertension cannot be guaranteed with the elimination of the apnea, and asymptomatic apnea patients tend not to tolerate the bother and discomfort of apnea treatment with nasal continuous positive airway pressure. Therefore, aside from a careful history regarding sleep symptomatology, polysomnographic studies of clinic populations with primary hypertension to search for apnea as a cause cannot be recommended.

Key Words: Sleep apnea syndromes, hypoxemia, high blood pressure, sympathetic nervous system, proteinuria

A few years ago, it might have been premature to contemplate a review of nocturnal disordered breathing and abnormalities of renal function. However, research into the mechanisms and treatment of obstructive sleep apnea in just the past 10 yr has led to our recognition of a relationship between sleep apnea and renal function. Certainly, the most important impetus to furthering research has been the recognition of the relationship between obstructive sleep apnea (OSA) and systemic hypertension (1–9). Interest in the sleep apnea syndrome as a comorbidity factor in other diseases has fueled this research. This was especially relevant both with the recognition of decreased longevity in OSA patients and with the realization that sudden death during sleep from apnea is probably a rare event. Finally, the recent recognition of the high frequency with which sleep-disordered breathing occurs in the general as well as in the healthy working population (15% of healthy workers and those snoring may have 5 to 15 disordered breathing events per hour of sleep) has further stimulated interest in the comorbidity of sleep apnea and other systemic diseases (10).

SLEEP APNEA AND SLEEP APNEA SYNDROME

Sleep apnea is defined as the appearance of 10-s periods of breathing cessation during sleep. Apneas may be classified as obstructive, central, or mixed. Obstructive apneas appear to originate from occlusion of the compliant upper airway somewhere between the velopharynx (behind the soft palate) and the supraglottic area. The obstructive nature is usually recognized by the combination of airflow cessation and some measure of continued respiratory effort such as ineffective movement of the chest or abdomen (measured by strain gauge), continued intrathoracic negative pressure deflections (measured by esophageal pressure transducers), or the cyclic surface electrical activity of the diaphragm. Central apneas are characterized by the cessation of airflow along with the absence of obvious respiratory efforts.
in these same monitoring parameters. Mixed apneas, as the name implies, are a combination of central and obstructive patterns. Initially, there is absence of airflow without obvious respiratory effort. This is followed by the onset of ineffective muscular efforts, usually in a crescendo pattern, terminating in the release of the obstruction and the movement of air. Lesser degrees of obstruction or decreased central drive may result in decreased air movement without complete cessation of breathing but some degree of oxyhemoglobin desaturation. These events are termed "hypopneas." The release of the obstructive and mixed apneas and hypopneas, as well as the termination of central apneas, is frequently heralded by central nervous system (electroencephalographic) arousal, which may be the result of building hypoxia, hypercarbia, and/or the crescendo effect of various thoracomechanical-neural reflex arcs. Many feel that arousal, which may be the result of building hypoxia, sympathoexcitation, and inappropriately high chemosensory thresholds that invoke effector neural activity (especially to upper airway pharyngeal muscles), thereby making apnea release possible. Obstructive apneas are felt to be associated with or brought about by increased pharyngeal airway resistance. This may in turn be the result of a decrease in the physical size of the airway, the result of an inappropriate phasic pharyngeal dilator muscle response to inspiratory negative airway pressure, or both. It is difficult to define sleep apnea in terms of the absolute number of apneas and hypopneas, but fewer than five apneas per hour of sleep (apnea index) is considered normal and more than 20 apneas plus hypopneas per hour (disordered breathing [DOB] event index) is often associated with symptoms.

The recurrent arousals or the combination of hypoxia and arousals with greatly disturbed sleep architecture is generally blamed for the chronic daytime hypersomnolence, inattentiveness, fatigue, and other symptoms that result in the sleep apnea syndrome (SAS: nocturnal sleep apnea with daytime symptoms). Among the immediate pathophysiologic events occurring during apnea are noticeable and often severe cyclic arterial and mixed venous oxygen desaturation (11), a crescendo increase in intraarterial and immediate postapneic blood pressure (12), frequent end-apnea bradycardia (13) and decreased cardiac output (14), and sometimes, supraventricular and ventricular arrhythmias (15). Generalized increased sympathetic activity accompanies obstructive apnea and may in part or totally account for the pressor response and arrhythmic activity (16). The long-term sequelae of chronic sleep apnea and SAS, aside from hypersomnolence, include pulmonary hypertension and right heart failure, systemic hypertension, and shortened lifespan (17). Extensive reviews of the topic of sleep apnea are available to the reader (18,19).

SLEEP APNEA SYNDROME IN CHRONIC RENAL FAILURE

Patients with chronic renal failure (CRF) on dialysis may suffer from many nonspecific symptoms and general subjective feelings of poor health, including tiredness, headaches, and disturbed sleep (20). Millman et al. (21) found two CRF patients with overt clinical sleep apnea in a dialysis facility. Those authors subsequently undertook a broader study of dialysis patients, discovering 12 (41%) of 29 patients to have symptoms of SAS. Eight patients consented to have overnight polysomnography, and six had obstructive sleep apnea with a mean sleep DOB index (number of apneas and hypopneas per hour) of 65 ± 22. Those authors postulated that the treatment of these subjects with testosterone might have contributed to the SAS, but restudy after 2 months without testosterone injection did not show a change in the DOB index. Kimmel et al. performed a similar study in 26 CRF patients, 22 of whom were undergoing chronic dialysis and 4 of whom subsequently joined a dialysis program (22). Twenty-two gave histories suggestive of SAS, and 16 (73%) of these had sleep apnea defined as a DOB index of greater than 30/h. Four asymptomatic patients had no apneas. Periodic leg movements, which may also cause frequent nocturnal arousals and daytime sleepiness, were present in 9 of the 16 patients. In seven patients, more than half of the DOB events were central; the remainder in all subjects were obstructive. Mendelson et al. (23) performed polysomnographic sleep studies on 11 dialysis patients both the day before and the day of (after) hemodialysis. Seven (63%) of the 11 had complaints of disturbed sleep, and 6 had more than 30 DOB events per hour. The group mean DOB events per sleep session was the same on the dialysis night (138 ± 154 events) versus the "off" night (132 ± 140 events), indicating that acute shifts in fluid and electrolytes during dialysis did not appear to play an etiologic role in the apnea. However, there was a trend toward longer apneas on the hemodialysis night. Using polysomnography, the same authors examined 15 peritoneal dialysis patients and 15 hemodialysis patients for the presence of sleep apnea. The prevalence of sleep apnea was not different between these groups. None of the 15 peritoneal dialysis patients and 8 of the 15 hemodialysis patients had apnea (24). One weakness of these studies is that no mention is made of concomitant medications or their discontinuation for the sleep studies, making evaluation of DOB event prevalence more difficult. Second, many of the subjects had concomitant diseases, such as diabetes, that are already known to be associated with sleep DOB.

There are several possible explanations for the high frequency of sleep DOB in CRF patients. First,
hypocapnia associated with chronic metabolic acidosis may be lowering the apnea-Pco2 threshold, predisposing to periodic breathing. Second, chronic acidaemia may alter the hydrogen ion set point for respiration (increased sensitivity), predisposing to a shortened feedback loop and unstable breathing patterns (25). Third, Fein et al. (26) have suggested that uremic toxins acting on the central nervous system may result in a reduction of airway muscle tone during sleep or an instability of respiratory control. They showed improvement in sleep DOB events in one subject after aggressive hemodialysis. Another recent study showed regression of sleep apnea in two patients treated for CRF with kidney transplants (27). Fourth, it has been suggested that hemodialysis itself may be a cause of apnea by inducing osmotic disequilibrium (26), but the study by Mendelson et al. (23) tends to refute this. Fifth, many patients with CRF have peripheral neuropathy on the basis of underlying disease (diabetes mellitus, etc.) or in relation to the CRF itself. Peripheral neuropathy may be associated with sleep DOB if nerves affecting the upper airway patency are affected. Several other factors including anemia (28), advanced age, sex, and hormone imbalance may contribute to ventilatory control instability and theoretically could predispose to apnea in CRF patients. Obesity, which is a strong predisposing factor in apnea patients, did not appear to be predictive in the above studies (21,22). A small anatomic size of the upper airway is also a strong predisposing factor toward apnea but has not been investigated in CRF patients. Further studies in this area, preferably in subjects not taking medications, will need to be done to shed additional light on this problem.

In a recent report, Soreide et al. administered branch-chain amino acid (BCAA) solution versus placebo to seven CRF patients on chronic hemodialysis (29). The BCAA infusion appeared to cause a return in the amount of rapid eye movement sleep from low levels toward baseline and significantly decreased end-tidal CO2 in all stages of sleep. Only one subject had sleep apnea (severe) and was also overweight. The BCAA night was associated with a decrease in the apnea index from 85 (placebo) to 31 apneas per hour, with a disappearance of all central apneas and marked improvement in oxygen saturation. The mechanism for this is unknown.

THE KIDNEY IN OSA

In addition to systemic hypertension, which will be discussed subsequently, there appears to be a functional and possibly anatomic change in the kidney associated with OSA. Chaudhary et al. observed a greater-than-expected frequency of dipstick proteinuria in OSA subjects (30) and subsequently quantitated this with timed overnight (recumbent) urine collections in 9 healthy subjects, 12 obese nonapnea subjects, and 14 obese apnea subjects (31). Patients with known renal disease, diabetes mellitus, elevated creatinine level, abnormal urinary sediment, evidence of renal tubular disease, or uncontrolled hypertension were excluded. Overnight urinary protein excretion was 16.2 ± 5.5, 29.3 ± 9.5, and 94.0 ± 31.8 μg/min in the three groups, respectively. Only 14% of the obese nonapnea subjects had proteinuria (defined as >46 μg/min), whereas 64% of the apnea subjects had proteinuria. Neither body weight nor indices of the severity of sleep apnea were significantly different between those obese apnea subjects with and without abnormal protein excretion. Four of the subjects had hypertension. Those same authors also demonstrated reversibility of proteinuria in two apnea patients successfully treated for apnea with tracheostomy (32). Urinary protein excretion in one patient fell from 2.66 to 0.136 g/24 h 10 days after tracheostomy. A renal biopsy from this subject showed glomerulomegaly and one sclerotic glomerulus. In the second patient, urinary protein excretion fell from 1.74 to 0.054 g/24 h 10 days after tracheostomy. Neither patient showed substantial dry body weight loss in the 10-day period between urine collections.

The single biopsy (32) suggesting glomerular enlargement has been substantiated in other studies. Jennette et al. describe a 49-year-old morbidly obese apnea patient excreting 2.2 to 6.0 g of urinary protein per 24 h but without significant urine sediment (33). This patient had renal insufficiency with serum creatinine ranging from 3.4 to 5.4 mg/dL during periods of respiratory failure. Light microscopy of an open renal biopsy showed glomerulomegaly with hypercellularity (Figure 1) and focal segmental sclerosis preferentially involving the perihilar segments. Immunofluorescence microscopy demonstrated focal, segmental, irregular glomerular immunostaining with antisera specific for immunoglobulin, C3, and C1q. Bailey et al. have also described a morbidly obese man (149 kg) with proteinuria (2.6 g/24 h) and bilateral enlarged kidneys (34). A percutaneous renal biopsy showed that all glomeruli were 50% larger than those from an age-matched healthy man. Of 13 glomeruli, one was totally sclerotic and two showed focal segmental sclerosis and hyalinosis. The patient was hypoxemic and hypercarbic and suffered from recurrent cor pulmonale.

Other authors (35,36) note that focal segmental glomerulosclerosis is the most common pathologic lesion in the kidneys of obese patients with nephrotic syndrome. Kasiske and Crosson found focal glomerulosclerosis in 53% of 17 morbidly obese patients with marked proteinuria but without obvious renal disease (35). Normal body weight controls in this
Study had a 6% prevalence of this lesion. Several authors have suggested that focal glomerulosclerosis may be related to increased glomerular capillary pressures and flows, citing data from humans as well as from animal models (37,38). Systemic hypertension is also a well-known accompanying condition of OSA (see below). Additional mechanisms could include abnormal lipid metabolism (elevated cholesterol and triglycerides) or glucose intolerance, common to morbidly obese individuals. Patients with massive obesity have increased GFR. Stockholm et al. showed, in 16 obese versus 16 normal-weight women, all without evidence of renal disease, that GFR were on the average 25% higher in obese women than in controls (39). Weisinger et al. observed elevated right atrial pressures and increased cardiac output in three massively obese patients with nephrotic syndrome but without evidence of cardiac failure (36). Right atrial pressures normalized and proteinuria decreased in two subjects who successfully lost weight. Glomerulomegaly is also associated with chronic hypoxic cor pulmonale (40), which in turn is frequently associated with obesity (obesity-hypoventilation syndrome) and with OSA. These observations suggest the intriguing possibility that massive obesity could be related to proteinuria and nephrotic syndrome via the chronic hypoxemia or episodic hypoxemia of SAS (with hypoxia, hypercapnia, pulmonary hypertension, central venous engorgement, and systemic hypertension). It is conceivable that glomerular adaptive hemodynamic changes in response to increased filtration may induce anatomic renal lesions, leading to proteinuria in morbidly obese patients with SAS.

This theory is supported by indirect evidence of increased RBF in the setting of sleep apnea without nephrotic syndrome. Increased urine excretion in apnea patients without cor pulmonale, which decreases with effective treatment of apnea, is well documented (41–43). Krieger et al. measured urinary volume and electrolytes overnight in eight normal controls and in 13 apnea patients at baseline and during the elimination of apneas with nocturnal nasal continuous positive airway pressure (NCPAP) (42). Patients with OSA had significantly higher fractional urinary flows, higher fractional sodium and chloride urinary excretions, and a lower percentage of filtered sodium resorption than did normal subjects. With NCPAP treatment, fractional urinary, sodium, and chloride flow decreased toward control levels. There were no differences in other parameters of renal function (including aldosterone, and antidiuretic hormone, as demonstrated by no change in free water clearance) between healthy controls and OSA patients. Other studies show similar results (43). Hypoxia is a potent stimulus to sodium and water excretion (44). Additionally, the Mueller maneuver (exaggerated negative intrathoracic pressure against a closed glottis), which occurs with each effort at overcoming the obstructed breath, is known to cause atrial dilation, which may stimulate the release of atrial natriuretic peptide (ANP), further promoting urinary excretion. The urinary excretion of cGMP (which is induced by ANP) is
OSA AND SYSTEMIC HYPERTENSION

Systemic hypertension has long been associated with sleep apnea, occurring in up to 90% of patients in some studies (1–3). The most convincing proof of the association is the reversal of hypertension by the treatment of apnea with tracheostomy (4–6) or NCPAP (7–9). In the mid-1980s, a series of articles appeared implicating occult sleep apnea as a cause of primary hypertension (50–53). Hypertensive populations were studied polysomnographically for evidence of apnea. The prevalence of OAS in these studies was approximately 30%. Some subsequent studies refute these findings, showing no higher prevalence of episodic desaturation or sleep DOB in hypertensive patients (54–56) or instead showing a correlation between hypertension and age or obesity (57).

The disappearance of systemic hypertension in treated apnea patients is presumptive evidence that apnea was a cause of hypertension. A cause-effect association is less clear in patients taken from hypertensive populations who are then discovered to have sleep apnea (see below). For example, although the treatment of sleep apnea in eight hypertensive men resulted in a lowering of the mean systolic and diastolic blood pressure from 149/95 to 139/90 mm Hg, four patients continued to have a diastolic blood pressure of more than 90 mm Hg when not taking antihypertensive medication (Table 1) (52). There have been reports of improvement of blood pressure in hypertensive patients treated with NCPAP. Jenum et al. observed a substantial decrease in blood pressure in five hypertensive subjects treated for a week with NCPAP (7). Another group treated 12 men with sleep apnea and hypertension with NCPAP for 6 months and found that the mean systolic pressure fell from 147.1 to 126.4 mm Hg whereas the diastolic pressure fell from 81.6 to 69.4 mm Hg (P < 0.05) (8). Similar studies find that only a subgroup of treated apnea patients experience corrections or improvements in their blood pressure (9).

The association of obesity with both OSA and primary hypertension makes proof of a cause-effect relationship difficult. Summarizing previously reported studies, among 194 patients with sleep apnea defined as more than 10 DOB events per hour, 8% of the variance in diastolic blood pressure was accounted for by body mass index, 4% by age, and 1.7% by apnea index (number of apneas per hour) (57).
Neither the relationship of obesity to apnea nor its relation to hypertension is understood. Obesity could be associated with increased fatty tissue in the pharynx, which increases airway resistance, or it could cause decreased lung volume (chest wall compression), which also affects upper airway caliber. The distribution of body fat may also be an important determinant of the presence or absence of apnea. One study examining 37 morbidly obese patients (body mass index >40 kg/m²) found a 76.9% prevalence of sleep apnea in men and 7.1% in women (58).

Sleep apnea as a potential cause of primary hypertension was first reported by Kales et al. (50). Those authors performed polysomnographic examination of 50 hypertensive and 50 nonhypertensive persons matched for age but not for weight. Thirty percent of the hypertensive subjects had OSA with a mean apnea index of 9.3 per hour. The diagnosis of sleep apnea was strongly related to obesity, but there was a similar portion of obese patients among sleep apnea, sleep apnea activity, and no sleep apnea groups. Blood pressure did not correlate with the severity of sleep apnea. In a similar study, Fletcher et al. found the prevalence of sleep apnea (apnea index, >10/h) among 46 men with essential hypertension to be 35% while finding only three apnea patients among 34 age- and weight-similar normotensive men (52). Williams et al. studied 23 hypertensive subjects and eight age/weight-matched normotensive controls and found that 35% of the hypertensive subjects had sleep apnea (53). Subjects were not removed from medications at the time of polysomnography, and apnea subjects were more obese than were patients without apnea (53).

Contradicting earlier studies, Hirshkowitz et al. were unable to find a difference in apnea index between 38 untreated hypertensive and 53 normotensive men (55). Using overnight arterial oxygen saturation as an indirect indicator of apnea, Stradling and Crosby were unable to find a difference in the number of dips, or in the nadir nocturnal desaturation during dips, between 30 men with untreated essential hypertension and 30 normotensive age-, height-, and weight-matched controls (56).

Several large epidemiologic surveys (not polysomnographic studies) report an association between hypertension, cerebral infarction, and ischemic heart disease in self-reported snorers (59-64). (Severe snoring may be an indication of increased upper airway resistance and a tendency toward OSA.) The role of apnea as a cause of primary hypertension remains controversial because of improperly weight-matched normotensive controls, the nonremoval of antihypertensive medications from study subjects, and the lack of broad-based polysomnographic surveys of large, unselected patients with longitudinal follow-up. Obesity remains a confounding factor that cannot be easily separated as causal in both diseases. One study even suggests the possibility that hypertension could be causal in sleep apnea, by showing that the treatment of hypertension in apnea patients with angiotensin-converting enzyme inhibitors not only significantly reduces blood pressure, but also reduces apnea index (65).

The possible mechanisms of blood pressure changes in both the acute and chronic settings of OSA are numerous. The acute elevation of systemic blood pressure occurs with each apnea and probably results from a combination of several mechanisms: (1) wide fluctuations in negative intrathoracic pres-
pressure; (2) hypoxemia and hypercarbia stimulating peripheral chemoreceptors (12); (3) bradycardia probably resulting from the activation of baroreceptors (13,66); (4) changes in stroke volume caused by right ventricular overfilling with septal shift and increased afterload caused by the greater transmural pressure from the deep negative intrathoracic pressure (67); and (5) a surge of sympathetic activity probably causing vasoconstriction in certain vascular beds (16). At the termination of the obstruction, normalization of cardiac preload and afterload probably contributes to a sudden increase in cardiac output, which may contribute to a postapneic increase in blood pressure.

The possible mechanisms for the development of long-term increases in blood pressure (not acutely associated with apnea) are: (1) the direct effects of episodic hypoxemia and hypercarbia; (2) an alteration in fluid balance (previously discussed) in response to marked fluctuations in intrathoracic pressure during obstructed breathing; and (3) stress resulting from chronic, nightly disruption of sleep architecture. Studies relating these mechanisms to chronic elevated blood pressure are sparse and contradictory. As mentioned above, atrial stretch causes the release of ANP in OSA (45-48), which would counteract fluid retention as a mechanism of chronic hypertension. Two studies have demonstrated an increase in PRA activity with the correction of apnea with NCPAP, suggesting that PRA is low during obstructive apnea and that perhaps chronic hypertension associated with OSA is a low renin type (68,69).

One of the more notable acute changes of OSA is hypoxemia. Chemoreceptors adapt in a long-term fashion to hypoxia and hypercarbia and may play a major role in determining diurnal blood pressure (70). Increased ventilatory and pressor responsiveness to isocapnic hypoxia has been demonstrated in young subjects with mild hypertension (71). Augmented resting ventilatory drive dependent on peripheral chemoreceptors has been demonstrated in hypertensive subjects (72). The potentiation of excitatory sympathetic nerve responses to hypoxia has been demonstrated in borderline hypertensive subjects (73). Trzebski has hypothesized that "long-term, repetitive episodic hypoxia during obstructive sleep apnea resets chemoreceptor reflex drive to a higher level and initiates hypertension" (70). One group reported recently that hypertensive sleep apnea patients demonstrated an augmented tonic ventilatory response, evidenced by brief hyperoxic inactivation of chemoreceptors, as compared with sleep apnea subjects without hypertension (74,75). Thus, carotid chemoreceptor output may reset to a higher level as a result of recurrent episodic asphyxia, causing a chronic increase in sympathetic tone. Recent studies in humans show that peripheral sympathetic activity continues long after the cessation of hypoxemia. Crabtree et al. have administered intermittent asphyxia (simulating episodic hypoxia-hypercarbia of apnea) to five healthy, awake humans over a 20-min period (76). Muscle sympathetic nerve activity increased throughout the period of asphyxia, remaining elevated above control for up to 20 min after the release of the stimulus. This group hypothesizes that the carotid chemoreceptors are sensitized to hypoxia, that is, there is a time-dependent increase in responsiveness to a given level of stimulus. This fits with the theory that, after a night of episodic asphyxia, sympathetic activity to the adrenals or peripheral vasculature may remain high, promoting daytime elevation of blood pressure. Fletcher et al. have demonstrated in OSA patients high urinary levels of noradrenaline, which normalize after tracheostomy, further suggesting a high sympathetic activity as a cause of daytime elevation of blood pressure (77). It could also be postulated that a vasoactive amine such as angiotensin, cleaved from the arterial vessel wall in response to repeated vasoconstriction/relaxation (sheer stress), may further contribute to the daytime blood pressure elevation (78,79).

Despite all of the epidemiologic as well as pathophysiologic studies relating sympathetic activity, chemoreceptor drive, etc., in OSA and hypertensive patients, direct prospective longitudinal evidence in humans that recurrent nocturnal asphyxia eventually leads to sustained hypertension is still lacking. Such experimental evidence may never be forthcoming because of the probable long time course of blood pressure changes in humans. The use of animal models, in which chronic blood pressure changes in response to asphyxia can be observed prospectively, may be more appropriate. Using hypoxic chambers in which rats can be exposed to rapid swings in ambient oxygen concentration, Fletcher et al. have exposed several strains of rats to repetitive episodic hypoxia, which simulates the changes in oxygen saturation of human apnea (80). Repeating the hypoxia cycle up to 800 to 900 times per 7 h of each sleep period on 35 consecutive days in Sprague-Dawley rats caused a 21 mm Hg increase in tail cuff systolic blood pressure. Male Wistar rats, with blood pressures measured intra-arterially, showed a 13.7 mm Hg increase in mean arterial blood pressure after 35 days of episodic hypoxia (80). Thirty-day-exposed rats also showed a significant increase in mean blood pressure over baseline ($P < 0.05$), but rats exposed for shorter time periods did not have elevations in their blood pressure. The blood pressure of rats exposed to episodic compressed air in the same chambers showed no change in blood pressure, indicating that cage stress was not the cause of the elevation. After carotid body denervation by the severing of the carotid sinus nerves, rats do not develop elevated blood pressure (Figure 3) following episodic hypoxia.
for bilateral carotid body denervation and received only 5 groups of rats. Group 3 showed a significant increase in mean arterial blood pressure from baseline. Reproduced by permission from reference 81.

Figure 3. Change in mean blood pressure from baseline in five groups of rats. Group 3 showed a significant increase in mean blood pressure (13 mm Hg) compared with Group 1 (unhandled controls). Group 2 underwent sham operation for bilateral carotid body denervation and received only intermittent compressed air. Group 3 underwent sham operation for bilateral carotid body denervation and received intermittent episodic hypoxia for 7 h/day for 35 days. Group 4 received bilateral carotid body denervation along with intermittent hypoxia for 35 days. Group 5 also received bilateral carotid body denervation but remained unhandled for 35 days. No group besides Group 3 showed a significant change in mean arterial blood pressure from baseline. Reproduced by permission from reference 81.

(81), further supporting the theory of chemoreceptor resetting. By the same recurrent episodic hypoxia model, peripheral sympathetic nervous system denervation by the ip injections of 6-OH dopamine (a peripheral sympathetic neurotoxin) in male Wistar rats prevented the increase in blood pressure in response to the recurrent hypoxia (82). These results suggest that peripheral chemoreceptors in combination with the sympathetic nervous system play a role in the diurnal increase in blood pressure in response to chronic, repetitive, episodic hypoxia.

CLINICAL IMPLICATIONS

Although not proven, OSA and chronic waking systemic hypertension appear to be causally related. This may be more true in younger patients or those in the early stages of hypertension as opposed to older patients with long-established hypertension. This is supported by the early reports of the resolution of systemic hypertension in young apnea patients with effective treatment of the sleep apnea. In older patients, or in those in whom systemic hypertension has been present for long periods of time, the relationship between apnea and hypertension may no longer be causal. Additional factors may have intervened, with elevated blood pressure being sustained through mechanisms other than the asphyxia or related factors that may have initiated the hypertension. In the majority of studies, the effective treatment of apnea by tracheostomy or more recent therapies such as NCPAP reduces blood pressure or makes hypertension easier to treat with antihypertensive medications.

Presently, there is no indication for massive sleep study screening of hypertensive patients to look for occult sleep apnea. The treatment of hypertensive but asymptomatic apnea patients may be difficult because of noncompliance with NCPAP therapy. Also, the elimination of hypertension is not certain with such therapy. In hypertensive patients, adequate historical and physical assessment should be accomplished to detect those patients who might have symptomatic apnea. Such patients should be referred for sleep studies to allow the prescription of therapy to relieve symptoms and perhaps ameliorate the hypertension. Antihypertensive medication remains the mainstay of therapy in such patients after the appropriate treatment of the apnea.

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