In Western societies, sleep apnea (SA) has emerged as a major medical problem with important social (1) and financial implications. The issue may be even more relevant in nephrology because some of the factors involved in the pathogenesis of renal disease are the same that cause, or are associated with, SA in the general population. The interest in this syndrome is continuously increasing in the renal community, but many nephrologists do not fully appreciate its potential clinical implications. Before reviewing in some detail the particular situation of SA in chronic renal diseases, we therefore briefly review definitions, general pathophysiology, and types of SA first (2).

**Definitions and Pathomechanisms**
SA is defined as an intermittent interruption of airflow at the level of nose and mouth during sleep. Episodes of apnea are considered important if they persist for longer than 10 s, but in some cases they may last as long as 2 min. The *SA syndrome* is the clinical consequence of frequent episodes of apnea during sleep. Usually patients with the full-blown syndrome have at least ten episodes of apnea per h. The syndrome is probably the most important cause of daytime somnolence. Its prevalence is at least 2% in middle-age women and 4% in middle-aged men. The following types of apnea can be distinguished: (1) obstructive, (2) central (i.e. neurally mediated), and (3) mixed. Obstructive SA (OSA) is characterized by a cessation of airflow caused by occlusion of the oropharyngeal tract and central SA (CSA) by a transient abolition of the neural drive to respiratory muscles. Mixed apnea represents a combination of the two forms.

**Obstructive Sleep Apnea**
OSA typically occurs in males in an age range between 30 and 60 y and is characterized by a history of snoring, excessive daytime sleepiness, nocturnal choking or gasping, and moderate obesity.

The underlying disturbance in OSA is transient airway occlusion, usually at the level of the oropharynx. The airway occlusion provokes progressive asphyxia, which in turn elicits a brief arousal reaction restoring airway patency. This phenomenon occurs in a cyclic fashion, sometimes up to 500 times per night, and causes sleep fragmentation. The airway collapse in OSA depends on the inability of the airway dilator and abductor muscles to maintain airway patency during inspiration, *i.e.* when subatmospheric pressure is generated inside the respiratory system. By reducing muscular tone of the upper airways, sleep has a permissive role on airway collapse. Alcohol may be an important contributory factor. Structural abnormalities, such as macroglossia, retrognathia, and adenotonsillar hypertrophy, may generate as well as aggravate OSA. By increasing the fat content of the pharynx, obesity is another frequent condition contributing to OSA. Snoring, *i.e.* high frequency vibration of the palatal and pharyngeal soft tissues that results from the reduced size of the upper airway lumen, may further exacerbate the process by inducing soft tissue edema. Snoring usually precedes by several years the development of full-blown OSA, but only a minority of snoring patients have OSA. Recurrent episodes of nocturnal hypoxemia and arousal eventually lead to the full-blown OSA syndrome, which is characterized by additional neuropsychiatric and behavioral disturbances. These include excessive and progressive daytime sleepiness which often reaches a disabling degree as well as memory and personality disturbances. In men, impotence is a relatively frequent complaint.

OSA induces also important cardiorespiratory complications, which are considered a consequence of the recurrent episodes of nocturnal hypoxemia. Cyclic bradycardia during the apneic episodes, followed by tachycardia during the ensuing ventilatory phases, is frequently found. In a minority of cases, bradycardia may end up in prolonged asystolic periods or in various forms of tachyarrhythmia, including ventricular tachycardia. Arrhythmias in OSA may cause sudden death during sleep. Arterial pressure rises abruptly at the termination of each obstructive event. OSA is typically associated with nocturnal hypertension and with an inverted 24-h arterial pressure profile. OSA is a recognized risk factor for systemic hypertension (3,4) and perhaps also for myocardial infarction, stroke, and death (5–7). It is important to bear in mind that obstructive SA may precipitate left ventricular failure in patients with heart disease. Increased afterload during obstructive events, nocturnal hypoxemia, and the ensuing elevated sympathetic adrenal activity all combine to impair left ventricular function (8). On the other hand, a minority of patients with severe OSA, usually obese patients with sustained daytime hypox-
emia, develops frank pulmonary hypertension, right ventricular failure, polycythemia, and chronic hypercapnia and hypoxemia. Upper airway collapse may also induce central sleep apnea by eliciting reflexes that inhibit the respiratory drive. The cardiovascular consequences of OSA will be discussed further in the paragraph dealing with renal diseases.

**Central Sleep Apnea**

In contrast to OSA, the apneic events in CSA are associated with a decreased or absent ventilatory effort. CSA depends on a defective central drive to the ventilatory muscles. The resulting apnea has pathophysiologic consequences that are similar to those of OSA.

Normally, the rate and depth of breathing are regulated by a negative feedback system that maintains the partial pressure of arterial CO2 (pCO2) within a narrow range. Changes in pCO2 lead to changes in ventilation: the greater the sensitivity to CO2, the greater the ventilatory response. Among normal persons, there is considerable variation in the sensitivity to CO2, which may in part be related to genetic influences. Diminished sensitivity to CO2 increases the risk of chronic hypercapnia in patients with established pulmonary disease. Conversely, an increase in CO2 sensitivity minimizes perturbations in the partial pressure of arterial CO2. In theory, this should offer protection against the long-term sequelae of hypercapnia in patients with cardiopulmonary disease. Although this protective mechanism is advantageous during waking hours, the increased sensitivity may destabilize breathing during sleep when ventilation decreases and the partial pressure of CO2 rises (approximately 5 mmHg). In persons with increased sensitivity to CO2, the negative feedback system that controls breathing elicits a large ventilatory response when the pCO2 rises; the consequent hyperventilation, by driving the pCO2 below a certain level (the apneic threshold) then results in central apnea. As a consequence of apnea, the pCO2 rises again, which leads to an increase in ventilation. In this fashion, cycles of central apnea and hyperventilation recur during sleep (Cheyne-Stokes respiration). Patients with hyperventilation (driven by cardiopulmonary disease, metabolic acidosis, fever, and other causes) often develop CSA because during the awake state hyperventilation reduces pCO2 below the critical value, which elicits CSA. Heart failure (see below) is frequently associated with CSA (8). Primary hypoventilatory syndromes that are caused by altered metabolic control of respiration or disease of respiratory muscles are a rare cause of CSA.

**Diagnosis**

The diagnostic criterion standard for SA and for differentiating OSA from CSA is polysomnography, *i.e.* an overnight sleep study that includes (1) neurophysiologic variables (EEG, electrooculogram, and submental myogram) that allow a clear identification of sleep stages, (2) measurements of respiratory effort (respiratory inductive plethysmography or esophageal pressure measurements) that are aimed at detecting and classifying apnea as of central (CSA) or obstructive (OSA) origin, (3) arterial O2 saturation by pulse oxymetry, (4) heart rate, and (5) transcutaneous pCO2.

The main informations derived from polysomnography are schematically summarized in Table 1. The diagnosis of OSA is established when episodes of airflow cessation at the nose and mouth (at least ten episodes of apnea per h) are documented despite simultaneous evidence of continuing respiratory effort. Because of the cost of polysomnography, there is considerable interest in simplified, unattended, ambulatory sleep monitoring for home studies. The most useful test is the recording of arterial O2 saturation by oxymetry. The reliability of overnight oxymetry in the diagnosis of OSA depends on the pretest probability of the disorder. In patients with a high pretest

| **Table 1. Main information derived from polysomnography (also see text)a** |
|-----------------|---------------------------------------------------------------------------------------------------------------|
| **Total sleep time** | Light (1 and 2) and deep (3 and 4) sleep stages and REM sleep |
| **Arousal** | Full awakening or 3 s EEG shift to a lighter sleep stage. The *arousal index* is the ratio of the number of arousals to total sleep time (h) |
| **Apnea** | Total absence of airflow for 10 s or longer |
| **obstructive** | An event with evidence of respiratory effort |
| **central** | An event with absence of respiratory effort |
| **mixed** | An event with initial absence of respiratory effort followed by a respiratory effort |
| **Hypopnea** | A decrease >50% in the amplitude of breaths lasting >10 s or a “clear” decrease in amplitude of breaths (<50%) associated with an arousal or a decrease in O2 saturation >3% |
| **Apnea index** | Ratio of the number of episodes of apnea to total sleep time (h) |
| **Apnea-hypopnea index** | Ratio of the number of episodes of apnea + hypopnea to total sleep time (h). Different authors gave different definitions of the normal limit, ranging from 5 to 15/h |
| **Oxygen saturation** | Number of episodes of O2 desaturation (a decrease >4%); mean O2 saturation; nadir of O2 saturation; average O2 desaturation |
| **Periodic limb movements** | Either as isolated events or associated with arousals |
| **Body position** | Dependence on apneic events |

a REM, rapid eye movement; EEG, electroencephalogram.
probability (based on clinical symptoms and witnessed episodes of apnea during sleep), overnight oxymetry is of proven usefulness to confirm the diagnosis by documenting episodes of arterial O₂ desaturation (at least ten episodes per h). However, negative results in those with a high clinical probability do not exclude the diagnosis, and polysomnography in these cases is mandatory to exclude OSA. When the pretest probability of OSA is low (in the occasional snorer with rare episodes of daytime disturbance), the absence of arterial O₂ saturation virtually excludes the diagnosis, rendering polysomnography unnecessary.

The key element for the diagnosis of CSA is the documentation of recurrent episodes of apnea (at least five per h) that are not accompanied by respiratory effort.

Relation of Sleep Apnea to Hypertension, Heart Failure, and Renal Disease

SA alters several mechanisms that regulate extracellular fluid volume and vascular tone. It is apparently also related to systemic hypertension. Furthermore, SA can be a complication of advanced renal insufficiency. As alluded to above, SA may be of particular relevance in heart failure because it aggravates ventricular afterload by direct and indirect mechanisms. Recognizing the link between SA and cardiorenal physiology is important because it has implications for the prognosis and the treatment of patients with primary and secondary forms of the syndrome.

Body Fluid Homeostasis

By profoundly altering cardiopulmonary dynamics, SA induces reflex circulatory responses that critically affect renal function and body fluid volume homeostasis. Nocturnal secretion of atrial natriuretic peptide (ANP) is increased and renin secretion decreased, suggesting increased cardiac preload as in a state of hypervolemia (19). When patients are awake, however, hypervolemia is not demonstrable, indicating that apneic episodes promote a volume shift from the peripheral to the central circulation, *i.e.* central hypervolemia.

Hypertension and Heart Failure

There are important links between OSA or CSA and hypertension or heart failure, respectively. OSA is associated with hypertension and CSA with heart failure. These two conditions are challenging problems in patients with end-stage renal disease.

It is well documented that BP rises in a very consistent fashion during apneic episodes. The mechanisms responsible for this phenomenon are complex because the direct effects of apnea (hypoxemia and low intrathoracic pressure) are modified by cardiopulmonary reflexes. Undoubtedly, the rapid increase in arterial pressure that occurs at the end of an apneic episode is mainly mediated by surges in sympathetic function during the arousal reaction. Whether periodic nocturnal hypoxemia induces sustained hypertension during daytime as well is somewhat controversial. The problem has considerable epidemiologic relevance given the high frequency of OSA in the adult population.

To clarify the relationship between OSA and hypertension, it is necessary to address the following issues. What is the nature of this relationship; is the risk of hypertension in patients with OSA truly independent of other risk factors? Is it possible to reverse hypertension by specifically treating SA with continuous positive airway pressure (CPAP)? As to the first question, age, gender, body mass index, and alcohol as well as tobacco consumption are major confounders of the relationship between SA and BP. In some studies, the link was markedly attenuated when these factors were appropriately accounted for (9). Furthermore, in some early studies, the techniques applied to diagnose SA, to measure arterial pressure, and to characterize patients were not adequate. Recent large-scale surveys and cohort studies have produced a convincing answer that is based on solid scientific evidence. The Wisconsin Sleep Cohort Study (3) included 709 individuals of both sexes and was based on polysomnography and well-standardized arterial pressure measurements. This study showed that there was a dose response relationship between sleep-disordered breathing at baseline and BP at follow-up. Importantly, this response was independent of known confounding factors such as obesity and alcohol and tobacco consumption. The contribution of SA to hypertension in this cohort was weak (odds ratios for hypertension at the 4-y follow-up: 1.4 [no apneic events] to 2.9 [≥15 episodes of hypopnea or apnea per h]). Similar observations were reported in a large cross-sectional analysis of 6132 subjects enrolled in the Sleep Heart Study (4). In cross-sectional studies that are designed to investigate whether SA is related to increased mortality, bias will lead to underestimation of the true relative risk of hypertension because survival of subjects with disordered breathing during sleep is less (prevalence/incidence bias).

As to the second question there is little doubt that CPAP virtually eradicates cyclic BP surges. However, the chronic effects of CPAP on daytime hypertension remain uncertain because most studies addressing this problem suffer from the methodological flaws discussed above. Further shortcomings are low compliance and/or short follow-up. A recent study by Dimsdale *et al.* (10) examined the BP effect of CPAP treatment for 1 wk in 39 patients with obstructive SA. The strength of this study is that it is the only one that includes a placebo arm, *i.e.* CPAP administered at an ineffective pressure. Nighttime mean arterial pressure levels decreased to a much greater extent over time in the patients who received active CPAP treatment. However, the daytime decrease was not significantly greater in the active treatment group than in the placebo group, suggesting that the response was in part nonspecific. The very short treatment period and the tendency for BP to decrease toward the end of the active treatment period are obvious limitations of this study. There is obviously a need for properly designed investigations to estimate the true effects of CPEP on arterial pressure. Despite the methodological difficulties encountered in this area, there is agreement that hypertensive patients with apneic episodes are a highly heterogeneous population. Some of them retain normal nocturnal BP dipping, and
others develop frank nocturnal hypertension. These nondippers may be at higher cardiovascular risk.

At variance with systemic hypertension, which is typically associated with OSA, patients with heart failure display a high prevalence of CSA (up to 40%). Low cardiac output causes respiratory instability because it prolongs the time lag between changes in blood chemistry induced by ventilation (pO2, pCO2, and pH) on the one hand and detection of these changes by the chemoreceptors on the other hand. Consequently, the ventilatory drive remains inappropriately high because pCO2 in the central nervous system lags behind pCO2 in the circulation. When pCO2 is reduced below the apneic threshold, respiration ceases. It starts again as CO2 accumulates in blood, thus generating periodic breathing. Individual sensitivity to CO2 plays an important role in precipitating CSA in patients with heart failure because CSA episodes are far more common in patients with relatively low CO2 sensitivity (11). As mentioned above, patients with OSA may develop heart failure because of the detrimental effects of episodes of obstructive apnea on myocardial performance. In these cases, CPAP, by alleviating OSA, reduces left ventricular afterload and improves arterial oxygenation during sleep. On this basis, CPAP has been proposed as a non-pharmacologic adjunct for reducing afterload during nighttime in patients who are on pharmacologic treatment for heart failure. When heart failure is associated with CSA, theophylline reduces the number of apneic episodes (12) and may represent an alternative, or complementary, approach to the administration of nasal oxygen.

Sleep Apnea in End-Stage Renal Disease (ESRD)

Disturbed sleep is common in uremia. Up to 80% of chronic dialysis patients complain of sleep disturbances and reduced daytime alertness. Sleep disruption is a problem of paramount importance that is still inadequately appreciated by nephrologists. In young subjects, restricting time in bed to 4 h per night for 6 d induces striking alterations in metabolic and endocrine function, including increased sympathetic tone and a state of insulin resistance (13). Both abnormalities are well known complications of chronic uremia. There are only a few valid studies, i.e. based on electrophysiologic recordings in the sleep laboratory, which documented the occurrence of sleep apnea in dialysis patients (14–23). Furthermore, these studies were performed in patients who complained of sleeping problems and are therefore not indicative of the true prevalence of this disturbance in the dialysis population. The reported prevalence rate in selected cases ranged from 53 to 75%. A very recent estimate suggests that the overall prevalence may be about 15% (21). Because sleep apnea is common in ESRD, the nephrologist ought to have a high degree of suspicion in patients complaining of the symptoms and/or presenting the signs indicated in Table 2.

The high frequency of SA in renal failure is in part explained by the fact that the most common comorbid conditions of ESRD, namely atherosclerosis and diabetes, are also independently associated with this syndrome. Although apnea in the general population is mostly of the obstructive type, the obstructive (OSA) and the central (CSA) types are almost equally frequent in patients with ESRD. Uremic patients with preexistent heart failure are likely to present a predominantly central SA pattern. Despite the confounding effect of preexistent cardiovascular disease, there is little doubt that uremia per se is associated with SA and that this disturbance plays a major role in disrupting sleep in dialysis patients. Sporadic observations that SA is at least partly reversible after renal transplantation is convincing proof that SA is a direct consequence of renal failure (22,23).

The factors responsible for SA in ESRD are unclear. Chronic metabolic acidosis impinges on an important stimulus for respiration by inducing a compensatory fall in pCO2. However, in the seminar study by Kimmel et al. (16) no relationship was found between metabolic acidosis and apneic episodes in dialysis patients. The pCO2 level below which the breathing stimulus ceases, i.e. the apneic threshold, increases during sleep. It has been suggested that this threshold is increased in chronic uremia, which would increase the risk of CSA. To our knowledge, pCO2 measurements during sleep have not been reported in chronic renal failure. Anemia is another hypothetical factor, but an unpublished observation by Benz et al. (24) shows that correction of anemia has no effect on sleep apnea. The hypothesis has been advanced that accumulation of endogenous substances, e.g. endogenous opioids (25,26) destabilize breathing, but supportive data have not been provided. Central uremic neuropathy may in theory reduce airway muscle tone during sleep or destabilize respiratory control, but again the issue remains a matter of speculation. The level of several cytokines, which may influence sleep, is elevated in dialysis patients (27).

As discussed above sleep apnea impinges heavily on the quality of life by disrupting the sleep. Another important reason why it should not be overlooked by the nephrologist is its association with various cardiovascular complications, ranging from cardiac ischemia, left ventricular hypertrophy, heart failure, and arrhythmia to cardiorespiratory arrest (9–13). It is reasonable to assume that SA contributes to cardiovascular morbidity and mortality in these patients, but until now no solid evidence has been provided in support of this hypothesis. In a recent retrospective study in a group of dialysis patients

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**Table 2. Symptoms and signs that point to sleep apnea**

<table>
<thead>
<tr>
<th>Symptom or Sign</th>
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<tbody>
<tr>
<td>Male gender, older age, and family history</td>
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<tr>
<td>Excessive daytime sleepiness in situations demanding alertness</td>
</tr>
<tr>
<td>A history of motor vehicle accident or near miss associated with sleepiness</td>
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<tr>
<td>High alcohol intake or use of sedatives</td>
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<tr>
<td>Anatomic abnormalities in the airways (macroglossia, short mandible, adenotonsillar hypertrophy) or large neck size (&gt;43 cm)</td>
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<tr>
<td>Obesity (body mass index &gt;30 kg/m²)</td>
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<tr>
<td>Habitual snoring</td>
</tr>
<tr>
<td>Witnessed apnea or gasping for breath during sleep</td>
</tr>
<tr>
<td>A high index of suspicion is appropriate in patients presenting with severe hypertension</td>
</tr>
</tbody>
</table>

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with sleep problems, periodic limb movements rather than sleep apnea predicted death (28). However, the interpretation of this intriguing study is difficult because of the small number of patients, the fact that they were selected, and the failure to control for confounding factors. The issue is a crucial one because SA may be a target for intervention.

Long-term sequelae of sleep apnea may be caused by direct sympathetic activation secondary to chemoreceptor stimulation by episodic hypoxemia and hypcapnia and stress from chronic disruption of sleep. Hypoxemia is dangerous, and increased sympathetic activity is a counter-regulatory response that is aimed at preserving organ oxygen supply by increasing cardiac output, modifying blood flow distribution, and improving delivery of O₂ to the tissues. Intermittent hypoxia causes sympathetic activation that outlasts the triggering stimulus (29). Fletcher et al. (30) observed that norepinephrine and epinephrine excretion is high in patients with SA, and this was true not only during nighttime but also during daytime. In the general population, the role of sympathetic overactivity as a cardiovascular risk factor involved in the genesis of hypertension and cardiac hypertrophy is well established (31). Increased sympathetic activity presumably explains the association of SA with insulin resistance (27,32), which is also frequent in chronic uremia. Endothelial cells are another target of SA because hypoxia triggers the production of endothelin 1, a long-lasting vasoconstrictor, which may induce cardiac and vascular hypertrophy (33) and impair the synthesis of NO, a vasodilator and antiproliferative compound (34). Endothelium-dependent vascular relaxation is defective in hypertensive patients with obstructive sleep disorder, and this defect is largely independent of hypertension (34). The link between obstructive SA and endothelial distress may in part explain the endothelial cell dysfunction in ESRD.

The evidence that SA induces cardiovascular complications in ESRD is circumstantial. It has been shown that nocturnal hypoxemia is associated with nocturnal hypertension in dialysis patients (35). It is even more strongly associated with cardiac remodeling in concentric hypertrophy (36). SA is commonly associated with disturbed autonomic control of the cardiovascular system (37), and this holds true also in dialysis patients as well (38). Observational and interventional studies are sorely needed to test the hypothesis that SA and the attendant nocturnal hypoxemia are causally related to the high cardiovascular risk in dialysis patients.

Although the formal diagnosis of SA requires polysomnographic studies, nocturnal pulse oximetry at home is a good screening procedure in patients with ESRD because of the high pretest probability of SA. A positive test most likely indicates the presence of true SA, but a negative test has relatively low negative prediction power (39). Nocturnal hypoxemia by ambulatory pulse oximetry is correlated with several biologic and socioeconomic parameters in ESRD patients (40). Reliable home techniques for the diagnosis (4) and screening (41) of SA are now emerging. Hopefully, these simpler and cheaper methods will allow appropriate diagnosis in many patients in whom it would otherwise remain undetected and untreated.

The treatment of SA depends on whether one deals with OSA or CSA. The treatment of OSA should address the underlying pathophysiology. In obese patients, the patenty of airways may be improved by weight reduction if appropriate oral or nasal prostheses should be provided. Avoidance of alcohol and sedatives may produce substantial improvement. Protriptyline is useful in mild to moderate SA, but it has marked side effects that range from excessive sedation to orthostatic hypotension. There is practically no controlled experience in uremic patients with OSA. In moderate to severe OSA, uvulopalatopharyngoplasty (resection of redundant soft tissue) and nasal CPAP during sleep are therapeutic options. Uvulopalatopharyngoplasty increases the pharyngeal lumen. Long-term benefit is reported in about half of the cases, but evidence on the efficacy of this surgical approach in ESRD patients is not available. Nasal CPAP keeps the pharyngeal airway open by delivering positive pressure through a nasal mask. It is undoubtedly the most efficacious approach. SA is relieved in about three quarters of the patients. CPAP has been tested in dialysis patients and proved to be beneficial (20). The effect of kidney transplantation on SA has been studied in only three dialysis patients and was curative in all (22,33).

Hypoxic patients with CSA usually respond favorably to nocturnal supplemental oxygen. CPAP is efficacious not only in OSA, but also in CSA. Perhaps the small increase in pCO₂ elicited by the added expiratory mechanical load in part explains the beneficial effect of this treatment in OSA. As discussed by Jahaveri et al. (8), CPAP and theophylline are valid options if CSA is secondary to congestive heart failure.

References