Central sleep apnea syndrome (CSAS) involves interruptions of breathing during sleep due to a transient loss of ventilatory control that results in an absence of respiratory effort or oscillations in intrathoracic pressure.\(^1,2\) Patients with CSAS represent a mere 4% to 10% of all individuals with sleep apnea syndrome in populations studied in sleep laboratories.\(^3\) CSAS may be hypercapnic, hypocapnic, or normocapnic. Hypercapnic CSAS forms part of the alveolar hypoventilation syndrome, whereas the nonhypercapnic variant is idiopathic or secondary to a range of causes. We report the case of a patient with nonhypercapnic CSAS that could have developed in response to a number of causes. The CSAS was treated with bilevel positive airway pressure (BiPAP, Respironics Inc, Murraysville, PA, USA), and the different triggers were also treated; subsequently, continuous positive airway pressure (CPAP) was applied, and the response was good.

### Case Description

A woman aged 75 years was referred by the internal medicine department of our hospital. The patient had been admitted with symptoms of disorientation, generalized weakness, and a reduced level of consciousness that had begun a month earlier. The pneumology department was consulted after an abnormal ventilatory pattern was detected. The patient’s medical history included hypertension, chronic atrial fibrillation with controlled ventricular response, hypertensive cardiomyopathy with a left ventricular ejection fraction of 55%, chronic renal failure secondary to nephroangiosclerosis (creatinine, 3.5 mg/dL), and primary hyperparathyroidism with chronic hypercalcemia due to parathyroid hyperplasia. Two years previously the patient had begun to experience daytime sleepiness, and apneas were reported by a family member. Home-based nighttime pulse oximetry had revealed a sawtooth wave pattern, and the patient was diagnosed with chronic sleep apnea. The patient was treated with CPAP nasal at 7 cm H\(_2\)O. At this point it was observed that the patient no longer experienced somnolence; moreover, polysomnography revealed partial improvement in the CSAS and normalization of ventilatory patterns on application of nasal CPAP at 7 cm H\(_2\)O. We discuss the pathogenesis of CSAS associated with chronic kidney failure along with the treatment options.

Key words: Central sleep apnea syndrome. Chronic renal failure. Home mechanical ventilation.
with obstructive sleep apnea syndrome (OSAS). She was prescribed nighttime nasal CPAP, which she rejected. During the physical examination, the patient was sleepy. Her breathing pattern was consistent with long-duration apnea, with no thoracic or abdominal movements and no snoring, and with occasional gasping episodes and intense cyanosis at the end of the apneas. Waking her was difficult and she remained disoriented with practically the same breathing pattern when awake. Blood count and coagulation factors were normal. The only values of note in the biochemical analysis were creatinine (3.2 mg/dL) and calcium (11.3 mg/dL). Analysis of tumor markers, urinalysis, and a chest x-ray were normal. The results of arterial blood gas analysis breathing ambient air were indicative of compensated metabolic acidosis with respiratory alkalosis (pH, 7.41; PaO₂, 86 mm Hg; PaCO₂, 26.2 mm Hg; HCO₃, 16.3 mmol/L; base excess, –7 mmol/L; and arterial oxygen saturation, 96.6%). Cranial computed tomography revealed a marked alteration of the periventricular white matter associated with small vessel ischemic disease. Because of the patient’s extreme somnolence, we were unable to conduct a full functional examination, although occlusion pressure—2.77 cm H₂O and 1.03 cm H₂O at the beginning of arousals and apneas, respectively—and end-expiratory carbon dioxide concentration—18 mm Hg and 24.8 mm Hg at the end of the apnea and at the end of arousals, respectively.

Respiratory polygraphy revealed a respiratory disturbance index (RDI) of 62 (consisting entirely of central apneas), an oxygen desaturation index (ODI) of 59 desaturations of 3% or more, and a cumulative percentage of sleep time with oxygen saturation below 90% (CT90%) of 2.5% (Figure 1A), leading to a diagnosis of CSAS with Cheyne-Stokes respiration. In order to assess the most suitable treatment for the patient, respiratory polygraphy was performed under the following conditions: with CPAP at 7 cm H₂O and with 2 L/min of oxygen; with BiPAP in spontaneous/timed mode at 10/6 cm H₂O; with BiPAP in spontaneous/timed mode at 14/6 cm H₂O, at 10 cycles/min, and with 2 L/min of oxygen (Figure 1B). The third option was considered to be the most suitable for home-based administration, given that it managed to generate airflow and thoracic and abdominal movements, reduce the RDI and ODI to 25 and 30, respectively, and maintain the CT90% at 0.5%. Given the patient’s history, parathyroid surgery and dialysis were prescribed while awaiting a kidney transplant. The parathyroidectomy (performed 3 months later) and the commencement of hemodialysis led to a spectacular change in the patient; she walked unassisted into the surgery and showed no evidence of sleepiness (Epworth sleepiness score of 7), even though she only used the ventilatory support for 2-3 hours daily. Spirometry, occlusion pressure, end-expiratory carbon dioxide concentration, and arterial blood gas values were all normal. Laboratory workup showed a small decrease in the creatinine concentration (to 2.6 mg/dL) and a return to normal calcium values. Split-night polysomnography was conducted 15 days later. The first part (Figure 2A) showed a sleep efficiency of 82% (stage 1, 18%; stage 2, 58%; stage 3, 6%; stage 4, 4%; rapid eye movement (REM) stage, 14%; arousal index, 36; RDI, 28 [exclusively central events]; ODI, 16; and CT90%, 1.3%). In the second part, pressure adjustments revealed a CPAP of 7 cm H₂O to be sufficient to maintain a residual RDI of 7; consequently, this CPAP level was prescribed and was found to be well tolerated (Figure 2B).
Discussion

Idiopathic CSAS, which needs to be distinguished from other CSAS variants, is defined as follows: excessive daytime sleepiness or frequent arousals that cannot be explained by other factors, at least 5 central apneas or hypopneas in 1 hour of sleep, and normocapnia or hypocapnia during wakefulness (PaCO₂<45 mm Hg).4,5 Increased PaCO₂ in the hypercapnic form of CSAS is the outcome of a reduction in breathing or apneas produced by depressed respiratory control. Nonhypercapnic CSAS, on the other hand, is not associated with a primary reduction in breathing or with respiratory muscle weakness; rather, the central apneas are caused by hyperventilation and hypocapnia episodes, and there is an increase in ventilatory drive.1 According to the few studies that exist of patients

![Figure 2. Split-night polysomnography after parathyroid surgery and the commencement of hemodialysis. Central apneas can be observed in the first part of the polysomnography recording period (A); the second part (B) was performed with continuous positive airway pressure (CPAP) at 7 cm H₂O. RDI indicates respiratory disturbance index.](image)
with symptomatic CSAS, this disorder largely affects middle-aged and older men. Although clinical characteristics are similar to those for OSAS, insomnia symptoms are more pronounced in CSAS. Nonthypocapnic CSAS usually presents with symptoms only after sleep, including drowsiness, heartburn, or pulmonary—possibly because there is no severe hypoxemia during sleep.1

During REM (NREM) sleep is controlled by the metabolic system (the carotid body for hypoxia, and the carotid body and hypothalamic centers for hypocapnea). Hypocapnic alkalosis reduces the hypocapnic ventilatory stimulus, and that may cause central apneas in healthy individuals. Furthermore, the ventilatory response to hypocapnia and hypocapnic is reduced during NREM sleep, but even more so, during REM sleep. PaCO2 is probably the greatest stimulus during sleep, and in this regard, the concept of an apnea threshold—the PaCO2 value at which an apnea is triggered—is fundamental to the pathophysiology of nonhypercapnic CSAS. In periodic breathing, apnea only occurs when the preceding PaCO2 is relatively low. This apnea can be avoided by raising PaCO2 above a predetermined apnea threshold (chemoreceptor control), which varies according to the individual. In addition to the notion of an apnea threshold, there are other hypotheses, such as a possible inhibition of respiration secondary to an increase in tidal volume that is vagal in origin. If sensitivity to carbon dioxide is low or absent, there will be minimal ventilatory drive and central apneas will occur (as happens in the Ondine or obesity-hyperventilation syndromes). Nonetheless, if sensitivity to carbon dioxide is high, one of 2 ventilatory patterns will be observed: hypocapnia during wakefulness and a poor hypocapnic ventilatory response, or low PaCO2 during wakefulness and a strong hypocapnic response (as happened with our patient).

These abnormal patterns may occur independently or secondary to a number of disorders. Neurological causes include isolated or combined lesions of the peripheral, central, or autonomic nervous system. Among the most frequent non-neurological causes are heart failure, chronic renal failure, hypothyroidism, exposure to high altitudes, and a poor hypercapnic ventilatory response, or low PaCO2 below the apnea threshold, they may reduce the hypoxia and give rise to more regular breathing with a reduction in both the number and duration of apneas.14 Since central apneas are provoked by fluctuations in PaCO2 below the apnea threshold, they could be abolished by an increase of just 1-3 mm Hg in PaCO2, by means of the inhalation of gas enriched with carbon dioxide. However, this treatment is not used as it results in hyperventilation.22 On the other hand, as was demonstrated in our patient, as a follow-up to dialysis and parathyroid surgery, CPAP may be effective in increasing

CPAP by physicians.1,6 For our patient we demonstrated in our patient, as a follow-up to dialysis and parathyroid surgery, CPAP may be effective in increasing
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PaCO₂ and keeping it above the apnea stimulus. There is a lack of consensus regarding the use of CPAP compared to BiPAP; what’s more, to our knowledge there are no reports of home ventilation treatment for patients with CSAS and chronic renal failure. A study by Bradley et al23 of 287 patients with left ventricular ejection fraction below 25% and CSAS demonstrated that CPAP attenuated central apneas, improved nighttime oxygenation, increased left ventricular ejection fraction, lowered norepinephrine levels, and increased the distance achieved in the 6-minute walk test; however, it did not affect survival. A number of methods have been designed specifically to treat CSAS, for example, adaptive servoventilation24 and high-frequency jet ventilation.25 However, these have not been studied with an adequate number of patients, nor has long-term efficacy been tested.

We conclude that treatment of CSAS needs to be adapted to each patient—particularly when the more frequent causes of CSAS have been ruled out—on the basis of an assessment of response to different treatment regimens, including home-based ventilatory support.

REFERENCES