

Treatment of Central Sleep Apnea Syndrome of Multifactorial Origin by Home Ventilatory Support

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We report the case of a patient with chronic renal failure and primary hyperparathyroidism who developed nonhypercapnic central sleep apnea syndrome (CSAS), which was multifactorial in origin and attributed to metabolic factors. Given an inadequate response to oxygen therapy and continuous positive airway pressure (CPAP) revealed by several polygraph studies, the patient was treated with bilevel positive airway pressure ventilatory support. Three months after treatment commenced, a parathyroidectomy was performed and hemodialysis was initiated. 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 H₂O. We discuss the pathogenesis of CSAS associated with chronic kidney failure along with the treatment options and conclude that treatment should be customized due to the lack of predictability of patient response.

Key words: *Central sleep apnea syndrome. Chronic renal failure. Home mechanical ventilation.*

Síndrome de apnea central de origen multifactorial tratado mediante soporte ventilatorio domiciliario

Se describe el caso de una paciente afectada de insuficiencia renal crónica e hiperparatiroidismo primario, que presentó síndrome de apnea central (SAC) no hipercápnico, de origen multifactorial, que se atribuyó a factores metabólicos. Fue tratada inicialmente con soporte ventilatorio bipresión tras comprobar, mediante diversos estudios poligráficos, la respuesta inadecuada a oxigenoterapia y presión positiva continua de la vía aérea (CPAP). Tres meses más tarde, tras paratiroidectomía e inicio de hemodiálisis, se observaron la desaparición de la somnolencia, mejoría parcial del SAC en la polisomnografía y normalización del patrón ventilatorio al aplicar CPAP nasal a 7 cmH₂O. Se discute la patogenia del SAC asociado a insuficiencia renal crónica, así como las opciones de tratamiento, que en cualquier caso debe ser individualizado, debido a su respuesta imprevisible.

Palabras clave: *Síndrome de apnea central de sueño. Insuficiencia renal crónica. Ventilación mecánica domiciliaria.*

Introduction

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, Murrysville, 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

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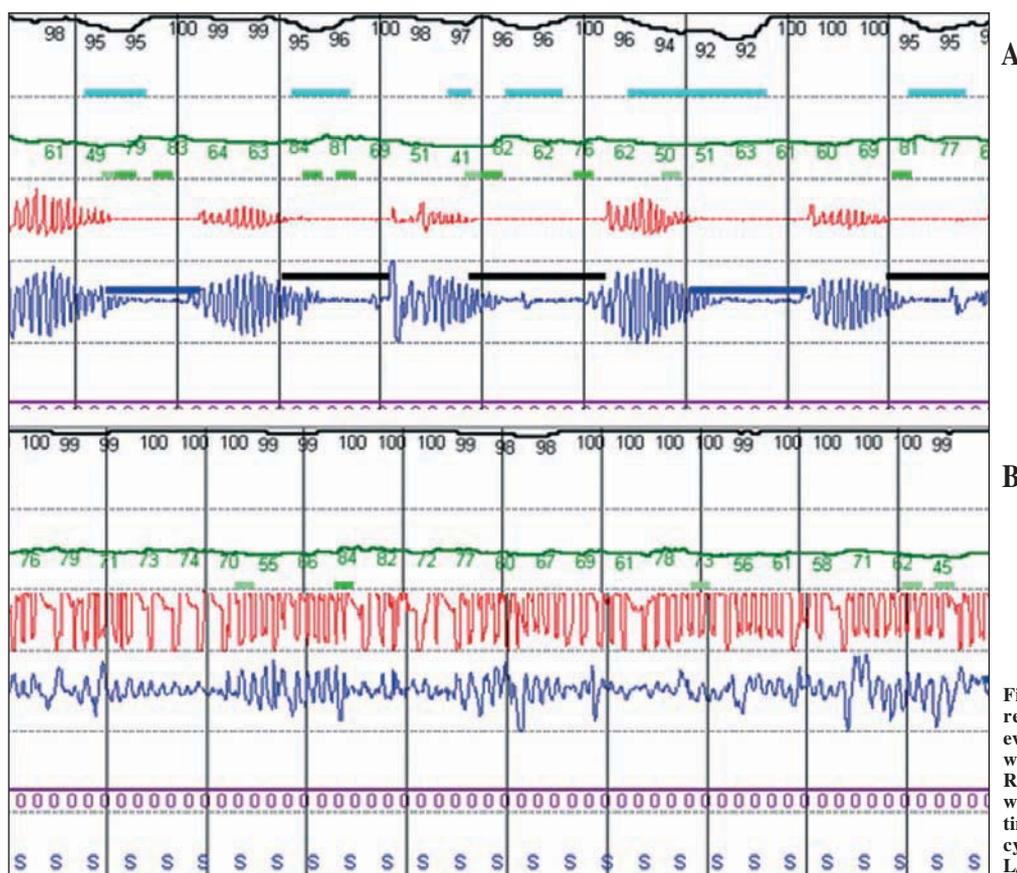


Figure 1. A) Trace obtained during respiratory polygraphy showing evidence of central apnea syndrome with Cheyne-Stokes respiration. B) Respiratory polygraphy performed with BiPAP in the spontaneous/timed mode at 14/6 cm H₂O, at 10 cycles/min, and with oxygen at 2 L/min.

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 it was possible to measure 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; and 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 ($\text{PaCO}_2 < 45 \text{ mm Hg}$).^{4,5}

Increased PaCO_2 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

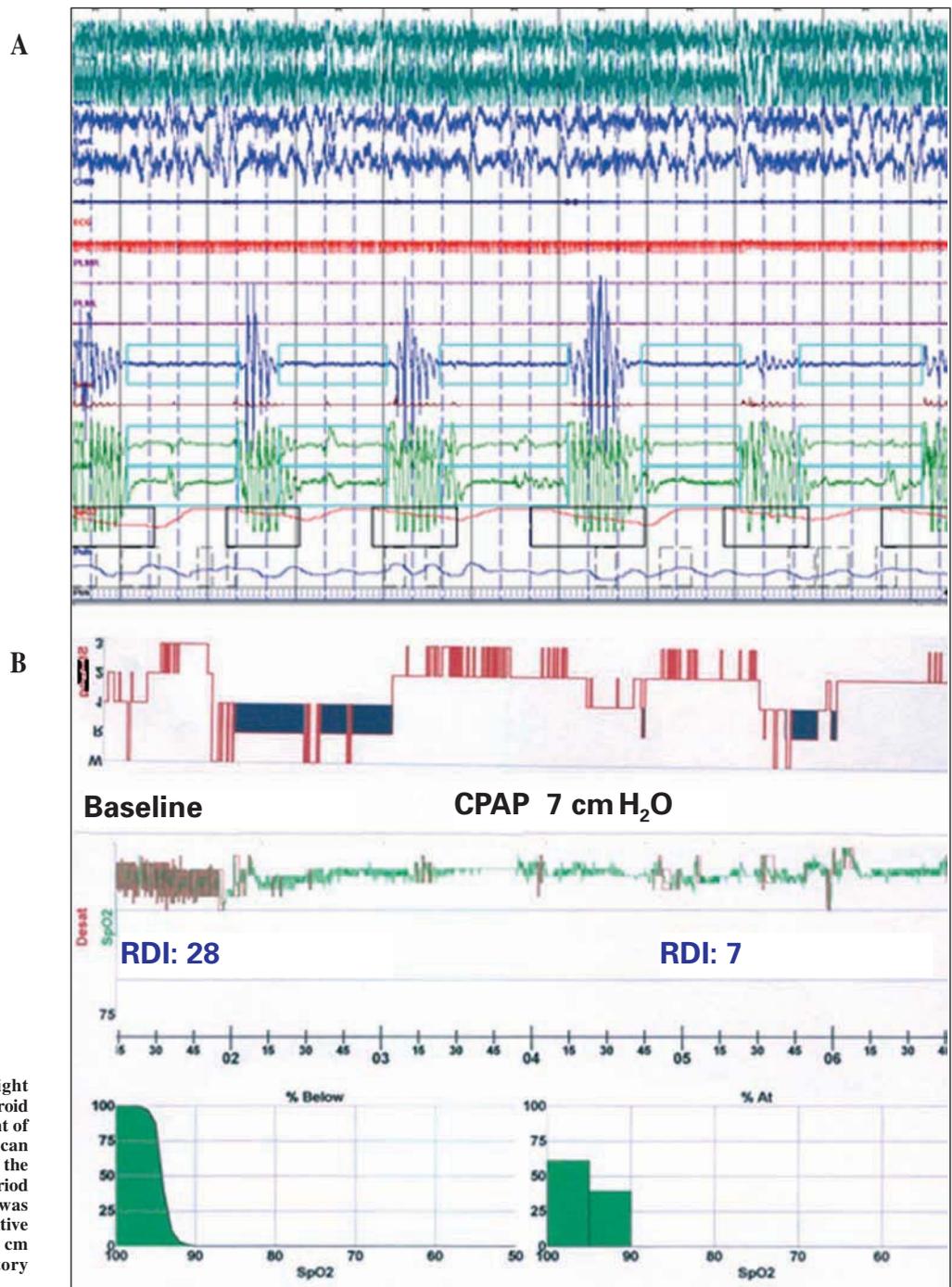


Figure 2. Split-night polysomnography after parathyroid surgery and the commencement of hemodialysis. Central apneas can be observed in the first part of the polysomnography recording period (A); the second part (B) was performed with continuous positive airway pressure (CPAP) at 7 cm H₂O. RDI indicates respiratory disturbance index.

with symptomatic CSAS, this disorder largely affects middle-aged and older men.³ Although clinical characteristics are similar to those for OSAS, insomnia symptoms are more pronounced in CSAS. Nonhypercapnic CSAS is not usually associated with polycythemia or cor pulmonale—possibly because there is no severe hypoxemia during sleep.¹

During non-REM (NREM) sleep (ie, sleep without rapid eye movements), ventilation is controlled by the metabolic system (the carotid body for hypoxia, and the carotid body and medullary chemoreceptors for hypercapnia). Hypocapnic alkalosis reduces the hypercapnic ventilatory stimulus, and that may cause central apneas in healthy individuals. Furthermore, the ventilatory response to hypoxia and hypercapnia 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-hypoventilation syndromes). Nonetheless, if sensitivity to carbon dioxide is high, one of 2 ventilatory patterns will be observed: hypercapnia during wakefulness and a poor hypercapnic ventilatory response, or low PaCO₂ during wakefulness and a strong hypercapnic response³ (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, certain drugs (opioids, phenothiazines in children), and titration of CPAP by physicians.^{1,6} For our patient we needed to establish which factors potentially concurred in order to produce CSAS—whether chronic renal failure, hyperparathyroidism, cerebral vascular disease, or heart failure.

It is known that 80% of patients undergoing dialysis experience sleep disorders.⁷ The most common disorder is OSAS (a prevalence of up to 73%), followed by other parasomnias such as restless legs syndrome and periodic leg movements.⁷ CSAS as experienced by our patient is exceptional, and can be attributed to hypocapnia secondary to metabolic acidosis, which predisposes a patient to an unstable breathing pattern and central apneas. Uremic toxins may also affect the central nervous system and reduce muscle tone during sleep, cause a lack of coordination between the diaphragm and the muscles of the upper airway, or destabilize respiratory control. Any of these factors might account for excessive daytime

sleepiness.⁷ Other aggravating factors deriving from a high degree of comorbidity (arteriosclerosis, diabetes mellitus, heart failure, and chronic metabolic acidosis) could provide a stimulus that would induce a compensatory fall in PaCO₂. The apnea threshold, furthermore, is raised in chronic uremia, and this represents an enhanced risk. Other factors that may contribute to the development of CSAS include anemia, endogenous opioids, uremic neuropathy, and an increase in cytokine levels.⁸ Conventional hemodialysis does not reduce the prevalence of OSAS, but nocturnal dialysis^{9,10} and kidney transplants have corrected both obstructive and central apneas.^{11,12} In the case of our patient, hemodialysis only partially corrected the CSAS. This was possibly because full correction of the metabolic disorders causing the syndrome was affected by factors such as the frequency of dialysis sessions, which, depending on the time elapsed between sessions, could cause a CSAS with alternating severity.

Our patient had hyperparathyroidism, for which a number of symptoms have been described that may have a bearing on poor sleep hygiene, such as restless legs, depression, irritability, anxiety, proximal muscle weakness, fatigability, and muscular atrophy. These symptoms show visible improvement following parathyroidectomy and normalization of parathyroid hormone and calcium values.¹³⁻¹⁶ As for cerebral vascular disease, any neurological disease that affects the metabolic respiratory control system potentially affects the ventilatory pattern and produces central apneas.^{6,17} Heart failure is frequently associated with Cheyne-Stokes respiration during both sleep and wakefulness. This periodic breathing is probably the consequence of instability in respiratory control resulting from a prolonged circulation time and an enhanced response to elevated PaCO₂.^{18,19} In one study, central apneas were detected in 40% of 81 ambulatory patients with heart failure due to systolic dysfunction (treated and stable).²⁰ Furthermore, CSAS with concomitant heart failure is associated with a poorer prognosis.¹⁹

Treatment of CSAS is problematic, given that it is an infrequent disorder for which no randomized studies have been conducted. Response to drugs such as theophylline, sedatives, medroxyprogesterone, tricyclic antidepressants, serotonin inhibitors, and acetazolamide is variable. In a recent study of patients with heart failure the administration of a single dose of acetazolamide prior to sleep improved the central apneas and daytime symptoms.²¹ Oxygen has a destabilizing influence on the hypoxic ventilatory response in respiratory control. When a patient experiences hypoxia, hyperventilation produces alkalosis and hypocapnia, both of which may inhibit respiration during sleep and cause central apneas. The addition of oxygen may reduce the hypoxia and give rise to more regular breathing with a reduction in both the number and duration of apneas.³ 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

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.⁶ 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.

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