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Case Report of Sleep-Related Hypoventilation Complicated by Obstructive Sleep Apnea and Substance Use Disorder

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Case Report

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Abstract

Sleep-related hypoventilation (SRH) is characterized by inadequate ventilation during sleep, leading to elevated partial pressure of arterial carbon dioxide ($PaCO_2$). The etiology of the condition is multifactorial, with obesity hypoventilation syndrome (OHS), chest wall deformities, neuromuscular diseases, and medical conditions such as stroke being the most common underlying factors. The condition often coexists with obstructive sleep apnea (OSA), and it is often overlooked clinically. Substance abuse is also an important contributing factor to SRH. Nevertheless, due to the fact that patients frequently conceal their history of substance abuse, and the underlying cause becomes obscured after detoxification, relevant case reports are infrequent. We present a 53-year-old man with poor sleep and snoring. Polysomnography (PSG) revealed severe OSA with atypical features, such as a higher frequency of respiratory events during non-rapid eye movement (NREM) sleep than during REM sleep and an ataxic respiratory pattern. A detailed review of the patient's medical history revealed a 15-year history of heroin abuse, with a 5-year period of abstinence. Following a thorough evaluation that excluded other potential secondary causes, the patient was diagnosed with severe OSA and substance (heroin)-related sleep-related hypoventilation, based on the patient's medical history and the characteristic findings from the PSG. Following treatment with noninvasive positive pressure ventilation and medication, the patient exhibited a marked improvement in both nocturnal and daytime oxygen saturation levels, with complete resolution of symptoms. This case highlights the critical importance of thorough history taking, meticulous PSG interpretation, and adjunctive overnight CO_2 monitoring for early identification of SRH and accurate etiologic differentiation, thereby preventing misdiagnosis.

1. Background

Sleep-related hypoventilation (SRH) is defined as insufficient ventilation that occurs primarily during sleep. It is characterized by a pathophysiological reduction in alveolar ventilation, leading to an abnormally elevated $PaCO_2$ in arterial blood during sleep(1). During normal sleep, all aspects of respiratory regulation are subject to a certain degree of inhibition, resulting in a physiological decrease in pulmonary ventilation. However, when this decrease exceeds the normal range and causes carbon dioxide retention, it constitutes a pathological condition. According to the third edition of the International Classification of Sleep Disorders (ICSD-3), sleep-related hypoventilation disorders are classified into six major categories, one of which is sleep hypoventilation caused by drugs or substances(2). Initially manifesting exclusively during sleep, SRH may signify an early stage of hypoventilation disorders. If not promptly identified and treated, it can gradually progress to daytime hypoventilation or even chronic respiratory failure(1). The present case report documents a case of heroin-associated sleep-related hypoventilation and provides a review of the relevant literature.

2. Case Presentation

The patient is a 53-year-old male. The patient's primary complaint was a 10-year history of poor sleep quality and snoring, with a noted exacerbation of symptoms over the past 2 years. The patient exhibited symptoms including difficulty falling asleep and maintaining sleep, loud snoring, and no daytime sleepiness, accompanied by irritability and memory impairment. Over the past 2 years, these symptoms have worsened, leading to insomnia throughout the night, loss of interest, and slowed reactions. The patient had previously been diagnosed with mild OSA at another hospital, and treatment with sleep aids and mood-stabilizing

medications proved ineffective. The patient has a medical history marked by hypertension and a 15-year history of heroin use, with a 5-year period of abstinence. The patient had no relevant family history. Physical examination: The patient's vital signs were recorded at body temperature 36.6°C, heart rate 108 bpm, respiratory rate 20 breaths/min, and blood pressure 164/114 mmHg. The patient was noted to be alert and exhibited cyanosis of the lips. The neck circumference was measured at 37 centimeters (cm), while the waist circumference was recorded at 112 cm. The patient's body mass index (BMI) was determined to be 29.4 kg/m², with a height of 168 centimeters and a weight of 83 kilograms. The patient exhibited an enlarged tongue with posterior displacement of the tongue base; however, no pharyngeal stenosis was observed. The patient exhibited symptoms of depression, including a depressed mood and impaired social functioning. Scale assessments: The Hamilton Depression Rating Scale (HAMD) score was 19 points, the Hamilton Anxiety Scale (HAMA) score was 13 points, the Epworth Sleepiness Scale (ESS) score was 3 points.

Secondly, the examination findings and diagnosis are as follows: Arterial blood gas analysis: pH 7.40, $PaCO_2$ 39.3 mmHg, PaO_2 47.2 mmHg, HCO_3^- 24.4 mmol/L, SaO_2 84.5%; complete blood count showed red blood cells 6.01×10^{12}/L, Hb 189 g/L, HCT 0.563 L/L. Cardiac injury markers, biochemical panel, BNP, thyroid function tests, infectious disease screening, and routine urine and stool examinations were unremarkable. The patient underwent a series of diagnostic tests, including the hyperventilation test, which yielded a positive result. The 6-minute walk test revealed a distance of 552 meters. Electrocardiographic (ECG) analysis revealed incomplete right bundle branch block and T-wave changes. Holter monitoring revealed sinus rhythm with prolonged ventricular pauses, occasional atrial and ventricular premature beats, and second-degree type I atrioventricular block. Chest computed tomography (CT) scan results showed evidence of pulmonary emphysema, pulmonary bullae, and chronic interstitial inflammatory changes. Pulmonary function testing revealed mild obstructive ventilatory impairment (after inhalation of a bronchodilator $FEV_1/FVC = 70.2\%$), which was not consistent with chronic obstructive pulmonary disease (COPD). The bronchodilator test yielded a negative result and diffusion capacity was found to be normal. Further evaluation of respiratory center function revealed a normal hypoxic drive response (-0.21 L/min/%) and a reduced hypercapnic drive response (0.38 L/min/mmHg). A comprehensive diagnostic evaluation was conducted, encompassing echocardiography, abdominal ultrasound, cranial MRI, electromyography, and diaphragm examination. These evaluations yielded no significant findings. PSG revealed an overall apnea–hypopnea index (AHI) of 35.4 events/h, all of which were hypopneas. The AHI was 35.4 events/h during NREM sleep and 7.5 events/h during REM sleep. The mean oxygen saturation (SpO_2) level during NREM sleep was 72%, with a minimum of 62%, while the mean SpO_2 level during REM sleep was 74%, with a minimum of 65%. Figure 1 illustrates the relationships among sleep stages, respiratory events, oxygen saturation, and body position throughout the night. Ataxic breathing was observed during sleep (see Fig. 2–3). Overnight transcutaneous CO_2 monitoring revealed a maximum value of 55.4 mmHg, which occurred during NREM sleep, with values > 50 mmHg exceeding 10 minutes. This represented an increase of > 10 mmHg compared to daytime $PaCO_2$, thereby supporting a diagnosis of hypoventilation. The final titrated settings were as follows: bi-level positive airway pressure (BPAP) S/T mode (EPAP 8 cmH_2O, IPAP 21 cmH_2O) along with backup respiratory rate 21 breaths/min, oxygen at 1 liter per minute, bed elevation to 30 degrees, and oronasal mask. The final diagnosis is as follows: substance (heroin)-related sleep-related hypoventilation, severe OSA, respiratory failure, and depressive state.

Due to the patient's intolerance to BPAP S/T, the mode was adjusted to Average Volume-Assured Pressure Support (AVAPS). Ventilator settings were as follows: tidal volume (VT) 720 mL, EPAP 8 cmH_2O, IPAP 19–23 cmH_2O (min–max), inspiratory time 1.2 s, and respiratory rate 16 breaths/min, with supplemental oxygen at 2 L/min. Mean SpO_2 was maintained at 92%, and the oxygen desaturation index was 4.7, with good tolerance. Concomitant medication included dimdazenil 2.5 mg/night, olanzapine 5 mg/night, paroxetine 20 mg/day, and bupropion sustained-release tablets 150 mg/day. Following treatment, the patient exhibited marked improvements in sleep quality and oxygenation.

3. Discussion

OSA and SRH often coexist. During sleep, alveolar ventilation is reduced due to factors such as impaired respiratory drive, COPD, or neuromuscular disorders. This results in an abnormal elevation of $PaCO_2$. The diagnosis of this condition is made on the basis of a combination of PSG and CO_2 monitoring. The most prevalent etiologies include obesity hypoventilation syndrome (OHS) and overlap syndrome (OS). Additional significant contributing factors include stroke, neuromuscular disorders, and thoracic deformities. Table 1 offers a concise synopsis of the pathophysiological mechanisms, high-risk populations, key differential diagnostic indicators, and treatment principles for the aforementioned conditions.

Table 1
OSA and Sleep -Related Hypoventilation: Differential Diagnosis

Etiology	Core Mechanism	High-Risk Populations/Clinical Clues	Differential Diagnosis Key Points	Key Treatment Considerations
OHS	Multifactorial: obesity-related thoracic restriction, central chemosensitivity blunting, and SDB(3).	BMI ≥ 30 kg/m², daytime hypercapnia ($PaCO_2$ ≥ 45 mmHg)(4), predominantly moderate-to-severe OSA.	Exclude other hypoventilation causes and differentiate from normocapnic obesity-related OSA(4).	PAP and weight loss are the mainstay, and combined therapy is required(4).
OS	OSA–COPD overlap(5).	History of long-term smoking; middle-aged and elderly individuals.	Pulmonary function shows persistent airflow limitation (FEV_1/FVC < 70%).	BPAP combined with long-term oxygen therapy.
Stroke	There is a bidirectional causal relationship between OSA and stroke(6).	Patients with acute or subacute stroke.	Requires evaluation of cranial imaging and neurological signs.	CPAP therapy may reduce stroke risk and improve neurological outcomes(6).
Neuromuscular disorders	Respiratory muscle weakness causes hypoventilation, with possible obstructive or central sleep apnea(7).	Patients with progressive neuromuscular disorders.	Clinical features (muscle weakness, atrophy, bulbar signs) with neurophysiology and craniospinal MRI.	Noninvasive ventilation (NIV) is the core treatment.
Thoracic deformities	Thoracic restriction causing restrictive ventilatory defect(8).	Patients with thoracic deformities.	Thoracic deformities warrant exclusion of neuromuscular causes.	Early NIPPV is superior to oxygen alone.
Opioids	Inhibit respiratory center drive and impair upper airway function(9).	Patients on long-term chronic opioid therapy (e.g., those with chronic pain).	NREM > REM: desaturation, events, abnormalities(10).	Opioid reduction/withdrawal + BPAP S/T mode or VAPS mode.
CCHS	PHOX2B-related chemosensitivity blunting(11).	Neonatal/infantile onset(11).	Genetic testing: PHOX2B mutation(11).	Lifelong ventilation: tracheostomy or noninvasive BPAP.

OHS: obesity hypoventilation syndrome; SDB: sleep-disordered breathing; OSA: obstructive sleep apnea; OS: overlap syndrome. COPD: chronic obstructive pulmonary disease; CCHS: congenital central hypoventilation syndrome.

SRH resulting from pharmaceutical agents, including long-acting narcotics, anesthetics, sedatives, and muscle relaxants, is currently characterized by a paucity of precise global epidemiological data. However, the clinical prevalence of this condition is gradually attracting attention. This phenomenon is closely associated with the widespread use of opioid medications. A study involving 98 patients with chronic pain receiving long-term opioid therapy(12) showed that 85% had some form of sleep-disordered breathing, with 24% having central sleep apnea (CSA) and 21% experiencing a combination of central and obstructive events. The heroin used by the patient in this case was diacetylmorphine, a μ-opioid receptor agonist. The mechanisms underlying its effects on breathing during sleep are illustrated in Fig. 4. This mainly includes the following four aspects: (1) The substance primarily activates μ-opioid receptors located in the brainstem respiratory centers, particularly in the medulla oblongata and pons(13). This activation results in a reduction of intracellular cyclic adenosine monophosphate (cAMP) levels via μ-receptors, leading to the inhibition of the function of respiratory neurons. The ventral anterior bundle of the medulla oblongata is the site where respiratory rhythms are generated and is also a region with a high concentration of opioid receptors(14). (2) During sleep, the body experiences a reduction in its capacity to regulate ventilation, with other forms of ventilatory control becoming significantly weakened or absent, apart from metabolic regulation. Opioids have been demonstrated to suppress the sensitivity of central and peripheral chemoreceptors, thereby reducing the body's ventilatory response to hypercapnia and hypoxemia(15). This effect prevents the body from effectively initiating compensatory ventilatory responses when CO_2 levels rise or oxygen partial pressure decreases. During NREM sleep, the respiratory center's pattern generator exhibits autonomous rhythmic activity that is highly dependent on chemical regulation. However, during REM sleep, neurons in the pre-Bötzinger complex no longer exhibit autonomous rhythmic activity. Instead, the frequency of inspiratory activity may be regulated by the brainstem or cortex. This results in central respiratory events during REM sleep being relatively milder compared to those during NREM sleep(16). (3) Opioids have also been demonstrated to markedly diminish sublingual nerve activity, consequently inhibiting chin-tongue muscle activity and potentially inducing upper airway obstruction(17). (4) Opioids have been demonstrated to increase loop gain, thereby rendering the respiratory control system susceptible to overreaction, resulting in erratic and highly unstable breathing patterns(18). Animal studies have indicated that chronic opioid use can give rise to various types of sleep-related breathing disorders, including SRH, CSA, and OSA(17). A study(10) was conducted in which polysomnography was used to examine three subjects who had been taking opioids long-term. The study identified four characteristic features. (1) During NREM sleep, the duration of apneas and the severity of hypoxia are significantly greater than during REM sleep. (2) Ataxic breathing, also known as Biot's respiration, occurs during NREM sleep. It is characterized by irregular breathing pauses and gasping without a periodic rhythm. (3) Recurrent episodes of prolonged obstructive hypoventilation lasting at least 5 minutes each, with a progressive and severe decline in blood oxygen levels, are observed only during NREM sleep. This phenotype does not occur during REM sleep. (4) Continuous positive airway pressure (CPAP) therapy is ineffective. With regard to treatment, the fundamental measure is the discontinuation of the causative substance. For patients with significant nocturnal hypoventilation and hypercapnia, BPAP or VAPS are effective treatment options(15).

The patient in question exhibited symptoms including poor sleep quality and snoring. PSG revealed severe OSA, with an apnea-hypopnea index (AHI) of 35.4 events per hour. Overnight transcutaneous CO_2 ($TcCO_2$) monitoring revealed a > 10 mmHg increase over daytime $PaCO_2$, with $TcCO_2$ values exceeding 50 mmHg sustained for more than 10 minutes, consistent with alveolar hypoventilation. However, with a BMI of 29.4

kg/m² and daytime $PaCO_2$ < 45 mmHg, the patient did not meet the diagnostic criteria for obesity-hypoventilation syndrome. Subsequent investigations, encompassing thyroid function tests, electromyography, chest CT, pulmonary function and diffusion capacity tests, and cranial MRI, excluded secondary causes of alveolar hypoventilation, including hypothyroidism, neuromuscular disorders, chest wall abnormalities, and pulmonary parenchymal lesions. A subsequent review of the patient's medical history revealed a history of long-term heroin abuse (having been abstinent for five years). The PSG findings were consistent with the typical characteristics of opioid-related respiratory abnormalities. The severity of hypoxia was found to be more pronounced during NREM sleep compared with REM sleep. Additionally, ataxic-like breathing patterns were observed during NREM sleep. The efficacy of continuous CPAP therapy in addressing these issues was not successful. In light of these findings, a clinical diagnosis of substance (heroin)-related sleep-related hypoventilation was established. However, CPAP therapy proved ineffective during pressure titration. Conversely, BPAP S/T mode effectively maintained blood oxygen saturation levels consistently above 90%. Nonetheless, the patient exhibited an adverse response to this mode of therapy. Following the transition to AVAPS mode, the tolerance levels were found to be satisfactory, and the therapeutic outcomes were deemed to be successful.

The distinctive element of this case is that despite the patient having been abstinent from heroin for a period of five years (as confirmed by a negative urine test), sleep-related breathing disorders persisted. The impact of protracted opioid use on the respiratory center endures even after its cessation. A potential mechanism(19) posits that protracted opioid exposure can lead to desensitization and internalization of μ-opioid receptors, thereby inducing intracellular adaptive changes (e.g., upregulation of adenylate cyclase), resulting in "tolerance" and "dependence."Even after the cessation of drug use, when the substance has been eliminated from the system, a considerable duration is required for the aforementioned homeostatic changes and signaling pathway activity to revert to normal. Concurrently, the respiratory center's chemical sensitivity to CO_2 remains diminished, and the arousal response to elevated CO_2 levels following withdrawal remains elevated. Nevertheless, certain literature reports(20) suggest that the discontinuation of opioids can improve or reverse sleep-related breathing disorders. For instance, a patient who had been on long-term fentanyl and oxycodone showed resolution of central sleep apnea on PSG five years after discontinuation. The resolution of the sleep-related breathing disorder in this patient will necessitate additional follow-up observation.

4. Conclusions

SRH and OSA frequently manifest in conjunction with one another; nevertheless, if alveolar hypoventilation is identified during the diagnostic evaluation of OSA, further inquiry into additional potential etiologies is imperative. Such etiologies may include central causes, neuromuscular disorders, chest wall disorders, pulmonary parenchymal lesions, and drug-related factors. In this particular instance, the PSG findings—namely, more severe hypoxia during NREM sleep in comparison to REM sleep, along with ataxic-like breathing—were consistent with the characteristics of opioid-related respiratory depression. When considered in conjunction with a documented history of protracted exposure to heroin, the diagnosis of substance (heroin)-related sleep-related hypoventilation was substantiated. This case underscores the significance of meticulous attention to these particular findings during sleep apnea monitoring in patients with a history of opioid use. It is imperative to promptly perform transcutaneous CO_2monitoring and pressure titration. The concurrent utilization of BPAP or VAPS modes in conjunction with medication has been demonstrated to effectively

ameliorate hypoxia and enhance sleep quality. Early identification and targeted treatment are imperative to improve the prognosis for these patients.

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Written informed consent for publication of this case report and accompanying images were obtained from the patient. The case report has been prepared in accordance with the CARE guidelines.

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All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

The participant has consented to the submission of the case report to the journal.

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Figures

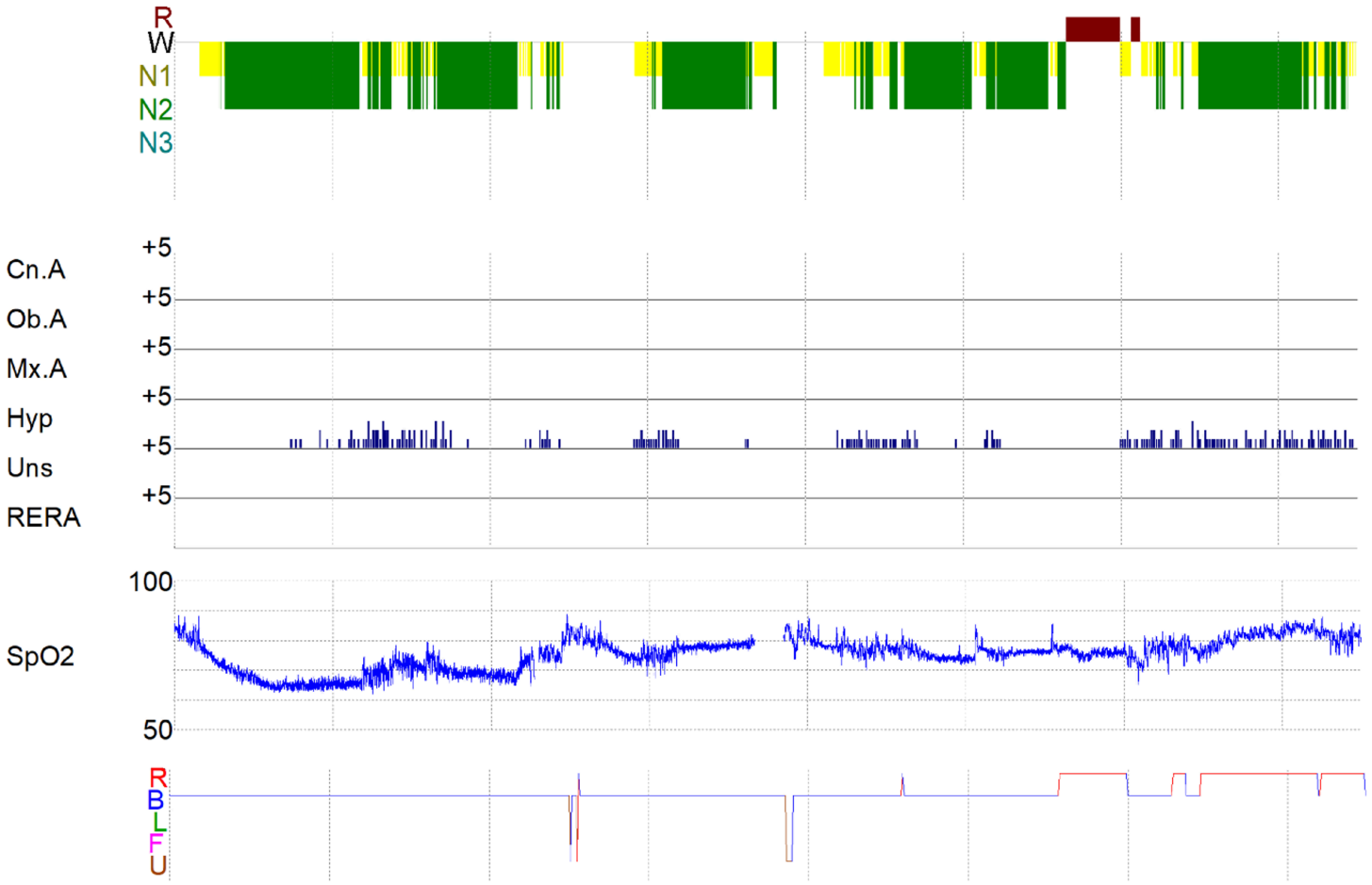


Figure 1

Respiratory events were predominantly characterized by hypoventilation and occurred primarily during NREM sleep. There was no significant correlation observed between the occurrence of these events and body position. Additionally, the lowest oxygen saturation was also observed during NREM sleep.

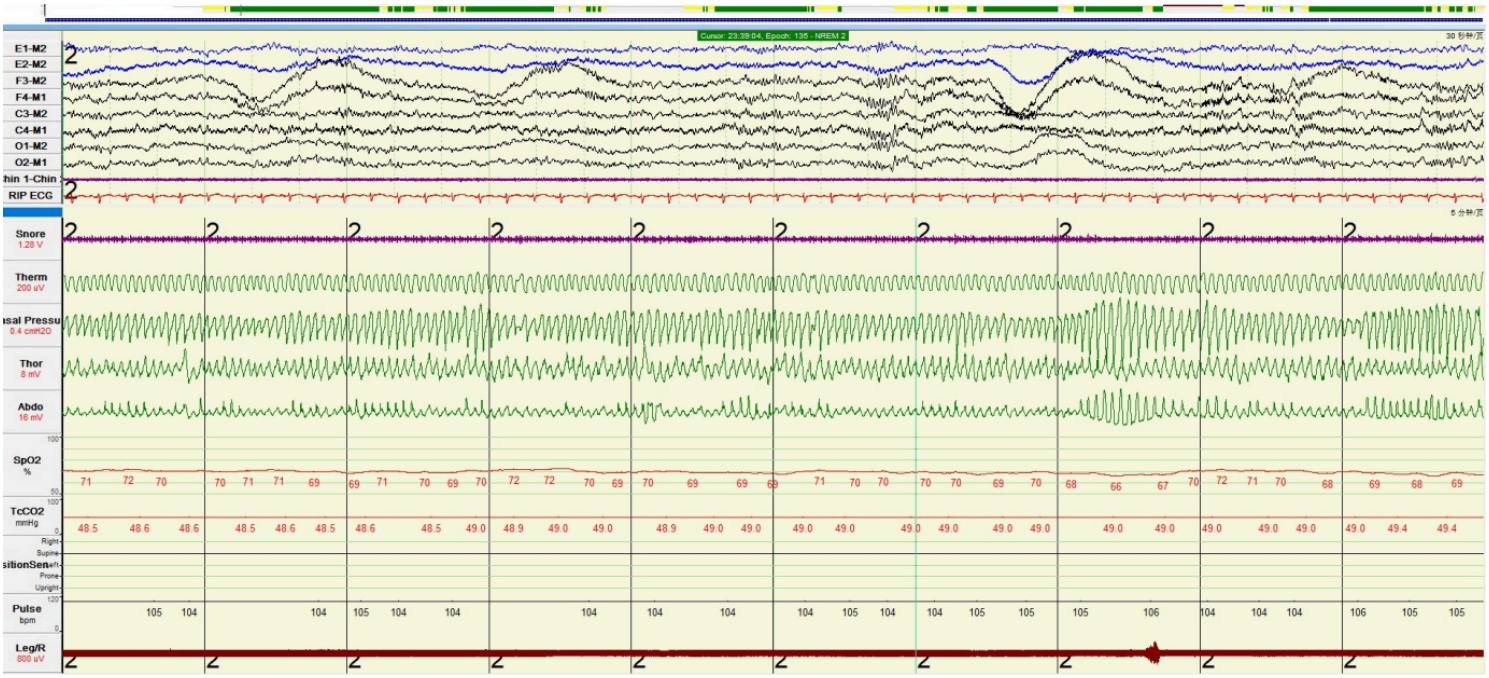


Figure 2

A 5-minute segment of a polysomnogram reveals a prototypical ataxic breathing pattern during stage N2, as indicated by the red arrow. This stage is distinguished by markedly irregular respiratory amplitude and rate. The respiratory rate was approximately 40 breaths per minute, with oxygenation levels of around 70%, which is consistent with central respiratory dysregulation.

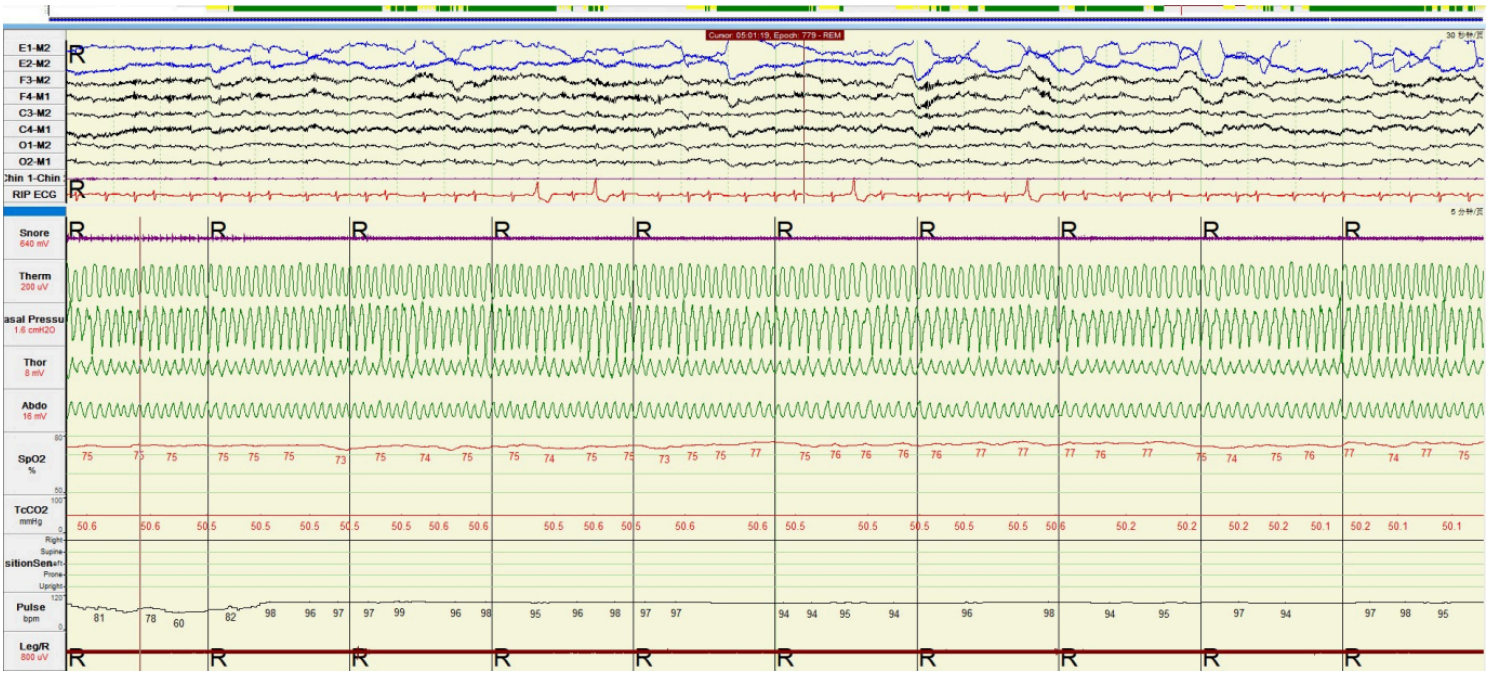


Figure 3

This 5-minute segment of the polysomnogram during stage R demonstrates a respiratory rate of approximately 30 breaths per minute and oxygen saturation of approximately 75%. A comparison with stage N2 reveals a slightly slower respiratory rhythm and marginally higher oxygen saturation levels.

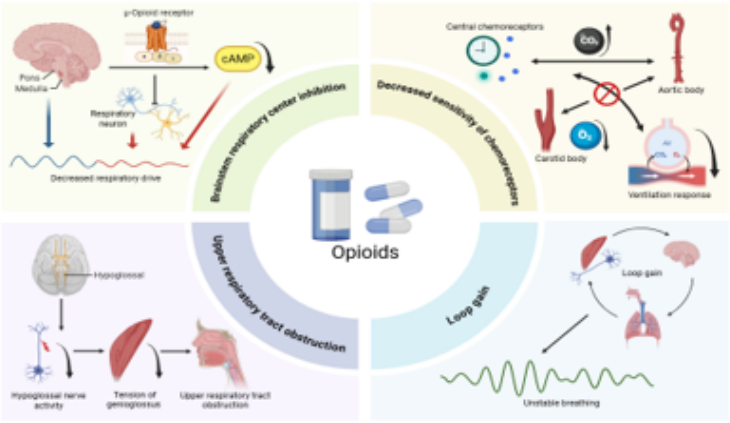


Figure 4

Mechanism of action of opioids on sleep-related breathing

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