A 45-year-old female who complained of frequent awakenings and excessive daytime sleepiness (Epworth Sleepiness Scale 16/24) was referred for a sleep study. Her husband reported that she had frequent pauses in her breathing during sleep with intermittent snoring and gasping. The patient began having sleep problems about 2 years before the sleep study. At that time she also developed severe pain associated with cervical degenerative joint disease requiring treatment with oxycodone. There was no history of recent weight gain or nasal congestion.

Physical examination: BMI 28
HEENT: oropharynx: Mallampati score 2, Neck 16 inches in circumference
Neurological examination: normal strength and sensation

Summary of sleep study results:

| Stage 1 (min) | 10.0 | Obstructive Apneas (no.) | 18 |
| Stage 2 (min) | 203.5 | Central Apneas (no.) | 267 |
| Stage 3,4 (min) | 128.0 | Mixed Apneas (no.) | 31 |
| Stage REM (min) | 59.5 | Hypopneas (no.) | 20 |
| AHI REM (/hr) | 13.1 |
| AHI NREM (/hr) | 55.7 | Minimum SpO₂ (%) | 85 |

*drop in SpO₂ > 4%

**Table 1—Summary of Sleep Study Results**

**Figure 2**—A 120-second segment from the patient’s sleep study is shown. C₄-A₁ and C₃-A₂ are the right and left central electroencephalographic tracings. O₂-A₁ and O₁-A₂ are right and left occipital electroencephalographic tracings. ROC-A₁ and LOC-A₂ are right and left electro-occulographic tracings. Chin EMG is the surface chin electromyographic tracing. EKG is an electrocardiographic tracing. Tracings of airflow by nasal pressure and chest and abdominal movements detected with piezo-electric belts are also shown along with a pulse oximetry (SpO₂) tracing.

**Question:** What is the cause of this patient’s breathing abnormality during sleep?
Chronic Opioid Therapy Producing Central Sleep Apnea

Surprisingly little information has been published about opioid induced sleep related breathing disorders. Patients taking narcotics may manifest a variety of changes in breathing during sleep. These include: 1) obstructive apneas of very long duration, 2) a mixture of central and obstructive apneas with predominant central events, 3) arterial oxygen desaturation that is more severe during NREM than REM sleep, 4) ataxic or irregular breathing pattern, and 5) prolonged periods of obstructive hypventilation. When central sleep apnea occurs, it may exhibit a periodic pattern (repeated central apneas separated by short periods of ventilation) or central apneas occurring randomly during regular or irregular ventilation. The pattern of respiratory abnormality (OSA with long events vs primarily central apnea) likely depends on the patient’s underlying upper airway anatomy. CPAP titration in some patients on chronic narcotics with primarily obstructive apnea may result in recurrent central apneas. The narcotic sleep related breathing disorders are usually associated with potent opioids such as oxycodone, methadone, morphine, or fentanyl.

Central sleep apnea (CSA) is often divided into hypercapnic and hypocapnic groups. Those patients with hypercapnic central sleep apnea typically have either a reduction in central drive or neuromuscular disease. They often present with evidence of right heart failure and typically have daytime hypercapnia and severe arterial oxygen desaturation during sleep. The hypocapnic group is composed of patients with a normal or low daytime PCO₂ who often have high ventilatory drives and instability in ventilatory control during sleep. The most common disorder in this group is Cheyne-Stokes breathing associated with congestive heart failure. The respiration in these patients is characterized by a crescendo-decrescendo pattern of ventilation between central apneas. Idiopathic central sleep apnea is characterized by patients in whom there is no explanation for the disorder. They have central apnea without the Cheyne-Stokes pattern. In both types of hypocapnic central sleep apnea, central events are uncommon during stage 3,4 sleep. The higher PCO₂ and arousal threshold typical of this stage of sleep is felt to stabilize breathing.

Patients with narcotic-induced CSA do not fit perfectly in either the hypercapnic or hypocapnic CSA groups. Unlike patients with hypercapnic CSA, patients with narcotic-associated CSA typically have daytime arterial PCO₂ values that are either normal or only slightly elevated. On the other hand, they do not have daytime hypocapnia or respiration with the Cheyne-Stokes morphology. A study of a group of 50 patients on methadone maintenance found that 30% had a central apnea index (CAI) > 5/hour and 20% had a CAI > 10/hour. The average peak overnight transcutaneous PCO₂ was 46 mmHg. Another study evaluating the same study group found that only 20% had a daytime PCO₂ > 45 mmHg.

The mechanism of central apnea is not well understood but likely involves effects of narcotics on ventilatory control centers. One study of ventilatory control in patients on chronic methadone maintenance found a reduced hypercapnic ventilatory response but an increased hypoxic ventilatory response. This interesting combination of ventilatory responses awaits confirmation by other studies. An earlier study of patients on methadone maintenance found that patients on methadone less than 2 months had diminished hypercapnic and hypoxic responses and mild increases in PCO₂ after taking methadone. A group of patients taking methadone longer than 8 months had reduced hypoxic but not hypercapnic responses. Thus, there is evidence of some ventilatory control adaptations to chronic methadone ingestion.

An obvious treatment for narcotic induced central sleep apnea is cessation of intake of the medication. However, this is often not possible for patients with chronic pain syndromes. While there has been no systematic study, clinical experience has shown that CPAP and bilevel PAP as typically administered are not very effective except in cases with predominantly obstructive events. The current patient was taking oxycodone SR 40 mg twice daily for pain associated with her cervical spine osteoarthritis. The sleep study results show predominant central apnea with an AHI that is much higher during NREM than REM sleep and relatively mild arterial oxygen desaturation. The first tracing illustrates a short central apnea occurring during stage 3,4 sleep. As noted above, this finding is uncommon in most types of central sleep apnea. The airflow preceding the apnea also has an irregular pattern typical of opioid use. The second tracing shows recurrent central apneas. The patient underwent a positive airway pressure titration (PAP) with both CPAP and bilevel positive airway pressure. The obstructive events were eliminated, but frequent central apneas persisted. A repeat titration using bilevel PAP with a backup rate reduced the apnea-hypopnea index to <10/hour. After long term treatment with bilevel positive airway pressures of 17/10 cm H2O with a backup rate of 12 per minute the patient’s sleep quality and daytime sleepiness improved (Epworth Sleepiness Scale 12/24).

PEERLS

1. Chronic opioid use can result in a variety of respiratory manifestations during sleep, including prolonged obstructive apnea/hypopneas; a mixture of obstructive and central apneas, often with predominantly central events; or a pattern of ataxic breathing (irregular respiratory pauses).
2. The central sleep apneas associated with chronic opioid treatment occur predominantly during NREM sleep. In contrast to other types of central sleep apnea, it is not uncommon for opioid-induced central apneas to be present during stage 3,4 sleep.
3. The central sleep apnea associated with chronic opioid treatment can either appear as a type of periodic breathing (repeated central apneas separated by brief periods of ventilation) or as a random pattern of central apneas that can be associated with ataxic breathing.
4. Patients with opioid-associated central sleep apnea usually have a normal or only mildly increased daytime arterial PCO₂.
5. Treatment for opioid-associated central apnea has not been studied systematically. Traditional treatment with CPAP or bilevel PAP is often not effective. Some patients have been treated with bilevel PAP with a back-up rate with success.

REFERENCES