related to the allograft rejection. It is known that eosinophilia is a marker for rejection in liver, kidney, and heart transplants. Graft eosinophilia is known to be a sensitive and specific marker of liver rejection. An association between graft eosinophilia as well as peripheral eosinophilia and kidney rejection has been observed. Blood eosinophilia is a marker of cardiac rejection, and the level of eosinophilia correlates with the severity of rejection.

In 1992, Yousem reported nine patients with tissue eosinophilia on lung allograft biopsy. Five of these cases were associated with acute rejection, and the other four were associated with infection. Each of the cases associated with rejection resolved with steroids, but one patient later acquired OB. Two of the cases associated with infection, Aspergillus and coxsackie A2 virus, resolved with treatment of the infection; two patients died of their infections.

Bewig et al. reported a series of four patients who presented with recurrent eosinophilic alveolitis on BAL. Only one patient underwent a concomitant transbronchial biopsy, and it revealed acute rejection. Each patient responded to treatment with steroids.

Several cases of sarcoidosis and pulmonary eosinophilia or chronic eosinophilic pneumonia occurring concomitantly have been described but not in the posttransplant period. A review of 140 patients with sarcoidosis found 14% had peripheral blood eosinophilia (absolute eosinophil count > 350/μL); however, the authors did not find an increase in parenchymal lung eosinophilia. Both of our patients had peripheral blood eosinophilia and pulmonary eosinophilia. Whether this was due to sarcoidosis, medications, graft rejection, or another etiology is unclear. Although there was no associated rejection on biopsy, perhaps the eosinophilic infiltrates foreshadow a decline in allograft function in patients with sarcoidosis.

In conclusion, we report two cases of acute eosinophilic pneumonia in lung transplant recipients for sarcoidosis. Although the significance of eosinophilic pneumonia is unclear, it is concerning that both patients went on to acquire OB within a relatively short time period. Eosinophils are known to release inflammatory mediators such as eosinophil chemotactic factor, interleukin 5, and leukotriene B4. Further studies may identify a role for these in the predisposition to OB. A higher suspicion for pulmonary eosinophilia in transplanted patients with sarcoidosis is warranted. Perhaps early and aggressive treatment when pulmonary eosinophilia is diagnosed would prevent the development of OB.

REFERENCES

Sleep-Disordered Breathing Associated With Long-term Opioid Therapy*

Robert J. Farney, MD, FCCP; James M. Walker, PhD; Tom V. Cloward, MD, FCCP; and Steven Rhondeau, MD

Three patients are described who illustrate distinctive patterns of sleep-disordered breathing that we have observed in patients who are receiving long-term, sustained-release opioid medications. Polysomnography shows respiratory disturbances occur predominantly during non-rapid eye movement (NREM) sleep and are characterized by ataxic breathing, central apneas, sustained hypoxemia, and unusually prolonged obstructive “hypopneas” secondary to delayed arousal responses. In contrast to what is usually observed in subjects with obstructive sleep apnea (OSA), oxygen desaturation is more severe and respiratory disturbances are longer during NREM sleep compared to rapid eye movement sleep. Further studies are needed regarding the effects of opioids on respiration during sleep as well as the importance of interaction with other medications and associated risk factors for OSA.

Key words: ataxic breathing; Biot respiration; opioids; sleep apnea

Abbreviations: BMI = body mass index; CPAP = continuous positive airway pressure; NREM = non-rapid eye movement; OSA = obstructive sleep apnea; REM = rapid eye movement; SaO2 = arterial oxygen saturation

Selected Reports
Editors, research studies, and patient surveys have consistently indicated that pain is inadequately treated, and physician education is woefully insufficient.1 Time-contingent, sustained-release opioids have now become the standard of care for patients with chronic, nonmalignant pain. Although the analgesic and respiratory depressant effects of μ-opioid receptor agonists are well known,2,3 the potential adverse respiratory consequences with long-term oral therapy are considered minimal:

It is now accepted by practitioners of the specialty of pain medicine that respiratory depression induced by opioids tends to be a short-lived phenomenon, generally occurs only in the opioid-naive patient, and is antagonized by pain. Therefore, withholding the appropriate use of opioids from a patient who is experiencing pain on the basis of respiratory concerns is unwarranted.4 The scientific basis for the assertion that long-term use of sustained-release opioids is safe is limited by the paucity of studies, particularly in persons who may be more susceptible to the respiratory depressant effects of opioids during sleep. Sleep may be associated with increased upper airway resistance, obstructive sleep apnea (OSA) syndrome, alveolar hypoventilation, and central apnea including Cheyne-Stokes breathing pattern.5–8 Restoration of ventilation and prevention of asphyxia is dependent on the interaction of peripheral chemoreceptors (carotid body) mediated through the carotid sinus nerve, mechanoreceptors in the chest wall and lungs mediated through the vagus nerve, and central respiratory controllers located in the brainstem.9,10 The carotid bodies appear to be responsible for immediate breath-by-breath dynamic control, while the central brainstem controllers establish the baseline minute ventilation and respond relatively slowly to changes in carbon dioxide levels.10 In all cases of sleep-disordered breathing, the control of breathing may be compromised by medications such as alcohol, sedatives, hypnotics, and opioids.11

We have observed numerous patients in whom we believe that opioid therapy not only contributed to the pathogenesis of their sleep-disordered breathing but also complicated therapy. If true, then there is currently a significant risk for many patients because of the concurrent increasing use of long-acting opioids coupled with the high prevalence of underdiagnosed sleep-disordered breathing. The following three cases illustrate distinctive patterns of abnormal breathing that seem to be associated with long-term opioid therapy.

Materials and Methods

The patients in this report were selected from our clinic and had been referred for evaluation of OSA. All three patients completed detailed sleep questionnaires and were examined by a pulmonologist certified by the American Academy of Sleep Medicine. Each patient was studied with attended polysomnography (Cadwell Easy II Sleep, software version 1.5; Cadwell Laboratories; Kennewick, WA). In addition to the initial polysomnogram, each was retested with nasal continuous positive airway pressure (CPAP) titration using a standard protocol for the laboratory. Electrophysiologic sleep parameters included the following: central (C3/A2 or C4/A1) and occipital (O1/A2 or O2/A1) EEG; right and left electrooculogram, and submentalis electromyogram. Periodic limb movements were monitored by anterior tibialis electromyogram, and single-lead ECG was recorded. Airflow was detected by nasal pressure transducers, and respiratory effort was determined by measurement of chest and abdomen motion using pneumatic bands. Arterial oxygen saturation (SaO₂) was measured with an Ohmeda 3700 oximeter (Datex-Ohmeda; Madison, WI) set in the fast-response (3-s) mode from the finger, and the SaO₂ was simultaneously recorded on a strip chart at slow speed. Raw data were manually scored in 30-s epochs for sleep stages using standard criteria.12 Apneas were scored on the basis of ≥10-s absence of airflow (0 to 20% of baseline signal). Hypopneas were scored when there was a clear reduction of airflow for ≥10 s associated with either a ≥3% decrease in SaO₂ or an arousal respectively.13 Obstructive events were defined by the presence of respiratory effort and/or characteristic flattening of inspiratory airflow pattern. Central apneas were defined by the absence of detectable effort using high-gain amplifier settings. The respiratory disturbance index was computed as the total of all respiratory events divided by the total sleep time in hours. All of the subjects in this report were not cigarette smokers, none had asthma or other clinical pulmonary disease, and all had normal SaO₂ for this elevation while awake (≥93%). The results of sleep and respiratory measurements obtained from polysomnography for all three cases are shown in Tables 1 and 2, respectively.

Case 1

A 35-year-old woman (height, 155 cm; weight, 87 kg; body mass index [BMI], 36; and neck circumference, 39 cm) presented with chronic fatigue; poor sleep quality; restless legs syndrome; frequent nocturia; snoring; and witnessed apneas. Previous diagnoses included depression and gastroesophageal reflux. Medications included the following: hydrocodone, 7.5 mg tid; time-release morphine sulfate, 15 mg bid; tramadol, 50 mg at bedtime; sertraline; nefazadone; amitriptyline; alprazolam, 0.5 mg; celecoxib; and omeprazole. Baseline polysomnography revealed obstructive sleep disturbances that were most severe during non-rapid eye movement (NREM) sleep (Fig 1, top, A). Many events defined only classification and were characterized by unusually prolonged obstructive hypventilatory periods each lasting 5 to 8 min and associated with gradually progressive severe hypoxemia to 78 to 80% (Fig 1, center, B). The inspiratory airflow pattern using a nasal air pressure transducer was consistent with increased upper airway resistance (Fig 1, bottom, C). The respiratory rate and qualitative tidal volume did not change over these periods but were finally reversed with one or two deeper breaths. The patient ingested a second dose of hydrocodone (7.5 mg) and alprazolam (0.5 mg) at 1:20 AM. Approximately 2 h later,
respiratory disturbances were more severe but only during NREM sleep. Subsequent polysomnography with CPAP titration showed decreased frequency of respiratory events, but supplemental oxygen was required to normalize hypoxemia (SaO₂, 70 to 86%) during NREM sleep.

**Case 2**

A 43-year-old woman (height, 160 cm; weight, 66 kg; BMI, 26; and neck circumference, 32 cm) presented with chronic fatigue, excessive sleepiness, and snoring. Previous diagnoses included depression, hypertension, and gastroesophageal reflux. Opioids had been prescribed for complex regional pain syndrome, chronic low back and severe unremitting leg pain. Medications included methadone, 40 mg/d; fentanyl, 50 μg/h patch every 72 h; nefazadone; quetiapine; bupropion; lisinopril; and famotidine. Baseline polysomnography showed decreased frequency of respiratory events, but oxygenation and breath-by-breath control of the ventilatory pattern were normal. Because of increasingly profound hypersomnia in spite of nightly use of nasal CPAP, polysomnography was repeated in February 2001 beginning with her previous therapeutic pressure of 10 cm H₂O and titrated to 16 cm H₂O. In contrast to her original study, polysomnography showed continuous central apneas and moderate hypoxemia but only during NREM (Fig 3, top, A, and bottom, B). Increasing the CPAP was well tolerated but was completely ineffective. Oxygen and CPAP were prescribed.

**DISCUSSION**

These three examples illustrate the types of breathing patterns that we are now recognizing with increasing frequency. In contrast with the typical respiratory abnormalities seen in opioid-free patients with OSA, we have observed the following unique distinguishing features in patients receiving sustained-release opioid medications: (1) apnea duration and severity of hypoxia are more severe during NREM sleep compared to rapid eye movement (REM) sleep; (2) ataxic or Biot breathing pattern²⁴ characterized by irregular respiratory pauses and gasping without periodicity present during NREM sleep; (3) recurrent and unusually prolonged periods of obstructive hypoventilation lasting at least 5 min resulting in progressive severe hypoxemia and not present during REM sleep; (4) ineffectiveness of nasal CPAP.

That opioids either contributed to the pathogenesis of sleep-disordered breathing or to the difficulty achieving satisfactory therapy with CPAP cannot be proven. These patients are complicated and there are obviously confounding factors; however, we believe that the distinctive aspects of their breathing patterns support our hypothesis. Recognition of airway occlusion, hypoxia, and breath-by-breath control of the ventilatory pattern is mainly the responsibility of the carotid bodies, especially during NREM sleep.⁹,¹⁰ The severity and unusual characteristics of the respiratory patterns ob-

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**Table 1—Sleep Variables Obtained From Polysomnography of Three Patients With Sleep-Disordered Breathing**

<table>
<thead>
<tr>
<th>Case No. (Date)</th>
<th>Test</th>
<th>TST, h</th>
<th>Sleep Efficiency, †</th>
<th>Stage 1, %</th>
<th>Stage REM, %</th>
<th>PLMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (February 28, 2000)</td>
<td>BL</td>
<td>6.0</td>
<td>84</td>
<td>12</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>1 (June 7, 2000)</td>
<td>CPAP†</td>
<td>6.4</td>
<td>90</td>
<td>5</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>2 (July 31, 2001)</td>
<td>BL</td>
<td>8.4</td>
<td>97</td>
<td>22</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>2 (August 1, 2001)</td>
<td>CPAP†</td>
<td>8.6</td>
<td>92</td>
<td>16</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>3 (September 1, 1995)</td>
<td>BL/CPAP‡</td>
<td>6.6</td>
<td>89</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>3 (February 4, 2001)</td>
<td>CPAP†</td>
<td>5.9</td>
<td>88</td>
<td>8</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

*BL = baseline (full diagnostic polysomnography); TST = total sleep time; Stage 1 = Stage 1 NREM sleep computed as time of Stage 1 NREM/total sleep time; Stage REM = REM sleep computed as time of REM sleep/total sleep time; PLMS = periodic limb movement index computed as No. of periodic limb jerks/total sleep time.
†Computed as (total sleep time/total recording time) × 100.
‡Polysomnography with nasal CPAP titration.
§Polysomnography performed with a split-night protocol with a diagnostic portion and a therapeutic CPAP portion.

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Selected Reports
Figure 1. Top, A: Sleep/wake hypnogram and \( \text{SaO}_2 \) across the night in case 1. Note the recurrent and gradual progressive declines of \( \text{SaO}_2 \) that were associated with prolonged obstructive hypopneas (minimum duration, 5 min). These episodes were more pronounced following the ingestion of additional hydrocodone at 1:10 AM. Also note that the severity of respiratory disturbances and hypoxemia were less during REM sleep compared to NREM sleep. Center, B: This 600-s sample corresponds with the area denoted as IB on Figure 1, top, A. There is no cessation of airflow or respiratory effort associated with the progressive decrease in \( \text{SaO}_2 \). Increasing tracheal sound implies increasing respiratory effort. Evidence of airway obstruction and hypoxemia are quickly reversed with a few deep breaths. Bottom, C: This 60-s sample corresponds with the area denoted as IC on Figure 1, top, A. The airflow signal obtained by nasal pressure transducer shows flattening, characteristic of increased upper airway resistance. Note the reversal of hypoxemia with a few deep breaths.
Figure 2. *Top, A:* Sleep/wake hypnogram and $\text{SaO}_2$ across the night in case 2. It can be seen that the most severe desaturations of $\text{SaO}_2$ occurred during NREM sleep. The earlier-than-normal REM onset and increased frequency of REM episodes can be associated with depression. Supplemental oxygen at 2 L/min was added at 3:00 AM and maintained the $\text{SaO}_2$ near 94%; however, respiratory disturbances continued (*bottom, C*). *Center, B:* This 300-s sample corresponds with the area denoted as 2B on Figure 2, *top, A* during NREM sleep and while breathing room air. The respiratory pattern is characteristic of Biot or ataxic breathing, the ventilatory equivalent of atrial fibrillation. Notice the irregularity of the respiratory rate, effort, and airflow associated with variable degrees of hypoxemia and that this pattern is present during NREM sleep. *Bottom, C:* This 300-s sample corresponds with the area denoted as 2C on Figure 2, *top, A* during NREM sleep and while receiving supplemental oxygen at 2 L/min. Hypoxemia was corrected; however, ataxic breathing pattern persisted.
All currently available opioids used for analgesia also suppress respiratory drive. The potential adverse effects of parenteral therapy used in the perioperative setting have been emphasized especially in patients with sleep apnea. It is widely believed that side effects from opioid therapy diminish with time and that analgesic tolerance may develop more rapidly than does respiratory tolerance. However, investigations pertaining to the effects of long-term administration are scant. To our knowledge, there have been no clinical sleep studies of patients with documented or suspected sleep-disordered breathing such as OSA receiving long-term opioid therapy. The majority of research concerned with the respiratory effects of opioids on respiration have been fixed on the results of parenteral administration in normal subjects during wakefulness. We are aware of only two studies that have examined the effects of oral opioids on respiration during sleep. Robinson et al examined the effects of a single dose of hydromorphone administered to healthy individuals, and there was no significant change in any measure of sleep-disordered breathing. Long-term use of methadone has been associated with central apneas and lower baseline SaO2 during sleep when compared to control subjects. However, ataxic breathing or Biot respiration has not been previously described in this setting but seems to be a particularly obvious characteristic in our population.

In summary, we have described three representative patients from our clinic with very unusual sleep-disordered breathing patterns in whom opioid therapy may have contributed to the pathogenesis of sleep-disordered breathing or complicated therapy. Ataxic breathing, unusually prolonged obstructive "hypopneas" with profound hypoxemia, and central apneas only during NREM sleep were characteristic, and nasal CPAP therapy without supplemental oxygen was consistently ineffective. There is potential for harm because patients with OSA syndrome continue to be underdiagnosed while at the same time the use of oral opioids for chronic pain control increases. Furthermore, opioids could interfere with providing effective nasal CPAP therapy. Patients receiving long-term, long-acting opioids need to be screened and monitored for sleep-disordered breathing. Symptoms of persistent fatigue with or without other features of OSA should possibly trigger a careful investigation for sleep apnea. Further prospective studies of the effects of sustained-release opioids on respiration during sleep are urgently needed. Questions to be answered relate to the dose, duration, of parenteral therapy used in the perioperative setting have been emphasized especially in patients with sleep apnea.

### Table 2—Respiratory Variables Obtained From Polysomnography of Three Patients With Sleep-Disordered Breathing

<table>
<thead>
<tr>
<th>Case No. (Date)</th>
<th>Test</th>
<th>RDI/h Overall</th>
<th>RDI/h Supine</th>
<th>RDI/h Nonsupine</th>
<th>Apneas Central</th>
<th>Apneas Obstructive</th>
<th>Hypopneas</th>
<th>Apnea Mean</th>
<th>Apnea Nadir</th>
<th>Apnea Lowest</th>
<th>Apnea Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (February 28, 2000)</td>
<td>BL</td>
<td>24</td>
<td>33</td>
<td>11</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>153</td>
<td>84</td>
<td>74</td>
<td>0</td>
</tr>
<tr>
<td>1 (June 7, 2000)</td>
<td>CPAP</td>
<td>10</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>61</td>
<td>86</td>
<td>70</td>
<td>4-15</td>
</tr>
<tr>
<td>2 (July 31, 2001)</td>
<td>BL</td>
<td>35</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>153</td>
<td>140</td>
<td>85</td>
<td>76</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2 (August 1, 2001)</td>
<td>CPAP</td>
<td>35</td>
<td>34</td>
<td>56</td>
<td>204</td>
<td>78</td>
<td>19</td>
<td>92</td>
<td>88</td>
<td>4-8</td>
<td></td>
</tr>
<tr>
<td>3 (September 1, 1995)</td>
<td>BL</td>
<td>69</td>
<td>20</td>
<td>76</td>
<td>15</td>
<td>85</td>
<td>139</td>
<td>88</td>
<td>84</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3 (February 4, 2001)</td>
<td>CPAP</td>
<td>16</td>
<td>17</td>
<td>15</td>
<td>13</td>
<td>15</td>
<td>17</td>
<td>92</td>
<td>86</td>
<td>4-12</td>
<td></td>
</tr>
</tbody>
</table>

*RDI = respiratory disturbance index computed as the total of all respiratory events divided by the total sleep time in hours. See Table 1 for expansion of abbreviation.

†Polysomnography with nasal CPAP titration.
specific opioid, and associated comorbid factors including interaction with other medications such as benzodiazepines and antidepressants.

REFERENCES


Figure 3. Top: Sleep/wake hypnogram, SaO₂, and nasal CPAP across the night in case 3. Note the presence of continuous desaturations during NREM sleep but not during REM sleep. There was no improvement as CPAP was increased from the previous therapeutic level of 10 to 16 cm H₂O. Bottom: This 300-s sample corresponds with the area denoted as 3B on Figure 3, top, A and shows the transition between NREM and REM sleep at a CPAP level of 16 cm H₂O. Note the progression from central apneas during NREM sleep to typical normal variable breathing pattern in REM sleep.
Leptospirosis Presenting as Diffuse Alveolar Hemorrhage*

Case Report and Literature Review

Andrew M. Luks, MD; Sambasiva Lakshminarayanan, MD; and Jan V. Hirschmann, MD

The literature on diffuse alveolar hemorrhage heavily emphasizes the causal role of vasculitides. We present a patient with diffuse alveolar hemorrhage caused by leptospirosis. Although the pathology in leptospirosis occurs secondary to a vasculitic process, this disease is not listed as a cause of diffuse alveolar hemorrhage in the review literature. In the right clinical scenario, the disease should be considered in a patient presenting with diffuse alveolar hemorrhage.

Key words: diffuse alveolar hemorrhage; hemoptysis; interstitial nephritis; leptospirosis; pulmonary hemorrhage; vasculitis

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; EIA = enzyme-linked immunoassay

The syndrome of diffuse alveolar hemorrhage consists of hemoptysis, bilateral airspace opacification on the chest radiograph, and a decreased hematocrit secondary to bleeding from the pulmonary microvasculature into the alveolar space. Many reviews divide its causes into those associated with vasculitis and those from other factors,1–5 while others focus solely on the vasculitides.6–12 Few, however, include an important cause of pulmonary hemorrhage—leptospirosis.

CASE REPORT

A 46-year-old homeless man complained of 5 days of nausea, watery diarrhea, myalgias, dizziness, and headache. While ill, he had little oral intake and spent most of his time sleeping in the woods. His temperature was 38.2°C (100.7°F), and his BP was 58/20 mm Hg while standing. Laboratory results were as follows: sodium, 133 mEq/L; bicarbonate, 21 mEq/L; BUN, 17 mg/dL; and creatinine, 1.5 mg/dL. Liver test results were as follows: aspartate transaminase (AST), 35 U/L (normal < 37 U/L); alanine transaminase (ALT), 24 U/L (normal < 40 U/L); alkaline phosphatase, 70 U/L (normal < 117 U/L); and total bilirubin, 2.6 mg/dL, with a direct component of 0.6 mg/dL. WBC count was 11.9 × 10^9/L, hematocrit was 40.2%, and platelets were 167 × 10^9/L. Urinalysis revealed 1+ protein, 3+ blood, 9 to 30 RBCs, 0 to 4 WBCs, and no casts.

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Work for this article was performed at the Veterans Affairs Medical Center and the University of Washington Medical Center in Seattle, WA.

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