Sleep-induced apnea

Part 1: A respiratory and autonomic dysfunction syndrome following bilateral percutaneous cervical cordotomy

ABBOTT J. KRIEGER, M.D., AND HUBERT L. ROSOMOFF, M.D.
Division of Neurological Surgery, University of Pittsburgh School of Medicine, and the Veterans Administration Hospital, Pittsburgh, Pennsylvania, and Department of Neurological Surgery, University of Miami School of Medicine, Miami, Florida

Data are reported on 10 patients who developed a syndrome of sleep-induced apnea preceded by lethargy and asthenia following bilateral percutaneous cervical cordotomy. Respiratory dysfunction occurred within 24 to 48 hours in most cases but appeared as early as 1 hour and as late as 6 days. One type of respiratory dysfunction was characterized by an attenuated CO₂ response with a normal vital capacity; in a second type an attenuated CO₂ response and a decreased vital capacity were both present. A variety of other autonomic dysfunctions were present in some of the patients; these included hypotension, hyponatremia, inappropriate antidiuretic hormone secretion, and difficulties in micturition. The syndrome lasted from 3 to 32 days in surviving patients. Five patients required endotracheal intubation. Three deaths were attributable to this syndrome; two occurred in patients who were not intubated and died in their sleep. The incidence of apnea during sleep, its reversal by arousal, and the absence of significant motor changes strongly suggest that the ascending reticular fibers in the ventrolateral segment of the spinal cord have been damaged.

KEY WORDS · sleep-induced apnea · percutaneous cervical cordotomy · hyponatremia · autonomic dysfunction · CO₂ response · respiratory function

RESPIRATORY and autonomic dysfunction are acknowledged complications of laminectomy and cervical cordotomy.¹,²⁷,²⁸ This dysfunction includes apnea and vasomotor collapse at the time of surgery as well as respiratory arrest, hypotension, hyponatremia, and urinary retention at varying intervals after cordotomy. While these features have been described as individual entities by numerous authors, no one has recognized them as part of a continuum comprising a syndrome.

Clinical Material

We have observed this spectrum of respiratory and autonomic dysfunction in 10
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patients with bilateral percutaneous cervical cordotomies (PCC). Sleep-induced apnea was the common denominator. Some patients had sleep-induced apnea alone, while in others this was accompanied by hypotension and/or hyponatremia. Almost all the patients had urinary retention.

There were three men and seven women in this group, most of whom were in the fifth decade (range 42 to 73 years). The underlying disease was malignant in four and benign in six; four suffered with lumbar radiculopathy. All patients were suitable candidates for general anesthesia. The chest films of four patients were abnormal, showing residual bronchogenic tumor and mediastinal shift in one, thoracotomy scars for bronchogenic carcinoma in one, a healed granuloma in one, and emphysema in the fourth. Pertinent clinical summaries are detailed in Tables 1 and 2.

The characteristic course of this syndrome began with the subjective sensation of asthenia associated with sighing respirations. At this time, objective clinical evidence of functional impairment was not always demonstrable, so that the uninitiated might disregard the symptoms by ascribing them to an anxiety reaction. The patient usually went on to hypoventilate and characteristically became apneic when asleep. If the patient was awakened, “normal” breathing resumed, but hypoventilation often persisted and apnea remained a constant danger with the resumption of sleep. If wakefulness could not be sustained, intubation and control of respiration became necessary. The condition was reversible if

TABLE 1
Clinical data in 10 patients with bilateral percutaneous cervical cordotomy (PCC)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, Sex</th>
<th>Underlying Disease</th>
<th>No. of PCC’s</th>
<th>Analgesia Level</th>
<th>X-ray Findings</th>
<th>Neurological Findings</th>
<th>Post-PCC Findings</th>
<th>Urinary Retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>osteoarthritis, F</td>
<td>2</td>
<td>high low</td>
<td>normal</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>lumbar radiculopathy, F</td>
<td>4</td>
<td>high high</td>
<td>normal</td>
<td>++</td>
<td>++</td>
<td>0 urecholine</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>laryngeal carcinoma, M</td>
<td>4</td>
<td>high high</td>
<td>normal</td>
<td>0</td>
<td>0</td>
<td>0 Foley catheter</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>lumbar radiculopathy, radiculopathy, F</td>
<td>2</td>
<td>low high</td>
<td>emphysema</td>
<td>0</td>
<td>0</td>
<td>Foley catheter</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>bronchogenic carcinoma, M</td>
<td>4</td>
<td>high high†</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>Foley catheter</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>bronchogenic carcinoma, M</td>
<td>2</td>
<td>low low*</td>
<td>residual tumor</td>
<td>0</td>
<td>0</td>
<td>Foley catheter</td>
</tr>
<tr>
<td>7</td>
<td>42</td>
<td>lumbar radiculopathy, radiculopathy, M</td>
<td>6</td>
<td>high high†</td>
<td>healed granuloma</td>
<td>+</td>
<td>0</td>
<td>urecholine</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>colonic carcinoma, M</td>
<td>3</td>
<td>high high</td>
<td>normal</td>
<td>++</td>
<td>+</td>
<td>Foley catheter</td>
</tr>
<tr>
<td>9</td>
<td>48</td>
<td>rheumatoid arthritis, F</td>
<td>2</td>
<td>high high</td>
<td>normal</td>
<td>0</td>
<td>0</td>
<td>Foley catheter</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>lumbar radiculopathy, F</td>
<td>2</td>
<td>low high</td>
<td>normal</td>
<td>+</td>
<td>+</td>
<td>0 Foley catheter</td>
</tr>
</tbody>
</table>

* No level No. 1.
† Hypotension during procedure.
‡ No level No. 3.
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TABLE 2
Course of respiratory dysfunction following bilateral percutaneous cervical cordotomy (PCC) in 10 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Onset (hrs Post-PCC)</th>
<th>Duration (days)</th>
<th>Intubation (days)</th>
<th>Lowest BP Post-PCC (mm Hg)</th>
<th>Medications Given Day of Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>3</td>
<td>0</td>
<td>200/140 pulse 100</td>
<td>percodan, librium 10 mg</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>4</td>
<td>0</td>
<td>140/100</td>
<td>librium 25 mg</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>32</td>
<td>30</td>
<td>150/90</td>
<td>100% O₂</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>8</td>
<td>8</td>
<td>90/0 pulse 92</td>
<td>thorazine 25 mg</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>34</td>
<td>30</td>
<td>90/50 pulse 60</td>
<td>librium 10 mg, thorazine 25 mg</td>
</tr>
<tr>
<td>6</td>
<td>144</td>
<td>11</td>
<td>0</td>
<td>100/70 pulse 96</td>
<td>codeine 60 mg</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>90/50 pulse 64</td>
<td>none</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>14</td>
<td>14</td>
<td>70/30 pulse 70</td>
<td>none</td>
</tr>
<tr>
<td>9</td>
<td>48</td>
<td>10</td>
<td>0</td>
<td>60/0 pulse 80</td>
<td>none</td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>5</td>
<td>2</td>
<td>140/90</td>
<td>demerol</td>
</tr>
</tbody>
</table>

respiration was maintained throughout this difficult period.

Summary of Cases

In surviving patients, the syndrome lasted from 3 to 32 days. All patients complained of vague feelings of lethargy and asthenia and appeared to be somewhat confused. Two patients complained specifically of the inability to "get enough air," and a third described a feeling of a "dead weight" in his chest. In one patient, the syndrome was interpreted as chest pain for which she was given Demerol. Table 2 summarizes the course of respiratory dysfunction in this series. Three deaths were attributable to the syndrome.

Fatal Cases

Two of the patients (Cases 1 and 2) had a very similar post-cordotomy course, and both were found dead in bed on the fourth postoperative night. Neither had been intubated, nor had they shown the need for this procedure. Physical examination a few hours prior to death had shown no functional impairment. Both, however, complained of nausea and the inability to sleep, and were anxious and apprehensive.

The third patient (Case 5) died 34 days after the onset of autonomic dysfunction. She had had bilateral cordotomies for intractable pain due to bronchogenic cancer and became hypotensive and hyponatremic with urinary retention requiring Foley catheter drainage. Within 24 hours after the last cordotomy she began to complain of breathing difficulty and showed limited chest movement. The next day she had a respiratory and cardiac arrest during sleep but was resuscitated. High doses of Ritalin were given which kept her awake all night, but on the third postoperative day she fell asleep and became apneic. She was intubated and maintained on positive-pressure ventilation with a Bird respirator. A tracheostomy was performed 9 days later, but she...
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TABLE 2 (continued)

<table>
<thead>
<tr>
<th>Blood Gases</th>
<th>Electrolytes</th>
<th>Mental Changes</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 7.35, pCO₂ 45.9, O₂ sat 97%</td>
<td>normal</td>
<td>nausea, disorientation, apprehension, insomnia, dyspnea</td>
<td>died in 4 days, sleep-induced apnea</td>
</tr>
<tr>
<td>pH 7.44, pCO₂ 47, O₂ sat 98%</td>
<td>normal</td>
<td>nausea, confusion, insomnia, dyspnea</td>
<td>died in 4 days, sleep-induced apnea</td>
</tr>
<tr>
<td>pH 7.33, pCO₂ 69, O₂ sat 80%</td>
<td>normal</td>
<td>lethargy, asthenia, dyspnea</td>
<td>died in 70 days, renal failure</td>
</tr>
<tr>
<td>pH 7.4, pCO₂ 40.5, O₂ sat 100%</td>
<td>normal</td>
<td>lethargy, asthenia</td>
<td>discharged</td>
</tr>
<tr>
<td>pH 7.42, pCO₂ 44, O₂ sat 86%</td>
<td>Na 116, K 5.0, Cl 86</td>
<td>nausea, asthenia</td>
<td>discharged</td>
</tr>
<tr>
<td>pH 7.44, pCO₂ 34.5, O₂ sat 98%</td>
<td>normal</td>
<td>lethargy, asthenia, dyspnea</td>
<td>discharged</td>
</tr>
<tr>
<td>pH 7.46, pCO₂ 31, O₂ sat 93%</td>
<td>normal</td>
<td>lethargy, dyspnea</td>
<td>discharged</td>
</tr>
</tbody>
</table>

continued to have pulmonary difficulties, with atelectasis due to inspissated secretions. She was never able to maintain adequate ventilation without assistance and died 30 days after intubation because of pneumonia.

Role of Drugs in Pulmonary Dysfunction

All of the patients, including those that died, had had large spinal cord lesions as indicated by the high levels of analgesia following the final cordotomy (Fig. 1). The only exception to this was a patient (Case 6) whose clinical course illustrates the precipitating influence of drugs.

Case 6. In this 66-year-old man with bronchogenic carcinoma and spinal metastasis, the first cordotomy was not successful; a D-8 level of analgesia was obtained at surgery but disappeared the next day. The following week a cordotomy done on the opposite side resulted in a D-6 level of anesthesia. He continued to have pain on the first side but as this was relatively mild he was discharged on codeine 60 mg as needed. One week later he was readmitted because of increasing pain and difficulty in breathing. He had been taking 6 mg of codeine every 3 or 4 hours at home. For several days prior to readmission his family had noted increasing confusion, particularly after the administrations of codeine. He complained of inability to take a deep and satisfying breath. On readmission he was lethargic, confused, and disoriented, with urinary retention requiring Foley catheterization. Blood gas analysis showed the PaCO₂ to be 69, pH 7.33, oxygen saturation 80%, and serum bicarbonate 35 mEq/l.

Pulmonary function studies revealed marked reduction in CO₂ response with only mild reduction of vital capacity. The patient was placed in the intensive care unit and all medications were discontinued. He was prevented from sleeping, and gradually his state of consciousness, orientation and pulmonary function improved. He continued to have pain but refused another cordotomy.
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Fig. 1. Cross sections of the spinal cord showing the extent of lesions at cordotomy. Upper Left: Case 2. Three discrete lesions are seen on the left side, the largest located anteriorly with involvement of the anterior horn. A second lesion involves the lateral margin while the third is located posterior medially. The right-sided lesion is well placed laterally. Upper Right: Case 3. Note the extent of necrotic lesions with almost complete obliteration of the ventrolateral cord. The anterior horn is not involved. Despite the size of the lesions, the patient survived the episode of sleep-induced apnea but succumbed to renal failure secondary to metastatic disease some 2 months after onset of his respiratory and autonomic symptoms. Lower Right: Case 5. Note the necrosis of the ventral aspects of the cervical spinal cord at the C-1 level. The necrosis is more extensive on the left side with involvement of the anterior horn. A second discrete lesion is present on the right ventrolaterally with sparing of the corticospinal tract.

and insisted on discharge. He was discharged and died at home 3 weeks later because of his primary disease. Permission for autopsy was refused.

Comment. This exceptional death emphasizes the fact that drugs depressing brain-stem function may cause apnea. Clinical studies on patients awake and asleep, with and without morphine, demonstrated that the pCO₂ required to drive alveolar ventilation to 20 l/min was increased significantly with sleep plus morphine. In our patient, the combination of a spinal cord lesion, codeine, and sleep was enough to precipitate the respiratory and autonomic dysfunction syndrome, even though the size of the cordotomy lesion was not as great as in other patients who had no difficulties.

Symptoms of Pulmonary Dysfunction

Clinically, all the patients experiencing pulmonary dysfunction appeared the same. However, on detailed study of their pulmonary function, two distinct types emerged. The first type is manifested by a normal vital capacity and an attenuated CO₂ response; Case 7 is an example of this type. The second type is manifested by a decreased vital capacity and an attenuated CO₂ response; Cases 9 and 10 are examples.

Case 7. This 42-year-old man had been injured in an automobile accident 3 years previously; multiple surgical procedures to relieve intractable pain resulting from spinal injuries had been unsuccessful, including two PCC's at another hospital. On admission to this institution, pulmonary function studies showed a marked reduction in vital
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Fig. 2. Case 7. Results of pulmonary function tests showing an unchanged FVC after several cordotomies despite fall of the VE(CO2). L/min/m² = liters per minute per square meter of body surface area; VE(CO2) = minute ventilation breathing 5% carbon dioxide; FVC = forced vital capacity as a percent of predicted; TV = tidal volume in cc; TV(CO2) = tidal volume breathing 5% carbon dioxide. Percutaneous cervical cordotomy (PCC) procedures are indicated by arrows. The abscissa is calibrated in arbitrary time units indicating the interval between pulmonary function tests.

capacity and a normal CO2 response. After cordotomy in August, 1967, the pain was relieved; the vital capacity improved significantly, probably due to the relief of pain. The CO2 response was unaffected in the immediate postoperative period, but when tested again 3 months later was found to be somewhat decreased. Pain recurred and a repeat cordotomy was performed on November 22, 1967, with transient relief of pain. The vital capacity remained unaffected, but the CO2 response decreased further. Another cordotomy 6 days later was followed by adequate pain relief. This time, while on the operating table, he complained of the feeling that he had "a dead weight on his chest." Later that afternoon he was lethargic and confused. That evening his pain returned, on sensory testing analgesia was spotty and his breathing was less labored. At this time pulmonary function studies (Fig. 2) showed an unaffected vital capacity and a marked decrease in CO2 response. Repeated pulmonary function studies indicated a gradual return of the CO2 response toward normal, with a consistently unaffected vital capacity. In January, 1968, still another cordotomy was performed because of recurrence of pain; once again this was effective. Following the procedure, he again became lethargic and dyspneic.

This continued into the evening and he was placed in the intensive care unit for closer observation. During the night his breathing was uneven and irregular (Fig. 3), and several times he became totally apneic. On each apneic occasion he was awakened and adequate respiration resumed. The next day his original pain recurred; with its return the breathing and state of consciousness improved. Pulmonary function studies performed the afternoon after the cordotomy and preceding the sleep-induced apnea showed another marked decrease in CO2 response and a normal vital capacity.

Case 9. This 48-year-old woman with long-standing rheumatoid arthritis had been
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bedridden for several months with extensive restriction of joint motion caused by pain. Pulmonary function studies (Fig. 4) prior to cordotomy were essentially normal. With each stage of the bilateral cordotomy, she sustained a marked reduction of both vital capacity and CO₂ response. Following the second cordotomy, she had a transient period of hypotension, and that night she was found to be apneic while asleep. After a short period of assisted ventilation she recovered. No further episodes of respiratory arrest occurred, but she required Foley catheter drainage for several days. Follow-up pulmonary function studies during the next 9 months revealed gradual recovery of the vital capacity to near pre-cordotomy levels but persistently impaired CO₂ response.

Another patient with this type of dysfunction was Case 6, with cordotomies for relief of lumbar radiculopathy pain.

Case 10. In this patient the first cordotomy had relieved the pain of lumbar radiculopathy for 6 months. Three days after the second cordotomy, she developed urinary retention and an unpleasant tightness in her chest which was initially interpreted as pain, and she was given Demerol. Shortly thereafter she had more overt respiratory distress. Cinefluoroscopy showed no right diaphragmatic movement and decreased movement on the left side. Pulmonary function study (Fig. 5), done prior to the second cordotomy, had shown essentially normal function. When repeated after the onset of respiratory symptoms, there was a marked fall in vital capacity with a significant reduction of the CO₂ response. On the basis of these studies she was intubated for 2 days. Subsequent pulmonary function testing revealed progressive improvement of vital capacity to near normal levels, but the impairment of the CO₂ response persisted.

Hyponatremia

Hyponatremia was present in three patients. Sodium values for two of the patients reached their lowest level 2 days post-

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Fig. 4. Case 9. Pulmonary function studies showing a parallel fall in FVC and VE(CO₂) after each cordotomy. However, during the recovery starting with test 3, dissociation between these two functions becomes apparent. Abbreviations as in Fig. 2.

Fig. 5. Case 10. Pulmonary function studies showing precipitous fall in FVC after the second cordotomy with a less dramatic fall of the VE(CO₂), which continues to fall while the FVC improves. Abbreviations as in Fig. 2.
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cordotomy (111 mEq/l and 117 mEq/l). Values for both patients were either normal or approaching normal by the sixth day after cordotomy (141 mEq/l and 134 mEq/l).

In the third patient sodium values continued to fall until 9 days after cordotomy, despite the fact that she had been given a total of 300 mEq of NaCl in a 5% NaCl intravenous solution during the previous 3 days. The sodium balance began to correct itself slowly, and intravenous NaCl was replaced by oral administration of 12 gm NaCl/day for the next 4 days. By that time (14 days after cordotomy) serum sodium values were normal, and oral sodium was discontinued (Fig. 6). She had excessive water retention which resulted from an inappropriate secretion of antidiuretic hormone (ADH), and persisted despite a reduction in the sodium concentration of her extracellular fluid.

Various other manifestations of autonom-ic dysfunction were present in most patients. Six patients were hypotensive; three of these did not compensate for the lowered blood pressure with an appropriate increase in heart rate, indicating a sympathetic interruption which was verified by a Horner's syndrome. The other three had the expected tachycardia and no Horner's syndrome.

Nine of the 10 patients had difficulty with micturition. Urinary difficulties always began the day each experienced respiratory difficulties. Three patients responded to Urecholine administration, but six patients required Foley catheter drainage.

Discussion

Mullan and Hosobuchi have reported that patients who seem to respond most adversely to bilateral cordotomy are those not able to withstand general anesthesia. This criterion is rather nonspecific, yet if

![Graphs showing positive water balance during first 14 days, accompanied by increased urine osmolarity and hyponatremia which persisted despite supplemental salt administration.](image-url)
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utilized, the 10 patients in our series would have been judged suitable candidates. There were three patients, however, in whom difficulty might have been anticipated. One became comatose subsequent to morphine administration, another became confused after the first cordotomy, and the third complained of shortness of breath after two ipsilateral procedures prior to the second cordotomy.

Various features were present concurrently with the respiratory distress syndrome, urinary retention, hypotension and hyponatremia. Nine of our patients were unable to void, and six required Foley catheter drainage; all but one (Case 6) retained awareness of bladder distension. This is a higher incidence than is seen in patients without respiratory problems.

Nathan and Smith analyzed the probable anatomic location of the afferent and efferent pathways of micturition. They located the afferent tract on the surface of the cord opposite the posterior angle of the anterior horn, and the efferent tract more medially in the lateral column on an equatorial plane passing through the central canal. White found that awareness of bladder filling was not significantly altered by bilateral anterolateral cordotomy. Other investigators have noted that although bilateral cordotomy resulted in urinary retention it was usually transitory.

Hypotension was present in six of our 10 patients. Foerster, reporting his observations on vasomotor alterations following bilateral cordotomies, concluded that vasomotor pathways to both sides of the body were represented in each anterolateral quadrant of the cord. Wang and Ranson reaffirmed this finding by showing that selective section of the ventrolateral column reduced the pressor responses from hypothalamic stimulation. Others have described orthostatic or postural hypotension as a result of bilateral cordotomy. Belmusto, et al., has been more specific in his localization of the vasomotor pathways in the spinal cord. In a small series of bilateral low cervical cordotomies, he placed the vasomotor pathways 3 to 5 \( \frac{1}{2} \) mm from the anterolateral surface of the cord. If hypotension with bradycardia after cordotomy is recognized as caused by sympathetic interruption, it can be treated effectively with volume replacement and atropine.

Hyponatremia was present in three of our patients. Saline corrected the deficit in the first two patients within 4 days. The last patient had the typical features of inappropriate secretion of antidiuretic hormone and saline was necessary for 14 days. The balance studies in this case progressed in the following sequence: hyponatremia, continued renal excretion of sodium, urine hyperosmolarity in the presence of serum hypoosmolarity, and normal renal and adrenal function.

Long and Story felt that hyponatremia was a rare finding after bilateral cordotomy, occurred chiefly in chronically ill patients, and was causally related to bilateral spinal lesions. Their suggestion that the descending sympathetic outflow is implicated might be...
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applicable in our cases since all three were hypotensive after the bilateral procedure. It is also true that all three of our cases had endotracheal intubation and intermittent positive pressure-assisted ventilation.

It has been adequately demonstrated experimentally\textsuperscript{25} that breathing against a continuous positive pressure decreases the rate of urine flow and results in water retention. This is probably due to an increased ADH release initiated by cardiovascular reflexes.\textsuperscript{11} Gauer and Henry\textsuperscript{11} presented evidence for a left atrial-vagal afferent mechanism which influences renal function, and this work has served as the basis for the hypothesis of vagal inhibition of ADH secretion. In experiments designed to determine volume regulatory reflexes, it was found that the effects of hemorrhage and transfusion on renal function could be duplicated by changes in the intrathoracic blood volume by negative and positive pressure breathing, immersion of the body in water, or inflation of a balloon in the left atrium. It has been further demonstrated that carotid arterial afferents serve a similar function.\textsuperscript{26} Mills and Wang\textsuperscript{26} reported experimental evidence of a central pathway connecting the visceral afferent system (vagus nerves) to the supraoptico-hypophyseal system. They stimulated various parts of the brain stem that inhibit diuresis, an indirect method of determining ADH release. Responses were obtained from the tractus solitarius, lateral reticular formation, and rostral reticular formation, suggesting that impulses from the visceral afferent system mediating ADH release ascend via extralemniscal pathways.

To understand the actual factors directly precipitating the syndrome we have identified, one must consider elements related both to sleep and respiration and the evolution of events leading to respiratory dysfunction and apnea. During the period 12 to 24 hours after cordotomy the patient may hypoventilate, but this alone could be well tolerated; what is not clearly understood is that during sleep the patient may become apneic. While the occurrence of respiratory depression during sleep is well known,\textsuperscript{21} the mechanism of profound respiratory depression leading to apnea and death is pure conjecture.

The reticular formation has been thoroughly studied in relationship to the states of consciousness,\textsuperscript{21} and it might be causally inferred that respiratory depression during sleep is related to inactivation of the reticular system. Fink, \textit{et al.}\textsuperscript{7,8} believes that the respiratory-depressant effects of sleep are due to the loss of the stimulating influence of wakefulness on respiration. The stimuli from the brain-stem reticular formation are diminished during sleep and respiration is more dependent on the PaCO\textsubscript{2} for adequate stimulation. This can be shown by hyperventilating an anesthetized individual so that he becomes apneic with a PaCO\textsubscript{2} drop of 10 mm Hg. All of our patients complained of generalized weakness, lethargy, and asthenia as though certain activating or arousing mechanisms were disrupted. This further deprivation of reticular influences might potentiate the normal mechanisms that produce respiratory depression during sleep and thus cause apnea.

Drugs may also depress brain-stem function and so cause apnea. This notion was nicely demonstrated in the clinical studies of Forrest and Bellville\textsuperscript{10} who reported CO\textsubscript{2} response curves on four subjects, awake and asleep, with and without morphine. The pCO\textsubscript{2} required to drive alveolar ventilation to 20 l/min was increased 1 to 6 mm Hg with morphine, 4 to 10 mm Hg with sleep, and 13 to 24 mm Hg with sleep plus morphine.

One of our patients (Case 3) became apneic after 100% oxygen administration. The specific cause of respiratory depressant effects of high pO\textsubscript{2} is not yet known. It is known that high partial pressures of O\textsubscript{2} reduce the reaction of the peripheral chemoreceptors to hypercapnea and acidaemia.\textsuperscript{15} Thus, it appears that 100% O\textsubscript{2} may remove another stimulus to the respiratory center via the reduction of CO\textsubscript{2} effect on the peripheral chemoreceptors. Therefore, the administration of O\textsubscript{2} to patients complaining of dyspnea after cordotomy must be considered hazardous.

Respiratory problems after cordotomy have prompted several studies to delineate spinal respiratory pathways in animals and man.\textsuperscript{5,4,26} Almost all have investigated the role of the descending pathways in respiratory failure. In 1927, Allen\textsuperscript{1} suggested that
the reticulospinal tracts conduct impulses to the respiratory motor nuclei. Subsequent work supported the initial impression that the reticulospinal tract in the anterolateral quadrant of the cervical spinal cord carried respiratory impulses. Since these tracts are closely related topographically to the pain fibers of the spinothalamic tracts, Belmusto, et al., concluded that damage during cervical cordotomy to the reticulospinal tracts produced the respiratory dysfunction. In a recent series of studies it has been shown that small discrete bilateral ventrolateral cord lesions which had little effect on spontaneous respiration led to profound changes on rate regulation, as well as pH and PaCO₂ in response to CO₂ inhalation. Furthermore, electrical stimulation of the inspiratory center after ventrolateral cervical cord lesions did not result in a substantially reduced depth of inspiratory spasm. Prior to that study only two major afferent inputs to the respiratory center were known, the vagal inflow and that from the pneumotaxic center. Ablation of both these inputs results in apnea. In this experimental study apneustic breathing was produced in animals with bilateral ventrolateral cervical cord lesions when an additional midpontine transection or bilateral vagotomy was performed. That study strongly suggested that another afferent pathway exists in the ventrolateral cervical cord for the regulation of normal respiration.

A possible clinical counterpart to sleep-induced apnea is the respiratory dysfunction present in some cases of bulbar poliomyelitis without chest wall paralysis. Pathological studies particularly by Baker, et al., demonstrated major damage in the lateral reticular formation, the identical region of the spinoreticular projections of spinal afferents demonstrated after experimental anterolateral cordotomies. In a series of 20 cases reported by Plum and Swanson there were 13 with irregular breathing and variable periods of apnea. All 13 had a reduced CO₂ response. Linderholm and Werneman in a study of 71 patients convalescing from polio noted a similar decrease in CO₂ response in patients with predominantly cerebral symptoms. He was able to identify a group with decreased vital capacity and maximum breathing capacity but a normal CO₂ response, which suggested that motor impairment was not a prerequisite for an impaired CO₂ response.

The importance of afferent inflow to the respiratory center from the reticular system has been described by several investigators, and documented experimentally by Hugelin and Cohen who showed that stimulation of the diencephalic and mesencephalic reticular formation increased the amplitude of the inspiratory discharge (phrenic nerve) and the frequency of the respiratory cycle. This effect was identical to that achieved by stimulation of the central end of a mixed nerve (median, ulnar, or radial). Thus, with depression of the reticular system one would expect decreased amplitude of inspiratory discharge resulting in decreased tidal volume, increased duration of expiration resulting in decreased rate, and a decreased slope of the phrenic discharge resulting in decreased instantaneous air flow. The changes in phrenic activity produced by reticular or afferent stimulation have always been accompanied by EEG desynchronization. When phrenic activity occurred spontaneously, it was always associated with cortical activation; conversely, spontaneous episodes of cortical activation were always associated with an increase in respiratory rate. Thus, in a wide variety of situations there is a relationship between cortical activation and respiratory changes which are similar to those evoked by reticular stimulation. Such correlations between cortical and respiratory changes have also been observed in man by Bülow and Ingvar. These findings taken together indicate that afferent impulses impinge on suprapontine reticular neurons and modify their discharge. This in turn produces changes in cortical and respiratory activity.

In the single published study of pulmonary function following percutaneous cordotomy, it was noted that vital capacity and peak flow rate decreased after cordotomy, the reduction being greater in patients who developed respiratory symptoms following the procedure. Although some of these patients developed phrenic palsy, the majority did not, and some of those with phrenic palsy had no symptoms. One patient with
Sleep-induced apnea after cervical cordotomy

Sleep-induced apnea was noted to have an impaired response to inhaled CO₂.

In our study of the effect of cordotomy on pulmonary function, the three significant changes were a decreased tidal volume, a decreased ventilatory response to CO₂ and an irregular respiratory pattern. The most clearly demonstrable change in the patients with symptomatic respiratory dysfunction was the marked reduction of minute ventilation in response to CO₂ brought about by a major decrease in tidal volume and an inadequate compensatory increase in respiratory rate. The results of these two clinical studies correlate quite well with the experimental data.

Conclusions

Clinical and experimental evidence supports the assumption that there are three separate identifiable patterns of respiratory dysfunction. There is a group which involves efferent mechanisms where the vital capacity, as a measure of motor function, is decreased preferentially. This type usually includes phrenic paralysis and is the one we have not found. There is another group in which the CO₂ response is attenuated and the vital capacity is not affected. Significant chest wall or diaphragmatic weakness is not present. The third and most common group is a mixture of the first two, with a decrease in both the CO₂ response and vital capacity. These findings imply that the ascending tracts relaying the afferent impulses to the respiratory center are interrupted. The miscellaneous autonomic dysfunctions are thought to result from interruption of the descending reticulospinal tracts originating from the hypothalamus and the brain-stem reticular formation. Interruption of spinoreticular fibers must also be important since massive degeneration of collaterals to the reticular formation occurs after cervical cordotomy. The relatively high incidence of autonomic and respiratory changes occurring together suggests some relationship not clearly understood. The presence of large spinal cord lesions in the ventrolateral quadrant that prevent impulse transmission via collaterals is the most logical explanation.

References


Address reprint requests to: Abbott J. Krieger, M.D., Division of Neurological Surgery, New Jersey Medical School, 65 Bergen Street, Newark, New Jersey 07107.