Recent Advances in the Management of Chronic Airway Obstruction

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Recent advances in our understanding of the natural history of chronic airway obstruction have identified aspects of this process that may enhance the morbidity and mortality of patients with a progressive increase in airway resistance. These advances have helped us to be more specific in the investigation and quantitation of the disease in the pulmonary function laboratory and to be more precise in our therapeutic management. Experience has taught us that the most useful measurement with which to characterize the degree of disease and its rate of progression is the forced expired volume in one second (FEV₁). The comprehensive studies of Dr. Charles Fletcher in London have demonstrated that the single most important therapeutic factor is avoidance of all airway irritants.¹ The application of aggressive bronchial hygiene in patients with obstructive airways disease may produce an initial improvement in the FEV₁ but will not in itself alter the rate of decline in pulmonary function. As the degree of airway obstruction increases, a number of interrelated physiologic abnormalities develop including hypoxemia, hypercarbia, polycythemia, cor pulmonale, and eventually, acute or chronic respiratory failure. These abnormalities account for most of the morbidity in this condition and the majority of patients who develop them have a high degree of airway obstruction. It is not unusual, however, to see patients with a moderate degree of airway obstruction who also manifest these problems. The purpose of this paper is: (1) to review the relationship between a progressive increase in airway obstruction and the associated physiologic abnormalities, and (2) to discuss the therapeutic interventions that show promise of reducing the morbidity from these accelerated physiologic abnormalities.

Hypercarbia and Airway Obstruction

In order to identify those patients whose clinical condition is significantly worse than anticipated from their level of airway disease, we need a readily applicable laboratory marker such as the elevated arterial carbon dioxide tension (PaCO₂). Several years ago, the relationship between airway obstruction characterized by the FEV₁ and the PaCO₂ was investigated.² It was noted that when the FEV₁ was 1500 cc or greater, the PaCO₂ was normal (PaCO₂ < 44 mm Hg). When the FEV₁ fell below one liter, the patient was as likely to have an elevated PaCO₂ as he was to have a normal PaCO₂, and when the FEV₁ was 500 cc or less, the PaCO₂ was almost always in excess of 44 mm Hg. Hypercarbia has been identified as an adaptive response in those patients who must balance the increased work of breathing against adequate carbon dioxide clearance and, indeed, this may be true in patients with severe airways disease. Such a state, however, has two major disadvantages; increased arterial hypoxemia and promotion of metabolic alkalosis, which contribute to a cycle of events that leads to premature metabolic deterioration. We have identified patients with moderate obstructive airway disease whose hypercarbia, previously attributed to the

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airway disease, was in fact, related to conditions amenable to medical management. Furthermore, there are patients who have severe obstructive airway disease whose hypercarbia is made worse by these same factors. These conditions include respiratory disturbances during sleep, metabolic alkalosis, and respiratory muscle weakness.

**Respiratory Alterations During Sleep**

Recent studies using an ear oximeter have clearly demonstrated that gas exchange is not stable from moment to moment during the day and that a single arterial puncture is not satisfactory to describe an individual’s blood gas composition, particularly during exercise and during sleep. Healthy adults develop periodic breathing during light sleep with an overall reduction in minute ventilation of one to two liters. Rapid eye movement (REM) sleep may include apneas of 15 to 20 seconds in normal individuals. Accompanying these episodes, there is an elevation in \( \text{PaCO}_2 \) of 4 to 8 mm Hg and a reduction in arterial oxygen tension (\( \text{PaO}_2 \)) of 3 to 10 mm Hg. In patients with chronic obstructive airway disease, similar fluctuations are found but with more profound blood gas disturbances that are not directly related to the degree of respiratory impairment when awake. There are three major abnormalities of respiration that may occur during sleep. These are (1) hypventilation, (2) central apnea, and (3) obstructive apnea. Patients with chronic airway obstruction may suffer from any of these entities; however, the two former problems are far more common than obstructive apnea. Episodes of hypoventilation causing hypoxemia and hypercapnia are usually brief but have been reported to last up to one hour. Alterations in chest wall mechanics and airway tone during REM sleep may increase these episodes. Normal, brief central apneas may be prolonged by alterations in the ventilatory control of the central nervous system. An increase in hypoxic drive produces a Cheyne-Stokes breathing pattern. Depression of either the hypoxic or hypercapnic drives may prolong the apneic spells.

Spells of nocturnal hypoxemia have been demonstrated to cause episodic pulmonary arterial hypertension, fluid retention, and polycythemia. It has been suggested that recurrent arterial hypoxemia during sleep produces a sustained elevation of the pulmonary arterial pressure and cor pulmonale. A major factor contributing to the prolongation of these episodes of hypoxemia is the depression of the central ventilatory response to hypercarbia. As the \( \text{PaCO}_2 \) rises, respiratory acidosis develops and repeated and prolonged bouts of acidosis stimulate a compensatory metabolic alkalosis. This renal adjustment to hypercarbia is a "compromised adaptation" in which the respiratory acidosis is buffered by an increase in serum and extracellular bicarbonate, but this elevated bicarbonate in turn promotes a readjustment of the respiratory control mechanism favoring perpetuation of the hypercapnic state. This effect of an elevated serum bicarbonate on the respiratory control mechanism has been demonstrated in patients with and without respiratory compromise. Nocturnal hypercapnia in a patient with modest airway disease may initiate progressive elevation of the serum bicarbonate which in turn will alter the respiratory control of the central nervous system and lead to a sustained elevation of arterial carbon dioxide tension during the waking hours. Furthermore, such an alteration prolongs the nocturnal apneic spells increasing both the arterial hypoxemia and hypercapnia.

This unfortunate situation may be magnified by the administration of chloride-depleting diuretics that are often given for fluid retention. Clinical experience has impressed upon us the fact that patients with moderate-to-profound arterial hypoxemia respond poorly to large doses of diuretics until their arterial oxygenation has been improved, which alone is often sufficient to promote a diuresis. The interrelationships among these abnormalities that occur during sleep are shown in Figure 1. There are several points in this cycle in which the physician may intervene. The most quickly reversible problem is diuretic-induced alkalosis. When we encounter a patient with a marked elevation in serum bicarbonate who has been on chloride-depleting diuretics, we discontinue the diuretic therapy and treat the patient with either a carbonic anhydrase inhibitor such as acetazolamide or by the administration of ammonium chloride. The effect of reducing the serum bicarbonate in a group of patients with severe obstructive lung disease whose metabolic alkalosis was in excess of that appropriate for the arterial carbon dioxide tension has been reported. In these patients diuretic therapy was discontinued and
METABOLIC ALKALOSIS

ACIDOSIS

CHLORIDE DEPLETING DIURETICS

DEPRESSED CENTRAL RESPIRATORY DRIVE

\[ \text{P.A.P.} \]

FLUID RETENTION

HYPOVENTILATION

HYPERCARBIA

HYPOXEMIA

SLEEP

Fig 1—Abnormalities of gas exchange during sleep.

acetazolamide 500 to 750 mg/day in divided doses or ammonium chloride 3 to 6 gm/day in divided doses was administered until the serum bicarbonate, \( \text{PaCO}_2 \) and arterial pH stabilized. The effect of this therapy on the arterial blood gas composition of 11 patients is summarized in Table 1.

Following the line of reasoning that a central control mechanism may be abnormal in patients with prolonged nocturnal hypoventilation, a number of physicians in this field have been investigating the use of medroxyprogesterone. This agent has been used in an attempt to increase minute ventilation in a variety of pulmonary problems with variable success. The most striking benefit seems to occur in those patients whose apneic spells are limited to hypoventilation on a central basis. Impressive improvement in arterial blood gas composition has been reported in patients with obesity hypoventilation\(^5\) and chronic airway obstruction.\(^6\) While correction of metabolic alkalosis and the use of progesterone can be of significant benefit to these patients, the administration of low-flow oxygen during sleep may be a necessary addition, especially for patients whose \( \text{PaO}_2 \) when awake is less than 60 mm Hg. The effect of nocturnal ox-

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>BEFORE CORRECTION</th>
<th>AFTER CORRECTION</th>
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<tbody>
<tr>
<td>( \text{HCO}_3^- ) mmol/L</td>
<td>36.9 ± 1.7</td>
<td>28.1 ± 1.0</td>
</tr>
<tr>
<td>( \text{PaCO}_2 ) torr</td>
<td>60.8 ± 2.6</td>
<td>47.6 ± 2.2</td>
</tr>
<tr>
<td>( \text{PaO}_2 ) torr</td>
<td>52.4 ± 3.1</td>
<td>69.1 ± 2.1</td>
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MATHERS: CHRONIC AIRWAY OBSTRUCTION / 93
TABLE 2
Hypoxemia During Sleep in 10 Patients with C.O.A.D. on Room Air and Supplemental O₂

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>Asleep</th>
<th>Change</th>
<th>Awake</th>
<th>Asleep</th>
<th>Change</th>
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</thead>
<tbody>
<tr>
<td>Mean S.Ø</td>
<td>95</td>
<td>68</td>
<td>-26</td>
<td>97</td>
<td>86</td>
<td>-11</td>
</tr>
<tr>
<td>S.D.</td>
<td>4</td>
<td>12</td>
<td>11</td>
<td>2</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
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Oxygen therapy has been described in a group of patients with moderate airway obstruction (Table 2). The data here are in terms of arterial oxygen saturation (S, O₂) and not PaO₂. The mean waking arterial oxygen saturation was 95% while the mean sleep saturation was 68% (a value associated with pulmonary arterial hypertension and polycythemia). The administration of low-flow oxygen to this group of patients significantly improved the oxygenation during sleep.

Abnormalities of ventilation during sleep remains a fertile field for investigation and the application of therapeutic modalities. We at the Medical College of Virginia are most interested in the documentation of breathing disturbances during sleep in patients believed to have accelerated physiologic deterioration. In conjunction with the Department of Neurology, we have developed a Sleep Study Center in which the presence of episodes of hypoventilation, central apnea or obstructive apnea may be readily determined and correlated with the stage of sleep. It is believed that after careful documentation of these abnormalities and the application of appropriate therapy, we may significantly reduce the morbidity that develops in the group of patients with moderate airway obstruction and premature carbon dioxide retention.

Respiratory Muscle Weakness

A great deal has been learned about the function of the respiratory muscles in recent years. The ability of patients with obstructive airways disease to sustain ventilation and avoid hypercapnic respiratory failure depends upon the strength and endurance of the respiratory muscles. The major causes of muscle failure in obstructive airways disease are (1) hyperinflation of the lung, (2) increase in airway resistance increasing the work of breathing, and (3) generalized muscle weakness. The development of respiratory muscle failure may be divided into two phases; muscle hypertrophy and muscle atrophy.

In the early stages of airway obstruction,
hyperinflation of the lung pushes down on the diaphragm shortening its resting length; as the muscle is progressively shortened, the ability to develop contractile force is reduced. At the same time, the increase in airway resistance and the increase in required minute ventilation increase the demands on this compromised muscle. In this early stage, it appears that there is hypertrophy of the diaphragmatic muscle. As the disease progresses, some patients begin to lose weight, most frequently because of inadequate diet, or an inability to eat a complete meal because of dyspnea. These patients develop a negative nitrogen balance and their loss in general muscle mass is shared by the diaphragm, to the point of producing hypercapnic respiratory insufficiency. In the Pulmonary Function Laboratory we test inspiratory and expiratory muscle strength with a pressure manometer but the presence of this problem can often be suspected during the physical examination by noting generalized muscle tone, evidence of recent weight loss and asynchronous breathing. Asynchronous breathing develops when the diaphragm becomes so weak that it no longer acts as an inspiratory muscle with depression of the abdominal contents and protrusion of the abdomen during inspiration. Instead, it becomes passive and is sucked up into the chest when the accessory muscles of inspiration are called into play causing retraction of the abdomen during inspiration. The events leading to this condition are seen in Figure 2.

There are a number of points of therapeutic intervention. The increased airway resistance may be treated with bronchodilators and aggressive airway hygiene to mobilize secretions. Hypoxemia may be reversed with supplemental oxygen, and malnutrition may be treated by ensuring an adequate diet. Frequently, several small feedings, high in protein content, are necessary in patients who become dyspneic during eating. Two other forms of therapy are currently under investigation and may add significantly to our management of these patients. One is breathing training and exercise programs; the other is the use of intermittent mechanical support. The former may be useful in those patients whose condition is caused by purely mechanical factors while the latter is reserved for those who have developed evidence of diaphragmatic atrophy. When a patient with evidence of marked muscle weakness is placed on either positive pressure ventilation or in the tank respirator, there is a marked decrease in inspiratory muscle contractile effort and relief of dyspnea. Many physicians now feel that periodic rest for this overworked muscle combined with an adequate diet will improve the patient's ability to sustain ventilation. Patients with this problem are currently being managed at home with Drinker-type tank respirators in which they may sleep or spend several hours per day. The initial result of this therapy has been a marked reduction in the amount of hospitalization these patients require.

In summary then, there are a number of factors, previously often unnoticed, that complicate the clinical picture of chronic obstructive airway disease. With the recent advances in our knowledge and diagnostic techniques, we may more precisely define patients whose deterioration is premature. Premature deterioration may be suspected when the PaCO\textsubscript{2} is elevated in an individual whose FEV\textsubscript{1} is in excess of 800 cc and who is able to reduce the PaCO\textsubscript{2} with voluntary hyperventilation. The presence of sleep abnormalities, metabolic alkalosis or muscle weakness may then be confirmed by further investigation as outlined in Table 3. Appropriate therapeutic intervention may produce significant improvement in the patient's condition and reduce the frequency of hospitalization.

Table 1 is adapted by permission from the Canadian Medical Association Journal (117:900–903, 1977).
Table 2 is adapted by permission from Annals of Internal Medicine (86:725–730, 1977).
REFERENCES


