Reversing the Irreversible

Some aspects of the therapy of chronic airflow obstruction (CAO), have become fairly routine. When the diagnosis is made, the patient will almost always be given a bronchodilator drug as a part of the therapeutic program, usually a theophylline of some kind. Once begun, the drug will frequently be continued indefinitely. As the patient’s dyspnea worsens, the dose of the theophylline will often be adjusted to provide what is considered to be an optimum blood level and oral β2 agonists are sometimes added to the therapeutic program in an attempt to maximize the patient’s remaining pulmonary function.

Unfortunately, this approach may not be completely justified. Most of the data indicating the value of bronchodilators on airflow obstruction have been developed from studies with patients who have reversible airway obstruction, usually idiopathic bronchial asthma. The value of the bronchodilator drugs in CAO has not been well documented since well-controlled clinical trials of this class of therapeutic agent in CAO are remarkably few. As a result, therapy with this class of drugs has been based largely upon the assumption that if there is a reversible component among the factors that produce increased airway resistance in patients with CAO, bronchodilator drugs such as theophylline may provide the patient with relief of dyspnea, the patient’s most disabling symptom. The FDA-approved package insert, for example, states that theophylline may be useful for the treatment of a reversible component in bronchitis and emphysema.

The advice of the package insert needs to be emphasized. There is a limited amount of data that indicate a large majority of patients who have CAO do not benefit from therapy with theophylline, the bronchodilator drug most commonly used in CAO.

In this issue of Chest, Eaton et al (see page 538) report that neither high nor low-dose theophylline therapy improved exercise tolerance or perceived breathlessness in patients with CAO, and the drug had only a relatively minor effect on FVC or FEV1.

A mean improvement in the FEV1 of less than 15 percent was observed during therapy with theophylline, but this was not reflected in exercise performance or in the perception of dyspnea by the patients. Since all the patients had baseline FEV1 of less than 1.2 L (mean FEV1, 0.74 L), it may be worthwhile to reflect if an increase of less than 150 ml in this group of severely impaired individuals is clinically important.

A study in a similar group of patients by our group had the same result.1 In this trial, 30 days of therapy with optimum doses of theophylline also produced a significant increase in forced expiratory flow rates. The FEV1 improved about 15 percent during theophylline therapy as compared to the value obtained during use of a placebo. Despite this improvement in observed FEV1 during theophylline therapy, there was no significant difference in symptoms such as dyspnea, wheezing, exercise tolerance, or how the patient felt. While there were small but significant changes in objective parameters such as air flow, these changes were not reflected in the patients’ perception of their symptoms. In another study, Eaton et al observed the effects of single-dose theophylline therapy on pulmonary function in patients with CAO and found results similar to those reported here.

In their most recent study, in this issue, Eaton et al have identified a subgroup of patients who seemed to have a greater than average objective response in their flow rates when given theophylline.

We have also observed a similar responder subgroup among patients we have studied in roughly the same proportion as Eaton et al, about one patient in five.

Further evaluation of our data indicated it was usually possible to identify these potential theophylline responders by the widespread but previously undocumented practice of noting the effect of an inhaled bronchodilator on expiratory flow rates. As has been suspected, those patients with CAO who responded to inhaled bronchodilators also had a much better than average response to theophylline therapy. As a result, based on the data available, it seems that only a small proportion of patients with CAO responded to theophylline and they can often be identified.

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Where does this leave us? It may be time to thoughtfully reevaluate our therapeutic approach to CAO, specifically to the almost universal practice of prescribing theophylline for these individuals without documenting improvement. Unless there is evidence of response, either by screening with an inhaled bronchodilator or by a therapeutic trial with theophylline, monitored with appropriate pulmonary function testing or both, the drug should not be prescribed routinely to patients with CAO. Selective use of this drug in only those instances where a positive objective or subjective response can be discerned should be encouraged and would reduce the cost, trouble, and potential toxicity of theophylline therapy.

What about the other oral bronchodilator drugs such as terbutaline? There are no data concerning the usefulness of these drugs in CAO that has come to our attention. It seems reasonable that until there is evidence terbutaline has objective beneficial effect in patients with CAO, enthusiasm for its use should be restrained and it should be used in the way we have proposed for theophylline, only when benefit can be measured.

Lastly, there is no substantial evidence of the usefulness of theophylline or other bronchodilator drugs during an acute exacerbation of bronchitis in patients with CAO or in respiratory failure, but it should be recognized that these conditions may be a special problem. All studies which indicate that theophyllines have only limited usefulness in CAO have been done with patients who are clinically stable. Reflecting on the complications that can occur during acute bronchitis or in respiratory failure in patients who have CAO, physicians should continue to use theophylline in these patients until there is or is not acceptable evidence of its usefulness. Eaton et al have reminded us that theophylline has many pharmacologic effects beyond bronchodilation, including respiratory stimulation, increased cardiac output, and increased muscle strength which might be useful in certain instances, such as in a period of acute respiratory decompensation.

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REFERENCES

1 Alexander MR, Dull WL, Kasik JE. Treatment of chronic obstructive pulmonary disease with orally administered theophylline. JAMA 1980; 244:2286-90

The Jack Spratt Connection

Mr. Spratt of nursery rhyme fame is usually pictured with a long neck, drooping shoulders and a large Adam's apple. Such physiognomy virtually precludes the presence of severe emphysema, but one wonders... did Jack know something we're just now discovering? The links between nutrition and chronic obstructive lung disease are being busily re-explored. Thus far, at least three have been proposed: 1) the slow wasting that characterizes the terminal stages of this disease; 2) the effects of superimposed acute respiratory failure on respiratory muscle metabolites; and (3) the relationship between our old friend the respiratory quotient (RQ) and blood gases. These factors are all probably interrelated.

We have known since at least the 19th century that emaciation accompanies advanced emphysema. It is now clear that this relationship is not a simple cause and effect, and that the old explanations of flat diaphragm, gastric distention and the dyspnea of eating no longer suffice. Some patients who lose weight eat more than they should. Underweight patients are sometimes eucapnic, despite having blunted $O_2$ and $CO_2$ drives and testosterone levels closer to normal than their hypercapnic peers. In some patients, weight loss does not reflect their degree of airway obstruction.

However, poor intake is associated with prognosis—patients die sooner when they have lost weight. In this issue of Chest (see page 506), Driver et al demonstrate that patients who entered the hospital with sufficient failure to require mechanical ventilation had significantly lower body weights, muscle size and visceral proteins than patients who did not require mechanical ventilation. A number of studies have demonstrated a similar association in ambulatory patients. We now know that the sudden appearance of respiratory failure superimposed on chronic respiratory insufficiency does terrible things to nutrition and metabolism. Both respiratory and limb muscles are depleted of their metabolites, apparently reversibly. The link between muscle metabolites and muscle fatigue is debated; the links between nutrition and muscle failure are unknown. The body's wisdom induces it to burn muscle protein during food deprivation. The intriguing observation that severe starvation appears to pre-