Session 9

Management of COPD
State of the Art

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I am pleased that this conference is ending on a clinical note. This helps us focus on what I consider to be the major goals of research in this area—that is, (1) improve the care of patients with COPD and (2) prevent the development of COPD.

I plan to present this state-of-the-art review from the point of view of a clinician who is an expert in none of the specific areas covered (eg, bronchial hyperreactivity, respiratory muscles, sleep abnormalities, control of breathing), but who has to assimilate the aspects with therapeutic potential and make decisions regarding application of this information to the individual patient with COPD. I will point out what I think are important changes or new information in the last several years. This may be a provincial view in some areas—especially drug therapy—in that what is new in the United States may have been available for 10-20 years in other parts of the world. In general, the disease processes making up COPD are relatively difficult to study. I will build on the theme that the pulmonary community has done a commendable job, especially of critically reviewing the more expensive forms of generally accepted therapy. Although no major breakthroughs in therapy have occurred, steady progress has been made. It struck me while listening to Whitney Thurlbeck's excellent state-of-the-art review on morphology and clinical morphologic correlations that, at the risk of oversimplification, much of the research presented at this meeting could be divided into two areas. The first encompasses those studies, whether basic or clinical, which explore the concepts of pathogenesis and mechanisms of disease. I think that most of us would agree that these studies are most important in part because they will result in the development of new forms of treatment. The second area involves critical evaluation of what we already do. The first area of study may lead to the development of concepts or theories which may provide the basis for new types of therapy. Sometimes these researches are employed without appropriate testing. Once therapy becomes common, clinical impressions result which may make this therapy very difficult to study but which also can be very wrong. A necessary final step on which the clinician or clinical investigator should insist is evidence from a well-designed study to answer the question "Does it work?" I will be stressing this second area of investigation—wherever these data are available.

Smoking Cessation

An appropriate place to begin a clinical review of management of COPD is smoking cessation. Since smoking is identified as the major cause of COPD, it seems logical that if cigarette smoking is avoided or if a subject stops smoking early, the disease can be prevented. An important question concerns the effect of smoking cessation on the disease course if disease is already present. The data major in this area are from Charles Fletcher et al in longitudinal studies which suggest that if mild but definite abnormalities of airflow obstruction (on the basis of a reduced FEV1) are identified in the group which stopped smoking, though not returning to the mean values of FEV1 for the population who never smoked, would return to the expected decrease in pulmonary function of nonsmokers as opposed to the progressive more rapid deterioration in lung function in those who continue to smoke. I have heard these data criticized at a previous Aspen Lung Conference on the basis of the statistical methods employed. I accept that criticism in that these methods are beyond my expertise, but I also believe that until this possibility is definitely disproved it is reasonable to operate on the possibility that smoking cessation may lead to less progression of airflow obstruction. Therefore, these data allow a logical basis for practical action in encouraging patients with mild-to-moderate airflow obstruction to stop smoking.

Clearly more work is needed in the methods of smoking cessation, primarily in the area of behavior modification. One new element soon to be available in the United States is nicotine chewing gum which can be slowly withdrawn in subjects in whom an element of nicotine addiction is suspected. I have no experience in this area, but based upon thorough review of the existing data by colleagues, it appears that nicotine addiction may play a role in a minority of patients and this may prove to be a helpful adjunct in this subset of smokers.

Another important question is what should the physician's role be in smoking cessation. Surveys of exsmokers indicate that a major influence in the decision to stop smoking was the advice of their physician. I interpret this as placing a considerable responsibility on the physician to clearly encourage the patient to stop smoking and to support them in that effort in any way possible. At the same time, I firmly believe that the patient who is unable to quit smoking should receive the same level of medical care from the physician as any other patient.

Bronchial Reactivity

This conference has helped me place bronchial reactivity in COPD patients in more appropriate perspective, although several unanswered questions of clinical relevance remain. Ramsdell et al studied 22 subjects with chronic bronchitis and airflow obstruction with methacholine bronchial provocation tests to evaluate the incidence of bronchial hyperactivity. All patients were very sensitive to inhaled methacholine, and no normal responses were seen. Ann Woolcock et al presented similar data from an epidemiologic study in Australia in which all of the subjects studied who had existing airflow obstruction had a positive histamine challenge test. The total clinical relevance is not yet clear but these data certainly suggest the possibility of airway responsiveness in patients with COPD even when there is no response on testing to a single dose of inhaled β-adrenergic bronchodilator.

Semantics continue to raise problems in the area of bron-
cholinergic bronchodilator treatment of the COPD patient. I would emphasize to the clinician that it is less important what a reversible element is called than identifying and treating that reversible component. Let us not allow semantic difficulties to confuse us to the extent that they impair therapy. It is a common impression that a small but clinically important reversible component is frequently seen in COPD patients. This component may be called asthma, but several studies suggest that it is impossible to identify and separate these patients from those without bronchodilator responsiveness on usual clinical grounds short of an empiric bronchodilator trial. So the art lies in deciding when and how to perform a therapeutic trial. I believe that any patient with significant symptoms including dyspnea resulting from airflow obstruction should receive a trial of theophylline and β-adrenergic bronchodilators and that, as the disease worsens, trials of anti-cholinergic agents and corticosteroids should be added. My own practice is to accept a subjective response to β-adrenergic and theophylline drugs, since I consider them to be relatively safe, but to insist on objective response for others because of either the potential of increased side effects or the expense of administering the medication.

Keep in mind that the lack of a β-adrenergic response may or may not predict responsiveness of other drugs. Marini and Lakshminarayan have shown that patients not responsive to inhaled bronchodilator may be very responsive to inhaled atropine. On the other hand, Dull and coworkers have demonstrated that the response to inhaled β-adrenergic drugs did predict responsiveness to theophylline with a sensitivity and specificity of 75% and 96%, respectively.

While I review advances in bronchodilator use in the United States, I hope our international guests will indulge my provincialism while silently gloating. New β-adrenergic drugs (metaproterenol, terbutaline, albuterol) have become available which are both more β2-selective and longer-acting. Since the inhaled route of bronchodilator use already confers a significant β2-selectivity, and since the oral administration is often limited by muscle tremor, which is a β2 effect, in many ways the longer duration of action of these newer drugs is the more important advance.

Much new information regarding theophylline drugs has become available in the past 10 years, particularly information on the important issue of attempting to choose the correct dose for any given patient. These advances are generally known to clinicians. I would mainly like to issue a word of caution in the face of these advances that a wide range of theophylline levels still is achieved for any given dose because of the many variables involved including liver function and drug-drug interactions. Also in sick patients the blood level achieved by any given dose is less predictable because of the increase in the number of variables affecting this.

At this meeting we have heard the latest in a series of elegant studies by Aubier and co-workers that aminophylline improves diaphragmatic contractility. Previously this was demonstrated in an animal model and in normal subjects, and during this meeting data were presented that diaphragmatic contractility in patients with COPD was improved with aminophylline administration. This is exciting information and may justify administration of theophylline drugs even when an acute bronchodilator effect cannot be demonstrated.

Atropine as a bronchodilator is making a comeback in the United States, but judging from information presented at this meeting, has evidently never left the Netherlands as well as other countries. Klock et al from Renzetti’s group had suggested in 1975 that atropine may have an even more important bronchodilator effect in COPD patients than in asthmatics. Marini and Lakshminarayan demonstrated that of 15 COPD patients who did not show a 15% improvement following inhalation of isoproterenol did have a 15% or greater increase in FEV1 following inhaled atropine. Even more striking was the fact that 6 of these subjects demonstrated more than 25% improvement and some greater than 40%. Marini and Lakshminarayan then went on to establish a dose-response curve of inhaled atropine in adult patients (Fig 1) which was similar to that previously established for children by Cavanaugh and Cooper. Based upon this dose-response curve, it is a practice in our institution to begin inhaled atropine at a dose of .02 mg/kg body weight. We select subjects who still have considerable airflow obstruction despite β-adrenergics and theophylline ± corticosteroids. Because at the present time atropine must be given as a solution with a compressor driven nebulizer, raising both the expense and hassle of administration, we currently test all candidates in the pulmonary function laboratory to determine whether an objective response is obtained. The average duration of effect is approximately 4 hours using an inhaled solution of atropine sulfate. In the near future ipratropium will be available in a metered-dose inhaler.

New data are available in the last several years on the use of corticosteroids in patients with COPD. Albert et al in a nicely designed study of patients with COPD and acute respiratory failure, demonstrated that subjects receiving corticosteroids in a dose of 0.5 mg/kg of body weight every 6 hours IV had significantly greater improvement in FEV1 compared to control subjects receiving placebo but with other therapy being similar (Fig 2). In this study patients who would usually be considered to have asthma were excluded as carefully as can be done on a clinical basis.
Two studies are now available demonstrating the efficacy of corticosteroids in outpatients with COPD. Shim et al., in a double-blind crossover study, demonstrated a significant improvement in FEV₁ with 30 mg of prednisone daily compared to placebo control. There was no relation of improvement in airflow obstruction to total eosinophil count; however, there was a positive relationship between improvement in pulmonary function and sputum eosinophils. Mendella et al. from Antochsen's group in Winnipeg also showed a beneficial response to steroids in some patients. This study clearly demonstrated the importance of a placebo control in studies of pulmonary function in COPD patients in that many patients had a 10 to 15% improvement with placebo (Fig 3). However, a number of patients had a significantly greater improvement with prednisone treatment. This steroid responsiveness was predicted in part by the response to a β-adrenergic agent in that none of the responders had less than a 10% increase to inhaled isoproterenol. There was no relationship in this study between response to steroids and either blood or sputum eosinophils.

INFECTION

No new evidence has been developed demonstrating a beneficial role of antibiotics in the treatment of patients with COPD and an acute exacerbation of bronchitis. Most of the existing studies have limitations in study design which limit the interpretation of both positive and negative results. Antibiotics are still used widely by clinicians in patients with an acute exacerbation probably because of some evidence that they may shorten the exacerbation but primarily because they are relatively inexpensive and relatively safe if used with appropriate caution. Use of influenza vaccine in patients with COPD is recommended by the CDC. Pneumococcal vaccine is also now available and has also been recommended, although no firm data in COPD patients have been available prior to this conference. Ann Logan Davis et al. presented much-needed information regarding the immunologic effectiveness of the pneumococcal vaccine in subjects with COPD.

HOME OXYGEN THERAPY

Our use of home oxygen therapy is being influenced by data from two major trials. The British Medical Research Council study evaluating oxygen for at least 15 hours per day vs no oxygen and the Nocturnal Oxygen Therapy Trial sponsored by the National Heart, Lung, and Blood Institute studying 12 vs 24 hours per day of oxygen. Taken together these two studies provide important new information. The BMRC study entry criteria included severe airflow obstruction, a PaO₂ of 40–60 mm Hg, and evidence of cor pulmonale. Men receiving oxygen showed increased survival after 500 days of therapy as compared to control subjects receiving no oxygen. The benefit was even more striking in women and was evident at all time points studied. The NOTT study entry criteria were similar, but cor pulmonale was not necessary. Subjects had to have a PaO₂ of less than 55 mm Hg or less than 60 mm Hg if clinical cor pulmonale was present. An increase in survival was demonstrated in the continuous oxygen patients as compared to the nocturnal oxygen group. Results from the two studies are shown in Figure 4. One surprise from the NOTT study was that cor pulmonale was not one of the variables which correlated with increased survival. This has resulted in changing our criteria of selection of patients.
for continuous home $O_2$. Previously we limited oxygen therapy to patients who not only demonstrated hypoxemia on arterial blood gas, but also had some evidence of deleterious end-organ response to that hypoxemia, the most common being some evidence of cor pulmonale. However, from the NOTT study, continuous oxygen appears to be indicated simply with the presence of hypoxemia defined as a PaO$_2$ of less than 55 mm Hg during clinical stability.

The NOTT study also provided information useful to the clinician in selecting candidates for home oxygen therapy. Their criteria specified that the patient have a resting PaO$_2$ of 55 mm Hg or less once the patient was considered clinically stable for one month. Forty-five% of hypoxemic patients identified as candidates for outpatient oxygen therapy had improvement in their PaO$_2$ to 60 mm Hg or greater during one month of stable outpatient observation. This suggests that patients discharged from the hospital with a PaO$_2$ of 55 mm Hg or less are not necessarily candidates for home oxygen and should be observed for one month while stable outpatients. This study also found that 97% of patients with stable clinical status had a resting PaO$_2$ of greater than 40 mm Hg; if the PaO$_2$ is lower than 40 mm Hg, the clinician should question whether the patient is truly stable or whether COPD is the only cause for hypoxemia. Of the patients started on oxygen, nasal prong oxygen flow rates from 1–3 L/min were adequate to provide a resting PaO$_2$ between 60 and 80 mm Hg. If a resting flow rate of greater than 3 L/min is required, again the clinician should consider whether the patient's condition is truly stable, whether the oxygen delivery system is faulty, or whether some other type of cardiopulmonary disease exists and contributes to the hypoxemia.

Pharmacologic therapy other than oxygen for pulmonary hypertension and cor pulmonale has been disappointing in terms of widespread clinical applicability. A paper reports a reduction in pulmonary artery pressure at comparable cardiac outputs with nifedipine in patients with COPD and pulmonary hypertension. Again, the clinical usefulness of this information remains to be proven.

**Use of Drugs Affecting Ventilatory Drive**

In this section I will review some interesting new information involving drugs which affect ventilatory drive, both stimulating and depressing drives. I group these studies together under this heading for purposes of simplicity and classification. However, it is not at all clear that the major effects I will describe are actually due to effects on ventilatory drive; in fact, some of the data contradict this notion. I would place these studies in the area of interesting new ideas which need further investigation before they should be applied clinically. Progesterone has been used therapeutically as a respiratory stimulant and has been shown to increase alveolar ventilation and lower PaCO$_2$ in patients with obesity-hyperventilation syndrome. It has also been used with variable effects in patients with COPD. Skatrud and co-workers, in a study designed to investigate the physiologic determinants of chronic CO$_2$ retention as well as the chronic effect of medroxyprogesterone on ventilatory drive and acid-base status, studied 17 patients with chronic CO$_2$ retention of...
whom 14 had COPD. Four weeks of medroxyprogesterone caused “correction” of PaCO₂ in 10 of these 17 patients with a mean decrease in PaCO₂ from 51 to 42 mm Hg. As expected, the correctors had a greater increase in alveolar ventilation than did the noncorrectors. However, both groups had an increase in P_{a1}, suggesting that ventilatory drive increased in both groups. In addition, Neil Pride at this conference has shown us that central drive is not depressed to account for hypercapnia in COPD patients. At any rate the study from Skatrud demonstrates that some patients with COPD and CO₂ retention may respond to chronic progestosterone therapy with improvement in arterial blood gases. In a related study, at this conference, Connaughton and coworkers⁴⁶ from the University of Edinburgh demonstrated effectiveness of oral almitrine on gas exchange and sleep hypoxemia in “blue and bloated” COPD.

In another paper, Woodcock and coworkers⁴⁷ used a drug with a depressive effect on central ventilatory drives, dihydrocodeine, in patients with severe breathlessness with the rationale that codeine would reduce breathlessness by reducing the ventilatory drive to CO₂, hypoxia, inspiratory flow resistive loading, and exercise. Oral dihydrocodeine reduced breathlessness and increased exercise performance in these patients with severe airflow obstruction and normal or low PaCO₂ (Fig 5 and 6). This effect was probably not due to a simple reduction in ventilatory drive, since there was only a modest decrease in minute ventilation, but a greater relative decrease in oxygen consumption. This study certainly raises the possibility that opiates may be useful therapy for the treatment of breathlessness in selected patients in whom life is made miserable by their severe dyspnea. As these authors conclude, further evaluation is needed, particularly regarding long-term benefits and safety, since this was a short-term study. In addition, a preliminary single-blind study using a varying protocol in four patients with severe COPD and severe dyspnea suggested a beneficial effect of diazepam in moderate doses for the relief of dyspnea.³⁸

One of the dangers of these sorts of therapy that need to be evaluated in a chronic study is whether patients on ventilatory drive suppressants suffer adverse effects when they develop an acute exacerbation, for example, with acute bronchitis superimposed upon their COPD.

**Physical Measures**

Exercise training has previously been shown to increase exercise performance in COPD patients. Recent studies have demonstrated that resistive loading training of inspiratory muscles has resulted in increased respiratory muscle endurance⁴⁹,⁵⁰ and increased exercise performance.³⁰ Pardy and associates³¹ compared a regimen of inspiratory muscle training by inspiring continuously against a resistance for two 15-minute sessions daily to physical therapy with exercise training on a treadmill, cycle, stairs, and lifting small weights three times weekly. Results were measured at one and two months of these training regimens. Inspiratory muscle training was superior to this regimen of physiotherapy with improvement in both endurance time and in distance walked in 12 minutes. This resistive inspiratory muscle training regimen is a simple one which can be carried out as part of the home-based “rehabilitation” program. In contrast, Belman and associates,³⁸ in work presented at this meeting, found that ventilatory muscle training did not add to the functional (excluding improved exercise tolerance) and symptomatic benefits attained by a pulmonary rehabilitation program alone. However, whether ventilatory muscle training provided any benefit to these patients if they developed an acute exacerbation of COPD was not studied and remains a plausible hypothesis.

In addition to muscle training, respiratory muscle rest can be important in selected patients. Norma Braun⁴⁸ showed data at this conference suggesting a dramatic beneficial effect of periods of respiratory muscle rest in selected COPD patients using a method of ventilatory muscle resting which is practical for home use.

**Sleep Abnormalities in COPD**

The management aspects of sleep abnormalities in COPD, which has become an area of practical importance in the last several years, has been discussed in a separate state-of-the-art review at this meeting and will not be discussed further here.

**Psychosocial Aspects of Management**

There are still important aspects of “art” in the “state-of-the-art” management of COPD patients. Much of this deals with the psychosocial aspects of management, one of the most important areas of caring for the patient with severe COPD. A recent series of articles by Dudley et al⁴⁸ reviewed psychosocial aspects of treatment, covering therapy for both the anxiety and depression which are common in patients with severe COPD. Techniques for management of anxiety

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**Figure 6.** Change in distance walked until exhaustion. The distance walked at 45 minutes after a drink was compared with the baseline before the drink on the same day (from Woodcock et al, *N Engl J Med* 1981; 305:1611-16, by permission).
include breathing retraining, meditation, relaxation training, and biofeedback. In general, medications for anxiety are not helpful, and they may aggravate the psychologic problem. Exceptions to this are also reviewed. The treatment of depression involves helping the patient face his feelings of fear, anger, and sadness over his limitations and losses. Open discussion of death and dying in the later stages of the disease process in encouraged. Individual drug therapy is also reviewed. One generalization suggested by these authors is the greater the age and the more chronic the disease, the lower the dose of psychopharmacologic agent that should be employed.

REFERENCES


Nifedipine Reduces Pulmonary Artery Pressure at a Comparable Cardiac Output in Patients with Chronic Obstructive Pulmonary Disease and Pulmonary Hypertension*

A. Muramoto, M.D., F.C.C.P.; J. Caldwell, M.D.; B. Albert, M.D.; S. Lakshminarayan, M.D., F.C.C.P.; J. Butler, M.D.

Vasodilating medications have been shown to increase cardiac output (CO) and decrease pulmonary vascular resistance, but their effects on pulmonary artery pressure at a comparable cardiac output have not been well documented. This pilot study was designed to evaluate the effects of nifedipine on pulmonary artery pressure and flow at a comparable cardiac output in patients with chronic obstructive pulmonary disease and pulmonary hypertension. Nifedipine reduced pulmonary artery pressure at comparable cardiac outputs in patients with chronic obstructive pulmonary disease and pulmonary hypertension.

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