with increasing airway resistance, it is likely that the abnormal mechanics of ventilation affected left ventricular filling. Hooper and Whitcomb have also observed abnormal PEP/LVET ratios in COPD subjects with a marked reduction in the forced expiratory volume in one second.

What are the results of other approaches to the assessment of left ventricular function in COPD? The ejection fraction was normal in the patients studied by Unger et al. Although it was decreased in the subjects studied by Frank et al.,11 the left ventricular muscle performance was normal, when judged by a contractility index derived from isovolumetric contraction. Left ventricular function curves obtained during methoxamine infusion were usually normal.13 In contrast, curves derived during angiotensin infusion were interpreted as abnormal, but no age-matched control group was studied.17

Although the weight of evidence indicates normal left ventricular function in COPD, we cannot exclude minor alterations in left ventricular compliance until simultaneous measurements of left ventricular diastolic pressure and volume are available, nor should we overlook the occasional coexistence of COPD with another disease that typically causes left ventricular dysfunction.

In the absence of a clear history of left ventricular disease, the diagnosis of left ventricular dysfunction in COPD is probably best approached by the direct recording of LVEDP (which may require correction for intrathoracic pressure shifts), by the use of indices of isovolumetric contraction, and by the measurement of ejection fraction.

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The New Oral Bronchodilators

The treatment of reversible airway disease by the oral route has been dominated for years by theophylline and ephedrine preparations. Unfortunately, in the dosages usually formulated for these drugs, the bronchodilator is not always significant, nor is its duration sufficiently prolonged. Increasing dosages frequently led to toxic or undesirable effects, particularly in the gastrointestinal, cardiovascular, or central nervous systems; and as a result, we are witnessing a flourish of drug-combination prescriptions where various arrays of tranquilizers, "expectorants," "mucolytics," etc., are added to theophylline and/or ephedrine without, however, any material increase in the bronchodilator effects of the basic drugs.

Since the discovery of isoproterenol, a new breed of sympathomimetic bronchodilators was introduced for aerosol use with claims of specific action on β-adrenergic receptors. However, only recently have orally administered bronchodilators of this type become available; most notable among them are metaproterenol (oriprenaline), salbutamol (al-
buterol), and terbutaline. Of these, metaproterenol sulfate (Alupent; Metaprel) and terbutaline (Bricanyl) sulfate have been approved by the Food and Drug Administration for general clinical use in the United States. In this issue of Chest (see page 155), an excellent study by Tashkin et al offers additional proof of the efficacy of orally administered terbutaline.

This group of new bronchodilators stimulate the production of adenosine 3':5'-cyclic phosphate (cyclic AMP) by activation of the enzyme, adenyl cyclase. This raises the level of cyclic AMP in the mast cell which prevents the release of histamine and other mediators of anaphylaxis. In addition, stimulation of $\beta_2$-adrenergic receptors provides for a selective action on bronchial smooth muscle with minimal cardiac stimulation. This has been particularly evident in laboratory and clinical trials of terbutaline, but avoidance of cardiovascular effects is still dose-dependent.

Another undesirable side effect seen with many sympathomimetics, namely a decrease in arterial blood oxygen pressure, has not been reported with the use of $\beta_2$-adrenergic receptor stimulants. This further supports the contention that these new drugs do not increase the perfusion of underventilated lung areas, which is the mechanism responsible for the hypoxemia observed with other bronchodilators.

The newer agents seem to have minimal effects on the central nervous system, thus obviating the need for concomitant administration of sedatives, such as hydroxyzine or barbiturates. As with other sympathomimetic amines; however, patients may experience fine tremor of the limbs which apparently results from $\beta_2$-adrenergic receptor stimulation of skeletal muscle.

To be attractive, an orally administered bronchodilator must also demonstrate a long duration of action. This has been an outstanding feature of the $\beta_2$-adrenergic receptor agonists. In the experience of Tashkin et al and that of Dulfano and Glass, terbutaline given in oral doses of 2.5 and 5.0 mg induced a significant degree of bronchodilatation lasting up to six hours. Metabolic studies suggest that this may result from resistance to degradation by liver-$0$-methyltransferase. About 33 to 50 percent of this drug is absorbed following oral intake, and excretion of the drug and its metabolites is complete within 96 hours.

We are apparently entering a new period in the pharmacologic approach to reversible airway disease where we are able to manipulate molecular specificity to achieve $\beta_2$-adrenergic receptor agonism while excluding undesirable effects of adrenergic stimulation. It is also reasonable to expect that such products given orally will provide convenient and effective round-the-clock bronchodilatation without significant side effects.

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