Physiologic Effects of Oral Bronchodilators during Rest and Exercise in Chronic Obstructive Pulmonary Disease*

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At rest and during exercise, noninvasive studies of cardiopulmonary physiology in patients with chronic obstructive pulmonary disease (COPD) were carried out to determine the objective benefits of commonly used oral bronchodilator drugs in 15 stable patients without cardiovascular disease or reversible obstruction of airflow. Theophylline, terbutaline, a combination of theophylline and terbutaline, and placebo were given for ten days each in a randomly sequenced double-blind protocol for outpatients. Spirometric values, the ratio of physiologic dead space to tidal volume (Vdp/Vt), and the alveolar-arterial oxygen pressure difference (P[A-a]O2) were studied at rest on each regimen. During steady-state exercise the changes in Vdp/Vt and P(A-a)O2, as well as the ventilatory equivalent for oxygen and oxygen pulse, were measured. When compared with placebo, no significant change was noted in the previously mentioned measurements with any regimen, with the exception of a small improvement in the forced expiratory volume in one second, which was significant for all regimens. These findings suggest that commonly used oral bronchodilator drugs in usual doses may have small effects on airflow even in "irreversible" COPD but that the objective effect of these agents on gas exchange during rest and exercise is not significant.

Treatment of reversible disease of the airways with bronchodilator drugs is generally advocated because of subjective and objective improvement in the obstruction of the airways. A more difficult question arises in the patient with chronic obstructive pulmonary disease (COPD) without evidence of reversible disease of the airways. Various methods of selection of such patients with COPD for treatment with bronchodilator drugs have been proposed. Reports of improvement in cardiac function and reduction of pulmonary vascular resistance with parenterally administered aminophylline and terbutaline, along with supporting evidence from radionuclide studies of cardiac ejection fraction, suggest that there may be a role for such agents beyond the simple involvement of spirometric measurements of disease. These studies also suggest a possible role for these drugs in the improvement of cardiopulmonary function during exercise, which might translate into a patient's greater sense of well-being; however, the clinical applicability of the information from these studies to the ambulatory patient with irreversible obstruction of the airways is uncertain, since the information was obtained after parenteral administration of the drug, and in patients in whom reversible disease of the airways had not been rigidly excluded.

The purpose of our study was to evaluate cardiopulmonary physiology both at rest and with exercise in carefully selected patients with irreversible obstruction of the airways. The patients' responses to ordinary oral doses of bronchodilator drugs were compared to placebo in a double-blind crossover study and constitute the basis for this report.

**Materials and Methods**

Selection of Patients

Fifteen male veterans (aged 50 to 69 years) were studied; all were ambulatory stable outpatients with a clinical diagnosis of COPD. Their disease was graded as severe, each having a forced expiratory volume in one second (FEV1) less than 50 percent of his predicted value. Means (± SD) for spirometric values and blood gas levels were as follows: FEV1, 1.03 ± 0.34 L; forced vital capacity (FVC), 2.26 ± 0.58 L; mean forced expiratory flow during the middle half of the FVC (FEF25-75%), 0.43 ± 0.15 L/sec; arterial oxygen tension (PaO2), 69.1 ± 10.6 mm Hg; and arterial carbon dioxide tension (PaCO2), 44.3 ± 6.5 mm Hg. All patients had a smoking history of greater than 20 pack-years. All had been dyspneic for many years without a significant symptom-free interval, despite various therapeutic regimens including bronchodilators. No patient had evidence of cor pulmonale; none was receiving oxygen at home.

Criteria for exclusion are listed in the following tabulation (the presence of any of these factors disqualified the patient):

- Reversible Obstruction of Airflow:
  - History of bronchial asthma
  - History of episodic, acute wheezing dyspnea
  - Presence of greater than 5 percent eosinophils on peripheral blood smear

Following inhaled isoproterenol: improvement of FEV1 by

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more than 10 percent of the patient's predicted value or rise in FEV, to 50 percent of predicted
Primary Cardiovascular Disease:
Ventricular arrhythmia (ventricular extrasystoles paired, multifocal, or numbering more than 10/min)
Coronary arterial disease (history or angina or myocardial infarction; angiographically documented coronary occlusion)
Sustained systemic hypertension
Valvular heart disease (other than mild tricuspid regurgitation)
Evidence of left ventricular decompensation
Other Complicating Systemic Illness

Care was taken to define patients with an "asthmatic" component to their obstruction of airflow and to avoid those with evidence of cardiovascular disease.

Baseline Studies

After informed consent was obtained, all medications with cardiopulmonary effect were discontinued for 72 hours. History and physical examination, complete blood count and chemistry profile, serum theophylline level, spirometric studies, chest roentgenogram, and 24-hour ambulatory electrocardiogram were performed on the first day. On the second day an incremental exercise test was performed to exhaustion on equipment and in surroundings identical to those to be used in subsequent tests. The patient was placed in the supine position on a cycle ergometer (Collins), with the back and head elevated 30° to the horizontal. Four-lead electrocardiographic monitoring was continued throughout exercise.Expired air was collected directly into the mouthpiece of a metabolic measurement cart (Beckman) calibrated daily for both zero and upscale values for all measurements for analysis of the expired gas. Work load, oxygen consumption (\(\dot{V}O_2\)) carbon dioxide production (\(\dot{V}CO_2\)), heart rate (HR), respiratory rate, tidal volume (VT), minute ventilation (VE), actual respiratory quotient (RQ), and expired carbon dioxide fraction were recorded for each minute of exercise. The work load on the ergometer was increased each minute in increments of 50 kilopond-meters/min; this was continued, with careful supervision and encouragement of best effort, until the patient signaled exhaustion. The work load at which this occurred was recorded as maximal for that patient.

After an overnight rest the patient was exercised at a constant work load for six minutes. The work load used in each case was 60 percent of the maximal work load determined on the previous day and has been shown in such patients to represent a physiologic stress while allowing attainment of steady-state conditions.\(^{17}\) The measurements noted previously were recorded during each of the six minutes, thus confirming the presence of steady-state exercise; values from the last two minutes were averaged to serve as values during "exercise" for each measurement. Samples of arterial blood were obtained by radial arterial puncture at rest and during the last minute of steady-state exercise, thus allowing calculation at the actual RQ of the alveolararterial oxygen pressure difference (PA-aO\(_2\)) and the ratio of physiologic dead space to tidal volume (Vdp/VT), corrected for anatomic dead space (VdAN) and mechanical dead space (VdM) by the following standard equations:

\[
P(A-a)O_2 = (P_a - 47)FIO_2 - [(L/\text{RQ} \times P_aCO_2) - P_aCO_2]
\]

where \(P_a\) is barometric pressure and where \(FIO_2\) is the fractional concentration of oxygen in the inspired gas and equals 0.21 for room air.

The equation for Vdp corrected for VdAN and VdM is as follows:\(^{18}\)

\[
Vdp = Vd - \left(\frac{P_aCO_2 \times VT}{(P_aCO_2 VT - VdAN - VdM)}\right)^{19} \times VdM
\]

where \(P_aCO_2\) is the partial pressure of carbon dioxide in the expired air, \(VdAN\) equals 4.5 \(\times 10^{-3}\) height (cm),\(^{1,4}\) (from Wood et al\(^3\)), and \(Vd\) is the Bohr dead space and equals \((P_aCO_2 - P_aCO_2)P_aCO_2 \times VT\).

The equations for predicted maximal values during exercise are as follows:

\[
HR_{max} (\text{beats/min}) = 210 - 0.65 \times \text{age (yr)}^{14}
\]

\[
\dot{V}O_2\max (L/min) = 4.2 - 0.032 \times \text{age}^{15}
\]

\[
\dot{V}E_{max} (L/min) = 35 \times \text{FEV}_1 (L)^{19}
\]

Radial arterial puncture may not be ideal but has not been shown to introduce significant error. "Oxygen pulse" was obtained by dividing \(\dot{V}O_2\) (in mL/min) by the corresponding HR; the ventilatory equivalent for oxygen (\(\dot{V}E_{O_2}\)) was obtained by dividing \(\dot{V}E\) (in L/min) by \(\dot{V}O_2\) (in L/min).

Protocols for Medication

With baseline studies having been completed, the patient was discharged on one of four regimens of oral medication: (1) theophylline (Elixophylline), 200 mg four times daily; (2) terbutaline (Brethine), 5 mg three times daily; (3) a combination of theophylline (150 mg) plus terbutaline (2.5 mg), both four times daily; and (4) matched placebo. The regimens were assigned and coded in the pharmacy, randomly sequenced (to avoid any "training" effect), and double-blinded.

A printed "patient's log" was given and explained to the patient, wherein he was asked to record the date and time of each dose of medication, along with symptoms of shortness of breath or wheezing (severity graded subjectively from zero to three) recorded daily. A "symptom score" was later calculated for each of the two symptoms by averaging the daily scores over the period of medication.

Each regimen of medication was prescribed for ten days. The patient then returned to the hospital while receiving the medication and underwent repeat spirometric studies and measurement of the serum theophylline level. While still taking the medication, the patient performed another six-minute steady-state exercise test, at the same previously determined work load, and in the manner defined in the preceding section.

The patient was then sent to the pharmacy for the next regimen of medication in his sequence, to return ten days later to repeat the previously described testing, until he had completed testing on all four regimens of medication.

Analysis of Data

Measurement at rest and during the last two minutes of steady-state exercise were compared with placebo for each regimen. Student's \(t\)-test for paired data was used for comparison; a value for \(p\) less than 0.05 was considered significant.

RESULTS

Incremental Exercise Test to Maximal

Heart rate at maximal exercise reached an average of 109 ± 11 beats per minute (mean ± SD); this represented 64 ± 7 percent of the age-predicted maximum. The \(\dot{V}O_2\) at maximal exercise was 792 ± 173 mL/min, representing 34.7 ± 8.6 percent of the predicted maximum. The \(\dot{V}E\) at maximal exercise was 27.9 ± 6.6 L/min, which was 82 ± 25 percent of the predicted maximum.

Compliance with Medication

Patients' logs revealed excellent compliance with schedules for medication; no patient missed more than
three doses of any regimen of medication. This was confirmed by checking bottles of medication after the dosing interval. No patient withdrew from the study, and on only two occasions was it necessary to abort a regimen because of a patient's intolerance, once from theophylline and once from terbutaline. The code was not broken under any circumstances until completion of the entire study. "Peak" theophylline levels in eight patients receiving theophylline alone averaged 13.84 mg/L, ranging from 8.7 to 22.5 mg/L. Peak levels were not available in the remaining subjects. When measured, peak theophylline levels for those receiving theophylline plus terbutaline were in the subtherapeutic range (mean level, 5.18 mg/L; range, 2.5 to 10.2 mg/L; n = 8).

**Symptom Scores**

The symptom scores calculated from the daily logs of the nine patients with complete records are summarized in Table 1. Nine of 16 patients who completed the symptom scores reported more wheezing and shortness of breath while receiving placebo than with any drug regimen, but the differences were not statistically significant.

**Spirometry**

Spirometric values with each regimen are illustrated in Figure 1. Values for all three tests of pulmonary function were slightly improved relative to placebo by all drug regimens, although improvement was most consistent with the combination of aminophylline plus terbutaline (for FEV₁, p<0.01; for FVC, p<0.02; for FEF₂₅₋₇₅%, p<0.06). Not shown in Figure 1 is the fact that values for FEV₁ and FEF₂₅₋₇₅% while receiving placebo were slightly lower than during the baseline period of study, and these differences approached statistical significance (mean ± SE for FEV₁: baseline, 1.03 ± 0.09 L, and placebo, 0.93 ± 0.09 L, p<0.05; and for FEF₂₅₋₇₅%: baseline, 0.43 ± 0.04 L/sec, and placebo, 0.39 ± 0.05 L/sec, p<0.15).

**Gas Exchange at Rest**

As expected for this group of patients, both Vdp and P(A-a)O₂ were elevated at rest with placebo; Vdp/VT was 44.0 ± 4.8 percent, and P(A-a)O₂ was 25 ± 7.2 mm Hg (mean ± SD). No drug regimen affected Vdp/VT. Each drug regimen widened P(A-a)O₂ slightly, calculated using actual RQ value obtained during the measurement (Fig 2). None reached statistical significance.

**Steady-State Exercise Studies**

The Vdp/VT during the last two minutes of steady-
state exercise with placebo fell slightly (to 40.6 percent; average fall, 3.4 ± 4.7 percent [± SD]); and there was a trend toward a greater fall with exercise on each drug regimen (Fig 3), but this did not reach statistical significance.

The P(A-a)O\textsubscript{2} increased slightly during exercise with placebo (to 27.4 mm Hg). This increase with exercise averaged 3.3 ± 8.4 mm Hg (± SD) and was unaffected by any drug regimen.

Ventilatory equivalent for oxygen during exercise was elevated with placebo (mean ± SD, 33.1 ± 5.1 L \text{VE}/L \text{VO}_2 normal, 20 to 25), reflecting the expected inefficiency of ventilation in COPD. The \text{VE}/\text{VO}_2 was even further elevated on both regimens using terbutaline (terbutaline alone, 35.0 ± 4.8, p = 0.01; theophylline plus terbutaline, 34.3 ± 4.9, p = 0.12).

Oxygen pulse during exercise with placebo was slightly reduced in our study (mean ± SD, 6.34 ± 1.4 ml \text{VO}_2/beat; normal 7.3 \text{SD}). This was unchanged by any drug regimen.

**DISCUSSION**

Millions of people suffer from the chronic dyspnea and disability of COPD and are understandably des-

**FIGURE 2.** Effect of medications on P(A-a)O\textsubscript{2} at rest. Bars represent means; lines above bars represent SE. PL, Placebo; A, theophylline alone; T, terbutaline alone; and A + T, theophylline plus terbutaline.

**FIGURE 3.** Effect of medications on fall in ratio of V\text{D}/V\text{T} during exercise. Bars represent means; lines above bars represent SE. PL, Placebo; A, theophylline alone; T, terbutaline alone; and A + T, theophylline plus terbutaline.

perate for any treatment of benefit. Many of these patients have some degree of reversibility of their obstruction of airflow, and bronchodilator medications serve them well, both subjectively and objectively; however, many patients without such reversibility also claim improvement from these drugs, despite a lack of significant demonstrable objective benefit at rest. Because of the vast scope of the problem, many dollars and potential side effects are at stake; it is therefore essential to determine whether subjective improvement is truly reflected in demonstrable physiologic improvement. Our study tested whether such improvement might be found in gas exchange or spirometric data at rest, or in exercise-associated measurements of ventilatory and cardiovascular efficiency and gas exchange. Our population for study was purposely restricted to include only patients with irreversible obstruction of airflow, and our criteria are.
similar to those previously employed. Also, to simulate the usual clinical situation, the studies were done in ambulatory patients given commonly prescribed bronchodilator drugs in normal therapeutic doses.

Maximal incremental exercise testing was done to establish reproducible levels of exercise for each patient and also served to confirm the mechanism of physiologic impairment of exercise in our group. We found that exercise tolerance was severely limited (VO2 max, 35 percent of predicted) and that this limitation was ventilatory in origin (VEmax, 82 percent of predicted), rather than cardiovascular (HR max, 64 percent of predicted). These findings are similar to the observations of Jones et al in a large group of such patients.

Our patients tended to decrease wheezing and dyspnea with bronchodilator drugs, compared with placebo (Table 1); however, statistical significance was not demonstrated. Absence of symptomatic benefit in such patients receiving theophylline has been previously reported.

Spirometric data improved slightly with all bronchodilator regimens (Fig 1). The response of greatest magnitude was that of FEV1, to the combination of theophylline and terbutaline, averaging 200 ml. These improvements occurred during careful attempts to exclude patients with reversible obstruction of airflow and illustrate that small increases in expired volumes often occur with bronchodilator drugs even in "irreversible" obstruction of airflow.

Of interest is the decrease in FEV1 and FEF25-75% with placebo compared to the values obtained during the baseline evaluation. Theophylline was unmeasurable in the serum of all patients after 72 hours off medications, making persistence of active drug during the baseline evaluation an unlikely explanation. It can be speculated that a decrease in mucociliary transport or an alteration in respiratory drive might, over the ten-day period with placebo, allow reaccumulation of secretions or microatelectasis to decrease pulmonary function, while only 72 hours off medications might be insufficient time for these effects. Whatever the reason, this observation points out the need for more than 72 hours off bronchodilator drugs to establish true baseline conditions in future studies.

Some degree of pulmonary vascular disease is thought to be uniformly present in severe COPD, and several reports have suggested that pulmonary vasodilatation with theophylline and terbutaline given parenterally might contribute to the salutary effects of these agents. Some have suggested that an elevation of VD/Vr at rest and its failure to fall with exercise are reflective of pulmonary vascular disease, although a recent study has called this conclusion into question, at least in patients with collagen vascular disease. The VD/Vr was in fact elevated in our patients (44 percent) and fell only slightly with exercise (3.4 percent). The regimens of medication used in our study did not affect the resting VD/Vr, nor did they result in a statistically significant change with exercise associated with modest but not significant fall in Vr (Fig 3) as compared with placebo.

Efficiency of gas exchange in our patients was poor, as expected, and is reflected in their elevated VD/Vr and P(A-a)O2 (25 mm Hg). Our regimens further widened the resting P(A-a)O2 slightly (Fig 2). In subjects without cardiopulmonary disease, exercise results in a small narrowing of the P(A-a)O2 in patients with COPD, the P(A-a)O2 widens slightly, and this was observed in our patients (increase averaged 3.33 mm Hg). This was completely unaffected by the regimens studied, and our data indicate that these drugs fail to improve gas exchange at rest or during exercise in this group of patients. This has been shown previously for parenterally administered terbutaline.

Ventilatory equivalent for oxygen, a gross measurement of ventilatory efficiency during exercise, was elevated in our patients. This measurement was unaffected by theophylline. Terbutaline causes an increase in ventilation at rest and during exercise, and this effect could explain the increased VeO2 seen in our study with terbutaline-containing regimens, although there is no evidence that the drug improved exercise performance.

An increase in oxygen pulse during exercise is thought to reflect the increase of left ventricular stroke volume in response to exercise. In our group of patients receiving placebo, this measurement was slightly lower than predicted for the level of work performed. Whether this reflects undetected poor left ventricular contractility, interference by right ventricular overload with left ventricular filling, or some other mechanism is speculative; and, in fact, the small decrease may have no significance. In any case, there was no change in this measurement of cardiac function with any drug regimen, although several investigators have reported improvement in the function of both ventricles with theophylline and terbutaline in such patients. The difference in our findings may reflect the method used, oral administration of drugs, or our rigidly defined population of patients.

In summary, we have shown that ordinary doses of commonly prescribed oral bronchodilator medications produce little objective physiologic change, either at rest or with exercise, in a carefully selected group of ambulatory patients with COPD; however, despite this careful selection, a small improvement in spirometric data was observed, along with slight symptomatic improvement. Nevertheless, this should be weighed
against the expense and toxicity of long-term use of these medications for each patient individually. These findings are limited by the fact that only noninvasive techniques were used, and the findings should not be extended to other types of patients without further study; however, this group is representative of many outpatients cared for by internists and family practitioners, and our findings should be considered when prescribing these medications to such patients.

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