A rise in cardiac output and a fall in arterial oxygen tension are well known side effects of bronchodilator drugs, particularly β-adrenergic agonists. In recent years, fenoterol (Berotec), an effective β-adrenergic agonist, has been used at increasing rates in asthmatic subjects, as well as in patients with chronic obstructive pulmonary disease (COPD). The effects of fenoterol on systemic hemodynamics or arterial oxygenation (or both) in patients with COPD have not been investigated; in these individuals, who often have increased sympathetic tone and hypoxemia even at rest, cardiovascular stimulation and a fall in arterial oxygen tension would be particularly undesirable side effects. In 14 patients with COPD (seven without a reversible component of airflow obstruction [group 1]; and seven with a reversible component of airflow obstruction [group 2]), we studied all of the important parameters of oxygen transport before and after administration of fenoterol. Studies were performed at rest and after exercise. At baseline, group 1 showed a faster heart rate, a lower cardiac output, a lower arterial oxygen flow, a wider arteriovenous oxygen content difference (\(C(a-v)O_2\)), and a higher fraction of oxygen extracted by the tissues from a given arterial oxygen flow. In both groups, all measured parameters, including cardiac output and arterial oxygen pressure (\(PaO_2\)) remained statistically unchanged one hour after administration of fenoterol; with exercise, the heart rate, blood pressure, minute ventilation, oxygen consumption, (\(C(a-v)O_2\)), and the percentage of oxygen extracted from arterial oxygen flow, as well as cardiac output and \(PaO_2\), increased in all instances; the exercise responses were not affected by the drug. These results suggest that at the time of its maximal effect on the airways (60 minutes), fenoterol has no untoward effect on the oxygen transport system, at rest or during exercise, in patients with COPD with or without a reversible component.

The long-term management of patients with chronic obstructive pulmonary disease (COPD) quite often encompasses the use of bronchodilator drugs, including β-adrenergic agents, for control of a documented, or presumed, bronchospastic component. These drugs, by increasing cardiac output via sympathetic stimulation or by redistributing blood flow within the lungs (or both), may exaggerate preexisting ventilation-perfusion inequalities and cause a fall in arterial oxygen pressure (\(PaO_2\)).

Fenoterol is a relatively new, effective β-adrenergic agonist, seemingly free of significant side effects or tolerance. The responses of systemic hemodynamics and of arterial oxygenation after therapy with fenoterol have been evaluated, but in disparate studies and only in normal subjects or in patients with reversible airflow obstruction. There is no available comprehensive study of such responses in patients with COPD, who typically exhibit increased sympathetic tone and hypoxemia even at rest. In this state, side effects such as cardiovascular stimulation or decreased \(PaO_2\) would be particularly undesirable.

We studied all of the parameters of oxygen transport before and after a single dose of fenoterol in two groups of patients with COPD, those with fixed and those with reversible airflow obstruction. Since disturbances in oxygen transport induced by drugs may become apparent only when the cardiorespiratory system is stressed, observations were also made after standardized exercise.

Materials and Methods

Fourteen patients with COPD, defined by standard criteria, who were free of cardiac disease by clinical and routine laboratory data, were studied. They were all in stable condition with therapy, which included β-adrenergic agonist drugs. Two days before the study, all bronchodilator drugs were discontinued. One day before the study, the ventilatory response one hour following 400 μg of inhaled fenoterol was tested; seven patients in whom the forced expiratory volume in one second (FEV₁) increased by <15 percent were considered to have fixed airflow obstruction (group 1; all male patients); and in the other seven patients, FEV₁ was increased by >20 percent, and the patients were considered to have a significant reversible component of airflow obstruction (group 2; six male patients and one female patient). The pertinent baseline characteristics of the two groups are given in Table 1.

Maximal work capacity was assessed on the day preceding the study by exercising the patients, in the supine position, on a bicycle ergometer (Bosch ERG and ELP 500) with workloads increased by 25 W every two minutes until 90 percent of the maximal predicted heart rate was reached. Exercise was terminated sooner if exhaustion ensued or if systolic blood pressure rose to 200 mm Hg or more.

The experimental design on the day of study is shown in Figure 1. Baseline measurements after one-half hour of rest in the supine position included the following: heart rate and cardiac output by impedance cardiography (Minneapolis Impedance Cardiograph 304B and Microcomputer Surcom Inc.); oxygen consumption (\(Vo₂\)) by an...
open-circuit face mask (Oxylog; P.K. Morgan Ltd); arterial blood gas levels (Radiometer analyzer BMS 2 Mk2); arterial blood hemoglobin and oxygen saturation (MBA Co-oximeter). Using the tracings obtained with the impedance technique (Fig 2 and 3), values for the following variables were determined for each heart beat: instantaneous heart rate, from the R-R interval preceding each heart beat; \( dZ/dt \) (in ohms per second) from the impedance wave (maximal signal height from the baseline); and left ventricular ejection time (in seconds) from the first and second heart-sound intervals. Stroke volume (SV) was calculated by computer using the standard impedance formula of Kubicek et al.\textsuperscript{a} SV = \( pt \times (dZ/dt) \) (\( L/Vo \)), where blood resistivity (\( \rho \)) was calculated for each subject based on venous hematocrit,\textsuperscript{b} and \( L \) was the anterior midsternal distance between the inner electrodes.\textsuperscript{c} t, \( dZ/dt \), and \( Z_0 \) were as defined previously.

Immediately after collection of baseline data, patients performed submaximal exercise with a fixed workload (25 W less than maximal) for five minutes (zero to five minutes). During the last minute of exercise, all of the previous measurements were repeated. Thirty minutes were then allowed for complete recovery (5 to 35 minutes). At 35 minutes, fenoterol (400 mg by inhalation) was given. Approximately one hour later (90 to 95 minutes), baseline and exercise measurements were repeated using a protocol identical to the one described previously.

The following calculations were applied: \textsuperscript{1,29}

1. Arterial oxygen content (CAO\(_2\); in milliliters per liter) = (Hb; in grams per liter) \times (4) arterial oxygen saturation (SaO\(_2\); in percent).
2. Mixed venous oxygen content (CVO\(_2\); in milliliters per liter) = CAO\(_2\) - \( \Delta(\text{a-v})O_2 \)
3. Arteriovenous oxygen content difference (AC(a-v)O\(_2\); in milliliters per liter) = VO\(_2\) (in milliliters per minute)/cardiac output (CO; in liters per minute).
4. Oxygen extraction (OE; in percent) = (VO\(_2\) (in liters per minute) \times 100)/AF (in liters per minute).

Workload with the first exercise was 39 \pm 5 W (\pm SE) for group 1 and 54 \pm 9 W for group 2; in each case the workload was the same after administration of the drug. Increases in heart rate with exercise were comparable in the two groups (group 1, + 36 beats per minute before fenoterol and + 32 beats per minute after; group 2, + 36 beats per minute before and + 36 beats per minute after).

Baseline data were compared between groups with Student's t-test. The effects of exercise before and after administration of fenoterol were analyzed by two-way repeated-measures analysis of variance.

Informed written consent was obtained from all patients before inclusion in the study.

RESULTS

At baseline, in contrast to group 2, where all measured and calculated parameters of oxygen transport were within the range for age-matched normal subjects in our laboratory, the patients in group 1 (with FEV\(_1\), PaO\(_2\) comparable to group 2) showed evidence of impaired oxygen transport. Cardiac output and arterial oxygen flow were decreased; hence, in order to maintain a normal VO\(_2\), the \( \Delta(\text{a-v})O_2 \) had to be widened, and the fraction of arterial oxygen flow extracted by the tissues had to be larger (Table 1). In

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**Table 1—Pertinent Basal Values in Two Groups**

<table>
<thead>
<tr>
<th>Data</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>66 \pm 7</td>
<td>56 \pm 11</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area, m(^2)</td>
<td>1.8 \pm 0.2</td>
<td>1.8 \pm 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, beats per min</td>
<td>84 \pm 2</td>
<td>68 \pm 4</td>
<td>0.01</td>
</tr>
<tr>
<td>FEV(_1), L/s</td>
<td>1.4 \pm 0.2</td>
<td>1.4 \pm 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Forced vital capacity, L</td>
<td>2.7 \pm 0.2</td>
<td>2.3 \pm 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>PaO(_2), mm Hg</td>
<td>72 \pm 8</td>
<td>76 \pm 5</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO(_2), mm Hg</td>
<td>39 \pm 4</td>
<td>39 \pm 1</td>
<td></td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.38 \pm 0.01</td>
<td>7.38 \pm 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin level, g/dl</td>
<td>15.3 \pm 0.4</td>
<td>15.3 \pm 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.5 \pm 0.2</td>
<td>5.1 \pm 0.4</td>
<td>0.005</td>
</tr>
<tr>
<td>( \Delta(\text{a-v})O_2 ), ml/L</td>
<td>85 \pm 6</td>
<td>59 \pm 4</td>
<td>0.005</td>
</tr>
<tr>
<td>VO(_2), ml/min</td>
<td>291 \pm 26</td>
<td>297 \pm 13</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial oxygen flow, ml/min</td>
<td>657 \pm 43</td>
<td>1,044 \pm 43</td>
<td>0.010</td>
</tr>
<tr>
<td>Oxygen extraction, percent</td>
<td>45 \pm 4</td>
<td>30 \pm 3</td>
<td>0.010</td>
</tr>
</tbody>
</table>

*Data are means \( \pm \) SE.
†NS, Not significant.
‡PaCO\(_2\), Arterial carbon dioxide tension.
both groups (Tables 2 and 3) at one hour after administration of fenoterol, all parameters of oxygen transport were unchanged. In particular, PaO₂ and cardiac output were not affected by the administration of the drug, PaO₂ was 72 ± 8 mm Hg (± SE) (before) vs 70 ± 7 mm Hg (after) in group 1 and was 76 ± 5 mm Hg (before) vs 77 ± 5 mm Hg (after) in group 2, and cardiac output was 3.5 ± 0.2 L/min (before) vs 3.7 ± 0.3 L/min (after) in group 1 and 5.1 ± 0.4 L/min (before) vs 5.2 ± 0.3 L/min (after) in group 2. In addition, when changes in PaO₂ were looked at in all 14 patients before and after administration of fenoterol, there was still no significant change. Even though several of the parameters of oxygen transport in group 1 differed at baseline from those of group 2, responses to exercise before therapy with fenoterol were as expected in both groups. Heart rate, VO₂, cardiac output, arterial oxygen flow, ΔC(a-v)O₂, and oxygen extraction, as well as PaO₂, all increased; after therapy with fenoterol, responses to exercise in each group were statistically the same as before administration of the drug (Tables 2 and 3).

**DISCUSSION**

In healthy subjects after administration of fenoterol, cardiac output may remain normal⁴¹ or may increase;⁴¹,⁴² responses of PaO₂ have not been studied. After fenoterol in patients with reversible airflow obstruction, cardiac output has been found to be unchanged or increased⁴³ and PaO₂ unchanged⁴⁰,⁴⁴ or decreased.⁴⁵ The contrasting responses may be explained by differences in dosage or route of administration of the drug or by differences in the timing of the observations (or both). There is only one report in the literature⁴⁶ on the effect of fenoterol upon the cardiac output of the PaO₂ of patients with fixed airflow obstruction; it suggests that in normoxemic patients with chronic disease of the airways, fenoterol has no effect on PaO₂ (measured at the end of three hours), but hemodynamic observations were not included in this study.

The increase in cardiac output after bronchodilator drugs, particularly conspicuous with β-adrenergic agonists, has been uniformly attributed to the stimulatory effect of the drugs on the smooth muscle of blood vessels supplying skeletal muscles, with consequent decrease in peripheral vascular resistance and reflex tachycardia.⁴⁶ Arterial desaturation after administration of these drugs has been explained by various mechanisms: lack of distribution of the drug, when given by inhalation, to poorly ventilated pulmonary regions; reversal of the hypoxemia-induced pulmonary vasoconstriction in those same regions; and sympathetic stimulation with increased cardiac output and excessive perfusion of hypoventilated alveoli.⁴⁶,⁴⁷,⁴⁸,⁴⁹

In this study, we measured cardiac output, PaO₂, and all other major indicators of tissue oxygenation, the physiologic parameter ultimately important,⁵⁰,⁵¹,⁵² at 60 minutes after 400 μg of fenoterol by inhalation; we believed that this experimental design would be the most relevant clinically, since we have shown previously that the effect of fenoterol on the airways is maximal at one hour with this dosage. We used a noninvasive method, impedance cardiography, to measure left ventricular stroke volume (LVSV) and thus calculate cardiac output; the validity of this method is well documented.⁵³,⁵⁴ Pertinent to our study, measurements of LVSV by impedance cardiography have been found to be reliable, even during exercise.⁵⁵ The origin of the impedance signal has not been entirely established, but there is agreement that the major portion of Z comes from blood ejected into the ascending aorta.⁵⁶ This view is supported by the good linearity observed between LVSV determined impedance cardiography and LVSV determined simultaneously with the use of an electromagnetic probe in the ascending aorta.⁵⁶,⁵⁷ At our institutions, impedance cardiography has been used extensively for measuring cardiac output in human and animal studies.⁵⁸,⁵⁹ The reproducibility of the technique has been confirmed.⁶⁰ Like others, we have documented good correlations between impedance cardiography and thermodilution measurements in two separate studies, one on 20 cardiac patients with a cardiac index greater than 2.0 but less than 4.5 L/min/m² (r = 0.784)⁶¹ and the other on ten dialysis patients with a cardiac index greater than 2.5 but less than 5.0 L/min/m² (r = 0.88).⁶² Most

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### Table 2—Oxygen Transport Parameters in Group 1*

<table>
<thead>
<tr>
<th>Data</th>
<th>Before Fenoterol</th>
<th>After Fenoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
</tr>
<tr>
<td>Heart rate, beats per min</td>
<td>84 ± 2</td>
<td>114 ± 4</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>72 ± 8</td>
<td>77 ± 8</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.5 ± 0.2</td>
<td>7.4 ± 0.7</td>
</tr>
<tr>
<td>CaO₂, ml/L</td>
<td>200 ± 6</td>
<td>200 ± 6</td>
</tr>
<tr>
<td>ΔC(a-v)O₂, ml/L</td>
<td>100 ± 10</td>
<td>80 ± 10</td>
</tr>
<tr>
<td>VO₂, ml/min</td>
<td>291 ± 26</td>
<td>876 ± 63</td>
</tr>
<tr>
<td>Arterial oxygen flow, ml/min</td>
<td>657 ± 43</td>
<td>1,432 ± 102</td>
</tr>
<tr>
<td>Oxygen extraction percent</td>
<td>45 ± 4</td>
<td>61 ± 4</td>
</tr>
</tbody>
</table>

*Data are means ± SE.
recently, we have reported very reproducible values for cardiac output obtained by impedance cardiology in a group of patients with chronic obstructive pulmonary disease, at rest and during supine exercise. \(^{29}\)

Under the conditions of the present investigation, fenoterol showed no effect in either group, at rest or after exercise, on the oxygen transport parameters investigated, indicating that the drug-induced pathophysiologic disturbances discussed previously were not operative or were not detectable with the design of our study.

The negative findings in the patients with fixed airflow obstruction are of particular importance. At baseline, these patients exhibited evidence of impaired systemic oxygen transport, with significant reductions of cardiac output and arterial oxygen flow; adequate tissue oxygenation \((VO_2)\) was maintained through a widening of the \(AC(a-v)O_2\), i.e., an increase in the percentage of oxygen extracted by the tissues from a given arterial oxygen flow. The "hypodynamic" state of some subsets of patients with COPD and the compensatory mechanisms entering into play to insure adequate supply of oxygen to tissues have been commented upon in the past. \(^{60}\) With exercise, the \(VO_2\) of patients in group 1, although slightly lower, was not statistically different from that of group 2; the greater tissue oxygen demands imposed by the physical effort were met similarly in the two groups, in part by an increase in systemic blood flow and in part by a further widening of the \(AC(a-v)O_2\). In spite of their underlying physiologic limitations in oxygen transport, even these patients showed no untoward effect after fenoterol. Hence, when indicated, the use of this drug in patients with COPD is not a potentially harmful practice.

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REFERENCES


2 Kasik JE, Alexander MR. Reversing the irreversible. Chest 1982; 82:517-18


7 Harris L. Comparison of the effect of blood gases, ventilation, and perfusion of isoproterenol-phenylephrine and salbutamol aerosols in chronic bronchitis with asthma. J Allergy Clin Immunol 1972; 49:63-71


9 Heel RC, Brodgen RN, Speight TM, Avery GS. Fenoterol: a review of its pharmacological properties and therapeutic efficacy in asthma. Drugs 1978; 15:3-32


11 Branscomb BV. Efficacy and side effects of fenoterol compared with isoproterenol administered by metered dose inhalers in asthma. Chest 1978; 73(suppl):1002-04


17 Dakhil J, Clauzel AM, Michel FB. Effect of SCH 1000 and fenoterol inhalation on bronchial hyperreactivity. Respiration 1984; 46:370-78

18 Perri G, Giovannini M, Spada E. Salbutamol plus beclomethasone dipropionate (Ventolin Flogo) vs fenoterol (Dusberotec) in...
20 Ashraf M, Sharp J, Kehoe T, Cugell DW. A comparison of the effects of Th115a (fenoterol) and isoproterenol on spirometry and arterial blood gases. Chest 1978; 73(suppl):981
21 Siekmann U, Heilmann L, Irmer M. Indices of cardiac function during treatment with betamimetic drugs (fenoterol and hexoprenaline). Arch Gynecol 1983; 253:73-83
24 Meneely GR, Renzetti AD Jr, Steele JD, Wyatt JP, Harris HW. Accuracy of the stroke index as determined by the transthoracic electrical impedance method. Anesthesiology 1975; 42:201-05