Effect of Steroid Therapy on Exercise Performance in Patients with Irreversible Chronic Obstructive Pulmonary Disease*

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Many patients with irreversible chronic obstructive pulmonary disease (COPD) claim symptomatic improvement with steroid therapy, despite a lack of objective improvement in their spirometric data. To determine if steroids actually increase the exercise capacity of these individuals, 13 clinically stable patients (mean age, 63 ± 4 years; 12 male patients) were given methylprednisolone (32 mg once daily) or placebo in a randomized double-blind crossover fashion. Spirometric data and minute ventilation, oxygen consumption (\(\dot{V}_O_2\)), carbon dioxide production, and heart rate during incremental exercise were measured at each visit. Methylprednisolone did not produce a significant change in any of the measured parameters. Three patients had an increase in maximal \(\dot{V}_O_2\) of greater than 2 ml/kg/min during therapy with methylprednisolone, while two experienced a decline in maximal \(\dot{V}_O_2\) of similar magnitude. The change in exercise capacity was unrelated to the change in the forced expiratory volume in one second in individual patients \((r = 0.08)\). We conclude that in the absence of any improvement in the usual tests of airway mechanics, steroid therapy does not improve exercise performance in patients with COPD.

Patients with irreversible chronic obstructive pulmonary disease (COPD) often complain of dyspnea and exertional intolerance. Therapy with bronchodilators, including theophylline, \(\beta\)-adrenergic agonists, and corticosteroids, is frequently used in an attempt to relieve the obstruction of the airways and to improve the exercise tolerance. In a majority of these patients, expiratory airflow does not increase after administration of any of these medications, including corticosteroids.1-10 Despite a lack of improvement in their airway mechanics, some patients with irreversible obstruction of the airways claim symptomatic improvement with corticosteroids.7,8 We hypothesized that the subjective improvement reported with steroid therapy might reflect an increase in exercise tolerance that is independent of any measurable improvement in airway mechanics. To answer this question, we evaluated the effect of corticosteroids on the exercise capacity of patients with irreversible COPD and correlated the change in maximal oxygen consumption (\(\dot{V}_O_2\)) with improvement in symptoms and expiratory flow rates.

**Materials and Methods**

The medical records of all patients followed in the Shreveport (La) Veterans Administration Medical Center Chest Clinic were reviewed, and individuals with clinically stable COPD and a ratio of the forced expiratory volume in one second (FEV1) over the forced vital capacity (FVC) of less than 60 percent were invited to participate in the study. A number of eligible patients were unable to participate because of the distance lived from the hospital and problems of transportation with repeated visits. The protocol and consent form were approved by the Human Experimentation Committee of the VA Medical Center, and informed consent was obtained prior to initiation of the study. Those with a recent (within three months) exacerbation of their pulmonary disease, a history of asthma, or a strong family history of atopy, recent use of systemic or inhaled corticosteroids, active pulmonary infections, or physical conditions (such as severe exertional angina or musculoskeletal disease) which might preclude cycle ergometric testing were excluded.

A complete evaluation of each patient, including a medical history and physical examination, complete blood cell count, automated blood chemical analysis (SMA-18), urinalysis, chest roentgenogram, and electrocardiogram, was performed upon admission into the study. Based on this evaluation, none of the patients was considered to have cor pulmonale. Spirometric testing for determining the FEV1, FVC, and FEV1/FVC ratio was performed with a dry rolling-seal spirometer (Cardiopulmonary Instruments). Functional residual capacity (FRC) was determined by the open-circuit nitrogen-washout technique,11 and residual volume (RV) was calculated as the difference between FRC and the expiratory reserve volume measured by spirometric testing. Total lung capacity (TLC) was determined as the sum of vital capacity and RV. The diffusing capacity of the lung for carbon monoxide (DLco) was measured by the single-breath technique of Ogilvie et al.12 To confirm the unresponsiveness of the obstruction of the airways, ten minutes after the second of two puffs of isoproterenol from a metered-dose inhaler spaced five minutes apart, spirometric testing was repeated. All values obtained were also expressed as percent predicted using standard predictive formulas.13 Each patient then underwent an incremental exercise test to familiarize himself with the testing technique and to confirm that his exercise tolerance was limited by his pulmonary disease.

After the initial screening evaluation and exercise testing, the
patients were randomly assigned in a double-blind manner to receive either methylprednisolone (32 mg) or an identical placebo tablet once daily for 14 days. All patients were maintained on therapy with their usual bronchodilator medications (theophylline and an inhaled β-adrenergic agonist), which were not changed during the course of the study. The patients then returned to the clinic for a second visit and were questioned about any subjective change in their exercise tolerance. The patients were asked if they had been able to increase their activity while receiving the medication and about their sense of dyspnea during their customary activity. Spirometric testing was repeated as described previously, after which each patient performed an exercise test. A two-week washout period then ensued, after which the subject began a two-week course of the alternative medication (placebo or methylprednisolone). As on the second visit, a symptomatic evaluation, spirometric testing, and exercise testing were performed at the end of the washout period and at the conclusion of the final treatment.

Upon entry into the study and at each of the three subsequent evaluations, exercise capacity was determined during a multistage incremental exercise test on a cycle ergometer (Gould Lanono-type 18070) with instantaneous breath-by-breath measurement and analysis of gas exchange using a programmable desktop calculator (Hewlett-Packard 9825A). After resting data were obtained, the patient began unloaded cycling for one minute, after which the work rate was increased in 10-W increments each subsequent minute until the patient was unable to continue due to severe dyspnea or exhaustion. Heart rate was measured on a cardiotachometer (Hewlett-Packard 98332A). Expiratory airflow was determined with a Fleisch No. 3 pneumotachograph with a differential pressure transducer (Hewlett-Packard 98704A). While the patient was breathing through a high-flow, low-resistance low-deadspace valve (Koegel), the concentrations of carbon dioxide and oxygen in the expired air were determined by rapidly responding analyzers (Beckman LB-2 and Applied Electrochemistry S3-A, respectively). The analog outputs of these four instruments were connected to the calculator by an analog-to-digital converter (Hewlett-Packard 47310A). The VO₂ and carbon dioxide production (VCO₂) were calculated as previously described by Sue et al.14 Maximal work rate was defined as the highest work level that was reached and maintained for at least 30 seconds. Similarly maximal heart rate, oxygen uptake (VO₂max/kg), and minute ventilation (VÉmax) were the highest levels reached during the test. This VO₂max was believed to be an accurate reflection of the patients' aerobic capacity because, in all but one individual, VO₂ during the final exercise stage reached a plateau at a level similar to that observed during the preceding stage.

All data are presented as the mean (±SE). The significance of the differences between values observed with methylprednisolone and placebo was determined by Student's t-test for paired data.19 Differences were considered to be statistically significant when p<0.05.

### Table 1—Effect of Placebo and Methylprednisolone Therapy on Pulmonary Function and Exercise Performance*

<table>
<thead>
<tr>
<th>Data</th>
<th>Placebo</th>
<th>Steroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L</td>
<td>1.1 ± 0.1</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.3 ± 0.2</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>FEV₁/FVC%</td>
<td>48 ± 3</td>
<td>52 ± 3</td>
</tr>
<tr>
<td>Resting VO₂, ml/kg/min</td>
<td>4.1 ± 0.1</td>
<td>4.5 ± 0.3</td>
</tr>
<tr>
<td>VO₂max, ml/kg/min</td>
<td>13.0 ± 1.1</td>
<td>13.9 ± 1.1</td>
</tr>
<tr>
<td>VCO₂max, ml/kg/min</td>
<td>12.2 ± 1.3</td>
<td>13.1 ± 1.3</td>
</tr>
<tr>
<td>VÉmax, L/min</td>
<td>42.2 ± 2.8</td>
<td>43.5 ± 3.0</td>
</tr>
<tr>
<td>Maximal heart rate, beats per min</td>
<td>128 ± 4</td>
<td>127 ± 4</td>
</tr>
<tr>
<td>Maximal work rate, W</td>
<td>61 ± 7</td>
<td>65 ± 6</td>
</tr>
</tbody>
</table>

*Data are presented as means ± SE.

**Results**

Fourteen patients met the criteria for inclusion and agreed to participate in the study. One patient experienced a near-syncopal episode after taking the first dose of the tested medication (placebo) and was dropped from the study. The remaining 13 patients completed the study. Demographic data and results of baseline tests of pulmonary function in these patients were as follows (means ± SE):

- No. of male patients: 12
- Age, yr: 63 ± 4
- Weight, kg: 78 ± 3
- Smoking history: 13
- Blood eosinophils per cu mm: 147 ± 42
- FEV₁, L
  - Before bronchodilator: 1.16 ± 0.12
  - After bronchodilator: 1.23 ± 0.13
- FVC, L
  - Before bronchodilator: 2.43 ± 0.21
  - After bronchodilator: 2.58 ± 0.25
- FEV₁/FVC, percent
  - Before bronchodilator: 48.3 ± 2.6
  - After bronchodilator: 48.3 ± 2.7
- TLC, percent predicted: 106 ± 5
- Dsb, percent predicted: 55 ± 5

Five patients experienced symptomatic improvement in their exercise tolerance during the study. All five believed that they were less dyspneic during their usual activities, but none reported an increase in their level of activity. In four of these patients, the subjective improvement in exercise tolerance occurred while receiving steroid therapy, but in only one was there an increase in VO₂max (of 3.3 ml/kg/min) which exceeded 10 percent of the VO₂max with placebo. The exercise capacity of two patients who experienced symptomatic benefit with steroid therapy was essentially unchanged (within 10 percent of placebo values), while the VO₂max of the fourth patient actually decreased by 2.5 ml/kg/min (18 percent of placebo). The one patient who experienced symptomatic improvement with placebo had a decrease in VO₂max of 3.0 ml/kg/min. The mean improvement in FEV₁ of patients with symptomatic improvement was 1±6 percent, and the largest increase in FEV₁ was 15 percent with steroid therapy.

The results of the objective measurements during each period of evaluation are presented in Table 1. There was no significant difference in spirometric data between placebo and methylprednisolone therapy. Only one patient had an increase in FEV₁ of more than 30 percent during methylprednisolone therapy, and this individual's VO₂max was essentially unchanged during exercise.

The results of the exercise tests performed after two weeks of methylprednisolone therapy and placebo are also presented in Table 1. Oxygen consumption at rest and during maximal exercise was not significantly different during the periods of placebo and methylprednisolone therapy.
yprednisolone. Similarly, the maximal work rate during methylprednisolone therapy was not significantly different from that of the placebo period. As might be expected, \( \dot{V}CO_2 \) at maximal exercise during methylprednisolone was also similar to that during placebo. The differences in maximal heart rate and \( \dot{V}E \) between both study periods were also small and not statistically significant.

Three patients had an increase in \( \dot{V}O_2 \)max of greater than 2 ml/kg/min during methylprednisolone therapy, while in two patients, \( \dot{V}O_2 \)max decreased by more than 2 ml/kg/min during steroid therapy. To determine if the observed improvement in \( \dot{V}O_2 \) was related to individual improvements in FEV1 that were obscured by the lack of improvement in other patients, we examined the relationship between FEV1 and \( \dot{V}O_2 \)max in each patient while receiving methylprednisolone therapy (Fig 1). No significant correlation was found between the change in exercise capacity and the change in FEV1 while receiving steroids (\( r = 0.08 \)). Nine patients had a change of both FEV1 and \( \dot{V}O_2 \)max in the same direction (both improved in eight), whereas these parameters changed in different directions in the other subjects.

### Discussion

Previous investigators have observed that the subjective benefits of steroid therapy far outweigh the objective improvements.\(^7\)\(^8\) When steroids are administered to patients with chronic obstruction of the airways, only a minority of these individuals will experience symptomatic improvement and a definite improvement in their expiratory flow rates.\(^7\)\(^8\) Many of these "steroid-responsive" individuals have eosinophilia of sputum or peripheral blood or have a significant improvement in their FEV1 after inhaled isoproterenol, suggesting a possible asthmatic component to their disease.

In the present study, we sought to restrict our observations to those patients with nonasthmatic obstructive airway disease by excluding those patients with eosinophilia or significant improvement in FEV1 following an inhaled bronchodilator. The variability of FEV1 observed in the present study is similar to that reported by others.\(^4\) We found in these patients with stable COPD, methylprednisolone therapy produced neither an improvement in work capacity and \( \dot{V}O_2 \)max nor any measured change in airway mechanics.

![Figure 1. Changes in FEV1 (\( \Delta FEV_1 \)) and \( \dot{V}O_2 \)max (\( \Delta \dot{V}O_2 \)max) in individual patients during methylprednisolone therapy compared to placebo.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21495/ on 04/08/2017)
Subjective improvement with methylprednisolone therapy was observed in only four of the 13 individuals, only one of whom had an increase in $\bar{V}O_2$max of greater than 2 ml/kg/min. In accord with previous studies which found a poor correlation between symptomatic benefit and objective improvement, we found the subjective changes to be an unreliable indicator of an increase in exercise tolerance. Furthermore, the correlation between the change in FEV1 and $\bar{V}O_2$max was poor. Some investigators have reported a small increase in arterial oxygen pressure with corticosteroid therapy, which was attributed to improved ventilation-perfusion matching or to an increase in the diffusing capacity (or both), however, a more recent double-blind controlled study found no significant change in blood gas tensions with corticosteroids. Although we did not measure arterial blood gas levels in our patients, it is unlikely that there was a physiologically significant increase in arterial saturation during methylprednisolone treatment, since both $V_e$ and $\bar{V}O_2$max during exercise with steroid therapy was similar to the placebo values.

Although several patients experienced a large improvement in their exercise capacity while receiving steroid therapy, overall $\bar{V}O_2$max during treatment with methylprednisolone was similar to that observed with placebo. In view of the potential for significant side effects, we do not believe that the routine use of steroids can be advocated in patients with stable chronic obstruction of the airways. Furthermore, if an empiric trial of steroid therapy is to be employed in such patients, the efficacy should be objectively determined by comparing respiratory mechanics and work capacity before and after initiation of therapy.

ACKNOWLEDGMENTS: We thank Ms. Cathy Couvillon and Ms. Carol Potter for secretarial assistance. Methylprednisolone and placebo were supplied by the Upjohn Co., Kalamazoo, Mich.

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