Controlled Short-term Trial of Fluticasone Propionate in Ventilator-Dependent Patients With COPD*

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Background: There is no agreement about the efficacy of systemic corticosteroids in patients with COPD, but corticosteroids often are employed during exacerbations of the disease. The use of systemic or inhaled corticosteroids in patients in stable condition is even more controversial, even though the more severely affected patients seem to respond better. Unfortunately, in this subset of patients, the use of forced expiratory maneuvers frequently fails to detect significant functional response.

Study objectives: We evaluated the short-term effects of an inhaled corticosteroid, fluticasone propionate (FP), on FEV₁ and on the mechanical properties of patients in stable condition with severe COPD and chronic hypercapnic respiratory failure who were receiving long-term ventilatory support. This allowed us to measure respiratory mechanics (RM) passively, thereby avoiding any problems linked with voluntary maneuvers.

Design: Randomized, placebo-controlled, crossover study.

Setting: A respiratory ICU.

Patients: Twelve hypercapnic COPD patients (mean [± SD] PaCO₂, 60 ± 11 mm Hg; mean FEV₁, 13 ± 5% predicted; and mean FEV₁/FVC, 31 ± 7%) were enrolled.

Interventions: A daily dose of 2,000 μg FP or placebo was administered via metered-dose inhaler during mechanical ventilation for 5 consecutive days. A washout of 72 h was allowed between regimens.

Measurements: End-expiratory and end-inspiratory airway occlusions were performed to assess static intrinsic positive end-expiratory pressure (PEEPi,st), static compliance of the respiratory system (Cst,rs), maximal respiratory resistance (Rmax,rs), and minimal respiratory resistance (Rmin,rs). The bronchodilator response also was assessed by FEV₁ level.

Results: No significant changes were found in RM after administration of the placebo. By day 6, FP had induced the following significant decreases: PEEPi,st, 4.3 ± 2.4 to 3.1 ± 1.7 cm H₂O (p < 0.01); Rmax,rs, 19.0 ± 6.5 to 14.6 ± 6 cm H₂O/Ls (p < 0.001); and Rmin,rs, 14.8 ± 4.2 to 10.5 ± 3.4 cm H₂O/Ls (p < 0.001). The Cst,rs and the effective additional resistance of the respiratory system did not change significantly, the latter suggesting that the major effect of FP was on the airway caliber (Rmin,rs). FEV₁ changes significantly (p < 0.01) underestimated the bronchodilator response, as compared with changes in Rmin,rs.

Conclusions: We conclude that in patients in stable condition with severe COPD and chronic hypercapnic respiratory failure, a brief trial of FP may induce a bronchodilator response, mainly related to a reduction in airway resistances, that is not detected by the usual pulmonary function tests.

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Key words: COPD; fluticasone propionate; mechanical ventilation; respiratory mechanics

Abbreviations: Cst,rs = static compliance of the respiratory system; FP = fluticasone propionate; MDI = metered-dose inhaler; P₁ = sudden decrease in pressure at the airways from a peak value to a lower value; P₂ = value achieved after a sudden decrease in pressure at the airways from a peak value to a lower value followed by a more gradual and slow decrease until an apparent plateau is reached; Paw = pressure at the airways; PEEPi,st = intrinsic static positive end-expiratory pressure; Raw = airway resistance; RM = respiratory mechanics; Rmax,rs = maximal resistance of the respiratory system; Rmin,rs = minimum resistance of the respiratory system; VR = tidal volume

Systemic use of corticosteroids during exacerbations of COPD requiring hospitalization recently has been shown to improve the clinical outcome moderately,¹ and respiratory mechanics (RM) promptly, in COPD patients receiving mechanical ventilation for an episode of acute respiratory failure.² The prolonged use of corticosteroids in COPD patients in stable condition is still controversial, even though the subset of more severely affected patients...
(ie, those with an FEV₁ < 1 L) seems to respond better to the treatment than less compromised patients. The major guidelines on COPD treatment, therefore, recommend that reversibility testing to oral corticosteroids, lasting 1 to 2 weeks, should be performed in more severely ill COPD patients. The use of high doses of systemic steroids has been discouraged by their well-known side effects. The use of high doses of systemic steroids should be performed in more severely ill COPD patients.

The only short-term study on the effects of inhaled corticosteroids suggested that beclomethasone dipropionate was less effective than oral prednisolone, but was better than placebo, in improving pulmonary function tests. This study was, however, performed in patients affected by a moderate degree of the disease (mean FEV₁, 1.2 L), who theoretically would be less responsive to the treatment, and used a less powerful drug than those actually available. The possibility of recording passive RM in patients very severely affected by chronic respiratory insufficiency offers us the unique opportunity to monitor, objectively, the possible changes induced by pharmacologic agents on the resistive properties of the respiratory system, while avoiding forced expiratory maneuvers that frequently fail to detect significant functional responses in the most severely ill, spontaneously breathing patients.

The primary end point of this randomized, placebo-controlled, crossover study was to evaluate the short-term effects of fluticasone propionate (FP), given by metered-dose inhaler (MDI), on the RM of ventilator-dependent COPD patients and, in particular, to evaluate the effects on the resistive properties of the respiratory system and to compare the results with those obtained using classic tests of bronchodilatation.

**Materials and Methods**

**Patients**

Ventilator-dependent patients with COPD, as defined by American Thoracic Society criteria, were enrolled in this study, which had been approved by the local ethics committee. Oral informed consent was given by each patient. The patients had been considered eligible for receiving long-term ventilation in one of their previous admissions to our respiratory ICU. Briefly, at the time of an episode of severe acute respiratory failure, patients were intubated in one of the five ICUs connected to our center and, later, were transferred after a tracheostomy had been performed, if weaning from mechanical ventilation was proving difficult to achieve. During the first admission to our department, several attempts at weaning were performed, either with T-piece trials and/or with pressure support ventilation. At the same time, a comprehensive rehabilitation program was instituted, as described in detail elsewhere, together with nutritional support, counseling, and psychological support, and medical therapy for the underlying disease. If repeated attempts at weaning failed over a period of 4 to 6 weeks, patients were discharged and were enrolled in a home ventilation program. A follow-up admission in our department was scheduled every 3 to 4 months. Twelve patients in clinically stable condition were enrolled in the study 2 to 4 days after a routine follow-up admission to our respiratory unit. They were from the group of 19 ventilator-dependent patients who are followed-up by our center. The other seven patients did not participate in this study because they had one or more contraindications (see below) or because they did not consent. At the time of enrollment in this study, the patients were receiving ventilation for at least 12 h/d (range, 12 to 24 h).

Clinical stability was defined by the following criteria: (1) absence of hyperthermia; (2) stable hemodynamics (mean arterial BP not varying by > 10 mm Hg in the preceding 48 h, with systolic pressure of > 90 and < 170 mm Hg); (3) a conscious and cooperative state; and (4) no use of respiratory depressant drugs.

Patients were excluded if they had concomitant severe diseases (ie, neurologic or psychiatric diseases), cancer or other systemic diseases, severe arrhythmia, GI perforation or bleeding, trauma, diabetes, coagulopathy, other hematologic diseases, or osteoporosis. None of the patients had a preexisting diagnosis or history of asthma or radiologic evidence of pneumonia.

Table 1 illustrates the time between the institution of long-term ventilation and enrollment in the study. It also shows the main respiratory characteristics and arterial blood gas levels during a brief trial of spontaneous breathing. All the patients were receiving long-term oxygen therapy. They were also receiving standard therapy for COPD, including β₂-agonists (10 patients), theophylline (6 patients), anticholinergic agents (3 patients), and diuretics (4 patients). None of the patients was receiving long-term treatment with steroids, either systemic or inhaled. The diameter of the tracheal cannula (Shiley cuffed; internal diameter, 8 mm) was identical for all the patients who underwent a tracheotomy.

**Study Design**

This study had a double-blind, randomized, placebo-controlled, crossover design. Therapy with bronchodilators, inhaled or nebulized, was suspended at least 24 h before enrollment. Methylxanthine therapy was suspended on admission to the unit.

**Protocol**

The patients were randomized to receive placebo or FP using a computer program. During the study, the code was held by the chief nurse who was unaware of the aim and protocol of the study. She gave the nurse on shift the canister with placebo or FP, which had been approved by the local ethics committee. Oral informed consent was given by each patient. The patients had been considered eligible for receiving long-term ventilation in one of their previous admissions to our respiratory ICU. Briefly, at the time of an episode of severe acute respiratory failure, patients were intubated in one of the five ICUs connected to our center and, later, were transferred after a tracheostomy had been performed, if weaning from mechanical ventilation was proving difficult to achieve. During the first admission to our department, several attempts at weaning were performed, either with T-piece trials and/or with pressure support ventilation. At the same time, a comprehensive rehabilitation program was instituted, as described in detail elsewhere, together with nutritional support, counseling, and psychological support, and medical therapy for the underlying disease. If repeated attempts at weaning failed over a period of 4 to 6 weeks, patients were discharged and were enrolled in a home ventilation program. A follow-up admission in our department was scheduled every 3 to 4 months. Twelve patients in clinically stable condition were enrolled in the study 2 to 4 days after a routine follow-up admission to our respiratory unit. They were from the group of 19 ventilator-dependent patients who are followed-up by our center. The other seven patients did not participate in this study because they had one or more contraindications (see below) or because they did not consent. At the time of enrollment in this study, the patients were receiving ventilation for at least 12 h/d (range, 12 to 24 h).

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Arterial blood gas levels were measured during a brief trial of spontaneous breathing with a Venturi mask at a 33% fraction of inspired oxygen.

†Patient 4 was totally ventilator-dependent; therefore arterial blood gas levels were recorded during mechanical ventilation at a 35% fraction of inspired oxygen, 992 L/min; decelerating flow waveform; (RR), 12 breaths/min; positive end-expiratory pressure, 0 cm H2O. Before the administration of the puffs, the patients were asked to relax and to try to be captured by the ventilator frequency. The setting of the ventilator during the recordings of the RM was similar to that employed for drug delivery, with the exception of the flow waveform, which was switched from decelerating to constant.

From day 1 to day 5, the patients received one of the two treatments bid. On day 6, they received only the morning dose, after which their RM were measured (see below) and they passed a washout period of 72 h. After that, on day 10, they were crossed over to the other treatment for 5 days.

**Timing of Measurements**

Recordings of RM, pulmonary function tests, and arterial blood gas levels were performed on days 1, 6, 10, and 15, immediately before the administration of placebo or FP and 2 h after.

Mechanical ventilation for drug delivery was provided using dry ventilator circuits, during assist/control mode with the following settings: tidal volume (Vt), 12 mL/kg; respiratory rate (RR), 12 breaths/min; positive end-expiratory pressure, 0 cm H2O; inspiratory flow, 40 L/min; decelerating flow waveform; respiratory duty cycle, >0.3; and inspiratory trigger, −0.5 cm H2O. Before the administration of the puffs, the patients were asked to relax and to try to be captured by the ventilator frequency. The setting of the ventilator during the recordings of the RM was similar to that employed for drug delivery, with the exception of the flow waveform, which was switched from decelerating to constant.

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Mechanical ventilation was provided at the time of the measurements by a standard ICU ventilator (Cesar; Taema; Antony, France) set in the controlled mode. Patients were sedated with benzodiazepine to produce complete relaxation and adaptation, which was assessed by the absence of spontaneous efforts (ie, negative deflection in airway pressure) so that there was no change in inspiratory flow rate, Vt, or RR during the recordings. We induced neuromuscular blockade with succinylcholine in two patients who did not achieve these conditions. Each patient received ventilation during the recordings of RM using the same parameters throughout the time course of the study, except for patient 10 for whom the RR was increased from 10 breaths/min (day 1) to 14 breaths/min (days 6, 10, and 15) to obtain complete capture. Five minutes before the recordings, the patients had careful bronchial aspiration; this time interval has been shown to be sufficient to avoid the effects of the transient bronchoconstrictive response to suction. Three or four measurements for each occlusion test (see below) were taken at fixed intervals of 2 min to assess the reproducibility of the measurements.

Pulmonary function tests for the recording of dynamic volumes were performed through the endotracheal cannula during spontaneous breathing (usually about 5 to 10 min before the beginning of the mechanics), as described in detail elsewhere.

**Instruments**

Flow at the airway was measured with a heated pneumotachograph (Screenmate; Jaeger; Wurzburg, Germany) that was inserted between the proximal end of the tracheotomy and the “Y” of the ventilator, while Vt was calculated by the integration of the flow. Pressure at the airways (Paw) was sampled by means of tubing proximal to the pneumotachograph. A differential pressure transducer (Honeywell; Freeport, IL) setting, ±250 cm H2O) was employed to record the pressure. The equipment dead space, not including the endotracheal or the tracheotomy tube, was 120 mL. Pulmonary function tests were recorded with a portable spirometer at the bedside of the patients. Arterial blood gas levels were obtained from the radial artery and were measured with a blood gas analyzer (Radiometer; Copenhagen, Denmark).

**Measurements of Pulmonary Mechanics**

The patients were examined in a semirecumbent position. During the study, a physician not involved in the procedure was always present to provide care for the patients. The end-inspiratory and the end-expiratory occlusion method was employed to monitor RM. Static intrinsic positive end-expiratory pressure (PEEPi, st) was recorded by pressing the end-expiratory

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### Table 1—Patient Characteristics and Prestudy Arterial Blood Gas Levels*<sup>†</sup>

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Sex</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; % predicted</th>
<th>FVC L % predicted</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</th>
<th>pH</th>
<th>PaCO&lt;sub&gt;2&lt;/sub&gt; mm Hg</th>
<th>PaO&lt;sub&gt;2&lt;/sub&gt; mm Hg</th>
<th>Mech Vent, d</th>
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<tr>
<td>1</td>
<td>71</td>
<td>M</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7.38</td>
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<td>2</td>
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<td>3</td>
<td>76</td>
<td>M</td>
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<td>4†</td>
<td>44</td>
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<td>58.9</td>
<td>89.5</td>
<td>68</td>
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<tr>
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<td>65</td>
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<td>32</td>
<td>11.62</td>
<td>13.67</td>
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<td>SD</td>
<td>9.3</td>
<td></td>
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<td>0.148</td>
<td>8.6</td>
<td>0.02</td>
<td>11.62</td>
<td>13.67</td>
<td>266.4</td>
</tr>
</tbody>
</table>

*Arterial blood gas levels were measured during a brief trial of spontaneous breathing with a Venturi mask at a 33% fraction of inspired oxygen. Mech Vent = No. of days the patient received mechanical ventilation prior to enrollment in the study; M = male; F = female; NA = not applicable.

†Patient 4 was totally ventilator-dependent; therefore arterial blood gas levels were recorded during mechanical ventilation at a 35% fraction of inspired oxygen.
hold button that was incorporated into the ventilator and occluding the airway opening for 5 s at the end of tidal expiration. During this time, the increase in Paw, if any, was due to end-expiratory elastic recoil of the respiratory system. After these measurements, following several mechanical inflations, the airway opening was occluded again, but this time at end-inspiration, for approximately 5 s. Briefly, the end-inspiratory occlusion is always followed by a sudden decrease in Paw from a peak value to a lower value (P1), followed by a more gradual and slow decrease until an apparent plateau is reached (P2). P1 was measured by back extrapolation of a computer-fitted curve. P2 represents the static end-inspiratory elastic recoil pressure of the total respiratory system. The static compliance of the respiratory system (Cst,rs) was calculated as the ratio between the expired VT and the differences between P2 and PEEPi,st. The Cst,rs was corrected for the compliance of the ventilator tubing and the gas compression (0.8 mL/cm H2O). The end-inspiratory occlusion also was used to calculate the inspiratory resistive properties. The so-called minimal resistances of the total respiratory system (Rmin,rs) were computed by dividing the peak Paw minus P1 from the Paw tracing by the preceding constant flow and subtracting the resistance of the endotracheal tube. The slow decay in pressure (P1 − P2) divided again by the flow preceding the occlusion gives the so-called effective additional resistance of the respiratory system (ΔR,rs). The sum of Rmin,rs and ΔR,rs represents the total resistance or maximal resistance of the respiratory system (Rmax,rs). The flow-resistive properties of the tracheotomy tube were computed in vitro at various inspiratory flows, as described elsewhere. In the calculation of resistances, the error due to the closing time of the valve of the ventilator was corrected for.

Data Analysis

All the signals were first recorded on an eight-channel recorder (model TA 4000; Gould; Valley View, OH). They were also sampled at 100 Hz by an analog-to-digital converter and were stored on a personal computer (model 14/C; Philips; Amsterdam, the Netherlands) for subsequent analysis. The mean value from three measurements was used for each physiologic variable. The results are expressed as the mean ± SD. A Student’s t test for paired observations was used to compare the differences between baseline measurements. The values of RM at the various times of measurements (ie, days 1, 6, 10, and 15) were analyzed using one-way analysis of variance for repeated-measures analysis of variance, and, when allowed by the F value, the significance among treatments was computed using Fisher’s protected least significant difference test. Probability values < 0.05 were considered significant.

RESULTS

All the enrolled patients completed the study, and none of them showed any side effects due to the aerosol administration. In particular, serum glucose levels, arterial BP, and heart frequency were not affected by FP or placebo.

Table 2 shows the values of RM recorded on day 1. PEEPi,st was present in all the patients and varied from 1.2 to 9.6 cm H2O. Cst,rs was, on average, higher than that reported for healthy subjects and was similar to the values obtained in COPD patients receiving mechanical ventilation. Rmax,rs values were also four to five times higher than those usually recorded in healthy subjects.

As shown in Table 3, no significant variation was observed in the baseline values (pre-MDI administration) on days 1 and 10. However, in the patients randomized to receive FP as the first treatment, the 72 h of washout were not enough to achieve exactly comparable levels in PEEPi,st and resistances at day 10, even though the differences were far from being statistically significant. Cst,rs did not vary significantly after either FP or placebo.

As shown in Figure 1 (top) for each individual, 2 h after receiving the first dose of FP, a small reduction in PEEPi,st was observed, although this change was far from achieving statistical significance (4.33 ± 2.45 to 4.14 ± 2.24 cm H2O). FP induced a marked reduction in PEEPi,st at the sixth day of treatment compared to baseline, both preadministration (3.07 ± 1.7 cm H2O; p < 0.005) and 2 h after MDI administration (3.15 ± 1.7 cm H2O; p < 0.01). The change in PEEPi,st after administration of FP for 5 days varied among the patients; in particular, four of them did not show any change. As shown in Figure 1 (bottom), placebo administration did not induce significant or clinically relevant changes (baseline, 4.21 ± 2.81 cm H2O; day 1 after 2 h, 4.35 ± 2.50 cm H2O; day 6

| Table 2—Values of RM for Each Patient at Enrollment |
|-----------------|-----------------|-----------------|-----------------|
| Patient No. | PEEPi,st, cm H2O | Rmin,rs, cm H2O/L/s | Rmax,rs, cm H2O/L/s | Cst,rs, mL/cm H2O |
| 1 | 4.86 | 17.73 | 25.03 | 138.27 |
| 2 | 1.62 | 18.06 | 24.63 | 108.02 |
| 3 | 4.86 | 18.39 | 30.02 | 75.72 |
| 4 | 6.07 | 12.26 | 14.29 | 31.00 |
| 5 | 4.86 | 14.43 | 16.60 | 81.10 |
| 6 | 1.21 | 8.50 | 11.91 | 91.50 |
| 7 | 3.24 | 17.15 | 24.30 | 106.36 |
| 8 | 1.40 | 7.94 | 10.58 | 97.22 |
| 9 | 9.72 | 11.10 | 12.70 | 62.83 |
| 10 | 3.24 | 17.05 | 19.21 | 49.82 |
| 11 | 6.67 | 20.58 | 25.58 | 139.00 |
| 12 | 4.50 | 12.30 | 14.00 | 88.00 |

Mean 4.35 14.86 19.07 89.07
SD 2.45 4.20 6.39 32.31

| Table 3—RM Values at Baseline* |
|----------------|----------------|----------------|
| RM | Baseline Day 1 | Baseline Day 10 |
| PEEPi,st, cm H2O | 4.35 ± 2.4 | 3.68 ± 2.3 | 0.002 |
| Rmin,rs, cm H2O/L/s | 14.56 ± 4.2 | 13.62 ± 4.1 | 0.13 |
| Rmax,rs, cm H2O/L/s | 19.07 ± 6.6 | 17.91 ± 6.5 | 0.18 |
| Cst,rs, mL/cm H2O | 89.07 ± 32.3 | 83.31 ± 33.1 | 0.23 |

*Values given as mean ± SD.
preadministration, 4.44 ± 2.22 cm H$_2$O; and day 6 after 2 h, 4.39 ± 2.38 cm H$_2$O).

Figure 2 (top) shows the individual changes of R$_{max,rs}$. On day 1, 2 h after FP administration, the changes were not statistically significant (baseline, 19.05 ± 6.53 cm H$_2$O/L/s; and 2 h after administration, 18.02 ± 6.45 cm H$_2$O/L/s). On the sixth day of treatment with FP, a significant decrease was seen, both before MDI administration (14.82 ± 5.95 cm H$_2$O/L/s; p < 0.001) and 2 h after (14.39 ± 6.0 cm H$_2$O/L/s; p < 0.001). Figure 2 (bottom) illustrates the nonsignificant changes after placebo administration (baseline, 18.56 ± 7.21 cm H$_2$O/L/s; day 1 after 2 h, 18.89 ± 6.77 cm H$_2$O/L/s; day 6 preadministration, 19.16 ± 7.34 cm H$_2$O/L/s; and day 6 after 2 h, 18.73 ± 6.88 cm H$_2$O/L/s).

Figure 3 (top) shows the changes in R$_{min,rs}$. Compared to baseline, on day 1, 2 h after FP administration, we did not observe any significant difference (baseline, 14.81 ± 4.22 cm H$_2$O/L/s; and 2 h after administration, 13.73 ± 4.70 cm H$_2$O/L/s). By day 6, FP had induced a significant decrease before administration (10.99 ± 3.77 cm H$_2$O/L/s; p < 0.001) that was similar to that 2 h after MDI administration (10.52 ± 3.41 cm H$_2$O/L/s; p < 0.001). The response to FP on day 6 was more homogenous in decreasing both resistances, as compared to that of PEEPi,st, since only two patients did not show any change. Figure 3 (bottom) represents the nonsignificant change after placebo administration (baseline, 15.03 ± 4.57 cm H$_2$O/L/s; day 1 after 2 h, 14.98 ± 4.37 cm H$_2$O/L/s; day 6 preadministration, 15.17 ± 4.94 cm H$_2$O/L/s; and day 6 after 2 h, 15.44 ± 4.79 cm H$_2$O/L/s).

Since we did not observe any significant changes in $\Delta R_{rs}$, we can conclude that the decrease in R$_{max,rs}$ was caused mainly by a reduction in R$_{min,rs}$, ie, a reduction in the airway resistance (Raw).

Figure 4 is the identity plot comparing the bronchodilator response at day 6, using the R$_{min,rs}$ or FEV$_1$ changes from baseline, in the nine patients who could correctly perform the pulmonary function tests. It can be noted that $\Delta$FEV$_1$ significantly underestimated the degree of response in each patient (7.6 ± 6.7%) compared to the recorded measurements of the interrupter resistances (19.9 ± 7.8%; p < 0.01).

Arterial blood gas levels recorded during mechanical ventilation at 8 PM on the days that RM was measured and 1 h after the last recording (3 h after MDI administration) did not show any significant changes.
In this study, we have demonstrated for the first time (to our knowledge), as objectively assessed by the recording of passive RM, that in severely ill, ventilator-dependent COPD patients with chronic respiratory failure who are in stable condition, a topical steroid (FP) that is administered for a brief period may improve the degree of airway obstruction.

The benefit of the administration of systemic corticosteroids to patients in stable condition with COPD is controversial even though, in a significant proportion of patients with severe airflow obstruction, the obstruction can be demonstrated to be reversible. The American Thoracic Society and the British Thoracic Society recommend, in their guidelines for the management of stable COPD, the use of a corticosteroid reversibility test when FEV₁ drops below the threshold of 60% of predicted and/or when moderate to severe dyspnea ensues. This test consists of a course of oral prednisolone (eg, 30 mg/d) taken for 1 to 2 weeks. Unfortunately, systemic corticosteroids may have adverse effects, including altered bone metabolism, hypokalemia, sodium retention, hyperglycemia, psychotic reactions, or gastric bleeding if an ulcer is present. Indeed, they may produce alterations in skeletal and respiratory muscle function and structure. Even short-term treatment (up to 5 days) with massive doses of steroids may induce severe respiratory and limb muscle wasting with type IIb atrophy.

Long-term treatment with inhaled steroids at a relatively high dose in COPD patients in stable condition, as recently stated in a meta-analysis, benefits FEV₁. In particular, in their large, international, and multicenter, randomized study, Paggiaro et al compared, in more severely ill patients (ie, FEV₁, around 50% of predicted), the effects of FP at the daily dose of 500 µg bid with placebo over a 6-month treatment period. They found a small, though significant, improvement in pulmonary function in the actively treated group, with associated clinical benefits in terms of symptoms, exercise capacity, and severity of exacerbations.

To our knowledge, the present study is the first short-term trial, in very severely ill patients, using high doses of an inhaled steroid to justify the use of the reversibility test with this topical drug. We were able to show that only 5 days of treatment with FP induced a significant reduction (about 20%), compared to baseline values, in the resistive properties of the respiratory system. At enrollment, our patients

Figure 2. Individual and mean changes in Rmax.rs at the various times of the experiment. Top: the effects of FP administration at day 1 and day 6. Significant reductions in R.rs from baseline day 1 were obtained at day 6 before (p < 0.001) and after (p < 0.001) FP administration. Bottom: the effects of placebo. No significant changes were observed.
already had profound alterations of their RM, leading to the hypothesis that these relatively small decreases in resistance could be helpful in a case of very severe airway obstruction. Indeed, unlike asthmatics, COPD patients often do not respond dramatically to standard bronchodilators since COPD is, by definition, characterized in the stable phase by only partial or even irreversible obstruction. In fact, the majority of patients showed an improvement in both resistances or in PEEPi,st of > 10%, but some of them did not seem to respond at all. The changes recorded in the present study were similar to the ones observed in patients during an episode of acute respiratory failure about 2 h after the administration of IV methylprednisolone and to those recorded after 3 days of receiving the same drug parenterally.

No study, so far, has been able to show an acute response to inhaled steroids in a population in stable condition. There may be three main reasons for this. First, most of the studies of patients in stable condition with COPD were designed to assess the long-term effects, and, therefore, the very early response to the drug never was tested. The second reason is probably related to the selection of patients, since most of the studies enrolled patients with mild disease (the pooled mean FEV1 of the published studies is around 55 to 60% of predicted), while we focused our investigation on more severely ill patients (mean FEV1, 13% of predicted). The severity of airway obstruction is likely to be related to the time of the manifestation of the first symptoms and to the number of hospital admissions, both of which have been shown to be positively related to

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**Figure 3.** Individual and mean changes in Rmin,rs at the various times of the experiment. Top: the effects of FP administration at day 1 and day 6. Significant reductions in Rmin,rs from baseline day 1 were obtained at day 6 before (p < 0.001) and after (p < 0.001) FP administration. Bottom: the effects of placebo. No significant changes were observed.

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**Figure 4.** Identity plot comparing the bronchodilator response at day 6 using the Rmin,rs or FEV1 changes from baseline in the nine patients who could perform the pulmonary function tests correctly.
the response to steroid treatment. The last reason is that the lack of improvement reported in some studies may be related to methodological problems. The classical and routinely used methods to assess the effects of bronchodilators are the so-called forced expiratory maneuvers, in particular FEV₁, which have been shown to fail frequently to detect a significant functional response to bronchodilators.¹⁷ The lack of effect of this test on very severely ill COPD patients may be because of early airway collapse and subsequent airway decline causing underestimation of the real bronchodilator effects, which may be located more distally in the respiratory tract. In fact, the major site of resistance of patients with COPD is located very peripherally. The lack of sensitivity of FEV₁ in assessing functional improvement after a reversibility test in apparently poorly reversible COPD patients has been described recently by Maesen and coworkers.²⁸ They found that measurements of work of breathing and Raw had substantial advantages over FEV₁ in detecting changes in airway caliber. Similarly, we have found that the recording of the passive minimal resistances was significantly more sensitive than FEV₁ in assessing the bronchodilator response (Fig 4).

For these reasons, we decided to enroll a population of patients in stable condition with severe reversible COPD who were still receiving mechanical ventilation to allow us to have more objective measurements of RM. The end-inspiratory occlusion method during mechanical ventilation in sedated and, therefore, passive patients is able to determine the changes in airway diameters precisely. The end-expiratory occlusion method allows us to determine precisely the presence of PEEPi,st, which is a common finding in critically ill COPD patients, but one that could be measured only invasively or passively (i.e., when the respiratory muscles are quiescent).²⁹ In COPD patients, PEEPi,st is a consequence of dynamic hyperinflation and acts as an inspiratory threshold load that must be fully counterbalanced by the inspiratory muscles of the patient to start and maintain inspiration. The reduction in Raw produced, for example, by the action of bronchodilators, leads to a reduction in dynamic hyperinflation and, therefore, in PEEPi,st. The ΔR,rs did not change. This finding suggests that the major effect of FP was on the airway caliber.

Airway inflammation is central in the pathogenesis of airway obstruction not only in patients with asthma, but also in those with COPD.³⁰ In the latter group, airway inflammation is associated with an increased number of T-lymphocytes and macrophages in the submucosa and with an increased infiltration of neutrophils and macrophages in the bronchial glands of central airways. The recruitment of neutrophils, and neutrophil elastase in particular, to the lung and their activation lead to the release of proteolytic enzymes that, if not counterbalanced by their inhibitors, are thought to perpetuate this lung inflammation and progression of the disease. Llewellyn-Jones and coworkers³¹ have shown that the administration of FP may play a protective role in these patients, reducing the chemotactic activity of lung secretions and the recruitment of neutrophils, and at the same time may affect the proteinase-antiproteinase balance in favor of antiproteinases. These findings were questioned by Keatings et al³² who found no effect from a 4-week course of budesonide on some inflammatory markers, including neutrophil activation. Interestingly enough, and in keeping with our results, the only short-term study performed in COPD patients in stable condition using oral steroids demonstrated that only 5 days of treatment increased elastase inhibition, suggesting a beneficial effect on the antielastases.³³ Indeed, a direct action of FP on airway smooth muscles is also theoretically possible.³⁴

Despite the significant improvement in airway obstruction, no changes were recorded in arterial blood gas levels, but this is in keeping with other studies²,²⁷ Some methodological problems should be discussed at this point. The dose of FP used in the study is higher than that usually employed (2,000 μg vs 1,000 μg, respectively). It should be noted, however, that only a small fraction of the inhaled bronchodilators reach the pulmonary receptors, and this holds particularly true when the drug is delivered by MDI during mechanical ventilation because of the deposition of particles in the ventilatory circuit and in the tracheotomy or endotracheal tube.³⁵ We were very careful to control all the factors involved in optimizing drug delivery by MDI, such as ventilatory mode, Vt, inspiratory time, and duty cycle, and to avoid humidification and heating, which have been shown to reduce drug delivery.³⁶ The full control of these factors would reasonably lead to the delivery of about 35 to 40% of the drug (i.e., about 60% of that reported for spontaneously breathing patients). For this reason, the dose of FP was doubled to mimic the dose delivered to spontaneously breathing patients.

The measurement of RM in these patients with severe airflow limitation is fraught with difficulty. To minimize some of the problems, we occluded the inspiratory hold button for 5 s, which is the time recommended to allow true static recoil conditions to be reached.³⁷ We are also conscious that the recording of FEV₁ when a patient is breathing through a tracheotomy may be not reliable, even though this technique has been used in other published studies.¹⁸ Since the patients were studied in
the same manner before and after receiving treatment or placebo, most of these limitations apply at all times and, therefore, in our opinion, should not have biased the test results.

In this study, we did not specifically assess all the potential side effects of FP, but no major collateral events were recorded, including no increase in serum glucose.

In conclusion, we have shown that in patients in stable condition with severe COPD who are affected by chronic respiratory failure and are receiving long-term mechanical ventilation, the short-term administration of high doses of inhaled FP may improve their RM and, in particular, may decrease abnormally elevated resistive properties. This was assessed using a passive recording that limits errors due to effort-dependent maneuvers, like FEV1, in patients who are unlikely to be able to produce maximal efforts. The short-term course of inhaled steroids may usefully assess the reversibility of obstruction in these patients in an alternative to the classic bronchodilators and may eventually provide the conditions to improve patient-ventilator interaction in cases of prolonged mechanical ventilation.

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