Lung Function and Sputum Characteristics of Patients with Severe Asthma During an Induced Exacerbation by Double-Blind Steroid Withdrawal

JOHANNES C. C. M. in ‘t VEEN, HERMELIJN H. SMITS, PIETER S. HIEMSTRA, AELIKO E. ZWINDERMANN, PETER J. STERK, and ELISABETH H. BEL

Departments of Pulmonology and Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands

Some patients with severe asthma are difficult to control and suffer from frequent exacerbations, whereas others remain stable with anti-inflammatory therapy. To investigate mechanisms of exacerbations, we compared 13 patients 20 to 51 yr of age (11 female, two male) with difficult-to-control asthma (two or more exacerbations during the previous year) and 15 patients 20 to 47 yr of age (13 female, two male) with severe but stable asthma (no exacerbations) after matching for sex, age, atopy, lung function, airway responsiveness, and medication. Exacerbations were induced by double-blind, controlled tapering of inhaled corticosteroids (fluticasone propionate) at weekly intervals. FEV₁, airway responsiveness for methacholine (PC_{20} MCh) and hypertonic saline (HYP slope), eosinophils and soluble markers (ECP, albumin, IL-6, IL-8) in induced sputum were assessed at baseline and during exacerbation (peak flow ≤ 60% of personal best), or after 5 wk if no exacerbation occurred.

Steroid tapering caused a decrease (mean ± SEM) in FEV₁ (12.1 ± 3.1% pred; p = 0.045), PC_{20} MCh (2.1 ± 0.4 doubling dose; p = 0.004) and HYP slope (1.7 ± 0.3 doubling dose; p = 0.001), and an increase in sputum eosinophils (10 ± 3%; p = 0.008) and soluble markers for the two groups combined, without significant differences between the groups. Patients with difficult-to-control asthma had more exacerbations than did the stable asthmatics during both steroid tapering (7 versus 2; p = 0.022) and corticosteroid treatment (6 versus 0; p = 0.003). Exacerbations during steroid treatment in the patients with difficult-to-control asthma were associated with a decrease in FEV₁ and PC_{20} MCh, but not in HYP slope or increase in sputum eosinophils. We conclude that tapering of inhaled corticosteroids induces a rapid, reversible flare-up of eosinophilic airway inflammation. Patients with difficult-to-control asthma may develop exacerbations despite treatment with inhaled corticosteroids, which appear to have an eosinophil-independent mechanism. This implies that assessment of the nature of exacerbations may contribute to improved treatment for these patients.

Important progress has been made in the management and treatment of asthma during the last decades, resulting in a controllable disease in most patients (1). However, severe exacerbations do still occur, and there is evidence that morbidity and mortality from asthma are even increasing in most western countries (2–5). A history of multiple hospital admissions for asthma in the previous year has been shown to be a major risk factor for asthma mortality, and 20% of asthma deaths occur in patients with intermittent, severe exacerbations (6–10). A part from these important medical consequences, exacerbations have a significant socio-economic impact and contribute largely to the total cost of asthma (11).

The epidemiology of and risk factors for severe asthma have been studied extensively (2–9). However, it is as yet unclear why some patients with asthma have frequent exacerbations, whereas others remain stable with anti-inflammatory asthma treatment throughout the year.

We hypothesized that the pathophysiologic mechanisms of asthma exacerbations differ between patients with severe asthma with recurrent exacerbations and patients with equally severe but stable disease. Therefore, the aim of our study was to compare changes in lung function, airway responsiveness, and sputum characteristics during an induced exacerbation between two groups of patients with severe asthma: One group with at least two severe exacerbations requiring a course of oral corticosteroids during the preceding 12 mo, and one group without any exacerbations during the previous year.

We used an asthma model in which a (controlled) exacerbation was induced by double-blind, controlled, gradual taper-
ing of inhaled corticosteroids. During the development and recovery of an exacerbation airflow limitation was assessed by peak flow (PEF) and FEV₁, airway hyperresponsiveness was tested by direct (methacholine) and indirect (hypertonic saline) challenges, and airway inflammation was evaluated by cellular and soluble markers in induced sputum.

**METHODS**

**Subjects**

Two groups of patients with severe bronchial asthma participated in the study. A II patients had a history of episodic dyspnea and wheezing. Patient characteristics are summarized in Table 1. Classification of asthma severity was based on history, symptoms, clinical features, and medication requirement according to international guidelines (1). The FEV₁ was within the normal range (> 70% predicted) (12) after inhalation of 400 μg salbutamol per metered dose inhaler connected to an aerosol chamber. A II patients were hyperresponsive to inhaled methacholine (M Ch) as shown by a provocative concentration causing a 20% fall in FEV₁ (PC20 M Ch) of less than 8 mg/ml (13). A II patients except three were atopic as assessed by specific serum IgE to a panel of common allergens (Phadiatop; Pharmacia, Utrecht, The Netherlands). The group of asthmatic patients with recurrent exacerbations consisted of 13 patients 20 to 51 yr of age (11 female, two male) with severe asthma (difficult-to-control asthma), who had had two or more exacerbations during the preceding year requiring a course of oral corticosteroids for at least 7 d, despite high-dose inhaled corticosteroid maintenance therapy (beclomethasone dipropionate [BDP]/budesonide [BUD] 800 μg twice a day or fluticasone propionate [FP] 500 μg twice a day as multidose inhaler [MDI] or dry powder inhaler). The group of asthmatic patients without recurrent exacerbations (stable asthma) consisted of 13 matched control patients 17 to 51 yr of age (11 female, two male) with equally severe asthma, using an equivalent high-dose inhaled corticosteroid regimen (BDP/BUD 800 μg or FP 500 μg twice a day), without exacerbations during the previous year. They were recruited from the outpatient department and had been under specialist care.

Between the groups, the 13 pairs of patients were individually matched for age (two groups: 16 to 39 yr or 40 to 55 yr), FEV₁ postbronchodilator (70 to 85% or > 85% predicted), and PC20 M Ch (≥ 2 doubling doses), and for at least one of the following two criteria: sex and atopic status (two groups: atopy or no atopy). In addition, two more female patients with stable severe asthma were recruited but could not be individually matched. They were, however, included in the study.

None of the patients had a history of respiratory disease other than asthma, and none of them used any other medication except for study medication and short acting β₂-agonists or ipratropium bromide as needed for their asthma during the study. A II patients were non-smokers or ex-smokers (for more than 12 mo, with less than 5 pack-years). The patients were included during a clinically well-controlled episode, without symptoms of an upper respiratory tract infection for 4 wk prior to the study. The study was approved by the Hospital Med. Ethics Committee, and informed consent was given by all patients.

**Design**

The study had a double-blind, controlled, crossover design (Figure 1). The two study periods consisted of a 4-wk run-in phase, a 5-wk tapering phase, and a recovery phase of at least 2 wk. Before the start of the study patients were screened on two separate days. Long-acting β₂-agonists and theophylline preparations, if used, were discontinued at least 72 h before the first screening visit. On the first visit FEV₁ (before and after inhalation of 400 μg salbutamol per MDI connected to an aerosol chamber) was measured, and on the second visit a methacholine challenge test was performed. Inclusion criteria were checked and matching was completed. Thereafter, maintenance inhaled corticosteroid therapy of the patients was changed into fluticasone propionate 500 μg twice a day via a multi-dose dry powder inhaler (Rotadisk; Glaxo Wellcome, The Netherlands) in order to standardize anti-inflammatory therapy.

After the run-in phase of 4 wk in which medication compliance and disease stability were checked, an exacerbation was induced by weekly reduction of the daily dose of FP in a randomized, double-blind, controlled fashion. FP was tapered in a cross-over design over a 5-wk period during the exacerbation-induction phase, whereas the dosage remained FP 500 μg twice a day during the control phase. The patients visited the hospital at the end of the run-in period, at weekly intervals during the double-blind steroid tapering period, at the time of the exacerbation, and at remission (Figure 1). Before, during, and after the exacerbation measurements were performed on 2 consecutive days, at the same time of day, during which FEV₁ and airway hyperresponsiveness to M Ch were obtained on one day, and airway responsiveness to hypertonic saline (Hyp) and induced sputum on the other day. During the study the patients kept a diary to record morning and evening PEF measurements.

**Induction of an Exacerbation**

Induction of an exacerbation of asthma was performed according to a research model originally introduced by Gibson and colleagues (14).

### TABLE 1

**PATIENT CHARACTERISTICS***

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Atopy</th>
<th>FEV₁ (% pred)</th>
<th>PC20 (mg/ml)</th>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Atopy</th>
<th>FEV₁ (% pred)</th>
<th>PC20 (mg/ml)</th>
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* Patient with difficult-to-control asthma (DTC) have been individually matched with stable patients (S). FEV₁ values are expressed as individual values and as means and SEM. PC20 is expressed as individual values and geometric means and SEM in doubling doses.
as an open model. After the run-in phase of 4 wk, the dosage of FP was reduced from 1,000 μg to 750 μg daily during the first week, to 500 μg daily during the second week, and to 250 μg daily during the third week; no FP or any other corticosteroids were taken during the fourth and fifth week. The tapering phase lasted less than 5 wk if an exacerbation had occurred. In case of an exacerbation within this 5-wk period, tapering was discontinued and patients were treated as described elsewhere in this section.

During the 4-wk run-in phase (e.g., before FP tapering), all patients had to be stable (mean prebronchodilator diurnal PEF variability less than 25%) without lower respiratory tract infection (1). Only short-acting β₂-agonists (preferably Ventolin Rotadisk) or ipatropium bromide were allowed during the study as rescue medication. The patients were instructed in the correct use of a Rotadisk, a peak-flow meter, and a daily diary. A study physician was accessible by telephone 24 h a day. Patients faxed their PEF data daily to the physician during tapering of FP and during the remission period.

A n exacerbation was defined as at least one of three criteria: (1) reduction of PEF (best of three attempts) to less than 60% of the previous personal best (postbronchodilator) PEF value obtained during the run-in period (1), (2) a sudden, rapid decline in peak flow or deterioration in symptoms suggestive of the development of a severe exacerbation, (3) severe airway hyperresponsiveness, defined as a decline in FEV₁ of more than 20% after inhalation of diluent during the MCh challenge test. Measurements at the time of the exacerbation were then performed within 24 h. Thereafter, the dose of FP was increased to 1,000 μg three times daily for the first day, and 1,000 μg twice a day for the six following days to prevent further worsening. Then FP was again given in the previous dosage of 500 μg twice a day (Figure 1). No systemic corticosteroids were administered, unless there was further deterioration despite the increased doses of inhaled steroids. If systemic corticosteroids were given, patients were then withdrawn.

Remission was defined as normalization of PEF, with the mean morning and evening prebronchodilator PEF for 1 wk being at least 90% of the mean prebronchodilator PEF of the last week before FP tapering during baseline, and less than 25% diurnal PEF variation. At the remission visit, at least 2 wk after the exacerbation visit, measurements as described previously were performed. If no exacerbation of asthma had developed within 5 wk, the controlled withdrawal was discontinued, and measurements were performed as if there had been an exacerbation. Similarly, the doses of FP were increased and followed by additional measurements 2 wk later. The two steroid-tapering periods were separated by a “washout” phase of at least 4 wk, in which the patients received FP 500 μg twice a day.

**Lung Function Measurements and Challenge Tests**

Patients were instructed to perform morning and evening PEF measurements at home using a Mini-Wright peak-flow meter before taking bronchodilator medication (1). PEF was measured three times in the upright position and the best value was recorded. FEV₁ was measured using a dry rolling-seal spirometer (Spiroflow; P.K. Morgan, Rainham/Gillingham, U.K.) (12). No bronchodilator therapy was allowed within 6 h before measurements were made.

A irway hyperresponsiveness to methacholine was assessed using the method of Cockcroft and colleagues (13). MCh was inhaled by tidal breathing in doubling concentrations (0.015 to 32 mg/ml) for 2 min at 5-min intervals. Measurements of FEV₁ were made before the test and after each dose. The challenge test was discontinued if FEV₁ dropped 20% or more from baseline. The provocative concentration of MCh resulting in a 20% fall in FEV₁ (PC_{20}MCh) was calculated by linear interpolation of the log-dose response curves (13).

Hypertonic saline challenge tests were performed according to a recommended protocol (13). Sodium chloride aerosols 4.5% (HYP) (wt/vol) were generated by an ultrasonic nebulizer (Utnabn 2000; DeVilbiss, Somerset, PA) with a calibrated particle size (mass median aerodynamic diameter, 4.5 μm), and the output set at maximum (2.5 ml/min at the mouthpiece). The aerosols were inhaled by mouth while the nose was clipped. The exposure time was doubled as follows: 15 and 30 s and 1, 2, 4, and 8 min. FEV₁ measurements were made before and at 60 and 90 s after each exposure. The actual output delivered to the two-way valve was determined by weighing the nebulization chamber before and after nebulization. The challenge test was discontinued when FEV₁ had dropped more than 20% from baseline value, or when
the maximal dose had been given. Because not all subjects had a 20% fall in FEV₁ during the HYP challenge, the response to HYP was expressed as the slope of the dose-response curve (HYP slope), in which percent decline FEV₁ was defined as the decline in FEV₁ (from mean baseline value) after the final dose of HYP administered, and the dose was defined as the cumulative HYP dose delivered (15). Hyperresponsiveness to MCh and HYP were assessed at least 24 h apart. Bronchodilators were withdrawn at least 6 h before the challenge tests.

Sputum Induction and Processing

Sputum induction was performed in association with the hypertonic saline challenge test as described earlier (16) with modifications (17). After each inhalation period patients were asked to rinse their mouth and were encouraged to expectorate sputum. All subjects received 400 μg salbutamol by spacer device after completing the HYP challenge test. Thereafter, sputum induction was continued by inhalation of hypertonic saline with expectoration of sputum every 5 min to a maximum of 15 min. The volume of the whole sputum sample was determined, and an equal volume of dithiotreitol 0.1% (wt/vol) (Sputolysin; Calbiochem, La Jolla, CA) was added. The samples were gently mixed, an equal volume of dithiotreitol 0.1% (wt/vol) (Sputolysin; Calbiochem, La Jolla, CA) was added. The samples were gently mixed, placed in a shaking water bath at 37°C for 15 min, and centrifuged. The supernatant was aspirated and stored at −70°C pending analysis. The cell pellet was resuspended, filtered, cytocentrifuged, and stained (Diff-Quik; Baxter, Dübening, Switzerland). The total cell count was obtained by a standard hemacytometer. Differential cell counts were performed by counting at least 500 nonsquamous cells in a blind way, and are expressed as a percentage of nonsquamous cells. Sputum samples containing more than 80% squamous cells were excluded from the analysis because of poor cytospin quality (17).

Biochemical Assays

Albumin was assessed by turbidimetric assay (Hitachi 911 system; Boehringer Mannheim, Germany), interleukin-8 (IL-8) by enzyme-linked immunosorbent assay (ELISA) (Centrion Laboratory of The Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands), monocyte chemoattractant protein-1 (MCP-1) by ELISA using antibodies obtained from R&D Systems (A bingdon, U K), and eosinophil cationic protein (ECP) by fluoroenzyme immunoassay (generously donated by Pharmacia, Woerden, The Netherlands).

Analysis

Data are expressed as mean ± SEM unless otherwise stated. PC₂₀ MCh, HYP slope, and biochemical data are log-transformed before analysis and are expressed as geometric mean ± SEM in doubling dose or concentration. Differences were assessed by Student’s t test for paired and unpaired data and MANOVA, or by nonparametric tests (Mann Whitney U and Wilcoxon’s tests) when appropriate. A p value of 0.05 or less was considered significant.

**EXHIBIT **

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
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<tbody>
<tr>
<td><strong>MEASUREMENTS OF BASELINE VISIT AND THE VISIT AT EXACERBATION OR AFTER 5 WEEKS OF DOUBLE-BLIND TREATMENT OBTAINED DURING THE TAPERING PHASE AND THE CONTROL, FLUTICASONE-TREATED PHASE.</strong></td>
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<tr>
<td><strong>Difficult-to-control Asthma (n = 13)</strong></td>
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<td><strong>Fluticasone Propionate</strong></td>
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<td><strong>Exacerbation, n</strong></td>
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<td>PEF, L/min</td>
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<td>FEV₁, % pred</td>
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<td>PC₂₀, ng/ml</td>
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<td>Sputum neutrophil, %</td>
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<td>Sputum ECP, ng/ml</td>
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<td>Sputum albumin, μg/ml</td>
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<td>Sputum IL-8, ng/ml</td>
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<td>Sputum MCP-1, μg/ml</td>
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*p Data are expressed as mean ± SEM, or geometric mean ± SEM in doubling doses per concentration when appropriate.

† p < 0.05, changes during fluticasone treatment versus tapering for difficult-to-control versus stable asthma.

‡ p < 0.05, changes during fluticasone treatment versus tapering.

§ p < 0.01, fluticasone propionate versus tapering.

| Habit to-be-expected as the slope of the dose-response curve (HYP slope), in which percent decline FEV₁ was defined as the decline in FEV₁ (from mean baseline value) after the final dose of HYP administered, and the dose was defined as the cumulative HYP dose delivered (15). Hyperresponsiveness to MCh and HYP were assessed at least 24 h apart. Bronchodilators were withdrawn at least 6 h before the challenge tests.

**RESULTS**

**Patient Characteristics**

Patient characteristics at screening are summarized in Table 1. As expected, there were no significant difference between patients with difficult-to-control asthma and those with stable asthma for age (p = 0.84), FEV₁ postbronchodilator (p = 0.97), and airway responsiveness for MCh (p = 0.90). Aiso, sex and atopy were equally distributed between the two groups. In retrospect, also, prebronchodilator FEV₁ (% predicted) did not significantly differ between the patients with difficult-to-control asthma (77.6 ± 5.6) and those with stable asthma (81.0 ± 4.1, p = 0.62). Both the patients with difficult-to-control asthma (18.1 ± 3.6 yr) and the patients with stable asthma (19.3 ± 2.7 yr) had long-standing asthma (p = 0.77).

**Exacerbations**

Seven (54%) patients with difficult-to-control asthma developed an exacerbation during the steroid-tapering period as compared with six (46%) during the FP treated period (p = 0.99). Two (13%) patients with stable asthma developed an exacerbation during the steroid-tapering period as compared with zero (0%) during the FP treated period (p = 0.50). The patients with difficult-to-control asthma had significantly more exacerbations than did the stable asthmatics both during the steroid-tapering period (p = 0.022) and the FP-treated period (p = 0.003). A.11 but one subjects with an exacerbation reached a peak flow of 60% or less. Exacerbation in one subject (PEF = 67%) was defined on PC₂₀ MCh.

Systemic corticosteroids were required for an exacerbation with further deterioration despite FP in three patients with difficult-to-control asthma during the control period, and in two patients with difficult-to-control asthma as well as in two pa-
patients with stable asthma during the FP tapering period. All other patients recovered completely with high-dose inhaled FP.

### Lung Function and Challenge Tests

During the run-in phase in both study periods, asthma of all patients was well controlled as measured by the mean diurnal PEF variation, which was less than 15%. There were no significant differences in baseline data of PEF (mean morning and evening PEF of the last week of the run in phase, FEV₁, and PC₂₀MCh neither within nor between groups. The baseline airway responsiveness to hypertonic saline expressed as HY P-slope (geometric mean % fall/ml ± SEM in doubling dose) appeared to be steeper in the group with difficult-to-control asthma than in the stable asthmatics (1.55 ± 0.52 versus 0.40 ± 0.48, p = 0.005).

Results of the changes in lung function and challenge measurements comparing difficult-to-control and stable asthma are shown in Table 2 and Figure 2. When comparing the changes between baseline and exacerbation for patients with difficult-to-control asthma and the stable asthmatics for all lung function parameters, only the change in PC₂₀MCh appeared to be significantly different (p = 0.040). A further exclusion of the patients requiring oral corticosteroids during the remission period, reintroduction of FP resulted in normalization of all measured lung function parameters in both patient groups.

### Sputum Measurements

No significant differences were observed in baseline cell counts or soluble markers in induced sputum within and between patient groups. Squamous cell counts of induced sputum were always less than 80%; therefore none of the sputum samples was withdrawn from analysis.

Results of the changes in sputum parameters, comparing difficult-to-control and stable asthma, are summarized in Table 2 and Figure 2. When comparing the effect of FP tapering between the two groups, only the change in sputum albumin during the double-blind steroid tapering appeared to be significantly different (p = 0.043). A further administration of FP all values normalized, and no differences were observed when comparing baseline versus remission visits.

### General Effects of Steroid Tapering

Although it was not the primary aim of the study, we also assessed the effects of tapering of FP on lung function and sputum parameters for both patients with difficult-to-control asthma and those with stable asthma combined. Corticosteroid tapering resulted in a significant increase in airway obstruction and airway hyperresponsiveness to MCh and HYP.

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**Figure 2.** Effect of double-blind tapering of inhaled corticosteroids for the patients with difficult-to-control asthma (left panels) and stable asthmatics (right panels) on airway responsiveness to methacholine (A) and to hypertonic saline (B) and sputum eosinophils (C). Data were collected at run-in (Week 0), exacerbation (Week 5), and remission visit (Week 7), and they are expressed as mean ± SEM. The continuous line with closed triangles represents the FP tapering period, and the dashed line with open triangles represents the FP control treatment period (*p* < 0.01 comparing baseline visits of difficult-to-control asthma and stable asthma; *0.05 < p < 0.10, **0.05 ≤ p < 0.01, ***p ≤ 0.01, comparing changes between exacerbation and baseline and between remission and exacerbation within the two groups).
In addition, markers of inflammation in induced sputum increased significantly (Table 3).

DISCUSSION

The present study shows that double-blind tapering of inhaled corticosteroids in patients with severe asthma causes a reversible reduction in lung function and an increase in airway responsiveness to methacholine and hypertonic saline, associated with an increase in eosinophils and other markers of inflammation in induced sputum. There were no significant differences between patients with frequent asthma exacerbations and patients with stable disease, except for a more pronounced airway responsiveness to hypertonic saline in the former group at baseline. As expected, the patients with difficult-to-control asthma had significantly more exacerbations than did the patients with stable asthma, both occurring during the corticosteroid-tapering phase and the control-treatment phase with inhaled corticosteroids. In contrast to the steroid tapering-phase, the exacerbations occurring during the steroid-treatment phase were not associated with an increase in sputum eosinophils or airway responsiveness to hypertonic saline. This suggests an eosinophil- and possibly an inhaled corticosteroid-independent mechanism for recurrent exacerbations in patients with difficult-to-control asthma.

This is the first double-blind, controlled inhaled steroid tapering study in patients with severe asthma investigating pathophysiologic mechanisms of a controlled exacerbation. The results confirm and extend those of Gibson and colleagues (14) using a similar but uncontrolled exacerbation model in adults with asthma. They found an exacerbation of symptoms within 4 wk after the onset of steroid reduction, accompanied by a decrease in FEV₁, an increase in airway responsiveness to methacholine, and an increase in peripheral blood eosinophils. In their study, all patients developed an exacerbation during steroid reduction, whereas this was not the case in our study. The most likely explanation for this discrepancy is the stringent definition of exacerbation not based on symptoms but on a decrease in PEF of 40% or more from personal best PEF. A less strict criterion would have increased the number of exacerbations considerably. In retrospect, a fall in PEF of 30%, as suggested by Chan-Y Yeung and colleagues (18), might have been more appropriate. A nother explanation might be a bias factor, introduced by the uncontrolled design in Gibson's study. Three other articles also reported on lung function and airway responsiveness to methacholine after controlled tapering of inhaled corticosteroids in patients with mild asthma, and found significant changes after 3 to 12 mo (19–21). Our study adds to the above studies, in that it relates the changes in lung function parameters to the concurrent changes in sputum inflammatory markers during an induced exacerbation.

This is also one of the first studies investigating pathophysiologic mechanisms of frequent exacerbations in a subgroup of patients with severe asthma. At baseline, the patients with recurrent exacerbations were carefully matched with those without exacerbations for factors that have been reported to be associated with frequent hospitalizations for asthma such as sex, atopic status, airflow obstruction, and airway responsiveness to methacholine (4, 9, 22, 23). In addition, there was no difference in duration of asthma and diurnal peak flow variation. Still, it appeared that baseline airway responsiveness to hypertonic saline could separate the two groups. A low baseline responsiveness to hypertonic saline, studied while asthma was clinically well controlled, was significantly more severe in the patients with frequent exacerbations than in the group without exacerbations. This suggests that airway responsiveness to indirect stimuli is a more specific marker of instable asthma than are other lung function parameters. Interestingly, even sputum markers did not discriminate between the groups, which questions the additive information of sputum to physiologic markers in relation to the clinical control of asthma.

In the present study we observed that patients with difficult-to-control asthma, being selected on the basis of at least two exacerbations the previous year, continued to suffer from exacerbations, even during the nontapering phase. The number of exacerbations in this group of patients was significantly higher (6 versus zero) as compared with the group of patients with stable disease. This seems to confirm the observation by others that a history of frequent exacerbations is a risk factor for developing future exacerbations (6, 9). It indicates that among patients with severe asthma, a subgroup can be distinguished with an abnormally increased susceptibility to exacerbations. Apparently, the regular use of this dose of inhaled corticosteroids did not protect against deterioration. This suggests that these exacerbations might have been elicited by factors that were not, or only minimally, affected by corticosteroids such as viral respiratory infections, allergens, female hormones, psychologic factors, or unknown sensitizing factors (24).

The double-blind, controlled design of the study provided us with the unique opportunity to compare the pathophysiologic mechanisms of induced and spontaneous exacerbations in severe asthma. Both the exacerbations induced by steroid tapering, as well as the spontaneously occurring, were characterized by a decline in PEF and FEV₁ and an increase in airway responsiveness to methacholine. However, only the induced exacerbations were associated with increases in airway responsiveness to hypertonic saline and percentages of eosinophils in induced sputum. This suggests that changes in PEF, FEV₁, and airway responsiveness to methacholine are nonspecific, and reflect an exacerbation in general, thereby favoring their usage in clinical practice. In contrast, airway hyperresponsiveness to indirect stimuli and sputum eosinophilia are being suppressed by corticosteroid treatment, recur after discontinuation of treatment, and are not characteristic for all types of exacerbations in severe asthma (25). This fits in with the observation that inhaled corticosteroids do not suppress noneosinophilic airway inflammation in severe asthma (26).

The effects of steroid tapering can be explained by the effects of corticosteroids on the inflammatory airway process in asthma. Inhaled corticosteroids are known to improve lung function and airway responsiveness to direct and indirect stimuli (27–29), and to suppress eosinophilic airway inflammation (30–33). It is therefore not surprising that a study with an opposite design with tapering of inhaled corticosteroids shows a deterioration in lung function parameters with a flare-up in sputum eosinophilia as well as in other sputum markers of inflammation.

The clinical implications of the present study are first that tapering of inhaled corticosteroids in patients with severe asthma causes a rapid flare-up of eosinophilic airway inflammation with subsequent development of an asthma exacerbation. Second, patients with difficult-to-control asthma may develop exacerbations that cannot be prevented by even high doses of inhaled corticosteroids. These exacerbations are associated with changes in PEF, FEV₁, and PC₂₀M Ch, but not with increased bronchial responsiveness to hypertonic saline or eosinophilic airway inflammation, and they probably have a different underlying mechanism. It is, therefore, important to investigate the nature of the exacerbations in patients with difficult-to-control asthma in order to assess the need for high doses of (inhaled) corticosteroids to control the disease.
References


