Impaired Perception of Dyspnea in Patients with Severe Asthma: Relation to Sputum Eosinophils

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Poor dyspnea perception might be a risk factor for developing asthma exacerbations. We investigated whether severe asthmatics with recurrent exacerbations (brittle asthma) have different dyspnea perception and sputum cells compared with equally severe, but stable asthmatics, or patients with mild steroid-naive asthma. Fifteen brittle asthmatics (13 female, median age 28 yr [range, 20 to 47 yr]), 15 matched severe-stable asthmatics (14 female, median age 26 yr [range, 17 to 52 yr]), and 11 mild asthmatics (8 female, median age 25 yr [range, 19 to 43 yr]) underwent inhalation tests with methacholine (MCh), and hypertonic saline combined with sputum induction. Dyspnea was assessed by Borg and Visual Analogue Scale (VAS), plotted against the percent fall in FEV$_1$, and expressed as the slope of the regression line (Slope-Borg and Slope-VAS). The brittle and stable asthmatics had poorer perception than patients with mild asthma (Slope-Borg [p = 0.036], Slope-VAS [p < 0.001] for MCh). In patients with brittle asthma the perception was less as compared with severe-stable asthma (Slope-Borg for MCh: p = 0.05). In the severe asthmatics there was an inverse correlation between sputum eosinophilia and Slope-Borg and Slope-VAS (R$=−0.55$, p = 0.002 and R$=−0.37$, p = 0.049), whereas this correlation was a positive one in the mild asthmatics (R$=0.79$, p = 0.012 and R$=0.67$, p = 0.05). In conclusion, patients with severe asthma, particularly those with recurrent exacerbations, have blunted perception of dyspnea, which is related to the degree of sputum eosinophilia. This suggests that increased sputum eosinophilia is an indicator of clinical instability, and that eosinophilic airways inflammation might affect dyspnea perception in severe asthma.

Asthma is a chronic inflammatory disease of the airways, characterized by episodic symptoms of chest tightness and wheezing, associated with variable airways obstruction (1). In most patients symptoms are well controlled by current anti-inflammatory therapy. However, severe exacerbations do still occur in a minority of patients, potentially leading to near-death or even death (2–4). An important endogenous factor that could contribute to the development of frequent exacerbations in asthma is a diminished perception of breathlessness (5). Because of blunted perception, patients with severe asthma might not sense a forthcoming exacerbation, thereby not avoiding bronchoconstrictive stimuli nor seeking medical care (5, 6).

The scoring of perception during bronchoprovocation testing may help to detect patients who are at risk of not perceiving a worsening of their asthma (7). Previously, it has been shown that the severity of dyspnea appears to be greater in response to indirect stimuli (hypertonic saline) as compared with direct stimuli (methacholine) at the same reduction of FEV$_1$ (8, 9), which might be explained by differences in perception due to inflammatory activity within the airways (8, 10, 11). In addition, it has been confirmed recently that there is an association between perception of breathlessness and airway inflammation, as measured by eosinophilic infiltration and epithelial shedding in bronchial biopsies from asthmatic patients (12).

In the present study we hypothesized that asthmatic patients with recurrent exacerbations have a diminished perception of dyspnea as compared with asthmatic patients without exacerbations. The aim of our study was to compare the perception of dyspnea between patients with severe steroid-dependent asthma, with a recent history of recurrent exacerbations (brittle asthma) with equally severe, but stable matched asthmatic control subjects (stable asthma) by using the Borg score (13) and Visual Analogue Scale (VAS) score (14), during inhalation challenge tests with either methacholine or hypertonic saline. In addition, the perception of dyspnea in this...
group of severe asthmatics was compared with the perception of a group of patients with mild, corticosteroid-naive asthma. In order to study the relation between dyspnea and noninvasive markers of asthmatic airway inflammation, we also assessed the relation between the perception of breathlessness, and markers of inflammation in induced sputum.

**METHODS**

**Subjects**

Three groups of patients with bronchial asthma participated in the study. All subjects had a history of episodic dyspnea and wheezing. Classification of asthma severity was based on history, symptoms, clinical features, and medication requirement according to international guidelines (1). The forced expiratory volume in one second (FEV₁) was within the normal range (<70% predicted) at baseline, or after inhalation of 400 μg salbutamol per metered dose inhaler connected to an aerosol chamber. All subjects were hyperresponsive to inhaled methacholine (M Ch) as shown by a provocative concentration to cause a 20% fall in FEV₁ (PC₂₀) of less than 8 mg/ml (15). A topic status was assessed or excluded by specific IgE to a panel of common aeroallergens (Phadiatop; Pharmacia, Uppsala, Sweden). Group I (brittle asthma) consisted of 15 patients (13 female, 2 male, age 20 to 47 yr) with severe asthma, who had had two or more exacerbations during the previous year requiring treatment with oral corticosteroids, despite high dose inhaled corticosteroid therapy (beclomethasone dipropionate/budesonide 800 μg twice daily or fluticasone propionate 500 μg twice daily). Group II (stable asthma) consisted of 15 matched control subjects (14 female, 1 male, age 17 to 52 yr) with equally severe asthma, using equivalently high-dose inhaled corticosteroid therapy, without a history of exacerbations during the previous year. The patients were recruited from our outpatient pulmonary department. Most of them visited our hospital for many years, mostly on a 3 to 6 mo basis, and during exacerbations. Inhaled corticosteroids were routinely tapered to the lowest possible doses. The 15 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). Group III (mild asthma) consisted of 11 patients (8 female, 3 male, age 19 to 43 yr) with mild steroid-naive asthma. All subjects had inhaled short acting β₂-agonists on demand as rescue medication. None of the subjects had a history of other respiratory disease than asthma, and did not use any other medication for their asthma during the study. All subjects were nonsmokers or ex-smokers (for more than 12 mo, with less than 5 pack-yr). The subjects were studied during a clinically stable period, without symptoms of an upper respiratory tract infection for 4 wk prior to the study. The study characteristics are summarized in Table 1. The study was approved by the Hospital Medical Ethics Committee, and informed consent was given by all subjects.

**Design**

On a screening day inclusion criteria were checked, and the subjects were made familiar with bronchial provocation testing. The inhaled corticosteroid medication of all patients of Groups I and II was matched by changing it to fluticasone propionate 500 μg twice daily (Rotadisk) for at least 4 wk. Hereafter, the subjects underwent two inhalation challenge tests within one week on two different occasions at the same time of day: on the first day a methacholine challenge was performed, and on the second day a hypertonic saline challenge test followed by sputum induction. During the challenge tests, dyspnea was measured after each dose of agonist using Borg and VAS scales. Compliance with the inhaled corticosteroid medication was checked before each challenge by counting the used Rotadisk blisters.

**Methacholine Inhalation Challenge Test**

Methacholine challenge tests were performed according to a standardized tidal breathing method (15). Methacholine in isotonic saline was aerosolized at room temperature in doubling concentrations (0.015 to 32 mg/ml) by a DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, PA; output 0.13 ml/min), with the straw in fixed position, connected to a three-way valve with an expiratory filter (Pall Utitpor BB 507; Pall Biomedical, Portsmouth, England). The aerosols were inhaled by tidal breathing during 2 min at 5-min intervals through the mouth with the nose clipped. Measurements of FEV₁ were made in triplicate before the test (baseline), and in duplicate (30 and 90 s) after each increasing dose. The challenge test was discontinued if FEV₁ dropped 20% or more from baseline. The provocative concentration of M Ch resulting in a 20% fall in FEV₁ (PC₂₀ M Ch) was calculated by linear interpolation of the log-dose response curves (15).

**Hypertonic Saline Inhalation Challenge Test**

Hypertonic saline challenge tests were performed according to a recommended protocol (15). Sodium chloride aerosols (Hyp) 4.5% (wt/vol) were generated at room temperature by an ultrasonic nebulizer (Ultraneb 2000; DeVilbiss, Somerset, PA) with a calibrated particle size (mass median aerodynamic diameter 4.5 μm), with the output set at maximal (2.5 ml/min at the mouthpiece). The aerosols were administered to the subjects through a 100-cm-long tube with an internal diameter of 22 mm, and were inhaled by mouth through a two-way valve (No. 2700; Hans-Rudolph, Kansas City, MO), while the nose was clipped. The exposure time was doubled as follows: 15, 30 s, 1 min, 2, 4, and 8 min. Measurements of forced expiratory volume in one second (FEV₁) were made in triplicate before (baseline) and at 60 and 90 s after each exposure to the aerosol. The 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 dropped more than 20% from baseline value, or when the maximal dose had been given. The provocative cumulative dose of Hyp resulting in a 15% decrease (the cutoff point [11, 15] that should be regarded as abnormal) in FEV₁ (PD₁₅ Hyp) was calculated by linear interpolation of the log-dose response curves (15).

**Assessment of Perception of Dyspnea**

The severity of dyspnea during the challenge tests was assessed by a Borg scale and VAS scale, at 20 s after inhalation of each dose, just before the measurement of the FEV₁ curves. Each subject was asked by oral question to rate their asthma sensation (Borg) and breathlessness (VAS) in a standardized way. The Borg scale is a vertical list with labeled categories (0–10) describing increasing intensities of asthma sensations (0 = “nothing at all,” and 10 = “maximal”) (13). The subjects were asked directly after inhaling each dose the same standardized question: “How severe is your asthma during and directly after the inhalation? 0 is nothing, 10 is maximal.” The VAS scale is a hori-

<table>
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<th>TABLE 1</th>
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| **SUBJECT CHARACTERISTICS**
<p>| |
|  |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Brittle Asthma</th>
<th>Stable Asthma</th>
<th>Mild Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>28 (20–47)</td>
<td>26 (17–52)</td>
<td>25 (19–43)</td>
</tr>
<tr>
<td>FEV₁% pred, postbronchodilator</td>
<td>91.6 (72–124)</td>
<td>100.5 (72–118)</td>
<td>98.3 (81–114)</td>
</tr>
<tr>
<td>PC₂₀ M Ch, mg/ml</td>
<td>0.69 (0.03–8.65)</td>
<td>0.71 (0.10–5.82)</td>
<td>0.65 (0.07–5.80)</td>
</tr>
<tr>
<td>PD₁₅ Hyp, ml</td>
<td>5.0 (1.1–15.8) (n = 10)</td>
<td>10.2 (3.8–12.2) (n = 5)</td>
<td>4.1 (3.2–14.65) (n = 6)</td>
</tr>
</tbody>
</table>

* Values are median (range). No significant differences were observed between the groups.
A patient with stable asthma (triangle and the decrease in FEV1. The decrease in FEV1 fell more than 20% from baseline or the maximal dose given, all subjects received 400 

When FEV1 fell more than 20% from baseline or the maximal dose given, all subjects received 400 

\( \text{g salbutamol by spacer device.} \)

Calbiochem, La Jolla, CA) was added. The samples were gently mixed for 15 min. The volume of the whole, pooled 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 using a wide-bore plastic pipet, and placed in a shaking water bath at 37°C C for 15 min to ensure complete homogenization. The homogenized sputum was centrifuged at 350 × g for 10 min. The cell pellet was resuspended in 10 ml phosphate-buffered saline, filtered through a nylon gauze (pore size approximately 1 mm), cytocentrifuged for 3 min at 1,500 rpm (Shandon cytocentrifuge 3; Shandon Southern Instruments, Sewickley, PA), and stained with Diff-Quik (Baxter, Düdingen, Switzerland). The total cell count was measured by using a standard hemacytometer. Differential cell counts were performed by counting at least 500 nonsquamous cells in a blind way, and are expressed as percentage of nonsquamous cells. Sputum samples containing more than 80% squamous cells were excluded from the analysis because of poor cytospin quality (17).

**Analysis of Perception of Dyspnea**

Borg and VAS scores of all subjects were plotted against percentage of fall in FEV1 from baseline, and individual Borg/FEV1 and VAS/FEV1 slopes (Slope-Borg\(^{\text{MCh}}\), Slope-VAS\(^{\text{MCh}}\), Slope-Borg\(^{\text{Hyp}}\), and Slope-VAS\(^{\text{Hyp}}\), respectively), representing an index of dyspnea (12), and their corresponding intercepts, representing baseline Borg and VAS, were calculated by linear regression analysis for both MCh and Hyp challenges (Figure 1).

**Statistical Analysis**

Data are expressed as median (range). Nonparametric tests were used because the data of Borg/FEV1 and VAS/FEV1 slopes were skewed. Differences between the groups were analyzed by Mann-Whitney U-test. Correlation (R) between data was assessed by Spearman correlations test. At a p value of 0.05 or less, differences were considered to be statistically significant. Sample size estimations using data obtained in a pilot study showed that 15 patients in the brittle and stable asthma group would allow a detection of at least a 50% reduction in slope-Borg\(^{\text{MCh}}\) and slope-VAS\(^{\text{MCh}}\) (2-sided alpha = 0.05, 1-sided beta = 0.80). In order to evaluate whether differences in perception were associated with differences in sputum cell counts, an analysis of covariance was performed after ranking the data, with perception as dependent variable and percentage sputum cells as covariate (18).

**RESULTS**

**Subject Characteristics**

Subject characteristics are summarized in Table 1. There were no significant differences in age, FEV1 postbronchodilator, and airway responsiveness to MCh between the patients with brittle and stable asthma, as well as between the patients with severe (brittle and stable) asthma versus the patients with mild asthma. Although a larger number of patients with brittle asthma responded with a 15% or greater fall in FEV1 after hypertonic saline inhalation as compared with the patients with stable and mild asthma, the PD15 Hyp did not differ between the three groups.

**Perception of Breathlessness**

Baseline perception, as measured by the Borg/FEV1 and VAS/FEV1 intercepts for both challenges, did not differ signif-

**Figure 1.** Representative example of relation between Borg and decrease in FEV1. The closed line represents the linear regression of a patient with stable asthma (triangle) with adequate perception, and the dashed line represents a patient with brittle asthma (inverted triangle) with poor perception. The figure includes the correlation coefficient (R), the slope, and the intercept \((Xo)\) for both patients.

**Sputum Induction**

Sputum induction was performed in association with the hypertonic saline challenge test as described earlier (16) with some modifications (17). During the challenge, subjects were asked to rinse their mouth with tap water after each inhalation period and were encouraged to cough and expectorate sputum if present in a clean plastic container.

**Table 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intercept-Borg(^{\text{MCh}})</th>
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<th>Intercept-Borg(^{\text{Hyp}})</th>
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<td>0.59 (−0.17 to 2.0)</td>
<td>6.25 (−1.6 to 24.0)</td>
<td>0.68 (−2.5 to 3.0)</td>
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<td>Stable</td>
<td>0.57 (−0.1 to 3.0)</td>
<td>10.3 (−1.2 to 25.9)</td>
<td>0.47 (−0.8 to 1.8)</td>
<td>4.3 (−3.4 to 25.7)</td>
</tr>
<tr>
<td>p Value(^{a})</td>
<td>0.82</td>
<td>0.33</td>
<td>0.27</td>
<td>0.163</td>
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<td>Mild</td>
<td>0.71 (−0.6 to 2.1)</td>
<td>9.4 (−3 to 25.3)</td>
<td>0.31 (−0.3 to 2.5)</td>
<td>7.5 (−2.8 to 21.4)</td>
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<tr>
<td>p Value(^{a})</td>
<td>0.75</td>
<td>0.52</td>
<td>0.76</td>
<td>0.83</td>
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\(^{a}\) Intercepts of Borg/FEV1 (%fall FEV1\(^{-1}\)) and VAS/FEV1 (mm · %fall FEV1\(^{-1}\)) for MCh and Hyp challenge, respectively. Data are expressed as median (range).

\(^{b}\) Patients with brittle asthma compared with stable asthmatic control subjects.

\(^{c}\) Patients with mild asthma compared with the patients with severe (brittle and stable) asthma.

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\(^{a}\) Intercepts of Borg/FEV1 (%fall FEV1\(^{-1}\)) and VAS/FEV1 (mm · %fall FEV1\(^{-1}\)) for MCh and Hyp challenge, respectively. Data are expressed as median (range).

\(^{b}\) Patients with brittle asthma compared with stable asthmatic control subjects.

\(^{c}\) Patients with mild asthma compared with the patients with severe (brittle and stable) asthma.
Figure 2. The slopes of Borg/FEV\textsubscript{1} and VAS/FEV\textsubscript{1} (mm · %fall FEV\textsubscript{1} \textsuperscript{-1}) induced by MCh (A and B) and Hyp (C and D) for the patients with brittle (inverted triangles), stable (triangles), and mild (open circles) asthma. Data are expressed as median and individual scores.
Vera asthma, neither between the patients with severe (brittle and stable) asthma and mild asthma (Table 2). However, the slopes of Borg/FEV₁ and VAS/FEV₁ were different between the groups (Figure 2): the Slope-BorgMCH was significantly lower in the patients with brittle asthma as compared with the patients with stable asthma (Figure 2A: \( p = 0.05 \)), whereas similar trends for Slope-VASMCH, Slope-Borgexp, and Slope-VASexp did not reach significance (Figures 2B-2D: \( p = 0.085 \), \( p = 0.061 \), and \( p = 0.10 \), respectively). In addition, the Slope-BorgMCH and Slope-VASMCH scores were significantly lower for the patients with severe (brittle and stable) asthma as compared with the patients with mild asthma (Figures 2A and 2B: \( p = 0.036 \) and \( p < 0.001 \), respectively). However, perception during the inhalation of hypertonic saline was not perceived differently between the groups.

**Induced Sputum**

Two subjects, one with stable and one with mild asthma, were not able to produce any sputum. In addition, sputum from one patient with mild asthma contained > 80% squamous cells and was therefore excluded from analysis. No significant differences in cellular parameters were observed between the patients with brittle and stable severe asthma, except for a higher percentage of sputum eosinophils in the brittle asthma group (Table 3: \( p = 0.05 \)). The sputum of patients with mild steroid-naive asthma contained a lower number of nonsquamous cells per milliliter sputum, and a slightly higher percentage of epithelial cells as compared with the sputum of the group with severe asthma.

**Perception of Dyspnea versus Sputum Cell Counts**

In the group with severe asthma treated with fluticasone propionate there was a correlation between the percentage of bronchial epithelial cells and the Slope-BorgMCH (Figure 3A: \( R = 0.38 \), \( p = 0.04 \)). In this group there also appeared to be an inverse correlation between percentage sputum eosinophils and the Slope-BorgMCH \( (R = -0.31, p = 0.097) \), Slope-Borgexp \( (R = 0.55, p = 0.002) \), and Slope-VASMCH \( (R = -0.37, p = 0.049) \). In the patients with mild asthma the percentage sputum epithelial cells tended to be correlated with the Slope-Borgexp \( (R = 0.59, p = 0.09) \). Furthermore, the percentage sputum eosinophils was positively correlated with the Slope-Borgexp \( (R = 0.79, p = 0.012) \) and the Slope-VASMCH \( (R = 0.67, p = 0.05) \). No other significant correlations were observed between percentage sputum cells and the slopes of Borg/FEV₁ or VAS/FEV₁. When using percentage of sputum eosinophils as covariate in the analysis of variance, the observed difference in Slope-BorgMCH between brittle and stable severe asthmatics was no longer significant (\( p = 0.17 \)).

**DISCUSSION**

The results of the present study show that bronchoconstriction is less well perceived by patients with severe inhaled steroid-dependent asthma as compared with patients with mild steroid-naive asthma. In addition, in patients with severe asthma suffering from recurrent exacerbations, the perception of bronchoconstriction during well-controlled periods tends to be less as compared with patients with equally severe, but stable disease. In patients with severe asthma, the perception of bronchoconstriction is inversely correlated with the percentage of eosinophils in induced sputum, whereas there is a positive correlation in patients with mild asthma. The results suggest that ongoing airway inflammation in severe asthma, despite treatment with inhaled corticosteroids, is associated with a reduced perception of airflow obstruction, which might be a risk factor for recurrent exacerbations.

This study is the first to show a difference in perception of induced bronchoconstriction between patients with severe asthma with and without recurrent exacerbations during well-controlled periods. Two earlier reports showed a poor perception of breathlessness in patients with severe asthma during an ongoing exacerbation (6, 19), but this normalized after recovery from the exacerbation. Boulet and coworkers were not able to identify a difference in perception of laboratory-induced bronchospasm between a group of patients with near-fatal asthma attacks and an asthmatic control group, which might be due to a smaller sample size in their study (20). Our results extend the findings of Kikuchi and colleagues who showed that patients with near-fatal asthma attacks have a reduced ventilatory response to hypoxia as compared with patients without near-fatal asthma attacks as well as normal subjects (21). In their study the perception of breathlessness did not differ between patients with and without near-fatal attacks, which might be explained by the method of provoking dyspnea by breathing through inspiratory resistances (22).

One earlier study by Roisman and colleagues reports a relationship between perception of bronchoconstriction and airway inflammation in patients with mild-to-moderate asthma (12). They found that perception of bronchoconstriction induced by bradykinin was inversely related to the number of eosinophils in bronchial biopsies, which is in line with our observed correlation between sputum eosinophils and perception of bronchoconstriction induced by hypertonic saline. Another finding by the group of Roisman was that perception of dysnea was positively correlated with the percentage of basement membrane covered with epithelial cells, whereas we

**TABLE 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cells</th>
<th>% Squamous Cells</th>
<th>% Eosinophils</th>
<th>% Epithelial Cells</th>
<th>% Neutrophils</th>
<th>% Macrophages</th>
<th>% Lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brittle</td>
<td>1.45 (0.26–2.32)</td>
<td>23.7 (0.6–50.5)</td>
<td>2.7 (1.1–14.3)</td>
<td>1.1 (0.6–21.8)</td>
<td>0.5 (1.3–34.4)</td>
<td>0.1 (15.9–85.2)</td>
<td>0.5 (12.1–69.8)</td>
</tr>
<tr>
<td>Stable</td>
<td>1.72 (0.94–3.77)</td>
<td>14.6 (1.9–65.4)</td>
<td>3.5 (1.3–13.5)</td>
<td>1.3 (1.3–20.0)</td>
<td>0.1 (17.8–49.1)</td>
<td>0.1 (25.8–76.8)</td>
<td>0.1 (0.2–2.0)</td>
</tr>
<tr>
<td>Mild</td>
<td>0.62 (0.27–2.54)</td>
<td>19.4 (4.7–50.3)</td>
<td>1.6 (0.1–11.0)</td>
<td>0.7 (8.4–32.0)</td>
<td>0.8 (5.0–59.7)</td>
<td>0.0 (25.8–76.8)</td>
<td>0.1 (0.2–2.2)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>p Value¹</th>
<th>p Value¹</th>
</tr>
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<tbody>
<tr>
<td>0.036</td>
<td>0.006</td>
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</table>

¹ Total nonsquamous sputum cells (10⁶ cells · ml⁻¹) and sputum differential cell counts (%). Results are expressed as median (range).

² Patients with brittle asthma compared with stable asthmatic control subjects.

³ Patients with mild asthma compared with the brittle and stable asthmatic patients.
found that perception of dyspnea correlated positively with the number of bronchial epithelial cells in induced sputum. This discrepancy might be explained by the fact that the epithelial cells in induced sputum possibly do not reflect epithelial denudation, but shedding of an abundance of epithelial cells on an intact basement membrane.

It is unlikely that methodological errors influenced our results. First, the two groups of patients with severe asthma were individually matched for all factors known to influence perception of bronchoconstriction, including sex (23), age (23, 24), baseline lung function (25, 26), airway responsiveness (6, 25), recent exacerbations (6), and inhaled corticosteroid medication (5, 12, 27). The female gender was slightly, but not significantly overrepresented in the patients with severe asthma as compared with the patients with mild asthma. Theoretically, this could have biased our data, because women are known to have an improved perception of bronchoconstriction compared with men (23). However, this female dominance would have resulted in an improved perception in the severe asthmatics, whereas we observed the opposite.

In addition, the patients with mild asthma did not differ significantly from the patients with severe asthma with respect to age, baseline lung function, airway responsiveness to methacholine nor percentage sputum eosinophils. The latter findings might be explained by the use of high doses of corticosteroids in the patients with severe asthma. Second, the measurement of dyspnea perception was performed in a standardized way. All patients were clinically stable for at least 4 wk before the study, and dyspnea was scored by using validated Borg and VAS assessment scales (7, 13) presented on a monitor with a uniform verbal instruction during standardized bronchial provocation tests (15). Third, the sample size of 15 subjects might have been too small to detect significant differences in all dyspnea scores between the two groups of patients with severe asthma. However, for all parameters there appeared to be a consistent trend suggesting a blunted perception in the patients with recurrent exacerbations.

Our study shows that the perception of dyspnea in patients with severe asthma, in particular in those with recurrent exacerbations, is impaired. Theoretically, poor perception of dyspnea in patients with severe asthma could be explained by adaptation to more severe airway narrowing resulting in a higher threshold for experiencing dyspnea. Indeed, adaptation has been shown to influence perception of dyspnea after a recent exacerbation, but these effects do not appear to be long lasting (6). Because the patients in our study had to be recovered from any exacerbation for at least 4 wk, we expected the perception of dyspnea to be normalized. Therefore, it could be
postulated that the observed difference is not the consequence of, but a risk factor for recurrent exacerbations.

Perception of dyspnea is mediated by several mechanisms (28) including hyperinflation (29), increase in the work of breathing (28) possibly by activating proprioreceptors of respiratory muscles (30), and by direct stimulation of airway mechanoreceptors (31). In addition to these mechanical pathways, eosinophilic airway inflammation has also been proposed as a determinant of breathlessness (8, 10–12). Our study showed an inverse relationship between perception of dyspnea and sputum eosinophilia in patients with severe asthma, and a difference in perception and in sputum eosinophilia between patients with and without recurrent exacerbations. The latter finding was the more surprising, because the two groups were matched for the degree of airway responsiveness as well as anti-inflammatory medication. These data supply further evidence for a direct role of eosinophilic airway inflammation in the sensations of breathlessness in asthma. In addition, the difference in sputum eosinophilia suggests that patients with recurrent exacerbations have ongoing airway inflammation despite control of symptoms and airway hyperresponsiveness by inhaled steroid therapy.

Eosinophilic airway inflammation could influence dyspnea perception by several mechanisms. Activated eosinophils are known to release neurotoxins that might, as suggested by others (12), affect afferent nerves participating in perception of dyspnea. A potential explanation might be that eosinophilic inflammation of the small airways contributes to hyperinflation and early airway closure, thereby influencing mechanical pathways that control breathlessness (5, 28–31). Patients with severe asthma with recurrent exacerbations have indeed been shown to have an increased closing capacity as compared with patients with severe, stable asthma (32).

The difference in the relationship between the percentage sputum eosinophils and perception of breathlessness in the patients with mild steroid-naive versus severe steroid-dependent asthma is not easily understood. Because the major difference between the two groups was the use of inhaled corticosteroids and asthma severity, the most plausible explanation is that perception of bronchoconstriction is influenced by both factors. Our data are in keeping with the results of Higgins and Laszlo, who showed a reduction in perception of bronchoconstriction by inhaled corticosteroids (27), suggesting that inhaled corticosteroids may also modulate asthma symptoms, possibly by affecting airway inflammation or by a direct effect on the central nervous system (27, 33).

Taken together, the present study shows that perception of breathlessness is diminished in patients with severe asthma, in particular in those with recurrent exacerbations. Moreover, perception of dyspnea in this category of patients is correlated with the degree of eosinophilia in induced sputum, suggesting that eosinophilic airway inflammation directly impairs dyspnea sensation. These findings imply that in patients with severe asthma who have poorly controlled disease despite treatment with inhaled corticosteroids, progressive eosinophilic airway inflammation might result in an accompanying deteriorating perception of dyspnea. It cannot be excluded that this results in a vicious circle of clinical worsening (5, 6, 21, 24). Blunted perception leads to denial of a forthcoming exacerbation, and possibly to a life-threatening attack. Thus, although symptoms of dyspnea are important in the diagnosis and management of mild asthma (1), the present study implies that in severe asthma, objective measurements of asthmatic airways inflammation such as sputum eosinophilia, might add additional information in determining whether or not the disease is adequately controlled.

References


26. Noseda, A., J. Schmerber, T. Prigogine, V. de M aertelaer, and J. C. Y er-
nault. 1995. Perception of dyspnoea during acute changes in lung func-

27. Higgs, C. M. B., and G. Laszlo. 1996. Influence of treatment with beclom-
ethasone, cromoglycate and theophylline on perception of bronchoc-


29. Lougheed, M. D., M. Lam, L. Forkert, K. A. Webb, and D. E. O'Don-

30. Campbell, E. J. M., and J. B. L. Howell. 1963. The sensation of breath-


32. in 't Veen, J. C. C. M., P. J. Sterk, and E. H. Bel. 1996. Recurrent asthma
exacerbations in severe asthma are associated with enhanced airway

33. Pedersen, S. E. 1997. Efficacy and safety of inhaled corticosteroids in
children. In R. P. Schleimer, W. W. Busse, and P. M. O’Byrne, editors.
Inhaled Glucocorticoids in A sthma. Marcel Dekker, New York. 551–
606.