Perception of bronchoconstriction and bronchial hyper-responsiveness in asthma

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ABSTRACT

The inter-relationship between the perception of bronchoconstriction, bronchial hyper-responsiveness and temporal adaptation in asthma is still a matter of debate. In a total of 52 stable asthmatic patients, 32 without airway obstruction [forced expiratory volume in 1 s (FEV1)/vital capacity (VC) 84.1% (S.D. 7.9%)], and 20 with airway obstruction [FEV1/VC 60% (4%)], we assessed the perception of bronchoconstriction during methacholine inhalation by using: (i) the slope and intercept of the Borg and VAS (Visual Analog Scale) scores against the decrease in FEV1, expressed as a percentage of the predicted value; and (ii) the Borg and VAS scores at a 20% decrease in FEV1 from the lowest post-saline level (PB20). Bronchial hyper-responsiveness was assessed as the provocative concentration of methacholine causing a 20% fall in FEV1 (PC20FEV1). The reduction in FEV1 was significantly related to the Borg and VAS scores, with values for the group mean slope and intercept of this relationship of 0.13 (S.D. 0.08) and 1.1 (3.02) for Borg, and 1.5 (1.19) and 12.01 (35) for VAS. PB20 was 3 (1.75) with Borg scores and 34.6 (20.5) with VAS scores. Compared with the subgroup without airway obstruction, the obstructed subgroup exhibited similar slopes, but lower Borg and VAS intercepts. For similar decreases in FEV1 (5–20% decreases from the lowest post-saline values), the Borg and VAS scores were lower in the non-obstructed than in the obstructed subgroup. PC20FEV1 was significantly related to both Borg PB20 and VAS PB20 in the non-obstructed subjects, but not in the obstructed subjects. In neither subgroup was the log of the cumulative dose related to the Borg and VAS scores at the end of the test. We conclude that, unlike in previous studies, the ability to perceive acute bronchoconstriction may be reduced as background airflow obstruction increases in asthma. Bronchial hyper-responsiveness did not play a major role in perceived breathlessness in patients without airway obstruction, and even less of a role in patients with obstruction. The cumulative dose of agonist did not appear to influence the perception of bronchoconstriction.

INTRODUCTION

The assessment of perceived breathlessness during bronchoconstriction represents an outcome measure in the evaluation of the clinical condition and management of asthma. In asthmatic patients, the common finding is of a wide variation in perception of dyspnoea [1,2]. Airway inflammation [3–6], bronchial hyper-responsive-
Perceived bronchoconstriction has been reported to be weakly and negatively related to the level of bronchial responsiveness [1], but further studies [11,12] have not confirmed those results. The possibility has also been considered [13] that patients that perceive more bronchoconstriction experience a more systemic effect because a higher dose of agonist is needed, and this may influence their perception of bronchoconstriction [1]. In this regard, it has been shown that the cumulative dose of an agonist may account for variability in the perception of breathlessness in asthma [4]. However, without taking an agonist-induced decrease in FEV₁ (forced expiratory volume in 1 s) into account, these data are not easy to interpret.

The association between temporal adaptation and the perception of bronchoconstriction has yet to be defined, given the results of studies showing the lack of a relationship between the duration of the presence of asthma and the perception of bronchoconstriction [13–17]. In addition, other studies have shown a failure of asthmatics to recognize chronic changes, as a result of background airflow obstruction, which reduces the magnitude of the estimation of the severity of asthma [1,7]. Furthermore, the effects of temporal adaptation on the discrimination of changes in the severity of bronchoconstriction are conflicting. In fact, the ability to detect a further increase in resistance may be reduced [18], while the perception of acute exacerbations may be either increased [19] or normal [1]. However, in keeping with Weber’s Law, because of the relationship between the change in background load and the change in sensation, the possibility of a lower response to acute exacerbation is not unexpected.

Thus the following points are still open for debate: (1) the association between perception of bronchoconstriction and BHR is not completely understood; (2) the effect of the cumulative dose of an agonist on the perception of bronchoconstriction requires clarification; and (3) the ability to perceive acute bronchoconstriction may be increased, decreased or normal, as a function of an acute change in airflow obstruction. Here we report data from a study aimed at investigating these issues in two groups of asthmatic patients, with and without airway obstruction.

**MATERIALS AND METHODS**

**Patients**

A total of 52 consecutive asthmatic patients (25 males) aged 12–69 years (mean age 36.8 years), with stable chronic bronchial asthma according to the criteria of the National Heart, Lung and Blood Institute (NHLBI) [20], participated in the study. Asthma was characterized by a history of episodes of dyspnoea with wheezing and by BHR in response to methacholine [provocative concentration of methacholine causing a 20% fall in FEV₁ (PC_{20}FEV₁) < 8 mg/ml]. Subjects sensitized to pollens were studied out of the relevant season. The duration of the disease ranged from 1 month to 20 years. Each patient was in a clinically stable condition at the time of the study. A total of 20 out of the 52 patients had airway obstruction (FEV₁/vital capacity (VC) < 70%). At the time of the study, patients received inhaled corticosteroids. No patients had been given theophylline or oral corticosteroids in the previous 6 months. Bronchodilators were withheld for at least 12 h before the study. All subjects had been free from acute respiratory infections in the preceding 4 weeks. None of the patients had a history of smoking. Informed consent was given by each subject, and the study was approved by the Local Ethics Committee.

**Clinical scores**

The degree of asthma severity was assessed by a modified version of the asthma severity score (ASS), as proposed by Brooks et al. [21]. Possible scores ranged from 0 to 20. The ASS was based on the following. (1) The frequency of attacks of wheezing and/or chest tightness that occurred during the day: score from 0 to 4 (none; 1 or 2 per month; weekly; daily). (2) Frequency of asthma attacks that awoke the patient at night: score from 0 to 4 (none; 1 or 2 per month; weekly; daily). (3) Chronic exertional dyspnoea (from modified Medical Research Council dyspnoea scale [22]): score from 0 (no breathlessness) to 4 (breathlessness during dressing or undressing). (4) Therapy that patient required to control asthma: score from 0 to 4 (none; β₂ agonist bronchodilators 1 or 2 times per year; bronchodilators intermittently only; bronchodilators daily; bronchodilators in association with inhaled corticosteroids; oral corticosteroids). (5) Frequency of cough: score from 0 to 4 (no cough; 1 or 2 attacks/year; monthly episodes; weekly episodes; daily episodes).

**Measurements**

**Lung function**

Baseline pulmonary function testing was performed by measuring static and dynamic lung volume using a water-sealed spirometer (Pulmonet Godart; Sensormedics Corp., Yorba Linda, CA, U.S.A.), as reported previously [23]. The normal values for lung volume are those proposed by the European Community for Coal and Steel [24].

**Bronchial challenge**

Each patient was administered a methacholine aerosol...
inhalation test according to a standardized tidal breathing procedure [25]. Increasing concentrations of methacholine chloride in normal PBS (prepared by the University Hospital Pharmacy) were inhaled from a DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, PA, U.S.A.), resulting in an output of 0.13 ml/min. With this method, 4 ml of solution was placed in the nebulizer and inhalation was continued during tidal breathing for 2 min. The methacholine solution was stored at 4 °C and was nebulized at room temperature. Normal PBS was inhaled first, followed by methacholine, the concentration of which was increased 2-fold every 5 min from 0.016 to 32 mg/ml. The test was stopped at the concentration of methacholine that caused a decrease in FEV₁ of ≥ 20% compared with that obtained with PBS inhalation (provocative concentration). FEV₁ was measured 1–1.5 min after the inhalation of each concentration of methacholine. Two measurements of FEV₁ were performed, and the higher value was used. From the log dose–response curve, the PC₂₀FEV₁ was noted. For each subject the log of the cumulative dose of methacholine was also calculated.

Dyspnoea

The perception of bronchoconstriction during the challenge test was evaluated by assessing each patient using a Borg Scale and a Visual Analog Scale (VAS), in random order, just after the inhalation of each concentration of methacholine and before the measurement of FEV₁.

The Borg scale is a vertical list with labelled categories (0–10) describing increasing intensities of asthma sensation. Subjects were asked to rank the overall sensation of respiratory discomfort. The sensation of respiratory discomfort referred to the sensation felt by the subject during an asthma attack in the past. VAS and Borg scales were similarly labelled. The subjects were asked to rate their sensation of bronchoconstriction or asthma by answering the question: ‘How severe is your asthma at all’ at the left-hand end and ‘the worst asthma ever experienced’ at the right-hand end. The subjects were asked to place a vertical mark on the horizontal line; the VAS score was expressed as the distance from the mark to the left-hand end of the VAS, in mm [26].

Data analysis

Least-squares linear regression analysis was used to analyse the dose–response curves and the relationship between the perception of bronchoconstriction and the decrease in FEV₁. The Borg and VAS scores (perception of bronchoconstriction) at a 20% fall in FEV₁ (PB₂₀) were determined by interpolation. From the relationship between the perception of bronchoconstriction and the decrease in FEV₁, expressed as a percentage of the predicted value, the slope and intercept for the Borg and VAS scores were obtained by linear regression. PC₂₀FEV₁ values were log-transformed for statistical analysis. The Borg and VAS slopes and intercepts were compared using a t test. Differences in perception of bronchoconstriction between the two subgroups (with and without airway obstruction) were assessed by using univariate analysis of variance [27].

RESULTS

The demographic and clinical characteristics and the baseline function data for the patients as a whole and for the two subgroups are listed in Table 1. Patients in the subgroup without airway obstruction (Subgroup 1) had FEV₁/VC values ranging from 75 to 96%, whereas FEV₁/VC values for the subgroup with obstruction (Subgroup 2) ranged from 48 to 66%. Clinical scores (P < 0.001), but not age, sex or PC₂₀FEV₁, differed between the two subgroups.

For each subject we observed a significant linear correlation (r ≥ 0.7) between the decrease in FEV₁, expressed as a percentage of the predicted value, and the concurrent score of perceived bronchoconstriction, expressed in terms of both the Borg scale (P = 0.04–0.0001) and the VAS (P = 0.03–0.0001), during methacholine inhalation. The individual regression lines are depicted in Figure 1. Similar results were obtained by expressing the reduction in FEV₁ as a percentage of the lowest post-saline value. The Borg and VAS slopes were similar for the two subgroups, while intercepts and the final FEV₁ values, expressed as a percentage of the predicted value, differed significantly (Table 2). Importantly, the Borg and VAS scores at various reductions in FEV₁ (5–20% decreases compared with the lowest post-saline value) were significantly lower (univariate analysis of variance: F = 16.818, P = 0.0001 for Borg; F = 13.210, P = 0.0001 for VAS) in the obstructed compared with the non-obstructed subgroup (Figure 2).

PC₂₀FEV₁ values were significantly related to both Borg PB₂₀ (r² = 18.6%, P = 0.0014) and VAS PB₂₀ (r² = 16.3%, P = 0.003) when all subjects were considered (Figure 3). When assessing the subgroups, PC₂₀FEV₁ was related to Borg PB₂₀ (r² = 19.2%, P = 0.01) and VAS PB₂₀ (r² = 15.9%, P = 0.02) in the non-obstructed subgroup, but not in the obstructed subgroup. In neither subgroup did log cumulative dose relate to Borg and VAS scores at the end of the test.

Borg and VAS slopes and Borg and VAS PB₂₀ values were not related to age, to duration of the disease (P > 0.5), or to baseline FEV₁ or FEV₁/VC.
Table 1 Demographic and clinical characteristics and baseline function data for the 52 patients
Values are means (S.D.); values for PC_{20}FEV_1 are the geometric means. a.u., arbitrary units; %pv, % of predicted value.

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>Age (years)</th>
<th>Sex (F/M)</th>
<th>FEV_1 scores (a.u.)</th>
<th>FEV_1/VC (%)</th>
<th>VC (%pv)</th>
<th>PC_{20}FEV_1 (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>52</td>
<td>36.8 (16.7)</td>
<td>27/25</td>
<td>7.29 (3.9)</td>
<td>93.2 (17.1)</td>
<td>74.63 (13.9)</td>
<td>102.0 (12.6)</td>
</tr>
<tr>
<td>Patients without obstruction</td>
<td>32</td>
<td>32.21 (14.7)</td>
<td>16/16</td>
<td>6.18 (3.7)</td>
<td>100.7 (12.9)</td>
<td>84.1 (7.9)</td>
<td>104.1 (10.1)</td>
</tr>
<tr>
<td>Patients with obstruction</td>
<td>20</td>
<td>44.15 (17.6)</td>
<td>11/9</td>
<td>9.05 (3.6)</td>
<td>80.2 (14.7)</td>
<td>60 (4)</td>
<td>92.6 (10.1)</td>
</tr>
</tbody>
</table>

Figure 1 Relationships of Borg score (left panel) and VAS score (right panel) to the fall in FEV_1 during methacholine inhalation
Individual regression lines are depicted. FEV_1 is expressed as a percentage of the predicted value (%pv), and Borg and VAS scores are expressed in arbitrary units (au).

Table 2 Slopes and intercepts of the relationships between perception of bronchoconstriction and the decrease in FEV_1 during methacholine administration in the two subgroups of patients
Perception of bronchoconstriction is assessed by the Borg and VAS scores. The fall in FEV_1 was expressed either as a percentage of the predicted value (slope and intercept) or as a percentage of the lowest post-saline value (PB_{20}). Final FEV_1 values are also shown (%pv, % of predicted value). P values are for comparisons between the two subgroups.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Borg</th>
<th>VAS</th>
<th>FEV_1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>Intercept</td>
<td>PB_{20}</td>
</tr>
<tr>
<td>Without obstruction</td>
<td>Mean</td>
<td>0.12</td>
<td>-0.04</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>0.08</td>
<td>2.06</td>
</tr>
<tr>
<td>With obstruction</td>
<td>Mean</td>
<td>0.13</td>
<td>-2.81</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>0.09</td>
<td>3.54</td>
</tr>
<tr>
<td>P value</td>
<td>0.89</td>
<td>0.0007</td>
<td>0.28</td>
</tr>
</tbody>
</table>

DISCUSSION
Our data show that, for any given decrease in FEV_1 induced by methacholine, Borg and VAS scores were significantly lower in asthmatic subjects with airway obstruction than in those without obstruction. Perceived bronchoconstriction was not related to the age of the patients, to the duration of the disease or to baseline airway function. VAS and Borg scores were mildly sensitive to BHR and not at all sensitive to the methacholine cumulative dose.

The mechanisms responsible for inter-individual differences in dyspnoea perception in airway disease are difficult to clarify, due to the wide variations in the perception of breathlessness that occur in normal subjects [28], in whom the experience of breathlessness may modify subsequent estimates of breathlessness [29]. In a disease state, it may not be possible to identify these inherent inter-individual differences, and this may confound attempts to identify effects due to disease. The existing evidence in asthmatic patients suggests a signifi-
Figure 2  Comparison of perception of bronchoconstriction at various falls in FEV₁ (5–20%) from the lowest post-saline value between patients with and without airway obstruction

Left panel, Borg score; right panel, VAS score (both expressed in arbitrary units (a.u.). Solid bars, patients without airway obstruction; open bars, patients with obstruction. Values are means ± S.E.M.

Figure 3  Relationship of Borg (left panel) and VAS (right panel) scores at a 20% reduction in FEV₁ from the lowest post-saline value (PB₂₀) to log₁₀ PC₂₀FEV₁

○, Patients without airway obstruction; ○, patients with obstruction.

cant influence of background airflow obstruction on the ability of asthmatics to perceive the severity of their disease [1,7]. As a result, the process defined as temporal adaptation reduces the magnitude of the estimation of the severity of asthma and indicates a failure to recognize chronic changes [1,14,17]. This is a pattern also found in the present study, where different intercepts in Borg and VAS were noted for patients with and without airway obstruction. On the other hand, the effects of temporal adaptation on the ability of a patient to discriminate changes in the severity of bronchoconstriction have not been defined. In fact, discrimination studies in asthma suggest that, as background resistance increases, the ability of a patient to detect a further increase in resistance is reduced [18]. At variance with this, normal [1] or even increased [19] perception of acute exacerbation has been reported. The latter finding suggests that the perception of acute exacerbation increases with deterioration of airway obstruction.

Unlike previous reports [1], our data show that the presence of airflow obstruction resulted in decreased awareness of a further increase in airflow obstruction. These discrepant results may be explained as follows. Downgrading of the sensory experience is consistent...
with the phenomenon of temporal adaptation. It is reasonable to believe that such downgrading takes a significant length of time, but this has not yet been defined [30]. This could explain the difference between the results of Burdon et al. [1] and the present ones. Nonetheless, in keeping with Weber’s Law, in patients with abnormal mechanics, larger changes in background load are required before changes in sensation occur. Therefore a difference in additional load between the present study and the study of Burdon et al. [1] may account for the discrepancies. In our study, when FEV₁ had fallen by 20% compared with control values, FEV₁ was 60.5% of the predicted value in obstructed patients compared with 75.5% of the predicted value in non-obstructed patients (see Table 2), whereas a larger difference (50% compared with 75% of the predicted value, on average) was found in the study by Burdon et al. [1]. These findings, along with the different VAS and Borg intercepts, may explain the difference in perceived bronchoconstriction for a further increase in airway obstruction in asthmatics with airway obstruction.

Attempts to relate perception of bronchoconstriction to BHR have shown that patients with high responsiveness to histamine show less perception of bronchoconstriction than less responsive subjects [1]. Burdon et al. [1] suggested that, with repeated episodes of bronchospasm, the subject’s tolerance to a comparable amount of stimulation may be greater, and result in a reduction of symptoms. However, the relationship between PC₂₀FEV₁ and breathlessness was weak in the study of Burdon et al. [1], and further studies on the same topic [5,6,11,12,31] did not confirm their results. Our data, indicating that the perception of bronchoconstriction was related to BHR in the patients as a whole, are only partly in line with the study of Burdon et al. [1], in which the effect of baseline airway function was not taken into account. In the present study, however, the perception of bronchoconstriction was independent of BHR in patients with airway obstruction. An alternative interpretation of the data of Burdon et al. [1] postulated that more perceptive subjects experienced a more systemic effect because a higher dose of an agonist was needed, and this may have influenced their perception of dyspnoea [13]. Our data, obtained using methacholine, are not comparable with those of Burdon et al., who used histamine, but may be compared with those of Roisman et al. [4], who found that in 18 subjects VAS scores were related to both the dose of agonist and the decrease in FEV₁. We show that in neither subgroup was the log of the cumulative dose significantly related to the final Borg or VAS scores. This does not seem to indicate that some other challenge-related effects are involved in perceived breathlessness.

Unlike in a previous study [32], baseline airway calibre (FEV₁, FEV₁/VC) was not significantly related to the perception of bronchoconstriction. This discrepancy may be due to differences in clinical history, smoking habits, the agonist employed for bronchial challenge and background resistance. Also in line with previous observations [5,14–16] is the finding that age, in the range reported in the present study, did not influence the perception of bronchoconstriction.

In conclusion, unlike previous studies, we suggest that the presence of airflow obstruction does result in a decrease in perception of a further increase in airflow obstruction in subjects with asthma. BHR did not play a major role in the perception of bronchoconstriction in patients without airway obstruction, and even less so in patients with obstruction. A systemic effect did not seem to be involved in the perception of bronchoconstriction.

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