Perception of bronchoconstriction in obstructive pulmonary diseases (disease-specific dyspnoea)

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ABSTRACT

The perception of dyspnoea differs between subjects with obstructive pulmonary diseases, partly because the underlying mechanisms for bronchoconstriction are different. We investigated the perception of bronchoconstriction in subjects with bronchiectasis, asthma and chronic bronchitis and possible contributing factors. Forty-seven non-smoking subjects with bronchiectasis, 50 subjects with asthma and 31 with chronic bronchitis were challenged with histamine. The Borg score was assessed before and after each challenge. The perception score corresponding to a fall in the forced expiratory volume in 1 s (FEV1) by 20% (PS20) was calculated. The mean values of \( \frac{\Delta \text{Borg}}{\Delta \text{FEV1}} \) (the Borg score change divided by the change in FEV1 as a percentage of the baseline FEV1) and PS20 of subjects with bronchiectasis and chronic bronchitis were significantly lower than in subjects with asthma after histamine challenge. The ratio of non-perceivers was higher in bronchiectasis (25.5%) and in chronic bronchitis (32.3%) than in asthma (4.0%). When all subjects were considered, \( \frac{\Delta \text{Borg}}{\Delta \text{FEV1}} \) values were significantly related to female sex \( \left( r^2 = 11.5\%, \ P = 0.0001 \right) \), but not to age, duration of the disease, PD20 or baseline FEV1 %.

The present study indicates that perception of histamine-induced bronchoconstriction is lower in patients with bronchiectasis and chronic bronchitis than in asthmatic patients, and that sex partially contributes to this difference.

INTRODUCTION

Perception of bronchoconstriction varies between individuals [1]. Although the sensory structures are common to all diseases, the conditions of stimulation may be different in the different disorders. The difference may be related to the type of constricted airway, the rapidity and duration of constriction, or characteristics of inflammatory components in airways [2]. Moreover, the range and duration of the stimulus and the state of adaptation of the sensory system may cause changes in the perceived response [3]. In addition, discrepancies in perception may be due to differences in the disease severity, in methods assessing the dyspnoea, or in cultural characteristics of the study population [4]. Reliable interpretation of bronchoconstriction provides appropriate treatment, whereas poor perception leads to inappropriate treatment. Thus failure to recognize the severity of bronchoconstriction causes life-threatening episodes [3]. However, studies have failed

Key words: asthma, bronchiectasis, chronic bronchitis, dyspnoea, perception.

Abbreviations: BHR, bronchial hyper-responsiveness; COPD, chronic obstructive pulmonary disease; CT, computerized tomography; FEV1, forced expiratory volume in 1 s; FEV1%, percentage of the predicted value for FEV1; PD20, provocative dose causing a 20% fall in FEV1; PS20, perception score corresponding to a fall in FEV1 by 20%; \( \Delta \text{Borg}/\Delta \text{FEV1} \), the Borg score change divided by the change in FEV1 as a percentage of the baseline FEV1.

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to clearly identify the mechanisms responsible for the differences in perception of dyspnoea in airway diseases [5]. It may be hypothesized that perception of dyspnoea may be different among subjects with bronchiectasis, asthma and chronic bronchitis, because the underlying mechanisms for bronchoconstriction are different.

To investigate the differences in dyspnoea sensation among patients with bronchiectasis, asthma and chronic bronchitis, the Borg scores were measured before and after histamine challenge. Moreover, the contribution of clinical variables to changes in perceived bronchoconstriction was assessed.

**METHODS**

**Study group**

We studied 128 consecutive patients, 47 with bronchiectasis, 50 with asthma and 31 with chronic bronchitis. All patients signed informed consent forms, and the study was approved by the Local Ethics Committee. Diagnosis of asthma and chronic bronchitis were done according to the American Thoracic Society criteria [6]. Detailed history, physical examination and spirometric measurements were obtained from each patient. Patients with chronic bronchitis were current smokers (mean pack-years = 33.67 ± 20.43, range 8–96). All the patients with bronchiectasis and asthma were non-smokers. Atopy was determined by skin-prick tests to common inhalant allergens (Center Laboratories, Port Washington, NY, U.S.A.). The following were taken as exclusion criteria: cardiac disorder, cognitive impairment, treatment with systemic corticosteroids and respiratory tract infection in the previous 4 weeks.

Thin-section computerized tomography (CT) scans of patients with bronchiectasis were obtained at end-inspiration and reinterpreted by a chest physician and a radiologist. The CT diagnosis of bronchiectasis was established according to adopted criteria [7,8]. Central bronchi, which were greater in diameter than the adjacent vessels and bronchi depicted in the peripheral third of the lung field in thin-section CT, were considered as bronchiectasis.

**Histamine challenge test**

Patients were asked to stop using bronchodilating agents for at least 12 h before the histamine challenge test. Pulmonary functions were measured by a flow-sensing spirometer connected to a computer for data analysis (Jaeger, Wuerzburg, Germany) [9]. Each subject inhaled doubling concentrations of histamine up to 16 mg/ml or until a 20 % decrease in forced expiratory volume in 1 s (FEV1), via a dosimeter with an output of 9 ± 0.3 ml/puff (Dosimeter APS Pro; Jaeger, Wuerzburg, Germany). Bronchial response to histamine was expressed as the provocative dose causing a 20 % decrease in FEV1 (PD20, in mg/ml) and was calculated by the same computer program (LAB, version 4.3; Jaeger). PD20 was expressed as the geometric mean ± SD.

**Perception of bronchoconstriction**

Perceived intensity of dyspnoea was estimated using a modified Borg scale labelled from 0 (no symptom) to 10 (maximum bearable) [10]. Patients were asked to select an appropriate definition to determine dyspnoea at the time of the test. They were completely free to decide their own self-scores, but warned to determine only dyspnoea and to disregard any irritation of the nose or throat during the scoring. Borg scores were recorded immediately before each percentage of the predicted value for FEV1 (FEV1 %) measurement during the challenge test and at the maximum fall of FEV1 %. The perception score corresponding to a fall in FEV1 by 20 % (PS20) was calculated by linear interpolation of the last two points on the perception/fall in the FEV1 % curve of the histamine challenge test [11]. The change in dyspnoea during bronchoconstriction was expressed as the Borg score change divided by the change in FEV1 as a percentage of the baseline FEV1 (ΔBorg/ΔFEV1) [12].

**Statistical analysis**

Clinical data were expressed as the geometric mean ± S.D. Differences between three groups were assessed using multivariate analysis of variance and Student’s t test. Multiple linear regression analysis was performed with the perception of bronchoconstriction (ΔBorg/ΔFEV1 or PS20) as the dependent variable and the baseline FEV1 %, PD20, sex, age, duration of disease and cigarette pack-year as predictor variables. Predictor variables were entered in the multivariate model using a stepwise procedure. Differences in the distribution of non-perceivers (ΔBorg=0) between groups were analysed using the χ² test. All tests were performed two-sided, and P < 0.05 was considered to be significant.

**RESULTS**

Demographic characteristics and spirometric data of patient groups are presented in Table 1. Subjects with bronchiectasis showed significantly lower baseline FEV1 % values than the asthmatic patients (P = 0.003). There were relatively more male subjects among patients with chronic bronchitis than in asthmatics (93.5 % and 18.0 %; P = 0.0001). Twelve out of 47 subjects with bronchiectasis, 10 with chronic bronchitis and 2 out of 50 asthmatics did not indicate any increase in sensation of dyspnoea (Borg score) with induced bronchoconstriction (25.5 %, 32.3 % and 4.0 % respectively). The mean values of ΔBorg/ΔFEV1 and PS20 in subjects with bronchiectasis
Table 1  Clinical features of patient groups

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Bronchiectasis</th>
<th>Asthma</th>
<th>Chronic bronchitis</th>
<th>P value*</th>
<th>P value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.91 ± 14.71</td>
<td>51.04 ± 9.74</td>
<td>52.16 ± 11.13</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>15/32</td>
<td>9/41</td>
<td>29/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopy (+/-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borg/FEV1</td>
<td>0.073 ± 0.068</td>
<td>0.099 ± 0.052</td>
<td>0.064 ± 0.061</td>
<td>P = 0.035</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>PS20</td>
<td>1.41 ± 1.27</td>
<td>1.98 ± 1.02</td>
<td>1.27 ± 1.24</td>
<td>P = 0.044</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Non-perceiver (%)</td>
<td>12 (25.5)</td>
<td>2 (4.0)</td>
<td>10 (22.3)</td>
<td>P = 0.002</td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>Symptom duration (years)</td>
<td>16.68 ± 14.57</td>
<td>10.22 ± 6.64</td>
<td>9.81 ± 4.91</td>
<td>P = 0.004</td>
<td>NS</td>
</tr>
<tr>
<td>PD20 (mg/ml)</td>
<td>0.97 ± 1.51</td>
<td>0.72 ± 1.62</td>
<td>0.58 ± 1.26</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1 %</td>
<td>74.45 ± 17.54</td>
<td>85.39 ± 19.25</td>
<td>79.36 ± 21.62</td>
<td>P = 0.003</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figure 1  Comparison of ΔBorg/ΔFEV1 between three groups of patients

Group 1, bronchiectasis; group 2, asthma; group 3, chronic bronchitis. The number of patients per group is also shown.

and chronic bronchitis were significantly lower than in subjects with asthma after histamine challenge (P < 0.05) (Figure 1). Neither ΔBorg/ΔFEV1 nor PS20 differed between bronchiectasis and chronic bronchitis groups. Individual changes in Borg during histamine challenge in three groups of patients are shown in Figure 2.

When all subjects were considered, female subjects had significantly higher ΔBorg/ΔFEV1 and PS20 than males (0.098 ± 0.062 compared with 0.056 ± 0.052, and 1.94 ± 1.21 compared with 1.12 ± 1.04 respectively; P = 0.0001). Consequently, female sex was the only variable correlated with ΔBorg/ΔFEV1 values in bronchiectasis (r² = 12.0 %, P = 0.01) and in chronic bronchitis group (r² = 22.6 %, P = 0.01), as well as in overall subjects (r² = 11.5 %, P = 0.0001). Similar results were obtained when PS20 was considered as the perception of dyspnoea. When assessing the bronchiectasis group with the asthma group, ΔBorg/ΔFEV1 was related to female sex (r² = 8.2 %, P = 0.004), but not to age, duration of the disease, PD20 or baseline FEV1 %.

Similarly, the relationship between ΔBorg/ΔFEV1 and females was significant (r² = 13.9 %, P = 0.001) in chronic bronchitis group compared with asthmatics.

DISCUSSION

This study demonstrates that the perception of histamine-induced bronchoconstriction was poorer in patients with bronchiectasis and chronic bronchitis than in asthmatic subjects.

The reasons for the difference in the perception of dyspnoea among these groups are unknown. However, the
discrepancies in the natural course of these three diseases could account for differences in dyspnoea sensation. It is known that asthmatic patients experience episodic bronchoconstriction, whereas those with chronic bronchitis and bronchiectasis have persistent bronchoconstriction and the chronicity of this symptom may lead to desensitization [12]. The obstructive defect associated with obliterative bronchiolitis, collapse of large airways on expiration, retention of endobronchial secretions, emphysema and airway hyper-responsiveness that is partially different from chronic bronchitis or asthma may play a role in poor perception of dyspnoea in bronchiectasis [13]. The differences in bronchial hyper-responsiveness (BHR) and in airway wall inflammation may be important for the difference in the severity of induced bronchoconstriction. BHR in asthma may result from lymphocytic inflammation and secretion of cytokines from Th2 lymphocytes [14], whereas in chronic bronchitis it is due to increased airway smooth muscle mass, loss of elastic recoil, airway inflammation and decreased airway diameter [12]. Damage to sensory nerves, as a result of prolonged bronchial suppuration or by increased access to toxins through infected or inflamed bronchial mucosa in bronchiectasis, not only causes BHR, but also plays a partial role in low perception [15].

Rutgers et al. [12] have shown that the perception of dyspnoea is lower in chronic obstructive pulmonary disease (COPD) than in asthma. In another study [16], it was reported that the smokers with airflow limitation had lower perception of methacholine-induced bronchoconstriction. Although several studies have compared the perception of dyspnoea between asthma and COPD [17–20], none indicated bronchiectasis. To our knowledge, the present study is the first study investigating the perception of bronchoconstriction in patients with bronchiectasis. Our results showed some similarities with the previous studies performed in patients with COPD and with asthma. Conversely, Ward and Stubbing [21] have shown that the perception of added resistive loads to breathing in chronic airway limitation and the perception of added elastic loads in chronic interstitial lung diseases are not different from normal subjects. However, comparisons between studies are difficult due to differences in disease severity, distribution of age and sex, the methods assessing dyspnoea or cultural characteristics of each particular community.

Some studies dealing with the relationship between dyspnoea and bronchodilation have described ‘perceivers’ and ‘non-perceivers’ after administration of a bronchodilator agent [19]. In the present study, a quarter of the subjects with bronchiectasis did not indicate an increase in Borg at all after histamine challenge, whereas one-third of patients with chronic bronchitis were non-perceivers. This group of patients should be followed closely, because early recognition and treatment of acute exacerbation could be delayed, causing an increase in the morbidity and mortality.

Killian et al. [22] showed that females were 13% more dyspnoeic than males after a 20% decrease in FEV1 during methacholine-induced bronchoconstriction in asthmatics. Likewise, identical magnitude of breathlessness was observed both in symptomatic obstructive airway disease and age/sex-matched control subjects. A similar distribution in this study may suggest the effect of sex on perception of dyspnoea. Our present data seem to support the findings that the perceived bronchoconstriction is related to sex.

In the present study, it was found that females reported a greater sensation of dyspnoea than males in all groups, as has been shown in other studies [23–25]. In contrast, Noseda et al. [18] neglected the effect of sex on low perception in COPD, whereas others found no difference between the sexes in asthmatic subjects [26, 27]. In a more recent study [12], sex was not important in explaining the variance in perception of bronchoconstriction, although there were relatively more male subjects in the COPD group. Despite the fact that the possible effect of sex distribution on differences of dyspnoea perception in different diseases has not been assessed thoroughly, we suggest that male predominance may play a partial role in poor perception in chronic bronchitis after multivariate analysis.

We also found that the perceptual characteristics (ΔBorg/ΔFEV1 and PS20 values) were unrelated to baseline airway function (FEV1, %) in obstructive lung diseases, as observed in other studies [20, 28–30]. It was suggested that subjects with resting obstruction develop temporal adaptation to poor lung function [31]. ΔBorg/ΔFEV1 and PS20 values were not related to cigarette pack-year in chronic bronchitis. Consistent with our present results, Ottaneli et al. [30] showed that patients with airflow limitation may variably perceive bronchoconstriction independent of smoking history. In contrast, it has been postulated that prolonged exposure to cigarette smoke may lead to chronic depletion of sensory nerve neurotransmitters and abnormalities in sensory nerves might diminish the perception of bronchoconstriction in smokers [16, 17].

In conclusion, acute decrease in airway caliber is perceived less in patients with chronic bronchitis and bronchiectasis than in asthmatics. It is not possible to estimate the underlying mechanisms responsible for the differences, because the aim of this study was to look at perception of bronchoconstriction in three groups of patients with bronchiectasis, asthma and chronic bronchitis. Whether the perception of dyspnoea during histamine-induced bronchoconstriction in bronchiectasis differs from that spontaneously occurring in chronic bronchitis remains to be determined in future studies. As the conclusive results of studies with various groups...
will be reproduced, mechanisms of disease-specific differences in perception of dyspnoea will be identified.

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