Perception of dyspnea in asthmatics with normal lung function

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Key words: asthma, dyspnea perception, bronchial hyperresponsiveness.

Summary. The perception of dyspnea varies widely among asthmatics and it is influenced by many factors.

The aims of our study were to investigate the perception of dyspnea during methacholine-induced bronchoconstriction in asthmatics with normal lung function and to evaluate the influence of bronchial responsiveness, age and gender to dyspnea perception in these patients.

A total of 192 outpatients (aged 16–77 years) with stable asthma and normal lung function were examined. Methacholine challenge test was performed to each patient. The provocative dose of methacholine that reduces forced expiratory volume in 1 sec. (FEV₁) by 20% (PD₂₀) was estimated. Dyspnea perception of bronchoconstriction was evaluated using a Borg Scale and calculating the perception score corresponding to a fall in FEV₁ of 20% (PS₂₀). According to PS₂₀ ±1 standard deviation subjects were divided into three groups: hypoperceivers, normoperceivers and hyperperceivers. From the hypoperceivers group we set up asthmatics with PS₂₀ =0 and defined them as nonperceivers.

We found out that 43 (22.4%) patients were hypoperceivers, 116 (60.4%) – normoperceivers and 33 (17.2%) – hyperperceivers. The nonperceivers presented 6.3% (n=12) of all subjects. PD₂₀ positively correlated with PS₂₀ (r=0.252, p<0.001). Hypoperceivers showed significantly higher bronchial hyperresponsiveness (PD₂₀ =174±28 µg) comparing with hyperperceivers (PD₂₀ =323±50 µg, p=0.013). Bronchial responsiveness to methacholine of nonperceivers (PD₂₀ =106±31 µg, range 15–253 µg) was the highest and PD₂₀ was significantly lower comparing with normoperceivers (p=0.005) and hyperperceivers (p=0.001). Age and gender had no significant effect on the perception of bronchoconstriction.

Conclusion. The part of asthmatics with normal lung function has impaired perception of dyspnea. Dyspnea perception depends on bronchial responsiveness, but not on age and gender of these patients.

Background

Asthma is a chronic inflammatory disease of airways, characterized by episodic or permanent symptoms and associated with variable airway obstruction (1). The perception of asthma symptoms is subjective and varies widely among individuals. Low perception of dyspnea may result in undertreatment of asthma, delay modification in treatment and even predispose patient to fatal asthma attacks (2). It has been shown that most patients with near-fatal asthma have blunted perception of dyspnea (3). To prevent severe asthma attacks or even death from asthma it is important to identify patients with a poor perception of bronchoconstriction (2).

The perception of dyspnea is influenced by many factors and this could explain its variability in asthma patients. It has been reported that patients with higher bronchial responsiveness have shown lower perception of bronchoconstriction than less responsive asthmatics (4, 5). However, other studies have not found relationship between airway responsiveness and perception of dyspnea (6, 7). P. Weiner et al. showed that women significantly higher perceive dyspnea than men (8). It was also reported that elderly asthmatics are poorer perceivers of dyspnea than younger (9). Other studies failed to show any influence of gender and age on the perception of dyspnea (5, 10, 11).

The existing evidence in asthmatic patients suggests a significant influence of initial airway obstruction on the ability of asthmatics to perceive dyspnea (11, 12). Asthmatics with initial airway obstruction perceive acute bronchoconstriction poorer than those
without obstruction. Therefore, it is not clear whether asthmatics with normal lung function perceive dyspnea adequately. The aims of our study were: 1) to investigate the perception of dyspnea during methacholine-induced bronchoconstriction in asthmatics with normal lung function and 2) to evaluate the influence of bronchial hyperresponsiveness, age and gender on dyspnea perception in these patients.

**Methods and materials**

**Subjects**

A total of 192 outpatients (aged 16–77 years) with stable asthma and normal lung function were examined. Asthma was diagnosed according to the criteria of the Global Initiative for Asthma (1). All subjects had been free of acute respiratory infections for 4 weeks before the study and inhaled steroids for 2 months. All treatment with short-acting bronchodilators was withheld for at least 12 h before the study.

The Kaunas Regional Ethics Committee for Biomedical Research approved the study protocol and each subject gave informed consent.

**Spirometry**

Lung function was tested by spirometry using a pneumotachometric spirometer “Custo VitM” (Custo Med, Germany). Predicted values were obtained from P. H. Quanjer and *et al.* (13). Spirometry was performed on two separate days with 1–7 day interval. Lung function was considered as normal if FEV\(_1\) ≥ 80% pred., FEV\(_1\)/VC ≥ 88% pred. for men and ≥ 89% pred. for women.

**Methacholine challenge test**

Methacholine challenge test was performed to each patient using a reservoir method (Provocations Test I, Pari, Germany) described by G. Klein (14). Methacholine was inhaled by tidal mouth breathing started with 15 mg dose. Doubling doses of methacholine were administrated at intervals of 5 min. until FEV\(_1\) had fallen by 20% or more from baseline value. FEV\(_1\) was measured 30 sec after the inhalation of each methacholine dose. The provocative dose of methacholine that reduce FEV\(_1\) by 20% (PD\(_{20}\)) was estimated by linear interpolation.

**Assessment of dyspnea**

The severity of dyspnea during the challenge tests was evaluated by assessing each patient using a Borg scale (15) after each methacholine dose just before the measurements of FEV\(_1\). Subjects were asked to rank the overall sensation of respiratory discomfort.

The Borg scale is a vertical list with labeled categories (0–10) describing increasing intensities of asthma sensations (0="nothing at all", 10="maximal"). The perception score corresponding to a fall in FEV\(_1\) of 20% (PS\(_{20}\)) was calculated by linear interpolation of the last two points on the perception/fall in the FEV\(_1\) curve of the methacholine challenge test.

According to PS\(_{20}\) subjects were divided into hypoperceivers, normoperceivers and hyperperceivers. Hypoperceivers (low perception of dyspnea level) were defined as a PS\(_{20}\) was more than 1 standard deviation (SD) under the mean, hyperperceivers (high dyspnea perception level) were defined as a PS\(_{20}\) more than 1 SD over the mean and normoperceivers when PS\(_{20}\) was between 1 SD of the mean (16). From the hypoperceivers group we set up asthmatics with PS\(_{20}\)=0 and defined them as nonperceivers.

**Statistical analysis**

Statistical analysis was performed using standard statistics program (SPSS Windows 11.0). The data were expressed as means±SEM. Parametric test was employed (Student’s test). Correlation was estimated by Pearson rank correlation. Multiple regression analysis was performed with PS\(_{20}\) as the depended variable and the age, gender and PD\(_{20}\) as predictor variables. PD\(_{20}\) values were log-transformed for statistical analysis. Statistical significance was assumed at p<0.05.

**Results**

The subjects’ demographics, clinical and baseline function characteristics are shown in Table 1. We have found out that hypoperceivers were with PS\(_{20}\)<0.95, normoperceivers with a PS\(_{20}\)³0.95 and ≤4.57 and hyperperceivers with a PS\(_{20}\)>4.57.

**Table 1. Subjects’ characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Subjects (n=192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.1±1.1</td>
</tr>
<tr>
<td>Range</td>
<td>16–77</td>
</tr>
<tr>
<td>Sex F/M</td>
<td>138/54</td>
</tr>
<tr>
<td>FEV(_1) (l)</td>
<td>3.22±0.07</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>1.70–5.81</td>
</tr>
<tr>
<td>FEV(_1) (% pred)</td>
<td>105±1</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>80–152</td>
</tr>
<tr>
<td>PD(_{20}) (µg)</td>
<td>223±17</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>15–1166</td>
</tr>
</tbody>
</table>

M – male, F – female, FEV\(_1\) – forced expired volume in one second.
Out of 192 patients 43 (22.4%) were hypoperceivers, 116 (60.4%) – normoperceivers and 33 (17.2%) – hyperperceivers (Fig. 1). The nonperceivers presented 6.3 % (n=12) of all subjects.

Results showed that PD_{20} positively correlated with perception of dyspnea (PS_{20}) (r=0.252, p<0.001) (Fig. 2). These results indicate that asthmatics with more severe bronchial responsiveness were more likely to show a lower perception of dyspnea during methacholine-induced bronchoconstriction.

Hypoperceivers showed significantly higher bronchial responsiveness (PD_{20}=174±28 µg, range 15–870 µg) comparing with hyperperceivers (PD_{20}=323±50 µg, range 32–1166 µg, p=0.013). However, no differences were found in PD_{20} between normoperceivers (PD_{20}=223±21 µg, range 15–1041 µg) and hypoperceivers (p=0.175) or hyperperceivers (p=0.073) (Fig. 3). Bronchial responsiveness to methacholine of nonperceivers (PD_{20}=106±31 µg, range 15–253 µg) was the highest and PD_{20} was significantly lower comparing with normoperceivers (p=0.005) and hyperperceivers (p=0.001) (Fig. 4).

Stepwise multiple regression analysis showed that PD_{20} was related to dyspnea perception. Age and gender had no significant effect on the perception of bronchoconstriction (Table 2).

**Discussion**

The aim of the study was to test perception of dyspnea in stable asthmatics with normal lung function. The results showed that dyspnea perception in such asthmatics was impaired: 22.4% of all subjects had decreased dyspnea perception. A small part (6.3%) of all tested asthmatics did not perceive dyspnea during acute bronchoconstriction at all. We have found that only bronchial hyperresponsiveness contributed to dyspnea perception in asthmatics with normal lung function.

Previous data showed a significant influence of initial airway caliber on dyspnea perception in asthmatics (11, 12, 17). Initial airway obstruction is related to poorer perception of dyspnea and this could be explained that such subjects are chronically adapted to their increased airway resistance. To exclude the influence of airway caliber to dyspnea perception we studied asthmatics with normal lung function. Despite this, in present study we have found out that 22.4% of patients without airway obstruction perceived dyspnea poorly.

Distribution of hypoperceivers and nonperceivers among stable asthmatics varies in different studies. A. Chetta et al. reported, that 26% of asthmatics were with diminished dyspnea perception (18), while the studies of E. Martinez-Moragon et al. (19) and R. Magadle et al. (2) showed that 28% and up to 33% of asthmatics, respectively, were hypoperceivers. Special attention was paid to asthmatics that did not perceive dyspnea at all. In present study we have found out 6.3% of nonperceivers of all studied asthmatics. K. J. Killian et al. found 6% (20) and E. Martinez-Moragon et al. 13% (18) of subjects who did not experience any dyspnea during acute bronchoconstriction. These differences could be explained by a variety of asthmatics enrolled in the studies. In previous studies asthma-
tics were examined with different initial lung function, meanwhile in present study not only obstructed asthmatics were included. Our findings suggest that the perception of dyspnea in asthmatics with normal lung function could be contributed by other factors as well. The eosinophilic airway inflammation is one of the main pathological factors contributing variability of dyspnea perception in asthma patients. Inhaled corticosteroids with their anti-inflammatory activity reduce bronchial hyperresponsiveness and enhance

Fig. 3. Bronchial responsiveness in hypoperceivers comparing to nomoperceivers and hyperperceivers

$PD_{20}$ – the provocative dose of methacholine that reduces FEV$_1$ by 20%.

Fig. 4. Bronchial responsiveness in nonperceivers comparing to nomoperceivers and hyperperceivers

$PD_{20}$ – the provocative dose of methacholine that reduces FEV$_1$ by 20%.
perception of dyspnea (12). $\beta_2$-agonists producing bronchodilatation by directly stimulating $\beta_2$-receptors in airway smooth muscle induce perception of dyspnea (21). To minimize the influence of medications on perception of dyspnea and airway responsiveness, patients included in the study did not use inhaled corticosteroids and bronchodilators.

The results of present study showed the relation between dyspnea perception and bronchial hyperresponsiveness. Hypoperceivers showed higher bronchial responsiveness than hyperperceivers. Moreover, non-perceivers demonstrated the severest bronchial responsiveness to methacholine than normoperceivers and hyperperceivers. Our data correlate with several studies, which have found that patients with increased bronchial responsiveness showed poorer perception of bronchoconstriction than less responsive subjects (4, 5, 11). Though, other studies have failed to show any influence of the severity of bronchial hyperresponsiveness on the perception of airflow obstruction (6, 22).

The relationship between bronchial hyperresponsiveness and perception of asthma symptoms could be explained by several mechanisms. First, J. Burdon et al. suggested that those patients who frequently develop acute bronchoconstriction acquire a degree of tolerance that reduces the sensory intensity of the experience compared with that in less reactive subjects (17). This mechanism is called temporal adaptation. Second, it has been shown that activated eosinophils release neurotoxins that might affect afferent nerves participating in perception of dyspnea in hyperresponsive patients. This is in agreement that the degree of sputum eosinophilia is related with blunted perception in severe asthma (23). Third, the airway epithelium is involved in the sensitivity of dyspnea associated with methacholine-induced bronchoconstriction. The more important shagging of bronchial epithelium is, the poorer is the perception of bronchoconstriction. Loss of epithelium cells reduces the production of epithelial-derived mediators that may be involved in the activation of airway sensory receptors (24).

In our study we have not found relation between $P_S_{20}$ and asthmatics’ age. This is in agreement with the results of a large study performed in six countries, in which age and gender had no significant effect on the symptoms of asthma (25). These results and the results of present study are in contrast with some other studies (2, 9, 26) where elderly asthmatics perceived less breathlessness for fall of 20% in FEV₁ than younger asthmatics did. These differences may be due to the chosen age distribution in the study concern.

A few studies have shown that female report more dyspnea than male (2, 8), but others have not (5). Possible reasons for the gender differences are that women with asthma experience poorer quality of life at the same level of obstruction, higher anxiety level, different in maximal inspiratory muscle strength than men. Otherwise, results of our study did not confirm any effect of gender on dyspnea perception in asthmatics.

The impaired perception of dyspnea in asthmatics may tend to erroneous assessment of asthma severity and inadequate treatment. It is well known that patients with more severe asthma have more responsive airways (27). The results of current study indicate that asthma patients with higher bronchial responsiveness are more likely to be hypo- or non-perceivers. R. Magadle et al. suggested that patients with low perception of dyspnea, even without a history of near-fatal asthma, were at an increased risk of hospitalization, a nearfatal asthma attack, or even death from asthma attack (2).

In conclusion, dyspnea perception in a part of asthmatics with normal lung function is impaired and contributed by bronchial hyperresponsiveness, but not by age and gender. This suggests that hypopereceivers and especially nonperceivers are at the risk group and should be identified by measuring the perception of dyspnea in order to avoid severe or even fatal asthma attack.

### Table 2. Multiple regression analysis with dyspnea perception ($P_D_{20}$) as a dependent variable

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Regression coefficient</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchial responsiveness (log $P_D_{20}$)</td>
<td>0.881</td>
<td>3.307</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.017</td>
<td>1.848</td>
<td>0.066</td>
</tr>
<tr>
<td>Sex (male=0, female=1)</td>
<td>0.274</td>
<td>0.928</td>
<td>0.355</td>
</tr>
</tbody>
</table>

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Astma sergančių pacientų, kurių plaučių funkcija normali, dusulio suvokimas

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Raktažodžiai: astma, dusulio suvokimas, bronchų hiperreaktyvumas.

Santrauka. Pacientai, sergantys astma, dusulį, kuriam įtakos turi daugelis veiksnių, suvokia skirtingai. 


Nustatėme, kad 43 (22,4 proc.) asmenys silpnai suvokė dusulį, 116 (60,4 proc.) – normaliai ir 33 (17,2 proc.) – stipriai. 12 (6,3 proc.) tirių įtakai visiškai nejuto dusulio metacholininio sukeltos bronchų obstrukcijos metu. PD₂₀ buvo tiesiosgialai susijusi su PS₂₀ (r=0,252, p<0,001). Pacientų, silpnai suvokiančių dusulį, bronchų reaktyvumas buvo didesnis (PD₂₀=174±28 µg) palyginti su stipriai suvokiančiais pacientais (PD₂₀=323±50 µg, p=0,013). Tiriųjų, kurie nejautė dusulio, bronchų reaktyvumas metacholinui (PD₂₀=106±31 µg) buvo didesnis nei normaliai (PD₂₀=223±21 µg) arba stipriai suvokiančių pacientų (p=0,005). Dusulio suvokimas nepriklausė nuo amžiaus ir lyties.

Išvada. Astma sergančių pacientų, kurių plaučių funkcija normali, dusulio suvokimas yra sutrikęs ir priklauso nuo tiriųjų bronchų reaktyvumo, bet nepriklauso nuo amžiaus ir lyties.

References

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