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 FEV₁≥80% pred., FEV₁/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 μg dose. Doubling doses of methacholine were administered at intervals of 5 min. until FEV₁ had fallen by 20% or more from baseline value. FEV₁ was measured 30 sec after the inhalation of each methacholine dose. The provocative dose of methacholine that reduce FEV₁ by 20% (PD₂₀) 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 FEV₁. 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 FEV₁ of 20% (PS₅₀) was calculated by linear interpolation of the last two points on the perception/fall in the FEV₁ curve of the methacholine challenge test.

According to PS₂₀ subjects were divided into hypoperceivers, normoperceivers and hyperperceivers. Hypoperceivers (low perception of dyspnea level) were defined as a PS₂₀ was more than 1 standard deviation (SD) under the mean, hyperperceivers (high dyspnea perception level) were defined as a PS₂₀ more than 1 SD over the mean and normoperceivers when PS₂₀ was between 1 SD of the mean (16). From the hypoperceivers group we set up asthmatics with PS₂₀ ≤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 PS₂₀ as the depended variable and the age, gender and PD₂₀ as predictor variables. PD₂₀ 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 PS₂₀ <0.95, normoperceivers with a PS₂₀ ≥0.95 and ≤4.57 and hyperperceivers with a PS₂₀ >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></td>
</tr>
<tr>
<td>Mean±SEM</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>FEV₁ (l)</td>
<td></td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>3.22±0.07</td>
</tr>
<tr>
<td>Range</td>
<td>1.70–5.81</td>
</tr>
<tr>
<td>FEV₁ (% pred)</td>
<td></td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>105±1</td>
</tr>
<tr>
<td>Range</td>
<td>80–152</td>
</tr>
<tr>
<td>PD₂₀ (μg)</td>
<td></td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>223±17</td>
</tr>
<tr>
<td>Range</td>
<td>15–1166</td>
</tr>
</tbody>
</table>

Perception of dyspnea in asthmatics with normal lung function

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<sub>20</sub> positively correlated with perception of dyspnea (PS<sub>20</sub>) (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<sub>20</sub>=174±28 μg, range 15–870 μg) comparing with hyperperceivers (PD<sub>20</sub>=323±50 μg, range 32–1166 μg, p=0.013). However, no differences were found in PD<sub>20</sub> between normoperceivers (PD<sub>20</sub>=223±21 μg, range 15–1041 μg) and hyperperceivers (p=0.175) or hyperperceivers (p=0.073) (Fig. 3). Bronchial responsiveness to methacholine of nonperceivers (PD<sub>20</sub>=106±31 μg, range 15–253 μg) was the highest and PD<sub>20</sub> was significantly lower comparing with normoperceivers (p=0.005) and hyperperceivers (p=0.001) (Fig. 4).

Stepwise multiple regression analysis showed that PD<sub>20</sub> 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 <i>et al.</i> reported, that 26% of asthmatics were with diminished dyspnea perception (18), while the studies of E. Martinez-Moragon <i>et al.</i> (19) and R. Magadle <i>et al.</i> (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 <i>et al.</i> found 6% (20) and E. Martinez-Moragon <i>et al.</i> 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 asthmas-

![Fig. 1. The percentage content of study asthmatics with initial normal lung function according to perception score of dyspnea at a 20% fall in FEV<sub>1</sub>](image)

![Fig. 2. Relationship between the perception score of dyspnea at a 20% fall in FEV<sub>1</sub> (PS<sub>20</sub>) and the provocative dose of methacholine that reduces FEV<sub>1</sub> by 20% (PD<sub>20</sub>) in asthmatics](image)
Fig. 3. Bronchial responsiveness in hypoperceivers comparing to normoperceivers and hyperperceivers

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

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

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

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
Table 2. Multiple regression analysis with dyspnea perception (PD_{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 PD_{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>

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. Hypocontrollers showed higher bronchial responsiveness than hypercontrollers. Moreover, noncontrollers demonstrated the severest bronchial responsiveness to methacholine than normopercipients and hypercontrollers. 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 airway obstruction (6, 22).

The relationship between bronchial hyperresponsiveness and perception of asthma symptoms could be explained by several mechanisms. First, J. Burden 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 \(PS_{20}\) 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 FEV, 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 hypopercipients and especially noncontrollers 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.
Astma sergančių pacientų, kurių plaučių funkcija normali, dusulio suvokimas

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Raktažodžiai: astma, dusulio suvokimas, bronchų hiperreaktyvumas.

Santrauka. Pacientai, sergantys astma, dusuli, kuriem įtakos turi daugelis veiksnių, suvokia skirtingai.

Tyrimo tikslas. Įvertinti dusulio suvokimą asmenų, sergančių astma, kurių plaučių funkcija normali, ir nustatyti bronchų reaktyvumo, amžiaus ir lyties įtaką dusulio suvokimui. Išsikišę 192 astma sergantys asmenys, kurių plaučių funkcija buvo normali. Kiekvienam pacientui atlikta bronchų provokacinis mėgynys su metacholinu ir apskaiciuota metacholinio dozę, mažinant fosforato išvępimo greitį per pirmąją sekundę (FEV1) 20 proc. (PD20). Dusulio suvokimą bronchų obstruktijos metu vertinome naudodami Borgo skalą ir apskaiciavę dusulio suvokimo intensyvumą (FEV1, sumažėjus 20 proc. (PS20)). Pagal PS20 (± 1 standartinis nuokrypis) pacientai buvo susirinkę į tris grupes: silpnai, normaliai ir stipriai suvokiantys dusulį. Atskirai nagrinėti pacientai, kurie bronchų obstrukcijos metu neįtraukė medulio (PS20 = 0).

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.) tariamųjų visiškai neįtraukė dusulio metacholinio sukeltos bronchų obstruktijos metu. PD20 buvo tiesiogiai susijusi su PS20 (r = 0,252, p < 0,001). Pacientų, silpnai suvokiančiųjų dusuli, bronchų reaktyvumas buvo didesnis (PD20 = 174±28 μg) palyginti su stipriai dusuli suvokiančiais pacientais (PD20 = 323±50 μg, p = 0,013). Tariamųjų, kurie neįtraukė dusulio, bronchų reaktyvumas metacholinio (PD20 = 106±31 μg) buvo didesnis nei normaliai (PD20 = 223±21 μg) arba stipriai dusuli suvokiančiųjų pacientų (p = 0,005). Dusulio suvokimas nepriskirė nuo amžiaus ir lyties.

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

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References

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