Eur Respir J 2000; 16: 486–490
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European Respiratory Journal
ISSN 0903-1936

# Borg scores before and after challenge with adenosine 5′-monophosphate and methacholine in subjects with COPD and asthma

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*Borg scores before and after challenge with adenosine 5′-monophosphate and methacholine in subjects with COPD and asthma. S.R. Rutgers, N.H.T. ten Hacken, G.H. Koeter, D. S. Postma. ©ERS Journals Ltd 2000.*

**ABSTRACT: Dyspnoea differs between subjects with chronic obstructive pulmonary disease (COPD) and asthma, partly because the underlying mechanisms for bronchoconstriction differ. This study investigated the possible role of inflammation and the contribution of clinical variables on dyspnoea in subjects with COPD and asthma.**

**Forty-eight smoking subjects with COPD and 21 nonsmoking subjects with asthma, were challenged with adenosine 5′-monophosphate (AMP) and methacholine. The Borg score was assessed before and after each challenge.**

**Mean increases in Borg score (per percentage decrease in baseline forced expiratory volume in one second ($FEV_1$)) were significantly smaller in COPD than in asthma ($p<0.01$), values being 0.055 and 0.045 in COPD and 0.122 and 0.093 in asthma respectively. This difference was largely due to the fact that one-third of the subjects with COPD did not increase their Borg score during bronchoconstriction. The increase in Borg tended to be larger during AMP than during methacholine challenge, both in asthma and COPD. Changes in Borg scores were explained by age in COPD and by the Borg score before AMP challenge in asthma.**

**The authors conclude that perception of dyspnoea during adenosine 5′-monophosphate and methacholine induced bronchoconstriction is lower in chronic obstructive pulmonary disease than in asthma and that age contributes to this difference. As adenosine 5′-monophosphate is regarded as an indirect marker of airway inflammation, the results suggest that inflammation is not important because both groups showed similar responses on such provocations.**

*Eur Respir J 2000; 16: 486–490.*

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Keywords: Adenosine 5′-monophosphate
asthma
chronic obstructive pulmonary disease
dyspnoea
hyperresponsiveness
inflammation

Received: December 31 1998
Accepted after revision May 23 2000

This study was supported by the Dutch Asthma Foundation and Astra Pharmaceutica BV.

Dyspnoea is a common feature both in subjects with chronic obstructive pulmonary disease (COPD) and asthma [1, 2]. Dyspnoea during bronchoconstriction differs between COPD and asthma, partly because the mechanisms for bronchoconstriction differ between COPD and asthma [3]. Dyspnoea during bronchoconstriction has been shown to be determined by inspiratory vital capacity and mid-maximal inspiratory flow in subjects with COPD [4]. In subjects with asthma changes in forced expiratory volume in one second ($FEV_1$) and inspiratory resistance have been shown to be the most important factors [4]. Until now, no other factors explaining the differences in dyspnoea between COPD and asthma have been reported. Airway wall inflammation differs significantly between COPD and asthma [5], and it is hypothesized that this might be an important factor.

One way to study the relation between inflammation and dyspnoea is the application of direct and indirect bronchoconstrictive stimuli. Methacholine (Mch) causes bronchoconstriction *via* direct stimulation of muscarinic receptors on the smooth muscle cells. In contrast, adenosine 5′-monophosphate (AMP) causes bronchoconstriction indirectly *via* stimulation of mast cells and nerves in the airway wall. These mast cells, and maybe nerves as well, subsequently release mediators [6], which may cause bronchoconstriction *via* stimulation of receptors on the smooth muscle cell. AMP induced bronchoconstriction depends on the degree of airway inflammation, *i.e.* the number and activation of mast cells in the airway wall [7]. Mch and AMP probably both induce dyspnoea *via* bronchoconstriction, but AMP may induce additional dyspnoea *via* stimulation of sensory receptors and airway wall oedema [8]. It has been reported that subjects with asthma experience more dyspnoea during a challenge with AMP than with Mch [8]. It is hypothesized that the difference between AMP and Mch induced dyspnoea would be smaller in subjects with COPD than in asthmatics, because of the differences in type and number of inflammatory cells in the airway wall.

To investigate the differences in dyspnoea sensation between patients with COPD and asthma, the Borg scores were measured before and after an AMP and Mch challenge. Moreover, the contribution of clinical variables to changes in dyspnoea were assessed.

## Methods

### *Subjects*

Forty-eight subjects with COPD and 21 subjects with asthma were recruited from the outpatient clinic of the Groningen University Hospital or *via* advertisements in local newspapers. All subjects gave written informed consent at the start of the study. Subjects using corticosteroids or antibiotics and subjects with an exacerbation or a respiratory tract infection within a month prior to the study were excluded. All subjects had to be hyperresponsive for AMP (provocative concentration causing a 20% decrease in FEV1 (PC20) ≤80 mg·mL$^{-1}$) and Mch (PC20 <8.0 mg·mL$^{-1}$). COPD was diagnosed according to the American Thoracic Society (ATS) criteria [1, 2]. Only current smokers between the ages of 45–75 yrs were recruited. Atopic patients were excluded. Subjects with asthma also had to be between 18–45 yrs of age. All asthmatics had to have symptoms of asthma, be nonsmoking and atopic. Atopy was defined by a positive skin test for at least 1 of 18 major aeroallergens [9] or a positive specific immunoglobulin (Ig)E for house dust mite, cat, dog, grass or trees. Serum total IgE (Kabi Pharmacia, Woerden, the Netherlands) and the number of peripheral blood eosinophils (in a Bürker chamber) were also determined.

### *Adenosine 5′-monophosphate and methacholine induced bronchoconstriction and dyspnoea*

Subjects had to stop using bronchodilating agents for at least 6 h before the test. Subjects did not use long-acting bronchodilators. Spirometry was performed using a calibrated water-sealed spirometer (Lode BV, Groningen, the Netherlands) according to standardized guidelines [10]. AMP and Mch challenges were performed according to a 2-min tidal breathing method adapted from JUNIPER *et al.* [11]. Doubling concentrations of Mch bromide (0.03–19.6 mg·mL$^{-1}$) and AMP (0.04–320 mg·mL$^{-1}$) were administered as aerosols generated from a starting volume of 3 mL in a DeVilbiss 646 nebulizer (DeVilbiss Co, Somerset, Pennsylvania, USA). Consecutive doses were administered until FEV1 had fallen by 20% of baseline FEV1. Intensity of dyspnoea was measured using a modified Borg score [12]. Borg scores were recorded immediately before the challenge test and at the maximum decrease of FEV1.

### *Analysis*

Clinical data were expressed in mean±SD or geometric means (range). 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). The difference in ΔBorg/ΔFEV1 between COPD and asthma was analysed using the Mann-Whitney U-test. The difference in ΔBorg/ΔFEV1 between AMP and Mch was analysed using Wilcoxon matched pairs signed-ranks test. Subjects were arbitrarily marked as high perceivers (increase of Borg score ≥2), low perceivers (0.5≤ increase of Borg score <2) or non-perceivers (increase of Borg is equal to 0). Differences in the distribution of high-perceivers, low-perceivers or non-perceivers between groups were analysed using the Chi-squared test. Variables explaining the variance of Borg score changes within the asthmatic or COPD group were tested by logistic regression. Changes in Borg were dichotomized in ΔBorg=0 *versus* ΔBorg >0, or 0.5≤ΔBorg <2 *versus* ΔBorg ≥2. Age, sex, total IgE, baseline FEV1, change in FEV1 percentage of predicted, baseline Borg, PC20AMP and PC20Mch were independent variables. Odds ratios were considered to be significant if the 95% confidence interval (CI) did not include the value 1. All tests were performed two-sided and p-values <0.05 were considered to be significant.

## Results

### *Subjects*

Forty-eight subjects with COPD and 21 subjects with asthma were included (table 1). There were relatively more male subjects in the COPD group. Subjects with COPD showed significantly higher PC20AMP and PC20 Mch values and lower FEV1 % pred values than asthmatic subjects.

### *Borg score changes after bronchoconstriction: chronic obstructive pulmonary disease* versus *asthma*

An increase in Borg score was reported in all subjects with asthma. In COPD an increase was reported in 35 (73%) subjects after AMP, and in 30 (62%) after Mch (table 2). Consequently, subjects with COPD had significantly lower ΔBorg/ΔFEV1 during AMP and Mch than subjects with asthma (p<0.001, table 3). ΔBorg/ΔFEV1 did not differ significantly between AMP and Mch challenge in patients with COPD (p=0.18) or asthma (p=0.11). Individual changes in Borg during AMP challenge in COPD and asthma are shown in figure 1.

### *Variables explaining the variance of Borg score changes in chronic obstructive pulmonary disease*

Age was the only variable significantly explaining the variance of Borg score changes, dichotomized in ΔBorg = 0 and ΔBorg >0, during AMP and Mch challenge (Odds ratio (OR) = 0.88 (95% CI = 0.78–0.98) with AMP; OR = 0.88 (0.79 - 0.98) with Mch). Age was also the only variable

Table 1. – Patient characteristics

| | COPD | Asthma |
|---|---|---|
| Number | 48 | 21 |
| Sex M/F | 39/9 | 11/10 |
| Age yrs | 60±7 | 32±9 |
| Cigarettes·day$^{-1}$ | 18±8 | 0 |
| Serum total IgE U·L$^{-1}$ | 47 (2–621) | 282 (49–2000)** |
| Eosinophils $10^6$·L$^{-1}$ | 191 (60–480) | 251 (80–540) |
| FEV1 % pred | 57±13 | 89±13** |
| PC20 AMP mg·mL$^{-1}$ | 6.02 (0.13–80) | 2.69 (0.187–22.8)** |
| PC20 Mch, mg·mL$^{-1}$ | 0.57 (0.04–7.79) | 0.46 (0.08–6.61) |

Data are presented as means±SD or geometric mean (range). COPD: chronic obstructive pulmonary disease; M: male; F: female; IgE: immunoglobulin E; FEV1: forced expiratory volume in one second; PC20: provocative concentration causing a 20% decrease in FEV1; AMP: adenosine 5′-monophosphate; Mch: methacholine; **: p<0.01, asthma *versus* COPD.

Table 2. – Distribution of Borg score changes after adenosine 5′-monophosphate and methacholine challenges

| Challenge | COPD | Asthma |
|---|---|---|
| **Adenosine 5′-monophosphate** | 48 | 21 |
| ΔBorg=0 | 13 (27%)* | 0 (0%) |
| 0.5 ≤ΔBorg <2 | 16 (33%) | 6 (29%) |
| ΔBorg ≥2 | 19 (40%) | 15 (71%) |
| Methacholine | | |
| ΔBorg=0 | 18 (38%)* | 0 (0%) |
| 0.5≤ΔBorg <2 | 12 (25%) | 10 (48%) |
| ΔBorg ≥2 | 18 (38%) | 11 (52%) |

Data are presented as n(%). COPD: chronic obstructive pulmonary disease; *: p<0.05, COPD *versus* asthma.

significantly explaining the change in Borg, dichotomised in 0.5≤ ΔBorg <2 and ΔBorg ≥2 (OR = 0.88 (0.78–0.99) with AMP; OR = 0.77 (0.63–0.94) with Mch). Age correlated negatively with change in Borg score in COPD correlation coefficient (ρ=-0.38, p=0.008).

*Variables explaining the variance of Borg score changes in asthma*

Baseline Borg before the challenge with AMP was the only variable significantly explaining the Borg score change, dichotomized in 0.5≤ ΔBorg <2 and ΔBorg ≥2, during the test (OR=0.20 (0.05–0.91)). Baseline Borg tended to be a determinant during Mch challenge (OR= 0.13 (0.01–1.24))

## Discussion

This study demonstrated that the increase in Borg score after AMP and Mch challenge was smaller in COPD than in asthma. One-third of the subjects with COPD did not indicate an increase in Borg at all after these challenges, whereas all subjects with asthma did. Boulet *et al.* [13] proposed perception scoring of induced bronchoconstriction as a useful additional parameter to recognize poor perceivers of breathlessness in asthma. This study extended their observation and showed that elderly patients with COPD will have an even higher chance of being poor perceivers.

Table 3. – Borg score changes during adenosine 5′-monophosphate (AMP) and methacholine (Mch) challenges in chronic obstructive pulmonary disease (COPD) and asthma

| | COPD | Asthma |
|---|---|---|
| ΔBorg | | |
| AMP | 1.41±1.32*** | 2.55±1.38 |
| Mch | 1.13±1.16*** | 2.26±1.27 |
| ΔFEV1 % of baseline | | |
| AMP | 26±5 | 25±6 |
| Mch | 26±4 | 23±7 |
| ΔBorg/ΔFEV1 $\%^{-1}$ | | |
| AMP | 0.055±0.056*** | 0.122±0.093 |
| Mch | 0.045±0.048*** | 0.093±0.053 |

Data are presented as mean±SD. FEV1: forced expiratory volume in one second; ***: p<0.001 COPD *versus* asthma.

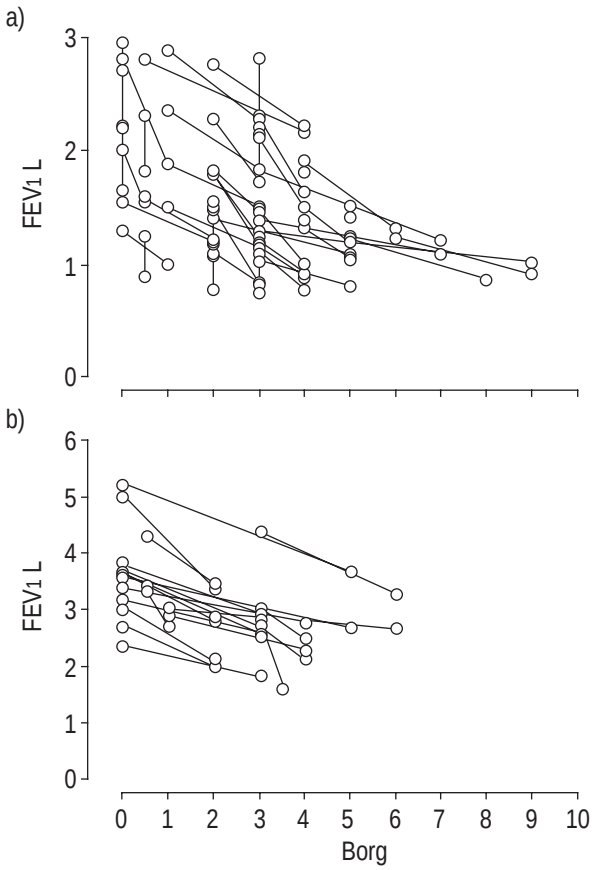


Fig. 1. – Individual changes in Borg score during adenosine 5′-monophosphate challenge in a) chronic obstructive pulmonary disease and in b) asthma. FEV1: forced expiratory volume in one second.

Theoretically, a 20% fall of FEV1 at a low baseline level increases airway resistance much more than at normal baseline level. Thus, the workload of breathing during AMP and Mch induced bronchoconstriction must have been significantly higher in the patients with COPD when compared with asthmatic patients. One explanation for the differences in reports for dyspnoea among COPD *versus* asthmatic patients may be experience. Whereas asthmatic patients experience episodic bronchoconstriction, those with COPD experience bronchoconstriction chronically. Familiarity with this symptom may lead to desensitization. Obviously, a reduced perception of bronchoconstriction may have important clinical implication. It may delay self-referral during exacerbations and lead to under treatment by physicians who base their therapy mainly on patients′ symptoms. Objective assessment of airway patency, therefore, remains important in the recognition of deterioration in lung function. Nevertheless, the authors do not suggest performing routine challenges in combination with Borg scores. After all, Boudreau *et al.* [14] could not demonstrate a relationship between the ability to sense breathlessness during histamine-induced and spontaneously occurring bronchoconstriction in asthma. The correlation with clinical outcome is probably even worse in subjects with COPD. This remains to be determined in future studies.

The hypothesis that AMP would induce more dyspnoea in asthma than in COPD could not be confirmed. Apparently, the rather large difference in airway wall inflammation between asthma and COPD is not important for the different feelings of dyspnoea during bronchoconstriction. Alternatively, it might be that activated mast cells are similarly involved in the airway inflammation of asthma and COPD. Another explanation is that factors other than inflammation are more important for inducing dyspnoea. Consequently, markers of inflammation, more direct than hyperresponsiveness testing to indirect agonists, are needed to give more insight in this issue.

The findings are in line with those of MARKS *et al.* [8], who showed larger differences in Borg score after AMP than after Mch challenge in a group of asthmatic subjects. They induced larger decreases in $FEV_1$ during provocation in the present study, which might explain the statistical significance in their study. The fact that an indirect agonist like AMP induced larger changes in Borg suggests that at least certain aspects of airway inflammation play a role in the perception of dyspnoea. It is possible that AMP not only causes smooth muscle contraction but also stimulates airway sensory nerves or causes airway wall oedema, and thus gives additional dyspnoea. In line with this, SONT *et al.* [15] showed that a challenge with hypertonic saline caused greater dyspnoea with higher maximal/partial ratios than with Mch.

Asthmatic subjects with lower Borg scores before AMP challenge had higher increases in Borg after the challenges. This higher increase in Borg was not due to the amount of stimulus administered, because the $PC_{20}$ values did not correlate with the changes in Borg. Also, the level of $FEV_1$ did not account for the change in Borg scores. It is speculated that asthmatics with active airway inflammation may have a continuous release of mediators, which stimulate irritant receptors and cause a relative insensitivity of these receptors. In contrast, subjects with low airway inflammation may have more sensitive irritant receptors and therefore perceive stimulation of these receptors better. Indeed, ROISMAN *et al.* [16] showed that perception of bradykinin induced bronchoconstriction correlated negatively with eosinophilic inflammation and epithelial shedding of the airway mucosa. Moreover, treatment with inhaled corticosteroids was associated with improved perception of bronchoconstriction. Another explanation for the larger increase in Borg scores in asthmatics with low baseline levels of dyspnoea may be that the asthmatic subjects in the present study felt a psychological barrier to classify their induced dyspnoea as "very severe" (Borg score=7). The maximum score given during the challenge test was 6, allowing the greatest increase in Borg scores to occur in asthmatics with low baseline scores. With respect to this problem, a visual analogue scale may be superior to the Borg score. Interestingly, CARRIERI *et al.* [17], using a visual analogue scale, found a positive relationship between dyspnoea at baseline and dyspnoea during Mch induced bronchoconstriction, which is opposite to the findings in the present study.

Several factors may contribute to hyperresponsiveness in COPD: increased airway smooth muscle mass, loss of elastic recoil, airway inflammation and decreased airway diameter. It is possible that airway diameter may have influenced the $PC_{20}$ values in some patients. However, there is data that suggest that airway inflammation also plays a role in hyperresponsiveness to AMP in COPD. It has been shown that histamine release by mast cells has a role in AMP induced bronchoconstriction [18]. Moreover, it was found that airway inflammation is associated with hyperresponsiveness to AMP in smokers with COPD [19].

Age was negatively associated with the perception of bronchoconstriction in COPD. The contribution of age to feelings of dyspnoea may be explained in several ways. One possibility is that the number and activity of those lung receptors transmitting sensory information to the central nervous system [20] may decrease with age [21], thereby lead to decreased perception of dyspnoea. Another possibility is that subjects become cortically less sensitive to the peripheral signals of dyspnoea with increasing age. Perception of resistive respiratory loads has been shown to diminish with age in elderly healthy subjects as does perception of tactile, visual, auditory and proprioceptive sensations [22]. Therefore, the subjects with COPD in the present study may have adapted more to the sensation of dyspnoea and did not perceive bronchoconstriction as well as the asthma group. This is in line with CONNOLLY *et al.* [23] who showed that 34 elderly subjects were less aware of methacholine induced bronchoconstriction than 33 young asthmatics or normal subjects.

Age did not contribute to the variation in dyspnoea in the asthmatic subjects. Several investigators have studied the influence of age on dyspnoea perception in asthmatics. BOULET *et al.* [13] demonstrated a positive correlation between age and perception of histamine induced bronchoconstriction in 50 asthmatics with a mean±SEM age of 37 (1.3) yrs. These findings are in contrast to those of KILLIAN *et al.* [24] who determined Borg scores during Mch challenges. They found 10 low-perceivers of dyspnoea out of 120 hyperresponsive asthmatics and showed that subjects with low (0), moderate (0–5) and high (>5) Borg score at 20% fall in $FEV_1$ had significantly different ages: 63 (2.8) *versus* 41 (1.5) *versus* 47 (4.0) yrs ($p<0.05$). This is in line with CARRIERI *et al.* [17] who found a negative relationship between age and magnitude of methacholine induced dyspnoea. MARKS *et al.* [8] also found a negative correlation between age (mean: 27 yrs) and perception of directly and indirectly induced bronchoconstrictions in asthmatic subjects. Results of the above studies may have been affected by an unequal distribution of inhaled corticosteroids use with age, whereas non of the patients in the presented study did use corticosteroids. HIGGS *et al.* [25] have shown that the use of inhaled corticosteroids results in lower perception of dyspnoea at baseline, whereas ROISMAN *et al.* [16] have shown an improvement in perception of bradykinin induced bronchoconstrictions.

The authors conclude that the increase in Borg score after adenosine 5′-monophosphate and methacholine challenges in chronic obstructive pulmonary disease was lower than in asthma. Many subjects with chronic obstructive pulmonary disease did not change their dyspnoea score during inhalation challenges at all. Both groups showed somewhat higher changes in dyspnoea after adenosine 5′-monophosphate as compared to methacholine, but the groups did not differ in this respect. It would appear that, the difference in airway inflammation between asthma and chronic obstructive pulmonary disease is not an important factor in the different perception of dyspnoea.

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