Chapter 2

Less small airway dysfunction in asymptomatic bronchial hyperresponsiveness than in asthma

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ABSTRACT

Background
Bronchial hyperresponsiveness (BHR) can be present in subjects without any respiratory symptoms. Little is known about the role of the small airways in asymptomatic subjects with BHR.

Methods
We investigated small airway function assessed by spirometry and impulse oscillometry, as well as Borg dyspnea scores at baseline and during a methacholine provocation test in 15 subjects with asymptomatic BHR, 15 asthma patients and 15 healthy controls.

Results
At baseline, small airway function (R_{5}-R_{20} and X_{5}) was comparable between subjects with asymptomatic BHR and healthy controls, whereas asthma patients showed small airway dysfunction as reflected by higher R_{5}-R_{20} and lower X_{5} values. During methacholine provocation, small airway dysfunction was more severe in asthma patients than in subjects with asymptomatic BHR. Interestingly, a higher increase in small airway dysfunction during methacholine provocation was associated with a higher increase in Borg dyspnea scores in subjects with asymptomatic BHR, but not in asthma.

Conclusion
Subjects with asymptomatic BHR may experience fewer symptoms in daily life because they have less small airway dysfunction.
INTRODUCTION

Bronchial hyperresponsiveness (BHR) is defined as exaggerated airway narrowing in response to various non-specific stimuli such as fog, perfume or cold air. Although BHR is a hallmark of asthma, it has been reported that subjects without any respiratory symptoms may also exhibit BHR. In a review by Jansen et al, a prevalence rate between 2.2 and 14.3% of this so-called ‘asymptomatic BHR’ was reported(1). Asymptomatic BHR is associated with an increased risk to develop asthma later in life(2-5).

The reason why some subjects do not have any respiratory symptoms, even though they do exhibit BHR is not clear, although several possible explanations have been investigated in the past decades, including the presence and extent of airway inflammation, airway remodeling and decreased perception of symptoms(6-9). Thus far, studies investigating asymptomatic BHR have focused mainly on the large airways. In recent years, there is increasing evidence that the small airways (i.e. those with an internal diameter < 2mm) are also involved in BHR and contribute importantly to the clinical expression of asthma(10-15). Mansur et al showed that small airway dysfunction during a methacholine provocation was associated with increased dyspnea perception in asthma patients(16).

In line with these recently found associations between small airway dysfunction, BHR, and asthma symptoms, we hypothesized that subjects with asymptomatic BHR have more small airway dysfunction than healthy controls, but less small airway dysfunction than subjects with symptomatic BHR, that is, patients with asthma. To investigate this, we performed a cross-sectional study measuring large and small airway function, both at baseline and during methacholine provocation, in subjects with asymptomatic BHR, patients with asthma and healthy controls.

METHODS

Study design

We performed a three-arm, cross-sectional, observational study. The three arms were controls (subjects without BHR, no respiratory symptoms and no history of asthma or COPD), asymptomatic subjects with BHR (subjects with BHR, but without respiratory symptoms and no history of asthma or COPD) and asthma patients (subjects with BHR and a doctor’s diagnosis of asthma). Subjects with asymptomatic BHR were available from a previous study aiming to obtain normal values of inflammatory variables in healthy individuals (the NORM study, NCT 00848406). During screening for the NORM

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study, these subjects, who were completely asymptomatic, showed BHR during a methacholine provocation test. For this reason, they were excluded from the NORM study. This observation led us to design the current study. We included subjects aged 18 to 65 years with a smoking history <10 packyears. BHR was defined as a provocative concentration of methacholine inducing a 20% fall in FEV\(_1\) (PC\(_{20}\) \(\leq 8\) mg/ml. Absence of BHR was defined as a PC\(_{20}\) >16 mg/ml. Respiratory symptoms were assessed as in a previous study(17). Briefly, asymptomatic subjects reported no symptoms of chronic cough or phlegm production, no shortness of breath when walking on level ground and no attacks of shortness of breath. Each subject was evaluated during 2 visits to our hospital. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen and all subjects gave their written informed consent.

**Pulmonary function tests**

Spirometry was performed according to international guidelines before and after administering 400µg salbutamol(18). Forced expiratory volume in 1 s (FEV\(_1\)), forced vital capacity (FVC), FEV\(_1\)/FVC and forced expiratory flow at 50% and between 25-75% of FVC (FEF\(_{50}\) and FEF\(_{25-75}\) respectively) were obtained. Reversibility to salbutamol was expressed as the change in FEV\(_1\) between the pre- and post-bronchodilator value as percentage of the predicted value. Impulse oscillometry (IOS) was used to measure the resistance at 5Hz (R\(_5\)), which reflects total airway resistance, resistance at 20Hz (R\(_{20}\)), which reflects the resistance in the large airways and the difference between R\(_5\) and R\(_{20}\) (R\(_5\)-R\(_{20}\)), reflecting the resistance in the small airways. In addition, reactance at 5 Hz (X\(_5\)) was measured, which reflects elastic properties of the small airways. Body plethysmography was used to measure total lung capacity (TLC), residual volume (RV) and airway resistance (R\(_{aw}\)).

**Methacholine provocation with IOS and Borg dyspnea score**

Methacholine provocation was performed according to the 2-minute tidal breathing method adapted from Crapo et al(19). Subjects inhaled doubling concentrations of methacholine (0.03 to 16 mg/ml). After each inhalation, the FEV\(_1\) was measured, impulse oscillometry was performed and the subjects were asked to score their perception of dyspnea by means of the modified Borg scale(20). This scale ranges from 0 (no dyspnea) to 10 (maximal dyspnea). The challenge was discontinued when the FEV\(_1\) had fallen by 20% or more from the pre-challenge level or when the highest concentration of methacholine had been administered. PC\(_{20}\) was calculated by linear interpolation between the last two data points of the logarithmic concentration-response curve.
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**Questionnaires**

All subjects filled out the Dutch version of the bronchial hyperresponsiveness questionnaire (BHQ) and the asthma control questionnaire (ACQ). The BHQ consists of 15 questions about symptoms and 19 questions about provoking stimuli associated with bronchial hyperresponsiveness in the last 3 months (0: no BHR, 6: worst score). The ACQ is used to assess asthma control (0: best control, 6: worst control)\(^{(21,22)}\).

**Statistical analyses**

Statistical analyses were performed using IBM SPSS Statistics, version 20 (IBM Corporation, Armonk, NY, USA). To analyze changes during methacholine provocation between the 3 groups, we calculated the slopes of FEV\(_{1}\), R\(_{5-R_{20}}\), X\(_{5}\), R\(_{20}\) and the Borg dyspnea score between the baseline measurement and the measurement at the last concentration of methacholine. A slope reflects the degree of change of a variable per mg/ml methacholine. In addition, to assess small airway dysfunction and dyspnea at the moment FEV\(_{1}\) had fallen by 20%, we calculated values at PC\(_{20}\) for R\(_{5-R_{20}}\), X\(_{5}\), R\(_{20}\) and the Borg dyspnea score in subjects with a positive provocation test, that is, subjects with asymptomatic BHR and asthma patients. Values at PC\(_{20}\) were calculated by interpolating between the second-to-last and the last value, similar to the way the PC\(_{20}\) is calculated\(^{(19)}\). Baseline values, slopes and values at PC\(_{20}\) in the groups were compared by one-way analysis of variance (ANOVA) or Kruskall Wallis tests with post-hoc Holm’s Bonferroni correction for multiple testing. To assess the association between changes in IOS parameters and change in dyspnea during a provocation test, we performed Spearman’s correlation analyses.

**RESULTS**

**Baseline characteristics**

A total of 45 subjects were included in the study: 15 healthy controls, 15 subjects with asymptomatic BHR and 15 asthma patients. The baseline characteristics of the three groups are presented in Table 1. The median age was 26 years in the control group, 24 years in the asymptomatic BHR group and 45 years in the asthma group. Body Mass Index (BMI) was significantly higher in asthma patients than in subjects with asymptomatic BHR and healthy controls. The PC\(_{20}\) methacholine was comparable between subjects with asymptomatic BHR and asthma.
Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=15)</th>
<th>Asymptomatic BHR (n=15)</th>
<th>Asthma (n=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26* (23; 32)</td>
<td>24* (23; 28)</td>
<td>45 (36; 52)</td>
<td>0.005</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>10/5</td>
<td>12/3</td>
<td>13/2</td>
<td>0.407</td>
</tr>
<tr>
<td>Smoking (n, %)</td>
<td></td>
<td></td>
<td></td>
<td>0.043</td>
</tr>
<tr>
<td>Current</td>
<td>5 (33)</td>
<td>8 (53)</td>
<td>2 (13)</td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>-</td>
<td>1 (7)</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>10 (67)</td>
<td>6 (40)</td>
<td>9 (60)</td>
<td></td>
</tr>
<tr>
<td>Packyears</td>
<td>5.6 (1.9; 8.3)</td>
<td>2.5 (1.3; 8.7)</td>
<td>4.7 (2.8; 8.9)</td>
<td>0.773</td>
</tr>
<tr>
<td>Family history of asthma (n,%)</td>
<td>4* (27)</td>
<td>5* (33)</td>
<td>13 (87)</td>
<td>0.002</td>
</tr>
<tr>
<td>Allergic rhinitis (n, %)</td>
<td>1 (7)*</td>
<td>3 (20)</td>
<td>9 (60)</td>
<td>0.008</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)‡</td>
<td>21.6 (20.6; 25.5)*</td>
<td>22.5 (20.8; 26.6)*</td>
<td>30.9 (28.4; 37.7) &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PC_{20} (mg/ml)†</td>
<td>-</td>
<td>1.9 (0.6; 8.0)</td>
<td>1.4 (0.04; 8.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>FEV₁ (% predicted)†</td>
<td>106 (10)</td>
<td>103 (14)</td>
<td>101 (15)</td>
<td>0.566</td>
</tr>
<tr>
<td>FEV₁, reversibility (% predicted)‡</td>
<td>1.8 (0.8; 4.1)</td>
<td>5.6 (3.0; 8.4)</td>
<td>5.0 (1.1; 9.4)</td>
<td>0.064</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>82.6 (79.0; 89.2)</td>
<td>82.7 (73.5; 89.5)</td>
<td>76.5 (67.4; 85.1) 0.110</td>
<td></td>
</tr>
<tr>
<td>FEF_{50} (% predicted)‡</td>
<td>92 (18)</td>
<td>85 (23)</td>
<td>76 (29)</td>
<td>0.179</td>
</tr>
<tr>
<td>FEF_{25-75}/FVC ((l/s)/s)‡</td>
<td>0.97 (0.76; 1.13)</td>
<td>0.91 (0.65; 1.08)</td>
<td>0.74 (0.54; 1.13) 0.346</td>
<td></td>
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<td>RV/TLC (% predicted)</td>
<td>0.83 (0.68; 1.04)</td>
<td>0.78 (0.58; 0.96)</td>
<td>0.62 (0.40; 1.00) 0.242</td>
<td></td>
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<tr>
<td>RV (l) (% predicted)†</td>
<td>88 (74; 97)</td>
<td>88 (77; 99)</td>
<td>90 (82; 110) 0.561</td>
<td></td>
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<td>R_{5} (kPa/l/s)</td>
<td>0.32* (0.27; 0.41)</td>
<td>0.35* (0.31; 0.40)</td>
<td>0.54 (0.41; 0.65) &lt;0.001</td>
<td></td>
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<tr>
<td>R_{20} (kPa/l/s)†</td>
<td>0.33 (0.08)</td>
<td>0.35 (0.09)</td>
<td>0.38 (0.06) 0.097</td>
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<tr>
<td>X_{5} (kPa/l/s)</td>
<td>0.00* (-0.01; 0.01)</td>
<td>0.02* (-0.01; 0.05)</td>
<td>0.12 (0.05; 0.25) &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Questionnaires</td>
<td>BHQ</td>
<td>0.0* (0.0; 0.2)</td>
<td>0.2* (0.0; 0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACQ</td>
<td>0.0* (0.0; 0.0)</td>
<td>0.0* (0.0; 0.2)</td>
<td>0.7 (0.3; 1.5) &lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

All values are presented as medians with interquartile ranges, unless stated otherwise; ACQ=asthma control questionnaire (0: best control, 6: worst control); BHR=bronchial hyperresponsiveness; BHQ=bronchial hyperresponsiveness questionnaire (0: no BHR, 6: worst score); FEV₁=forced expiratory volume in 1 s; FEF_{50}=forced expiratory flow at 50% of the FVC; FEF_{25-75}=forced expiratory flow between 25 and 75% of the FVC; FVC=forced vital capacity; PC_{20}=provoking concentration causing a 20% fall in FEV₁; R_{5}=resistance at 5 Hz; R_{20}=resistance at 20 Hz; R_{aw}=airway resistance; RV=residual volume; TLC=total lung capacity; X_{5}=reactance at 5 Hz; *Significantly different from asthma with Holm's Bonferroni correction; †Geometric mean with range; ‡Mean with standard deviation.
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There were no differences in small airway parameters between controls and subjects with asymptomatic BHR. Asthma patients had a significantly higher $R_{5}-R_{20}$ and a lower $X_{5}$, that is, more small airway dysfunction, than subjects with asymptomatic BHR and controls. Small airway airflow limitation reflected by $\text{FEF}_{50\%}$ predicted and $\text{FEF}_{25-75\%}$ predicted did not differ between the groups. Large airway parameters (FEV$_1$, % predicted and $R_{20}$) were comparable between the three groups. Scores on respiratory symptom questionnaires did not differ between controls and subjects with asymptomatic BHR, but were significantly higher in asthma patients. Since patients with asthma had a higher BMI than healthy controls and subjects with asymptomatic BHR, we investigated whether this would affect our main results. To this end, we also assessed the obese (BMI $\geq 30\text{kg/m}^2$) and non-obese (BMI $< 30\text{kg/m}^2$) asthma patients separately. This way, we found similar results, that is, $R_{5}-R_{20}$ values were higher in both obese and non-obese asthma patients compared to subjects with asymptomatic BHR ($p<0.001$ and $p=0.025$ respectively), whereas $X_{5}$-values were lower ($p=0.033$ and $p=0.010$ respectively).

Small airways and dyspnea score during methacholine provocation

During methacholine provocation, small airway resistance as reflected by the slopes of $R_{5}-R_{20}$ and $X_{5}$, increased to a higher extent in subjects with asymptomatic BHR and asthma than in controls (Table 2). Subjects with asymptomatic BHR had significantly higher slopes of $R_{20}$ than healthy controls. Furthermore, dyspnea increased significantly more both in subjects with asthma and asymptomatic BHR during the methacholine provocation test; that is, they had a higher slope of the Borg dyspnea score, than healthy controls. There were no significant differences in the slopes of FEV$_1$, $R_{5}-R_{20}$, $R_{20}$, $X_{5}$ and Borg dyspnea score between patients with asthma and subjects with asymptomatic BHR during methacholine provocation.

| Table 2. Changes in variables during methacholine provocation |
|-------------------|-------------------|-------------------|-------------------|-------------------|
|                   | Control (n=15)    | Asymptomatic BHR (n=15) | Asthma (n=15)      | p-value          |
| Slope FEV$_1$ (l/mg/ml) | -0.02 (-0.03 – -0.01) | -0.44 (-0.75 – -0.18)* | -0.38 (-0.60 – -0.09)* | <0.001          |
| Slope $R_{5}-R_{20}$ (kPa/l/s)/(mg/ml) | 0.00 (0.00 – 0.01) | 0.06 (0.02 – 0.13)* | 0.13 (0.04 – 0.56)* | <0.001          |
| Slope $X_{5}$ (kPa/l/s)/(mg/ml) | 0.00 (-0.01 – 0.00) | -0.05 (-0.14 – -0.02)* | -0.17 (-0.46 – -0.04)* | <0.001          |
| Slope $R_{20}$ (kPa/l/s)/(mg/ml) | 0.00 (0.00 – 0.01) | 0.02 (0.01- 0.04)* | 0.01 (0.00 – 0.05) | 0.049          |
| Slope Borg (score/mg/ml) | 0.06 (0.00 – 0.13) | 1.00 (0.25 – 1.00)* | 1.38 (0.53 – 2.19)* | <0.001          |

*Significantly different from controls ($p<0.05$ after Holm’s Bonferroni correction).

All values are presented as medians with interquartile ranges. BHR = bronchial hyperresponsiveness; FEV$_1$ = forced expiratory volume in 1 second; $R_{5}$ = resistance at 5 Hz; $R_{20}$ = resistance at 20 Hz; $X_{5}$ = reactance at 5 Hz.
Figure 1. Impulse oscillometry (IOS) measurements and Borg dyspnea scores at PC_{20}. a) R_5-R_{20}, b) X_5, c) R_{20} and d) Borg dyspnea score for subjects with asymptomatic BHR (●) and asthma patients (○) at PC_{20}. The lines represent medians. NS = not significant; PC_{20} = provoking concentration causing a 20% fall in FEV_{1}; R_5 = resistance at 5 Hz, R_{20} = resistance at 20 Hz, X_5 = reactance at 5 Hz.
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Figure 2. Correlation between the change in Borg dyspnea score ($\Delta$Borg score) and change in impulse oscillometry (IOS) measurements at $PC_{20}$ in asymptomatic BHR and asthma. a) $\Delta R_{5}-R_{20}$ in asymptomatic BHR, b) $\Delta R_{5}-R_{20}$ in asthma, c) $\Delta X_{5}$ in asymptomatic BHR, d) $\Delta X_{5}$ in asthma, e) $\Delta R_{20}$ in asymptomatic BHR, f) $\Delta R_{20}$ in asthma. $r_s$ = Spearman’s correlation coefficient; $PC_{20}$ = provoking concentration causing a 20% fall in FEV\(_1\); $R_{5}$ = resistance at 5 Hz, $R_{20}$ = resistance at 20 Hz, $X_{5}$ = reactance at 5 Hz.
At the provocative concentration causing the FEV$_1$ to drop by 20% (i.e., PC$_{20}$), significantly higher values of $R_5$-$R_{20}$ and lower values of $X_5$ were observed in asthma patients than in subjects with asymptomatic BHR (median $R_5$-$R_{20}$ 0.43 versus 0.17 respectively, Figure 1a; median $X_5$ -0.45 versus -0.20 respectively, Figure 1b), suggesting that asthma patients have more small airway dysfunction than subjects with asymptomatic BHR at a similar fall in FEV$_1$. Interestingly, $R_{20}$ did not differ between the groups at PC$_{20}$ (median 0.41 in both groups, Figure 1c). At PC$_{20}$, all asthma patients and some subjects with asymptomatic BHR experienced dyspnea, but asthma patients experienced significantly more dyspnea than subjects with asymptomatic BHR (median Borg score 3.4 versus 1.4 respectively, Figure 1d).

**Association between small airway dysfunction and dyspnea score**
In asymptomatic BHR, the increase in Borg dyspnea score from baseline to PC$_{20}$ ($\Delta$Borg score) was significantly associated with the concomitant increase in small airway dysfunction as reflected by both the increase in $R_5$-$R_{20}$ ($\Delta R_5$-$R_{20}$) and the decrease in $X_5$ ($\Delta X_5$) (Figure 2a-d). This was not the case in asthmatics. In contrast, an increase in large airway function, that is, a change in $R_{20}$ ($\Delta R_{20}$), was not correlated with the $\Delta$Borg dyspnea score neither in patients with asthma nor in individuals with asymptomatic BHR (Figure 2e-f).

**DISCUSSION**
The present study shows that subjects with asymptomatic BHR have a similar level of small airway function at baseline compared to healthy controls, whereas asthma patients show small airway dysfunction. During methacholine provocation, small airway dysfunction increases more in subjects with asymptomatic BHR and asthma than in healthy controls. At a 20% fall in FEV$_1$, subjects with asymptomatic BHR have less small airway dysfunction than asthma patients. The increase in large airway dysfunction, as reflected by the change in $R_{20}$, is not associated with the increase in dyspnea during methacholine provocation either in subjects with asymptomatic BHR or patients with asthma. In contrast and of importance, a higher increase in small airway dysfunction during the provocation test associates with more worsening of dyspnea in subjects with asymptomatic BHR, whereas this is not the case in asthma patients.

We show that the level of small airway resistance at baseline is similar in subjects with asymptomatic BHR and in controls. This is in line with two other studies(23,24), in which no baseline differences in small airway resistance and small airway inflammation between asymptomatic subjects with BHR and allergic rhinitis and controls were found. In contrast, we found an increase in small airway resistance in asthma patients.
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at baseline. In line with this, Tufvesson et al reported that the baseline level of exhaled alveolar nitric oxide, an indicator of small airway inflammation, was significantly higher in asthma patients than in subjects with asymptomatic BHR or controls. We extended the findings of previous studies by additionally analyzing changes in small airway function during methacholine provocation. Interestingly, we found that small airway dysfunction, as reflected by the slopes of $R_5-R_{20}$ and $X_5$, increased more in subjects with asymptomatic BHR and asthma than in healthy controls. These results are in line with those of Aronsson et al, showing that small airway resistance (i.e. the slope of $R_5-R_{20}$) during methacholine provocation increased the most in subjects with allergic rhinitis and asthma, followed by asymptomatic subjects with allergic rhinitis and BHR and finally subjects with allergic rhinitis without BHR(23). Thus, a methacholine provocation test induces small airway dysfunction not only in patients with asthma, but also in subjects with asymptomatic BHR.

Besides the change of small airway parameters during methacholine provocation, we also investigated the level of small airway dysfunction at a 20% fall in FEV$_1$, that is, at PC$_{20}$. At PC$_{20}$ we observed a higher degree of small airway dysfunction (a higher $R_5-R_{20}$ and lower $X_5$) in patients with asthma than in subjects with asymptomatic BHR. Of interest, large airway resistance ($R_{20}$) increased only slightly during provocation and did not differ between asthma patients and subjects with asymptomatic BHR at PC$_{20}$. Next, we investigated the perception of dyspnea during methacholine provocation. As could be expected, Borg dyspnea scores were significantly lower in subjects with asymptomatic BHR than in asthma patients at PC$_{20}$(9,25-27). Nevertheless, some subjects with asymptomatic BHR did experience an important increase in their Borg dyspnea score at the time their FEV$_1$ had dropped by ≥20%. This was a remarkable finding because these subjects were considered to be asymptomatic in their daily lives. However, it is in line with previous studies that also found subjects with asymptomatic BHR to report symptoms during a provocation test, albeit to a smaller extent than patients with asthma(25,26). A possible explanation for this observation may be that subjects participating in a study like ours are more attentive than usual to report dyspnea during a provocation test. Alternatively, it could be argued that these subjects may not encounter stimuli in their daily lives that cause bronchoconstriction as severe as occurs during a methacholine provocation. In this study, they were explicitly asked if they experienced dyspnea, and possibly they would not have considered this sensation as dyspnea in their daily lives. Another possible explanation could be that subjects with asymptomatic BHR are usually not or only minimally exposed to stimuli and therefore do not experience dyspnea in their daily lives. Interestingly, the increase in dyspnea during provocation ($\Delta$Borg score at PC$_{20}$) in subjects with asymptomatic BHR was significantly associated with the increase in small airway dysfunction ($\Delta R_5-R_{20}$ and $\Delta X_5$, Figure 2A), supporting...
the hypothesis that the dyspnea sensation is influenced by the small airways. In contrast to our expectations, we did not find an association between the ΔBorg score and the increase in small airway dysfunction in asthma patients. It is possible that no association was found in the asthma patients due to the limited size of this group in our study, as an association between dyspnea and small airway dysfunction during provocation in asthma patients has been found previously(16).

A strength of our study was the comparison between subjects with asymptomatic BHR and both controls and asthma patients. By comparing these three groups on several parameters, we not only obtained a broad overview of subjects with asymptomatic BHR alone, but we were also able to put these results in perspective with respect to the two other groups. A limitation of the study is the relatively small size of the study population which may have limited some variables to show a significant difference between the groups. Interestingly, subjects with asymptomatic BHR were frequently female, although female prevalence did not significantly differ between the three groups. This is in line with several studies showing that BHR is more common and more severe in women than in men and this may also be the case for asymptomatic BHR(28,29). Furthermore, asthma patients had a higher BMI than healthy controls and subjects with asymptomatic BHR. It has been reported that obese asthmatics have higher airway resistance and lower airway reactance than non-obese asthma patients(30). To investigate whether the higher BMI in asthma patients may have influenced our results we analyzed the small airway resistance in obese and non-obese asthma patients separately. We found that in both obese and non-obese asthma patients, small airway dysfunction was higher than in subjects with asymptomatic BHR. Based on this outcome, we think it unlikely that the higher BMI in asthma patients will have influenced our results. Finally, we provoked the airways with relatively large-particle methacholine, which will deposit mostly in the large airways. It would be interestingly, to provoke also the small airways with small-particle methacholine or other stimuli like AMP, as has been done previously in the study of Cohen et al(31).

In conclusion, our study shows that baseline small airway function of subjects with asymptomatic BHR is comparable to that of healthy controls, whereas asthma patients show small airway dysfunction. However, during provocation the small airways of subjects with asymptomatic BHR and those of asthma patients respond similarly. This results in significantly more small airway dysfunction at a 20% fall in FEV1 in asthma patients than in subjects with asymptomatic BHR. We speculate that subjects with asymptomatic BHR experience less symptoms in their daily lives because they have less small airway dysfunction.
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