

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 patients.

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

Bronchial hyperresponsiveness (BHR) is defined as exaggerated airway narrowing in response to various nonspecific 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. (1), a prevalence rate between 2.2 and 14.3% of this so-called ‘asymptomatic BHR’ was reported. 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 < 2 mm) are also involved in BHR and contribute importantly to the clinical expression of asthma (10–15). Mansur et al. (16)

showed that small airway dysfunction during a methacholine provocation was associated with increased dyspnea perception in asthma patients.

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 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 18–65 years with a smoking history <10 pack-years. 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 two 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 400 μ g 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 and 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 values as percentage of the predicted value. Impulse oscillometry (IOS) was used to measure the resistance at 5 Hz (R_5), which reflects total airway resistance, the resistance at 20 Hz (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 (0.03–16 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 prechallenge 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.

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 three 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 in 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 Kruskal–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.

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

Table 1 Baseline characteristics of the study population

	Controls (n = 15)	Asymptomatic BHR (n = 15)	Asthma (n = 15)	P-value
Age (years)	26* (23; 32)	24* (23; 28)	45 (36; 52)	0.005
Gender (female/male)	10/5	12/3	13/2	0.407
Smoking (n, %)				0.043
Current	5 (33)	8 (53)	2 (13)	
Ex	–	1 (7)	4 (27)	
Never	10 (67)	6 (40)	9 (60)	
Packyears	5.6 (1.9; 8.3)	2.5 (1.3; 8.7)	4.7 (2.8; 8.9)	0.773
Family history of asthma (n, %)	4* (27)	5* (33)	13 (87)	0.002
Allergic rhinitis (n, %)	1* (7)	3 (20)	9 (60)	0.008
Body Mass Index (kg/m ²)‡	21.6* (20.6; 25.5)	22.5* (20.8; 26.6)	30.9 (28.4; 37.7)	<0.001
PC ₂₀ (mg/ml)†	–	1.9 (0.6; 8.0)	1.4 (0.04; 8.0)	1.000
FEV ₁ (% predicted)‡	106 (10)	103 (14)	101 (15)	0.566
FEV ₁ reversibility (% predicted)	1.8 (0.8; 4.1)	5.6 (3.0; 8.4)	5.0 (1.1; 9.4)	0.064
FEV ₁ /FVC (%)	82.6 (79.0; 89.2)	82.7 (73.5; 89.5)	76.5 (67.4; 85.1)	0.110
FEF ₅₀ (% predicted)‡	92 (18)	85 (23)	76 (29)	0.179
FEF ₅₀ /FVC ((l/s)/s)	0.97 (0.76; 1.13)	0.91 (0.65; 1.08)	0.74 (0.54; 1.13)	0.346
FEF _{25–75} (% predicted)	95 (80; 112)	83 (59; 101)	69 (44; 114)	0.231
FEF _{25–75} /FVC ((l/s)/s)	0.83 (0.68; 1.04)	0.78 (0.58; 0.96)	0.62 (0.40; 1.00)	0.242
RV/TLC (% predicted)	88 (74; 97)	88 (77; 99)	90 (82; 110)	0.561
R _{aw} (% predicted)	80* (61; 91)	73* (66; 94)	120 (80; 193)	0.007
R ₅ (kPa/l/s)	0.32* (0.27; 0.41)	0.35* (0.31; 0.40)	0.54 (0.41; 0.65)	<0.001
R ₂₀ (kPa/l/s)‡	0.33 (0.08)	0.35 (0.09)	0.38 (0.06)	0.097
R ₅ –R ₂₀ (kPa/l/s)	0.00* (–0.01; 0.01)	0.02* (–0.01; 0.05)	0.12 (0.05; 0.25)	<0.001
X ₅ (kPa/l/s)	–0.07* (–0.09; –0.05)	–0.10* (–0.11; –0.06)	–0.16 (–0.23; –0.10)	<0.001
Questionnaires				
BHQ	0.0* (0.0–0.2)	0.2* (0.0–0.4)	2.4 (1.8–3.1)	<0.001
ACQ	0.0* (0.0–0.0)	0.0* (0.0–0.2)	0.7 (0.3–1.5)	<0.001

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; FEF₅₀, 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; PC₂₀, provoking concentration causing a 20% fall in FEV₁; R₅, resistance at 5 Hz; R₂₀, resistance at 20 Hz; R_{aw}, airway resistance; RV, residual volume; TLC, total lung capacity; X₅, reactance at 5 Hz.

*Significantly different from asthma with Holm's Bonferroni correction.

†Geometric mean with range.

‡Mean with standard deviation.

subjects with asymptomatic BHR and controls. Small airway airflow limitation reflected by FEF₅₀% predicted and FEF_{25–75}% predicted did not differ between the groups. Large airway parameters (FEV₁% predicted and R₂₀) 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. Because 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 ≥ 30 kg/m²) and nonobese (BMI < 30 kg/m²) asthma patients separately. This way, we found similar results; that is, R₅–R₂₀ values were higher in both obese and nonobese asthma patients compared with subjects with asymptomatic BHR ($P < 0.001$ and $P = 0.025$, respectively), whereas X₅-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 R₅–R₂₀ and X₅ 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 R₂₀ 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 FEV₁, R₅–R₂₀, R₂₀, X₅, and Borg dyspnea score between patients with asthma and subjects with asymptomatic BHR during methacholine provocation.

At the provocative concentration causing the FEV₁ to drop by 20% (i.e., PC₂₀), significantly higher values of

Table 2 Changes in variables during methacholine provocation

	Control (<i>n</i> = 15)	Asymptomatic BHR (<i>n</i> = 15)	Asthma (<i>n</i> = 15)	<i>P</i> -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

All values are presented as medians with interquartile ranges.

BHR, bronchial hyperresponsiveness; FEV₁, forced expiratory volume in 1 s; R₅, resistance at 5 Hz; R₂₀, resistance at 20 Hz; X₅, reactance at 5 Hz.

*Significantly different from controls (*P* < 0.05 after Holm's Bonferroni correction).

R₅−R₂₀ and lower values of X₅ were observed in asthma patients than in subjects with asymptomatic BHR (median R₅−R₂₀ 0.43 vs 0.17, respectively, Fig. 1A; median X₅ −0.45 vs −0.20, respectively, Fig. 1B), suggesting that asthma patients have more small airway dysfunction than subjects with asymptomatic BHR at a similar fall in FEV₁. Interestingly, R₂₀ did not differ between the groups at PC₂₀ (median 0.41 in both groups, Fig. 1C). At PC₂₀, 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 vs 1.4, respectively, Fig. 1D).

Association between small airway dysfunction and dyspnea score

In asymptomatic BHR, the increase in Borg dyspnea score from baseline to PC₂₀ (ΔBorg score) was significantly associated with the concomitant increase in small airway dysfunction as reflected by both the increase in R₅−R₂₀ (ΔR₅−R₂₀) and the decrease in X₅ (ΔX₅) (Fig. 2A–D). This was not the case in asthmatics. In contrast, an increase in large airway function, that is, a change in R₂₀ (ΔR₂₀), was not correlated with the ΔBorg dyspnea score neither in patients with asthma nor in individuals with asymptomatic BHR (Fig. 2E–F).

Discussion

The present study shows that subjects with asymptomatic BHR have a similar level of small airway function at baseline compared with 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 FEV₁, subjects with asymptomatic BHR have less small airway dysfunction than asthma patients. The increase in large airway dysfunction, as reflected by the change in R₂₀, is not associated with the increase in dyspnea during methacholine provocation either in subjects with asymptomatic BHR or in 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 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 (24). 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 R₅−R₂₀ and X₅, increased more in subjects with asymptomatic BHR and asthma than in healthy controls. These results are in line with those of Aronsson et al. (23), showing that small airway resistance (i.e., the slope of R₅−R₂₀) 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. 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 in small airway parameters during methacholine provocation, we also investigated the level of small airway dysfunction at a 20% fall in FEV₁, that is, at PC₂₀. At PC₂₀, we observed a higher degree of small airway dysfunction (a higher R₅−R₂₀ and lower X₅) in patients with asthma than in subjects with asymptomatic BHR. Of interest, large airway resistance (R₂₀) increased only slightly during provocation and did not differ between asthma patients and subjects with asymptomatic BHR at PC₂₀. 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 PC₂₀ (9, 25–27). Nevertheless, some subjects with asymptomatic BHR did experience an important increase in their Borg dyspnea score at the time their

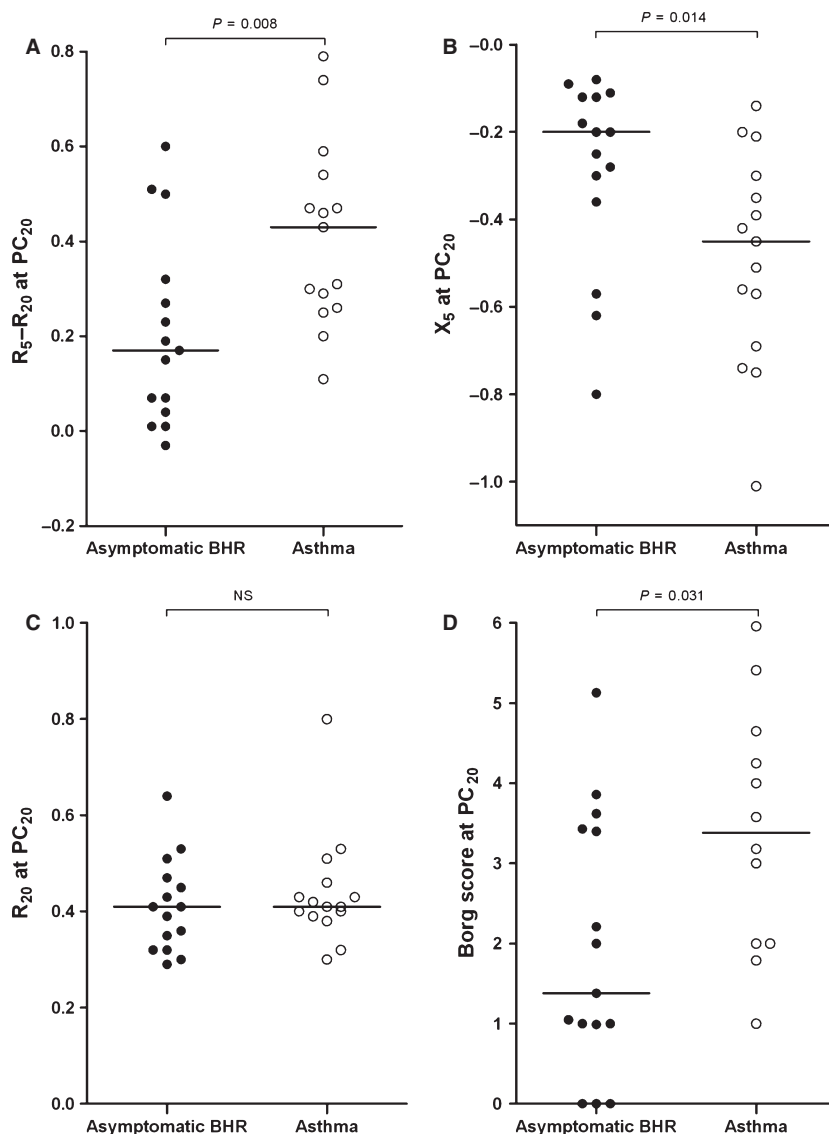


Figure 1 Impulse oscillometry (IOS) measurements and Borg dyspnea scores at PC_{20} . (A) $R_5 - R_{20}$, (B) X_5 , (C) R_{20} , and (D) Borg dyspnea score for subjects with asymptomatic BHR (●) and asthma patients (○) at PC_{20} . The lines represent medians. NS = not

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.

FEV_1 had dropped by $\geq 20\%$. 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 whether they experienced dyspnea, and possi-

bly, 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 (Δ 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 ΔX_5 , Fig. 2A and Fig. 2C), 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 Δ Borg score and the increase in small airway dysfunction in asthma patients. It is possible that no association

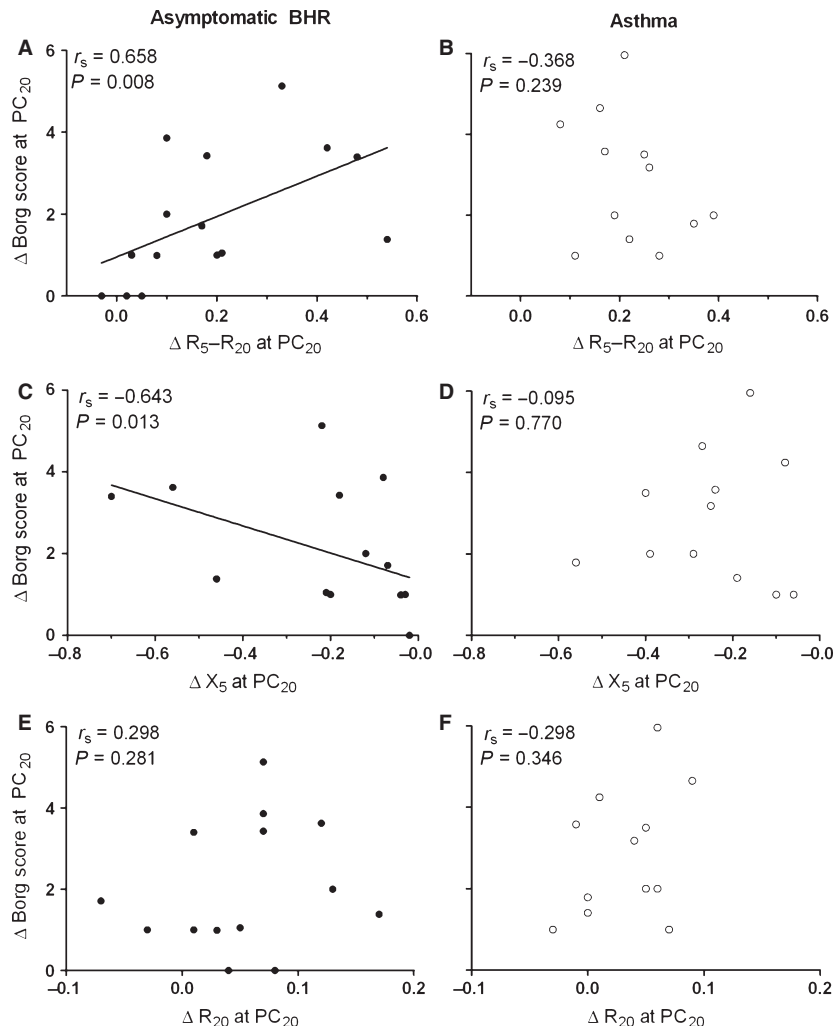


Figure 2 Correlation between the change in Borg dyspnea score (Δ Borg score) and change in impulse oscillometry (IOS) measurements at PC₂₀ in asymptomatic BHR and asthma. (A) Δ R₅-R₂₀ in asymptomatic BHR, (B) Δ R₅-R₂₀ in asthma, (C) Δ X₅ in asymptomatic BHR, (D) Δ X₅ in asthma, (E) Δ R₂₀ in asymptomatic BHR, (F) Δ R₂₀ in asthma. r_s = Spearman's correlation coefficient; PC₂₀ =

provoking concentration causing a 20% fall in FEV₁; R₅ = resistance at 5 Hz, R₂₀ = resistance at 20 Hz, X₅ = reactance at 5 Hz.

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 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 nonobese 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 nonobese asthma patients separately. We found that in both obese and nonobese 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 such as 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.

Author contributions

Ilse M. Boudewijn, Erica van der Wiel, Lieke Schiphof, Nick H.T. ten Hacken, Thys van der Molen, Eef D. Telenga, and Maarten van den Berge contributed to data collection. Ilse M. Boudewijn performed the statistical analyses under the supervision of Eef D. Telenga, Dirkje S. Postma, and Maarten van

den Berge. All authors contributed to interpretation of the data. Ilse M. Boudewijn wrote the first draft of manuscript under the supervision of Eef D. Telenga, Dirkje S. Postma, and Maarten van den Berge, which was then critically reviewed and approved by all authors.

Conflict of interest

Dr. M. van den Berge has received grants from Chiesi and Teva Pharma. Professor D. S. Postma has received consulting fees from Astra Zeneca, Boehringer Ingelheim, Chiesi, Nycomed, and Teva. Professor D. S. Postma has received grants or has grants pending from Chiesi and AstraZeneca. Professor T. van der Molen has received consulting fees from Chiesi, AstraZeneca, and Novartis; he received a grant or has grants pending from MSD and Allmiral and has received payment for lectures from Novartis and Chiesi. Professor T. van der Molen received royalties from Mapi. Dr. N. H. T. ten Hacken received grants from Chiesi and Nycomed. Drs. E. D. Telenga and L. Schiphof received grants from Chiesi. Drs. I. M. Boudewijn and E van der Wiel have no potential conflicts of interest to declare.

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