

Allergic rhinitis with hyper-responsiveness differ from asthma in degree of peripheral obstruction during metacholine challenge test

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Summary

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Allergic rhinitis (AR) is a risk factor for developing clinical asthma. Moreover, AR is often associated with bronchial hyper-responsiveness (BHR). The aim of this study was to compare the degree of involvement of the peripheral airways during metacholine (MCh) challenge test in asthmatics and patients with AR with or without BHR by using the impulse oscillometry (IOS) technique. Fifty-three patients with seasonal AR were investigated with MCh challenge test and IOS. Thirteen healthy non-reactive subjects served as controls. MCh challenge test was performed, cut-off value FEV_{1PD20} 2000 μ g. Linear regression analysis was used to calculate a MCh/FEV_1 slope ($Slope-FEV_1^{MCh}$), which was used as an index of BHR. IOS was performed, measuring respiratory resistance and reactance during the MCh challenge test. Twenty-six subjects had both AR and asthma symptoms, 27 patients reported AR only, without asthma symptoms, 17 (63%) manifested BHR by spirometric criteria. Patients with AR and symptoms of asthma manifested greater peripheral airway obstruction compared to those with AR only with BHR. Increased peripheral obstruction in the asthmatic group compared to patients with AR and BHR may explain previous findings that asthmatics perceive greater airway obstruction during MCh challenge tests.

Introduction

Allergic rhinitis (AR) is a risk factor for developing clinical asthma (Settipane et al., 2000). It is also known that approximately 45% of those with AR without diagnosed asthma have a bronchial hyper-responsiveness (BHR), which indicates pathology of the lower airways even in those who do not show any clinical symptoms (Alvarez et al., 2000), and non-invasive inflammation marker analyses have shown that these patients have evidence of lower airway inflammation (Braunsthahl et al., 2003). Moreover, in a previous study we found that asthmatics were more perceptive for degree of bronchial obstruction (Aronsson et al., 2005). We believe that this could be explained by asthmatics having more peripheral airway involvement than those with AR alone and that inflammation in the small airways is linked to clinical symptoms and exacerbations. Previous literature has defined small airways as those with a diameter of <2 mm and estimate that they account for approximately 80% total lung surface area (Youngmans, 1961). However, the small airways only accounts for 10% of the total airway resistance, which means that conventional tests of the lung function [e.g. forced

expiratory volume in 1 s (FEV_1)] fail to accurately reflect changes in peripheral resistance (Macklem & Mead, 1967; Hogg et al., 1968; Green, 1998). Hence, the term 'silent zone' is sometimes used for the small airways (Woolcock et al., 1969). For the purpose of this paper, small airways are defined as those which do not permit higher frequencies (>15–20 Hz and higher) of oscillation pressures to be transmitted through, which may have an approximate diameter of 2–4 mm.

Impulse oscillometry (IOS) is a forced oscillation technique (FOT) (Fisher et al., 1968; Oostveen et al., 2003), which only requires passive cooperation of the test subject to measure lung function (Bohadana et al., 1999; Goldman, 2001; Arets & van der Ent, 2004; Smith et al., 2005). Furthermore, it allows for discrimination between central and peripheral obstruction (Cuijpers et al., 1993; Navajas & Farré, 1999; Goldman et al., 2005).

The aim of this study was to compare the degree of involvement of the peripheral airways in asthmatics and patients with AR with or without BHR, specifically the degree of peripheral airway obstruction during MCh challenge test, by using IOS.

Materials and methods

Subjects

All subjects were non-smokers without upper respiratory tract infection within 3 weeks prior to the investigation. There were 23 male and 30 female subjects. The age ranged from 18 to 58 (mean 30). All subjects had clinically confirmed seasonal AR. Of those, 26 had concomitant clinically diagnosed mild asthma, according to Global Initiative for Asthma (1996) standards. Four of these patients inhaled corticosteroids daily (200–400 µg budesonide).

Caffeine was withheld 4 h before the investigation. Strenuous physical exercise was not allowed 2 h prior to the investigation. All subjects were patients attending the outpatient clinic of the Department of Lung medicine in Lund.

A control group of 13 non-smoking subjects, age ranging from 19 to 56 (mean 41), who did not report a history of AR or asthma, was recruited and investigated. These subjects had negative skin prick tests (SPT) and were not hyper-responsive to metacholine (MCh), and fulfilled all other inclusion criteria. FEV₁-slope data from healthy controls have previously been published in parts in another publication (Aronsson *et al.*, 2005).

All subjects gave written informed consent, and the ethical committee in Lund approved the study (LU412-03).

Methods

Allergy screening

Skin prick test (Alk Abello, Copenhagen, Denmark) was used to screen for sensitization to a panel of 10 common aeroallergens (birch, timothy, mugwort, cat, dog, horse, D. Pteronyssinus, D. Farinae, *Aspergillus fumigatus* and *Cladosporium herbarum*).

Spirometry and metacholine inhalation challenge test

A MasterScope spirometer, software version 4.5 (Erich Jaeger GmbH, Wurzburg, Germany) was used for flow-volume spirometry. The reference values were obtained from Crapo *et al.* (1981). The better of two measurements of FEV₁ with <4% variation was recorded as baseline. If the baseline value was below 70% of the predicted value, the MCh inhalation challenge test was aborted.

Presence of BHR was measured with a MCh inhalation challenge test, which was carried out with tidal volume triggered equipment (Aerosol Provocation System, APS; Erich Jaeger GmbH). The APS delivered a cumulative dose of 2000 µg MCh in five increments (50, 150, 300, 600 and 900 µg) following an initial dose of 0.9% NaCl. The challenge was discontinued if the FEV₁ declined more than 20% during the protocol. A positive test was defined as the cumulative dose that caused a decline in FEV₁ by 20% or more (PD₂₀FEV₁) from baseline. The PD₂₀FEV₁ was determined by interpolation by the last two points on the log dose–response plot. The amounts of

MCh given during every increment of the challenge test were plotted against the corresponding percentage fall in FEV₁ from baseline. Linear regression analysis was used to calculate a MCh/FEV₁ slope (Slope-FEV₁^{MCh}), which was used as an index of BHR. When FEV₁ fell below 80% of the baseline value or when the total amount of 2000 µg MCh was delivered, 400 µg of salbutamol were given to the subject. After 10 min a new flow-volume spirometry was carried out, to ensure that the subjects were recuperating properly.

Impulse oscillometry

A Jaeger MasterScreen Impulse Oscillometry System, Erich Jaeger GmbH, was used. Oscillometry was performed after each step of the challenge, prior to the spirometry, to avoid the influence of deep inspiration and subsequent maximal forced expiratory manoeuvres, which may induce bronchospasm, on IOS parameters. IOS was performed 90 s after each challenge step, FEV₁ performed 120–150 s after each challenge step. The subjects used nose clips and were told to press the palms of their hands against the cheeks to decrease the upper airways shunt. For about 30 s, oscillometric pressure impulses were superimposed on the tidal breathing of the subject, having a pulse sequence of 5 per second and a frequency spectrum between 5 and 35 Hz.

The IOS system produces a pulse-shaped pressure wave, sending it down the subject's lungs. The corresponding flow is then recorded to determine respiratory impedance. The oscillations provide a measure of total airway impedance, which reflects both resistive elements of the airways (resistance, R) and viscoelastic and inertive forces in the lungs and the chestwall (reactance, X). Reactance is the sum of inertance, which is the inertive force of the air column in the conducting airways, and capacitance, which reflects the elastic properties of the peripheral lung. Inertive forces dominate at frequencies above resonant frequency (F_{res}) whereas elastic forces are increasingly related to frequencies below F_{res}. Low frequent reactance is usually reported as X₅ (reactance at 5 Hz). X₅ reflects changes to the lung periphery and is nonspecific. Increased negative values can be seen both in restrictive and obstructive disease. Resonant frequency is the frequency where the inertance and capacitance are equal in magnitude and opposite in sign (phase), and is measured in Hz. The reactance area (AX) is a quantification of the respiratory reactance between 5 Hz and F_{res}, thus it will mostly reflect the capacitance part of the reactance. This makes AX a good index of changes of the degree of peripheral involvement.

Resistance is typically reported as R₅ and R₂₀ (resistance at 5 and 20 Hz respectively), where R₅ reflects total respiratory resistance of the airways and R₂₀ reflects resistance of the proximal airways. The ΔR₅-R₂₀ parameter is an indicator of peripheral properties of the respiratory tract.

The physiology and methodology of the IOS technique have recently been described in detail (Smith *et al.*, 2005). The IOS parameters were plotted against the MCh dose at each challenge

step and linear regression analysis was used to calculate a slope value, similar to how $\text{Slope-}\dot{\text{FEV}}_1^{\text{MCh}}$ was calculated.

Statistical analysis

For statistical analysis, the SPSS software was used (SPSS 12.0.1 for Windows; SPSS Inc., Chicago, IL, USA). Statistical comparison between the groups was done with Kruskal–Wallis test for independent samples. The Mann–Whitney U-test was used for comparison between two groups. A P-value of <0.05 was considered significant.

Results

Among the 27 AR patients with no concomitant asthma, 17 were hyper-responsive to MCh defined by spirometric testing, 23 of the asthmatics were hyper-responsive. The remaining three did not fall below 80% of the baseline value, but reported symptoms during the test. There was no significant difference in $\text{Slope-}\dot{\text{FEV}}_1^{\text{MCh}}$ between asthmatics and patients with AR and BHR (Fig. 1).

There was a general trend that asthmatics had higher peripheral obstruction compared to patients with AR with or without BHR, measured by IOS (Table 1). Furthermore, the patients with AR and BHR placed themselves as an intermediary state between the asthmatics and the patients with AR and no BHR (Figs 2 and 3).

Discussion

In the present study, we aimed to compare the degree of involvement of the peripheral airways in patients with AR with or without concomitant asthma by using IOS, which is a FOT (Smith et al., 2005).

Impulse oscillometry as a technique has distinct advantages over spirometry. It is not effort dependent and therefore not

affected by repeated measurements. It may be a more sensitive tool for evaluating drug effects on the lung (Houghton et al., 2005). Moreover, while $\dot{\text{FEV}}_1$ is a direct volume per time measurement, IOS measures both resistance and reactance and provides complementary information that can be used to discern which parts of the lung is affected (Cuijpers et al., 1993; Navajas & Farré, 1999; Goldman et al., 2005; Smith et al., 2005). We are well aware that the IOS model is based on theoretical assumptions. Very few physiological correlations between FOT parameters and direct evidence of airway function have been published. Therefore, one has to be careful of drawing too extensive conclusions from the results.

The interpretation of these IOS parameters representing preferably the peripheral lung can be complicated. It has been shown that Fres is increased in both restrictive and obstructive respiratory disease (Clement et al., 1983; Cauberghs & Van de Woestijne, 1992). Likewise, due to the nature of the X5 parameter, greater magnitudes can reflect both restriction and obstruction (Smith et al., 2005). However, the differentiation between restrictive and obstructive disease is normally not a problem in a clinical setting. Thus, in the present study, greater magnitudes of $\text{Slope-Fres}^{\text{MCh}}$, $\text{Slope-AX}^{\text{MCh}}$ and $\text{Slope-X5}^{\text{MCh}}$ in response to MCh in asthmatics compared with the other groups would indicate a higher degree of peripheral obstruction.

R5 reflects total respiratory resistance and is increased if obstruction occurs either centrally or peripherally. Higher frequencies of the oscillation, such as R20, measure more proximal resistance (Smith et al., 2005). The fact that the changes of R20-values during the provocation test did not significantly differ between the groups indicates that the increase of proximal resistance in all groups followed a similar pattern. However, asthmatics had a higher total resistance, indicating that peripheral resistance is increased more in asthmatics. This was confirmed by the indirect way of calculating peripheral resistance, $\text{Slope-}\Delta\text{R5-R20}^{\text{MCh}}$.

The IOS parameters show a clear difference between asthmatics and patients with AR and BHR. The median $\text{Slope-}\dot{\text{FEV}}_1^{\text{MCh}}$ of the asthmatic group was higher than that of patients with AR and BHR, indicating a stronger reaction to MCh in asthmatics also in terms of lowered $\dot{\text{FEV}}_1$. However, the difference was not significant. The IOS parameters further helped discriminate between central and peripheral airways, which indicating a stronger reaction in peripheral airways in the asthmatic group.

Interestingly, in a previous study comparing asthmatics and AR patients, the asthmatics perceived a greater degree of symptoms related to the same degree of MCh-induced bronchial obstruction (Aronsson et al., 2005). It is plausible to believe that the relative lack of symptoms in the AR plus BHR group may be explained by a lesser degree of peripheral airway involvement. Indeed, it has been shown that small airways play an important role in asthma (Bjerner, 2001). Wagner et al. (1998) measured small airways reactivity with a wedged bronchoscope technique and found that asthmatics had a higher degree of peripheral resistance in response to histamine compared with healthy controls. Moreover, there

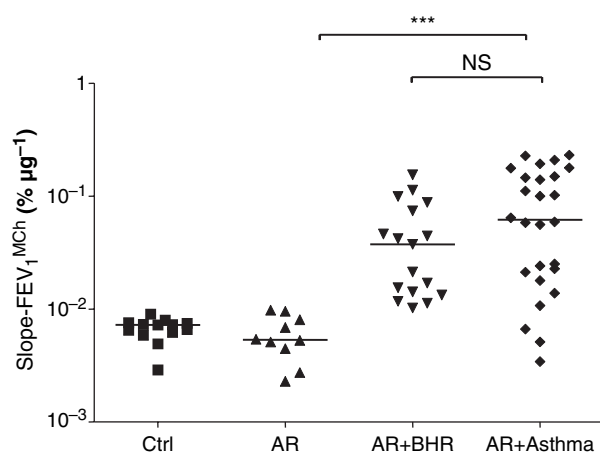


Figure 1 $\text{Slope-}\dot{\text{FEV}}_1^{\text{MCh}}$ for controls, patients with AR, with or without BHR and patients with AR and concomitant asthma. There was no significant difference between asthmatics and patients with AR and BHR. Data were expressed as individual scores and median.

Table 1 Baseline data and slopes of patients undergoing MCh challenge test. Median (range).

Parameter	Controls (<i>n</i> = 13)	AR (<i>n</i> = 10)	AR + BHR (<i>n</i> = 17)	AR + asthma (<i>n</i> = 27)
Age (years)	44 (19–56)	28.5 (22–55)	34 (18–53)	25 (18–58)
FEV ₁ , baseline (l)	4.10 (2.96–5.49)	3.97 (2.70–6.09)	3.64 (2.55–5.37)	3.90 (2.37–5.87) [†]
FEV ₁ , %pred (%)	107.3 (79.0–115.5)	100.8 (83.2–115.3)	107.4 (87.8–138.0)	95.5 (62.2–134.6) [†]
R5, baseline (kPa s l ⁻¹)	0.33 (0.20–0.73)	0.33 (0.22–0.59)	0.34 (0.22–0.62)	0.36 (0.23–0.70) [†]
R20, baseline (kPa s l ⁻¹)	0.29 (0.18–0.50)	0.33 (0.21–0.45)	0.31 (0.18–0.56)	0.32 (0.18–0.56) [†]
ΔR5-R20, baseline (kPa s l ⁻¹)	0.03 (0.0–0.29)	0.02 (–0.40 to 0.14)	0.03 (–0.12 to 0.32)	0.05 (–0.25 to 0.17) [†]
AX, baseline (kPa s l ⁻¹)	0.12 (0.06–0.34)	0.21 (0.00–1.20)	0.20 (0.04–0.36)	0.25 (0.06–1.11) [†]
Fres, baseline (Hz)	9.28 (7.37–30.50)	9.57 (5.85–22.14)	9.78 (6.68–13.64)	11.26 (7.00–20.77) [†]
X5, baseline (kPa s l ⁻¹)	–0.07 (–0.04 to –0.35)	–0.11 (–0.01 to –0.19)	–0.09 (–0.04 to –0.14)	–0.09 (–0.04 to –0.17) [†]
Slope-FEV ₁ ^{MCh} (10 ⁻³) (% per μg ⁻¹)	7.24 (2.89–9.04)	5.35 (2.29–9.80)	37.45 (10.24–154.80)	61.82 (3.43–231.80) [†]
Slope-R5 ^{MCh} (10 ⁻⁵) (kPa s l ⁻¹ μg ⁻¹)	4.87 (0.0–19.07)	6.80 (0.0–17.42)	24.52 (0.85–146.90)	71.62 (0.0–363.80)*
Slope-R20 ^{MCh} (10 ⁻⁵) (kPa s l ⁻¹ μg ⁻¹)	2.72 (0.0–11.33)	3.80 (0.0–11.43)	8.79 (0.0–62.31)	10.45 (0.0–93.85) [†]
Slope-ΔR5-R20 ^{MCh} (10 ⁻⁵) (kPa s l ⁻¹ μg ⁻¹)	3.51 (0.00–15.07)	2.41 (0.00–14.99)	11.90 (1.60–8.46)	51.70 (2.60–800.00)**
Slope-AX ^{MCh} (10 ⁻⁴) (kPa s l ⁻¹ μg ⁻¹)	2.82 (0.30–16.23)	1.53 (0.24–17.60)	9.32 (0.58–101.90)	45.48 (1.29–386.00)*
Slope-Fres ^{MCh} (10 ⁻³) (Hz μg ⁻¹)	2.17 (0.28–11.19)	3.28 (0.28–8.42)	7.10 (1.28–83.98)	30.65 (1.54–141.20) [†]
Slope-X5 ^{MCh} (10 ⁻⁵) (kPa s l ⁻¹ μg ⁻¹)	–2.31 (–0.11–12.18)	–2.33 (–0.60 to –11.28)	–7.20 (–0.50 to –7.32)	–37.40 (–3.8 to –320.0)*

*Significant difference from BHR group, *P* < 0.05; **Significant difference from BHR group, *P* < 0.01; [†]No significant difference from BHR group.

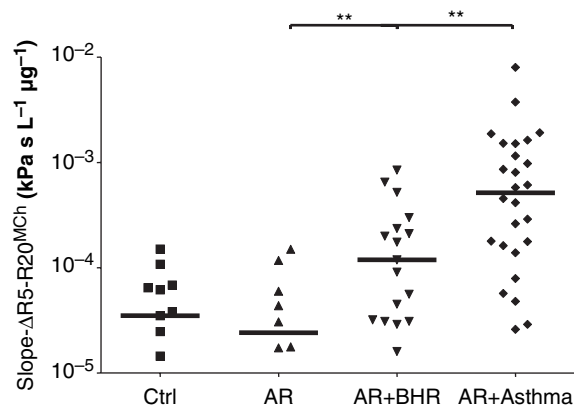


Figure 2 Slope-ΔR5-R20^{MCh} for controls, patients with AR with or without BHR and patients with AR and concomitant asthma. Significantly different levels of peripheral resistance were seen in the three groups of patients with AR. Data were expressed as individual scores and median.

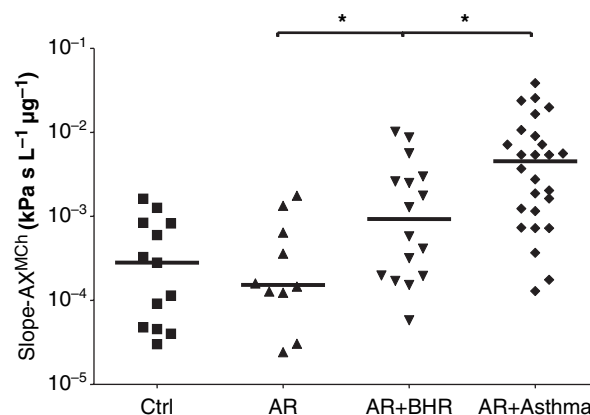


Figure 3 Slope-AX^{MCh} for controls, patients with AR with or without BHR and patients with AR and concomitant asthma. Significantly different levels of peripheral reactance were seen in the three groups of patients with AR. Data were expressed as individual scores and median.

was a strong correlation between the degree of BHR to histamine and to the degree of peripheral resistance, indicating a strong link between BHR and small airway involvement in asthma. That mild asthmatics are reactive in small airways is also indicated in a study by Brown et al. (2001). They found, by the use of high resolution computed tomography (HRCT), that patients with mild asthma and normal lung function in contrast to healthy controls had a narrowing of small airways after deep inspiration. However, HRCT scanning after MCh challenge showed more constriction of airways <3 mm in diameter in healthy subjects compared with mild asthmatics, quite in contrast to our findings. The reason for this discrepancy remains unclear.

In conclusion, asthmatics showed more peripheral obstruction compared to patients with AR with or without BHR, measured by IOS. This data indicates that asthmatics have a higher degree of involvement of the peripheral airways. These

findings could possibly explain our previous findings that asthmatics have a greater perception of bronchial obstruction (Aronsson et al., 2005). The group of patients with AR and BHR clearly located itself as an intermediate state between asthma and AR without BHR. Thus, the progress of AR alone to AR with concomitant asthma could be explained by the patient developing a higher degree of peripheral airway involvement.

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