

Effect of nasal allergen challenge on bronchial reactivity

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Allergic rhinitis offers a unique possibility for studying the impact of allergic inflammation of the nasal mucosa upon the lower airways. It is a common clinical observation that allergic rhinitis and bronchial asthma are closely related and that allergic rhinitis often antecedes asthma (1, 2). Moreover, prospective data from a 23-year follow-up study have demonstrated the presence of allergic rhinitis in adolescence to increase the risk of developing asthma in later life, approximately three times compared to non-rhinitic controls (3).

In patients with active allergic rhinitis, with no evidence of asthma, lung function parameters such as FEV₁ and FVC are seldom affected (4–6). In contrast, multiple studies have demonstrated that non-specific bronchial reactivity to histamine or methacholine is often increased in such patients compared to normal controls. In patients without rhinitis symptoms, bronchial hyperresponsiveness (BHR) has been observed in 11–16% (7, 8), while BHR was present in 24–60% of patients with active rhinitis (4, 6–10).

Several studies have focused upon the effect of environmental allergen exposure in patients suffering from seasonal allergic rhinitis (SAR) during their appropriate pollen season, notably patients having no history, signs or symptoms of asthma. In one study (8), 27 patients with grass pollen-induced rhinitis underwent bronchial carbachol challenge before and during the pollen season. Before the season, five of 27 were hyperresponsive (PD₂₀ < 1 mg), while this increased to 13 of 27 during the season, as well as a general increase was observed in a majority of the patients. Interestingly, patients increasing bronchial reactivity were significantly younger and had an earlier onset of symptoms when compared to the remaining patients. In another study (11), nine of 13 placebo-treated patients had an increase of bronchial reactivity during the pollen season. Recent results from the same group (12) were similar, as all 15 placebo

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treated patients presented an increased bronchial reactivity during the season. Moreover, the degree of bronchial reactivity was shown to normalize after the season.

The increase in bronchial reactivity following seasonal pollen exposure in SAR is both quantitatively and qualitatively interesting. This was demonstrated in a study of patients suffering from SAR as well as mild asthma (13). Seven of eight untreated patients increased their bronchial reactivity by more than one dilutional dose during the season. Furthermore, a recent study in SAR patients showed a doubling in the number of patients having a bronchial responsiveness to methacholine, in the asthmatic range, during the season, when compared to the number out of season (7).

In perennial allergic rhinitis (PAR), bronchial reactivity is increased, too. Eleven patients, with PAR and allergy to house dust mites, all showed a marked degree of BHR to carbachol, even though none of the patients presented with a history, signs or symptoms of asthma (14). In fact, bronchial reactivity in PAR patients seems to be increased more often and even to a higher extent, when compared to patients with SAR. One study (15) compared bronchial reactivity in 34 PAR and 38 SAR patients. Subjects sensitized to perennial allergens had a significantly lower mean PC₂₀ to methacholine than did pollen allergics, even when examined during their appropriate season. This observation is substantiated by data from 512 rhinitis patients comparing the levels of bronchial reactivity in SAR during the season, SAR out of season, and PAR (16). PAR patients revealed to be, by far, the most bronchially reactive.

When studying bronchial reactivity in rhinitis patients, environmental allergen exposure offers the advantage of a continuous exposure for a prolonged period of time. However, it cannot guarantee the allergic reaction to be localized exclusively to the nasal mucosa. To ascertain this, one must consider nasal allergen challenge, i.e. the artificial application of allergen to the nasal mucosa. Only a few studies have been carried out on this topic and interpretation of the data are clearly made difficult by the lack of a standardized methodology.

In one study (17), 11 patients with pollen induced rhinitis underwent a nasal challenge out of season, twice with saline and once with allergen nebulized to both nostrils. Each nasal challenge was followed by a bronchial methacholine challenge. PD₂₀ was not measurable in most patients after saline, but patients had a significantly larger decrease in FEV₁ after the highest dose of methacholine, when challenged with allergen. It is worth noticing that methacholine challenge was performed as soon as 10 min after

allergen challenge, thus indicating a very rapid interaction. Moreover, following allergen challenge, seven patients were designated as hyperresponsive. However, an unreasonably high limit was applied for this, i.e. PD₂₀ < 3100 mg.

Other preliminary data (18) in 13 patients with PAR and allergy to mites demonstrated that seven patients, subjected to nasal allergen challenge, had a significant increase in bronchial reactivity, expressed as mean PD₂₀ to methacholine, when comparing levels at baseline and as late as 36 h after allergen challenge. No change was seen in six patients, who did not undergo allergen challenge. These data could not be confirmed in another study on perennial allergy to mites, including 22 patients with PAR and eight patients with PAR as well as asthma (19). In this study, nasal allergen challenge was performed by unilateral application of a small paper disk, each patient receiving one of four different doses of allergen. No effect on PC₂₀ to methacholine was demonstrated, neither immediately nor 7 h after allergen challenge, in either patient group. However, BHR was already present prior to allergen challenge in the asthmatic patients and, probably, in most or all of the rhinitis patients according to the data available. A possible explanation could be that patients were already exposed from their allergenic environment prior to allergen challenge and, as a consequence, the single allergen dose was insufficient to further affect the bronchial reactivity.

The impact of nasal allergen challenge upon the lower airways in patients, with SAR as well as asthma, was examined in 10 patients out of the pollen season (20). Lung function parameters and bronchial reactivity were considered 30 min and 4.5 h after nasal spraying with placebo and allergen, respectively. Whereas no differences were observed regarding lung function in comparison to baseline, the diurnal variation of mean PC₂₀ to methacholine seen after placebo was eliminated at both timepoints, when patients were challenged with allergen. Moreover, all patients increased their bronchial reactivity, when comparing placebo and allergen PC₂₀ levels of each patient. However, it is noteworthy that there were large individual differences in the response to allergen.

Recently, our group has finalized a study in 10 patients with SAR, seasonal asthma and monoallergy to grass pollen outside the season. Nasal allergen challenge was performed three times with 24 h in between, by bilateral nasal spraying. Bronchial methacholine challenge was done before the first allergen dose as well as 6 h, 1, 3 and 7 days later. Preliminary data show a decrease of bronchial reactivity, expressed as mean change in PD₂₀ from baseline, at all timepoints after allergen dosing. However, when

regarding individual changes in patients, two were immediately bronchoreactive, three gradually increased in bronchial reactivity, while the rest remained at an almost constant level of reactivity throughout the study period.

Although current knowledge therefore seems to indicate a correlation between allergic rhinitis and bronchial reactivity, it also emphasizes the importance of considering changes in individuals or subgroups of patients and not merely applying mean levels. This view is supported by results from studies in which subgroups of patients have been possible to identify, based on their level of bronchial reactivity (16, 21). In one of these studies, subgroups were hence also applicable, when considering inflammatory parameters (21). Moreover, regarding a whole population, a considerable overlap of bronchial reactivity is present between different airway diseases (10).

Another important aspect of bronchial reactivity and, especially, the presence of BHR in allergic rhinitis, is the spontaneous variation. It is not a constant figure, but seems to be a dynamic parameter, changing in individuals over relatively short periods of time, i.e. a few years (22, 23). Moreover, in asthmatics, diurnal (24, 25) as well as day-to-day (26) variations of bronchial reactivity, are well-described phenomena.

Regarding the possible mechanisms underlying the interaction between an allergic reaction of the nasal mucosa and bronchial reactivity, based on present clinical data, quite a long time span is noticed, ranging from 10 to 30 min (17, 20) until 36 h (18) after allergen challenge. Whereas a short reaction time would suggest a reflex mechanism, a longer time period would indicate some kind of inflammatory

interaction. It could be argued that nasal spraying of allergen causes an inflammatory reaction by deposition directly in the lower airways. However, radiolabelled aerosol from a common nasal spray was not detectable in the lower airways, 1 and 6 h after spraying (20). Thus clinical evidence, so far, does not give a single answer, whether the interaction is based on reflexes or inflammation.

Only a few and conflicting data are available upon BHR in allergic rhinitis as a prognostic factor, i.e. whether it is able to predict future development of asthma. In one study 40 SAR patients were followed for a mean of 4.5 years after bronchial methacholine challenge (23). Three of 16 patients with initial BHR developed asthma, while asthma was not seen in patients with an initially normal level of bronchial reactivity. This finding could not be confirmed by data from a 6-year follow-up in 56 patients, suffering from SAR or PAR (27). 10.5% of initial hyperresponders to methacholine developed asthma, which was equal to 8.5% of patients with an initially normal responsiveness. However, in this study quite a high limit for designating BHR was used, i.e. $PC_{20} \leq 18$ mg/ml.

In conclusion, current clinical evidence supports a linkage between allergic inflammation of the nasal mucosa and bronchial reactivity in allergic rhinitis. Once again it must be emphasized that bronchial reactivity in patients with allergic rhinitis is a highly individual and dynamic parameter. Present data seem to indicate that nasal allergen exposure increases bronchial reactivity in most patients, while nasal allergen challenge increases bronchial reactivity in some patients. Further data are needed to clarify any prognostic value of BHR in allergic rhinitis.

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