

# Nasal allergen challenge: changes in nasal patency and in biochemical markers

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## Introduction

Nasal obstruction can be measured objectively by methods assessing nasal patency, and it can be evaluated subjectively by the patient as a feeling of impaired air passage through the nose and a sensation of stuffiness. There seems to be a fairly good overall correlation between an objective and a subjective evaluation, but a recent study by Sipilä and coworkers (1) has shown significant differences in some subjects. These authors asked a series of persons to breathe through four artificial nose models with varying diameters and resistance to airflow. About 10% of the subjects were not able to make a distinction between the narrowest and the widest tube. Because a subjective sensation of nasal blockage is not always a reliable parameter (2), it is important to add an objective measure of nasal patency in studies of rhinitis pathophysiology and drug efficacy.

## Allergen challenge studies

In the present review, we shall describe the results of a series of allergen challenge studies in which we have measured the changes in nasal airway resistance and the simultaneous changes in the concentration of biochemical markers in nasal lavage fluid.

### Early-phase response

In the early-phase response to allergen challenge, nasal obstruction is an important symptom and sign, but a full description of the response also involves evaluation of sneezing and hypersecretion. In a series of studies, we have compared these symptoms and signs with quantitative measurement of the release of mediators or biochemical markers (4–9). We have studied patients with pollen allergy out of the pollen season and com-

pared them with normal control subjects. A micro-suction technique for consecutive sampling of undiluted nasal secretions has been used to avoid a varying degree of dilution of the sample, which occurs when a nasal lavage technique is used. We measured histamine, tryptase and prostaglandin D<sub>2</sub> as markers of mast cell activation (and histamine also as a marker of basophil activation), ECP as a marker of eosinophil activation, and MPO as a marker of neutrophil activation.

The results during the early-phase response are presented in Table 1. There was a significant increase in nasal airway resistance in 94% of the patients, and this was associated with an increased concentration of mast cell markers whereas there was no increase in eosinophil and neutrophil markers.

### Late-phase response

The late-phase response in the nose is clinically characterized by persistent blockage with little sneezing and rhinorrhoea. When nasal obstruction is defined as a 100% increase in total nasal airway resistance, a clinical late-phase response occurred in only 41% of the patients, while 82% had a response defined as a 100% increase of unilateral nasal airway resistance (10). The study of biochem-

Table 1. Results of the measurement of biochemical mediators/markers of cell activation in suctioned nasal secretions in pollen-allergic patients before allergen challenge and during the early-phase response (median)

|                              | Baseline | Early-phase response |
|------------------------------|----------|----------------------|
| Histamine                    | 36 ng/g  | 214 ng/g*            |
| Tryptase                     | 0.1 µU/g | 28 µU/g*             |
| Prostaglandin D <sub>2</sub> | 410 pg/g | 226 pg/g             |
| Leukotriene C <sub>4</sub>   | 6.4 ng/g | 20 ng/g*             |
| ECP                          | 160 ng/g | 47 ng/g*             |
| MPO                          | 1.7 µg/g | 1.0 µg/g             |

\**P* < 0.01.

ical markers in nasal secretions showed a significant increase in ECP from 1 to 24 hours after allergen challenge in almost all the patients (94%). Twenty-four hours after allergen challenge, the histamine concentration was insignificantly higher (60 ng/g) than the baseline level, while the prostaglandin D<sub>2</sub> level was not increased; so it seems unlikely that mast cells are responsible for the late-phase nasal blockage. Leukotrienes are more likely candidates, but the peaks of leukotriene C<sub>4</sub> in nasal secretion correlated poorly with nasal airway resistance (11).

### Late-phase blockage

We have analysed the late-phase increase in nasal airway resistance in detail. During the early-phase response, the patients had a median increase of 262% in total resistance and of 316% and 361% in unilateral resistance (right and left). During the late-phase response, the corresponding values were lower, i.e. 79% and 183% and 192%. Allergic patients also showed a higher degree of fluctuation in nasal airway resistance during a 10-hour period after challenge. While the total maximal changes in the patients were 0.25 Pa/cm<sup>3</sup>/s for total resistance and 1.2 and 1.48 Pa/cm<sup>3</sup>/s for unilateral changes, the corresponding values for the normal controls were 0.16 Pa/cm<sup>3</sup>/s for total resistance and 0.44 and 0.42 Pa/cm<sup>3</sup>/s for unilateral changes. In other words, the fluctuations representing the nasal cycle, were increased with 56% for bilateral and by 236% and 185% for unilateral changes in patients as compared with normal subjects.

We could identify four different patterns of late-phase nasal blockage: (a) no response (18%), (b) unilateral blockage (29%), (c) synchronic bilateral blockage (6%), and (d) alternating unilateral blockage (47%). These changes disappeared within 24 hours in 50% of the patients, between 24 and 48 hours in 29% and between 48 and 56 hours in 21%.

### Allergen exposure

To study whether the allergic inflammation during natural pollen exposure during the pollen season is most similar to the early- or to the late-phase response after an artificial allergen challenge, we performed a comparative study of biochemical markers in nasal secretions before and after an allergen challenge outside the pollen season and during the season. Table 2 shows that the mediator profile during the pollen season – showing an elevated level of ECP, but not of tryptase and histamine – is similar to the late-phase response to artificial allergen challenge.

Table 2. Median concentrations of biochemical mediators in nasal secretions

|                            | Tryptase | Histamine | LTC <sub>4</sub> | ECP  |
|----------------------------|----------|-----------|------------------|------|
| Outside season             |          |           |                  |      |
| Baseline                   | 0.1      | 36        | 6.4              | 160  |
| Early-phase response       | 28*      | 214*      | 20*              | 47*  |
| Late-phase response (8 h)  | 1.9      | 56        | 6.6              | 267  |
| Late-phase response (24 h) | 0.1      | 60*       | 7.5              | 401* |
| During season              | 0        | 51*       | 23*              | 410* |
| Normal controls            | 0        | 19        | 5.7              | 105  |

\**P* < 0.01.

This comparative study indicates that allergic patients express a chronic state of inflammation in the nasal mucous membrane during the pollen season, which in the mediator profile is closer to the late- than to the early-phase response after artificial allergen challenge. This chronic inflammatory state is probably responsible for the increased responsiveness to specific exposure (priming) and to unspecific exposure (hyper-responsiveness) of the nasal mucosa during the pollen season. The typical early-phase response seems mainly to be limited to short and massive allergen exposure. However, the typical hayfever symptoms (itching, sneezing and watery rhinorrhoea) are more associated with the early- than with the late-phase response to allergen challenge. These observations may explain the apparent discrepancy between varying results of drug efficacy on the early-phase response and their therapeutic efficacy in disease: for example, the fact that H<sub>1</sub>-antihistamines are more effective than corticosteroids on the early-phase response, whereas the opposite is the case in the treatment of allergic rhinitis.

In the study of drugs for the treatment of allergic rhinitis, most authors examine only the effect of treatment on the subjective symptoms – i.e. sneezing, rhinorrhoea and blockage – based on diary cards (symptom scores or visual analogue scales). We recommend that also objective measurements of nasal airway patency (nasal peak flow, rhinomanometry, acoustic rhinometry) and of nasal inflammation are employed.

### Drug effect

#### H<sub>1</sub>- and H<sub>2</sub>-antihistamines

We have used a combined methodological approach, studying drug effect on the early-phase response to intranasal allergen challenge performed during the pollen season. In one such study, we compared the effect of a second generation H<sub>1</sub>-antihistamine (cetirizine, 10 mg/day) alone and together with an H<sub>2</sub>-antihistamine

(cimetidine, 800 mg/day) (12). Whereas the two therapies were equally effective on sneezing and rhinorrhoea, only combined H<sub>1</sub>- and H<sub>2</sub>-blockage had a statistically significant effect on allergen-induced nasal blockage ( $P < 0.01$ ). None of the therapies had any effect on the postchallenge-induced increase in mediators in nasal secretions or on the number of eosinophils.

These results accord with the results of nasal challenge tests with an H<sub>1</sub>-agonist (betahistine) and an H<sub>2</sub>-agonist (ipromodine) (13). Betahistine, but not ipromodine, induced itching, sneezing and hypersecretion, whereas both agonists increased nasal airway resistance. The effect of histamine (H<sub>1</sub>- and H<sub>2</sub>-agonist) was more pronounced than that of the H<sub>2</sub>-agonist which in turn was more potent than the H<sub>1</sub>-agonist.

In another study (14), pretreatment with both the H<sub>1</sub>-antihistamine (cetirizine) and the H<sub>2</sub>-antihistamine (ranitidine) inhibited the histamine-induced increase in nasal airway resistance, but the increase in lavage protein/albumin concentration was only inhibited by the H<sub>1</sub>-antihistamine. It can be concluded that whereas the H<sub>1</sub>-receptor is most important for plasma exudation and oedema formation, it is the H<sub>2</sub>-receptor that has the greatest effect on nasal obstruction.

H<sub>3</sub>-receptors have been identified in brain tissue, where they act mainly by modulating the effect on neural histamine release through a negative feedback mechanism (15). They have not been identified in the nasal mucosa, and it is doubtful whether H<sub>3</sub>-receptors play any role in rhinitis.

### Decongestants

In one study, we compared the decongestant effect of two intranasal vasoconstrictors, i.e. xylometazoline 0.1% and phenylephrine 0.5% (3). The objective evaluation clearly showed differences between the two drugs, in that xylometazoline caused a maximal reduction of nasal airway resistance of 33% and had a duration of action of 8 hours, compared with 17% and 2 hours for phenylephrine. In addition, xylometazoline showed a small rebound effect of 8% compared with 17% for phenylephrine.

### Immunotherapy

Finally, we have used measurement of nasal airway resistance to evaluate the results of immunotherapy in 25 patients with seasonal allergic rhinitis and in 25 patients with perennial allergic rhinitis (allergy to house dust mites). In an open study, the patients were challenged with three doses of allergen before treatment and every year during a

4-year immunotherapy period. There was a significantly reduced response to the allergen challenge during immunotherapy ( $P < 0.001$ ). The measurements of nasal airway resistance correlated with the patients' symptom scores, which did not show any correlation with change in RAST or in blood eosinophil count.

### Conclusions

In conclusion, nasal obstruction is an important symptom of allergic rhinitis, and it can be induced by artificial allergen challenge during both the early-phase and the late-phase response. The objective measurement of nasal blockage in these test situations can afford a precise and reliable evaluation, which is useful in both studies of pathophysiology and of drug effect. Measurement of nasal airway resistance can be combined favourably with the measurement of biochemical markers of inflammation in nasal secretions.

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