

# Unilaterality of obstruction after acute nasal allergen provocation. Relation of allergen dose, nasal reactivity and the nasal cycle

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## Summary

We examined unilaterality of obstruction after acute bilateral nasal allergen provocation in two groups of pollen-sensitive volunteers studied out of season. One group was challenged on one occasion with a threshold allergen dose and on another with placebo. We measured nasal airway resistance (NAR) unilaterally for 3.5 hr before the challenges and for 40 min after. Most subjects' noses had marked asymmetry of response. Over half showed marked obstruction on one side and none at all on the other side. The side which showed higher resistance and greater lability before challenge was typically more obstructed after. In a second group we compared responses to threshold and  $\times 10$  threshold doses. Threshold challenge produced results similar to those seen with the first group. After the higher allergen dose, there was some obstruction in the less responsive side and the rate of rise was much slower. Obstructive response after acute threshold allergen challenge is typically one-sided. This pattern may be related to the stage of the nasal cycle in which the challenge was delivered. Higher allergen doses produce more obstruction in the less responsive side but the response is still asymmetrical.

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## Introduction

Nasal blockage is a typical feature of allergic rhinitis [1]. Acute nasal allergen provocation, which shares some features with natural disease, also produces obstruction [2,3]. We have noted that bilateral allergen provocation usually produces obstruction on one side of the nose only. The immunological stimulus should be similar in both sides. Asymmetry in obstruction could result from differences in biochemical or reflex response to the stimulus. The latter seems more likely.

Reflex reactivity might vary with the nasal cycle. This cycle consists of reciprocal congestion and decongestion with variable periodicity [4,5]. The pattern occurs in diseased as well as in healthy people [6], and has been demonstrated in cats [7] and dogs [8] as well as in humans. It is thought to be under neural reflex control [7,9,10], but the exact mechanisms involved are not certain.

We postulated that the airway obstruction which follows acute allergen challenge is a product of the

biochemical results of mast cell triggering and the stage of the nasal cycle at the time of challenge. The studies described here were undertaken to examine the following issues: (i) confirm the unilaterality of the nasal obstruction after acute threshold allergen challenge; (ii) examine whether the unilateral response could be overridden by supra-threshold allergen doses; and (iii) look for congestion patterns preceding the challenge which might predict the side likely to show greater obstruction.

## Materials and methods

We performed two studies at different times in different populations. The provoking agents were major pollen allergens; ragweed in the majority, tree or grass pollen in a few. All studies were conducted well away from the season for the pollen being used. Nobody was symptomatic at the time of challenge.

The intake phases of both studies were similar. All participants gave informed consent. We did a limited medical work-up including screening skin-prick tests. Those with positive skin tests which correlated with their

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history underwent diagnostic nasal challenge. This consisted of a series of allergen dilutions dosed from a specially fabricated nasal sprayer [11]. The stock allergen extracts were obtained from Hollister-Stier div. Miles (West Haven, CT). The standard sequence of dilutions was 1/10 000, 1/3000, 1/1000 and 1/300. Each challenge consisted of 0.3 ml of allergen solution divided between the two sides of the nose. Each sequence began with a placebo challenge. Fifteen minutes separated challenges. We defined a positive response as more than one sneeze or more than 1 g of blown secretion in the 5 min following the challenge. The concentration that produced this response was the threshold dose and the challenge sequence was stopped. We performed two diagnostic challenges 1 week apart. To qualify, subjects had to react similarly both times.

The first study enrolled 26 subjects. Each was challenged twice; once with the threshold allergen dose, and once with placebo in random sequence. At least a week separated the two sessions. We conducted all challenges in the morning. Measurements of right and left sided nasal airway resistance (NAR) were made every 20 min, beginning 3.5 hr pre-challenge. After allergen provocation we measured NAR every 5 min for 40 min.

To verify that elevated NAR values did not reflect anatomic obstruction, we dosed each subject with two sprays of oxymetazoline given about 5 min apart. There were multiple measurements of NAR over the 10 min after dosing. This sequence was appended to the end of the placebo challenge session.

The second study enrolled 17 who qualified as described above. They were challenged twice in random order, once with the threshold concentration from the diagnostic series and once with a supra-threshold concentration, usually  $\times 10$  as strong. When the threshold concentration was 1/1000, we used 1/300 for supra-threshold. We measured NAR every 20 min, commencing 80 min before the challenge and at 3, 6, 10, 15, 20, 30 and 45 min after.

NAR was measured using a locally designed and fabricated system. The unit consists of a Fleisch pneumotachygraph coupled to a Statham pressure transducer and Gould bridge amplifier. These generate a voltage proportional to flow. The unit monitors posterior pharyngeal pressure with a second pressure transducer and bridge amplifier pair. Parallel traces of flow and pressure can be displayed for monitoring on a Gould Brush 220 recorder. This basic recording system has been automated with an Analog Devices MACSYM 150 computer, a 12-bit analogue to digital converter, a serial output board and a printer.

The system calculates resistance at a selected flow rate,

conventionally 0.25 l/sec. Values are displayed as they are measured. The operator looks for consistency and stops a measurement when at least three similar values have been recorded. At this point, the program selects and stores the median value.

NAR measurements are made unilaterally. The nozzle used to couple the pneumotachygraph to the naris is adapted from plastic sleeve packaging used for a 6-cc disposable syringe. The beveled end of this sleeve fits most nares acceptably. During the measurement the subject occludes the contralateral side manually and takes care that the occlusion and the nozzle are applied very gently. This is to minimize distortion and artifact in the NAR measurements.

Occasionally with very high resistances subjects could not generate the standard reference flow of 0.25 l/sec. This imposes an upper limit in our system (60 cm H<sub>2</sub>O/l per sec). We arbitrarily record unmeasured high values as 60. Our system has been calibrated against a water manometer and an independent flow sensor. We report resistance values directly in cm H<sub>2</sub>O/l per sec and have not applied the recommendations of Rhinomanometry Standardization Committee [12]. Since our primary concern is within-subject comparison, this should not detract from the interpretability of our data.

For analysis, we designated higher and lower resistance sides of the nose based on NAR values collected in the first 20 min after challenge. We analysed NAR results using an area-under-the-curve (AUC) per unit time response function. For each subject a pre- and post-challenge AUC (weighted mean using the trapezoid rule) was calculated. This was then adjusted for the number of minutes duration of each pre- or post-challenge period. The log of this adjusted AUC score met the distributional assumptions necessary for analysis with a repeated measures analysis of variance model incorporating factors for subjects, group, period and the group by period interaction. All analyses were done using PROC GLM from SAS (SAS Institute, Cary, NC). We interpreted the statistically significant group by period interactions for selected contrasts using pair-wise comparisons among the least squares means.

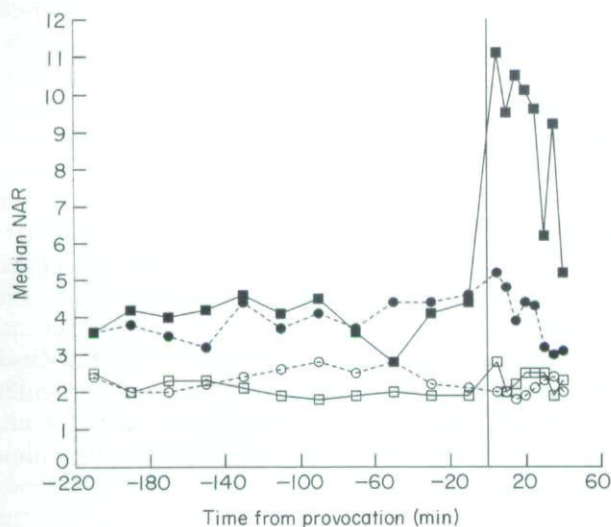
## Results

The first study examined unilateral NAR measurements made after placebo and threshold allergen provocation. To assure that elevations in these measurements did not reflect anatomic deformity, we determined minimal NAR after thorough decongestion with topical oxymetazoline after the placebo provocation session. Table 1 summarizes these results. Mean minimal resistance on the higher

**Table 1.** Smallest NAR measured after topical oxymetazoline decongestion

|                             | Higher resistance side | Lower resistance side |
|-----------------------------|------------------------|-----------------------|
| Mean minimal NAR $\pm$ s.d. | 1.52 $\pm$ 1.07        | 1.60 $\pm$ 0.96       |
| Range                       |                        |                       |
| Smallest                    | 0.5                    | 0.4                   |
| Largest                     | 5.8                    | 3.8                   |

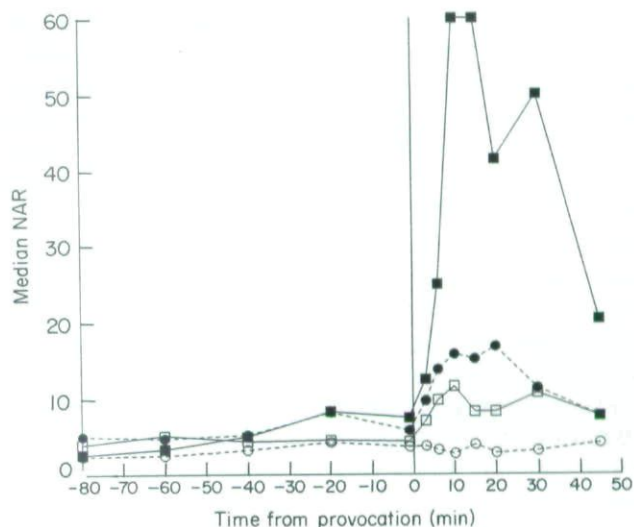
Designation of higher/lower resistance sides based on results from allergen challenge.

**Fig. 1.** Median nasal airway resistances (NAR) (cm H<sub>2</sub>O/l per sec) for higher and lower resistance sides of the nose, placebo and allergen provocation. ■, Allergen/higher; □, allergen/lower; ●, placebo/higher; ○, placebo/lower.

and lower resistance sides were similar. Fixed anatomic resistance seems not to have contributed to the NAR elevations seen in this study.

Obstruction after allergen provocation showed several patterns. Most commonly (14 out of 26), there was unilateral obstruction and essentially no change in the lower resistance side. Four subjects showed obstruction which was predominantly but not exclusively one-sided. Two showed small changes in both sides while two had essentially no change after challenge. Four subjects obstructed unilaterally but switched sides during the post-provocation observation.

Figure 1 shows median values for higher and lower resistance sides of the nose with threshold allergen or placebo provocation. These data represent the entire 26-subject study group. Pre-challenge resistances seemed

**Fig. 2.** Median nasal airway resistances (NAR) (cm H<sub>2</sub>O/l per sec) for higher and lower resistance sides of the nose, threshold and supra-threshold allergen provocation. ■,  $\times 10$  threshold/higher; □,  $\times 10$  threshold/lower; ●, threshold/higher; ○, threshold/lower.

to predict for post-challenge behaviour. The sides which showed higher resistance after challenge had also been the higher resistance sides during pre-challenge observation ( $P < 0.001$  for both placebo and allergen sequences). After the challenges, obstruction was substantially greater in the higher resistance, allergen-dosed side than in any of the others ( $P = 0.0001$ ). There was no difference in the lower resistance side challenged with allergen or placebo.

The second study compared behaviour after threshold allergen doses and supra-threshold doses, usually 10-fold higher, to see whether unilaterality of response would be overcome by larger amounts of allergen. Figure 2 summarizes the results. Response after threshold dosing was similar to that seen in the first study (Fig. 1). There was a pronounced rise in the NAR median values on one side and none on the other side ( $P < 0.001$ ). Increasing the provoking allergen dose increased the obstructive response on both sides, although they continued to differ significantly ( $P < 0.001$ ). The rise on the higher resistance side was very substantial compared with that seen with threshold dosing. NAR in the lower resistance sides after threshold and supra-threshold dosing also differed significantly ( $P = 0.0001$ ). The rise with supra-threshold dose was modest; there was essentially none after the threshold allergen dose.

## Discussion

This study shows that obstruction after acute allergen stimulation delivered to both sides of the nose is predom-

inantly unilateral. Only four out of 26 reacted similarly on both sides, two with no apparent obstructive response and two with very modest rises. No subject had large increases in resistance on both sides of the nose after threshold allergen provocation. That side which showed higher or more labile NAR before the challenge almost always exhibited greater obstruction after. This suggests that potential for reactivity differed in the two sides of the nose, possibly as a function of the nasal cycle. When similar allergen provocations were delivered to both sides of the nose only the side which was reactive before the fact had maximum congestive response.

Many investigators have examined responses to unilateral nasal provocation using a variety of challenging agents and measurements of response. Connell [13] described a 'reciprocal congestion-decongestion reflex'. He found that unilateral allergen provocation produced congestion on the allergen-exposed side with decongestion on the contralateral side. These observations suggested a crossing of reflex control signals. Haight and Cole [10] induced congestion with unilateral histamine and decongestion with unilateral oxymetazoline. They found no effect on the contralateral side and concluded that there were no feedback controls. Malmberg *et al.* [14] challenged noses unilaterally with allergen and found rises in resistance on the challenged side only. Secretion increased bilaterally. The amount of histamine in the secretion increased on the challenged side only.

Studies of mucosal blood flow after allergen exposure have produced a variety of findings. Konno *et al.* [15] challenged one side of the nose with allergen and found similar increases in blood flow in both sides. There was evidence of mucosal swelling on both sides of the nose. It was greater on the challenged side. With one-sided allergen challenge, Holmberg *et al.* [16,17] found a decrease in blood flow accompanied by a slight increase in air flow resistance in the side not challenged. Topical anaesthesia in the challenged side blocked the contralateral decrease in mucosal blood flow. These findings suggested reflex effects on mucosal circulation and vascular engorgement.

Though not entirely consistent in their findings and conclusions, these studies suggest that part of the response after acute provocation is reflex-mediated and part is due to local effects in the tissue, possibly attributable to mediators. After acute unilateral allergen provocation, mediator-induced changes should be most apparent near the site of release. Reflex effects apparently cross over and affect the non-provoked side.

Bende [18] found that unilateral decongestant treatment produced slight increase in congestion on the non-treated side, but the two sides tended to vary indepen-

dently. He concluded that congestion in the nasal mucosa was not affected by the state of the contralateral side. We have looked at unilaterality of decongestive response to infused phenylephrine [19]. Group median NAR values for the lower resistance sides of the nose were similar in normal and rhinitic subjects before and during phenylephrine infusion. In the higher-resistance side, the drug reduced obstruction in both normals and rhinitics. The mean minimal NAR achieved was higher in the rhinitics suggesting phenylephrine-resistant (non-vascular?) contribution to their nasal congestion. This study and the one here reported support each other. Both spontaneously occurring congestion and that induced by acute allergen provocation showed substantial asymmetry and a low resistance side which was not measurably obstructed.

Figure 2 shows that supra-threshold allergen provocation increased resistance in both sides of the nose, although asymmetry of response was preserved to a substantial degree. This pattern could result from recruitment of less responsive vascular elements in the lower resistance side, or it could reflect contributions from something other than vascular engorgement. This latter mechanism might be outside of reflex control. It might be present on both sides but inapparent where there is a large component of vascular engorgement. One possible explanation for this dose-response pattern is that threshold stimulation initiated sneeze, secretion and vascular engorgement but higher allergen doses caused more profound changes such as tissue oedema through non-reflex mechanisms.

Not much attention seems to have been paid to the relative contributions to nasal obstruction of vascular and non-vascular mucosal swelling. Combination of corticoid and topical decongestant has been shown to produce nasal patency comparable to that seen pre-seasonally. Decongestant alone was not able to approach this result [20]. One possible explanation for this observation was that mucosal swelling in the natural disease had several components, one vascular and readily reversible and the other less readily reversed and possibly non-vascular. It might be interesting to evaluate the relative protective effect of corticoids and decongestant vasoconstrictors against the patterns of obstruction seen in the present study.

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## References

- 1 Meltzer EO, Schatz M, Zeiger RS. Allergic and nonallergic rhinitis. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yuninger JW, eds. *Allergy: principles and practice* 3d edn. Saint Louis: CV Mosby, 1988:1253-89.
- 2 Taylor G, Shivalkar PR. Changes in nasal airways resistance on antigenic challenge in allergic rhinitis. *Clin Allergy* 1971; 1:63-73.
- 3 Corrado OJ, Ollier S, Phillips MJ, Thomas JM, Daview RJ. Histamine and allergen induced changes in nasal airways resistance measured by anterior rhinomanometry. *Br J Clin Pharmacol* 1987; 24:283-92.
- 4 Principato JJ, Ozenberger JM. Cyclical changes in nasal resistance. *Arch Otolaryngol* 1970; 91:71-7.
- 5 Eccles R. Cyclic changes in human nasal resistance to air flow. *J Physiol* 1977; 272:75P.
- 6 Stoksted P. The physiologic cycle of the nose under normal and pathologic conditions. *Acta Otorhinolaryngol* 1952; 42:175-79.
- 7 Bamford OS, Eccles R. Reciprocal nature of vasomotor oscillations in the cat. *J Physiol* 1982; 325:55P-6P.
- 8 Webber RL, Jeffcoat MK, Harman JT, Ruttimann UE. MR demonstration of the nasal cycle in the beagle dog. *J Comput Assist Tomogr* 1987; 11:869-71.
- 9 Wernitz DA, Bickford RG, Bloom FE, Shannahoff-Khalsa DS. Alternating cerebral hemispheric activity and the lateralization of autonomic nervous function. *Hum Neurobiol* 1983; 2:39-43.
- 10 Haight JSJ, Cole P. Nasal responses to local unilateral stimuli in man. *Rhinology* 1983; 21:67-72.
- 11 Brooks CD, Nelson A, Parzyck R, Maile MH. Protective effect of hydroxyzine and phenylpropanolamine in the challenged allergic nose. *Ann Allergy* 1981; 47:316-19.
- 12 Clement PAR. Committee report on standardization of rhinomanometry. *Rhinology* 1984; 22:151-5.
- 13 Connell JT. Reciprocal nasal congestion-decongestion reflex. *Trans Am Acad Ophthalmol Otolaryngol* 1968; 72:422-6.
- 14 Malmberg H, Binder E, Fraki J, Harvima I, Salo O, Holopainen E. Nasal reactions elicited by unilateral allergen challenge. *Acta Otolaryngol* 1989; 107:446-9.
- 15 Konno A, Togawa K, Nishihira S. Participation of vascular reflex in mucosal swelling in nasal allergy. *Acta Otolaryngol* 1982; 94:131-40.
- 16 Holmberg K, Bake B, Pipkorn U. Nasal mucosal blood flow after intranasal allergen challenge. *J Allergy Clin Immunol* 1988; 81:541-7.
- 17 Holmberg K, Bake B, Pipkorn U. Reflex activation in allergen-induced nasal mucosal vascular reactions. *Acta Otolaryngol* 1989; 108:130-5.
- 18 Bende M. Contralateral effects of unilateral nasal decongestion. *Acta Otolaryngol* 1989; 99:637-40.
- 19 Brooks CD, Spennner GC, Karl KJ, Heissler CT, Metzler CM. Nasal airway response to infused phenylephrine in normals and in patients with allergic and non-allergic rhinitis. *Rhinology* 1988; 26:51-8.
- 20 Brooks CD, Titus CR, Heissler CT. Vasoconstrictor and corticosteroid responsive components of allergic nasal mucosal swelling. *Ann Allergy* 1988; 61:151-6.

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