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Main Article

# The Allergic Rhinitis and its Impact on Asthma system: a new classification of allergic rhinitis and nasal responsiveness

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**Abstract**

Objectives and hypothesis: Allergic rhinitis has traditionally been classified into seasonal and perennial rhinitis. However, many subjects with dual sensitisation do not fit neatly into either category. Recently, the Allergic Rhinitis and its Impact on Asthma workshop has proposed a new allergic rhinitis classification, into intermittent and persistent forms. The purpose of the present study was to investigate whether the symptomatic and secretory responsiveness of allergic rhinitis sufferers correlated well with the Allergic Rhinitis and its Impact on Asthma classification, compared with the traditional classification.

Study design: Experimental study.

Methods: Forty subjects with allergic rhinitis and 13 normal controls underwent a unilateral nasal bradykinin challenge protocol. Symptom scores were recorded and secretion weights measured bilaterally using filter paper disks. The symptomatic and secretory responses of allergic subjects were analysed according to both the traditional and the Allergic Rhinitis and its Impact on Asthma classifications, and the two systems were compared.

Results: For both classification systems, the two groups of allergic subjects were clearly demarcated by secretory responses. However, after classification according to the traditional system, there was a lack of clear demarcation between the groups as regards symptomatic response, whereas clear demarcation of symptomatic responses was seen after using the Allergic Rhinitis and its Impact on Asthma classification.

Conclusions: In allergic rhinitis subjects, the degree of nasal responsiveness was closely related to their Allergic Rhinitis and its Impact on Asthma classification. Furthermore, this classification was not compromised by the inclusion of subjects with dual sensitisation. Thus, the Allergic Rhinitis and its Impact on Asthma classification may have advantages for future research studies on allergic rhinitis.

**Key words: Allergic Rhinitis; Classification; Bradykinin; Secretory Responses**

## Introduction

Allergic rhinitis has traditionally been classified according to the timing of symptoms and allergen exposure, into seasonal allergic rhinitis and perennial allergic rhinitis. In seasonal allergic rhinitis, symptoms are confined to a defined season, during which the offending aero-allergens are abundant in the outdoor environment. In perennial allergic rhinitis, symptoms are present throughout the year.[1] However, this classification is arbitrary, since many patients are sensitised to both seasonal and perennial allergens.[2] These patients with dual sensitisation are often excluded from studies in favour of subjects with sensitisation to one type of allergen. Nonetheless, this group is important as it reflects a large population of patients with allergic rhinitis. Practical issues exist concerning the degree of exposure to the allergen during the year, so exposure to seasonal allergens may be long-standing, while exposure to perennial allergens may be inconsistent throughout the year.[3] Thus, there are a number of limitations of this classification.[3]

Recently, the Allergic Rhinitis and its Impact on Asthma workshop has proposed a major change in the classification of allergic rhinitis, into intermittent allergic rhinitis (characterised by the presence of symptoms for fewer than four days per week, or for less than four weeks) and persistent allergic rhinitis (characterised by the presence of symptoms for more than four days per week, and for longer than four weeks).[3] While this new classification may appear easy to use from a clinical standpoint, its relationship to the underlying pathophysiological events has not been investigated.

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One method of studying the pathophysiological events in rhinitis is bradykinin challenge. Bradykinin is a peptide mediator involved in the acute allergic response,[4,5] which has direct effects on vasculature, leading to vasodilation and plasma extravasation.[6,7] Bradykinin does not directly stimulate nasal glands; however, in subjects with active allergic inflammation, reflex-mediated glandular secretion is seen. The contralateral secretory reflex to bradykinin is indicative of neurally-mediated secretory hyper-responsiveness in allergic rhinitis,[8] and can be induced in asymptomatic subjects with allergic rhinitis by nasal allergen challenge within the preceding 24 hours.[9]

The Allergic Rhinitis and its Impact on Asthma classification disregards the pattern of sensitisation and so neatly incorporates patients who are sensitised to either seasonal or perennial allergens or both. We hypothesised that, in subjects with allergic rhinitis, bradykinin challenge responses are more closely related to the Allergic Rhinitis and its Impact on Asthma classification than to the traditional classification. The results of this study may support the use of this new classification.

## Methods

### *Subjects*

Forty subjects (26 women, 14 men) with allergic rhinitis and 13 normal controls (11 women, two men) were recruited by volunteer advertisement.

All subjects underwent skin prick testing using a battery of common aero-allergens, including mixed grass, timothy grass, mixed spring trees, house dust mite and cat dander (HAL Allergenen Laboratorium BV, Haarlem, The Netherlands). Subjects with allergic rhinitis had positive skin prick tests to at least one allergen. Normal controls had no nasal symptoms and negative skin prick tests to all allergens tested.

Subjects with allergic rhinitis were classified according to both the traditional classification (i.e. into seasonal or perennial allergic rhinitis) and the Allergic Rhinitis and its Impact on Asthma classification (i.e. into intermittent or persistent allergic rhinitis).

Subjects were excluded if they had: suffered a respiratory infection within the previous month; used oral or nasal corticosteroids within the previous month; used astemizole in the previous three months; or used short-acting antihistamines or decongestants within the previous two days. All experiments took place outside the pollen season.

Subjects gave written informed consent, and the study was approved by the hospital research ethics committee.

### *Nasal bradykinin challenge protocol*

Nasal bradykinin challenge was performed and nasal secretions collected using paper disks punched from Shandon filter cards (Shandon, Pittsburgh, Pennsylvania, USA).[9,10] Challenge disks were impregnated with 10 μl of diluent (Hartman's solution, Baxter, Thetford, UK) or with 10 μl of bradykinin solution (Bachem, Basle, Switzerland) which contained 50 μg of bradykinin. Bradykinin solution was made by dissolving bradykinin (10 mg/ml) in Hartman's solution with an additional 1 g/l of sodium bicarbonate, to give a bradykinin stock solution, which was stored at −20°C. Immediately prior to use, 5 μl of this bradykinin stock solution was mixed with 5 μl of Hartman's solution. The Hartman's solution had a pH of 6–6.2 and an osmolarity of 278 mOsm/l. Bradykinin solution had a pH of 6.2 and an osmolarity of 302 mOsm/l. Collection disks were kept in numbered collection tubes and weighed before use.

Prior to performing nasal challenges, anterior rhinoscopy was performed to check for anatomical abnormalities, and any crusts or dried secretions were removed. Baseline secretions were then collected from both sides of the nose using the first two collection disks. Secretions were collected by placing these disks on either side of the anterior nasal septum for 30 seconds, after which they were replaced into their original collection tubes and reweighed. Nasal challenge with Hartman's solution was then performed. Challenge disks were placed onto the left side of the anterior nasal septum, beyond the mucocutaneous junction, for 60 seconds, and then removed. Thirty seconds after removal of the challenge disk, secretions were again collected from each side, this collection representing secretions obtained for the first two minutes after the challenge. Three minutes later, secretions were again collected, this time representing secretions obtained at five minutes. For each challenge, secretion weights at two and five minutes were added to give a total for each side of the nose. Following this, subjects were allowed to blow their nose.

Ten minutes after challenge with Hartman's solution, nasal challenge with bradykinin was performed, with secretions collected at two and five minutes as before.

### *Subjective assessment of nasal symptoms*

The subjective severity of the symptoms of nasal irritation, rhinorrhoea and obstruction was scored by subjects at baseline (i.e. before the experiment commenced) and after each challenge (i.e. after the collection of secretions at two minutes). Each symptom was graded on each side of the nose on a scale of zero to three (zero representing no perception of symptoms, and three representing greatest severity of symptoms imaginable) for a total score out of nine on each side. For each challenge, symptom scores at baseline were subtracted from this total.

### *Statistical analysis*

Data are presented as means ± standard error of the mean. Statistical analysis was performed using WinStat for Microsoft Excel software (version 2001.1). To test whether data were distributed normally, a chi-square test for discrete variables was performed. The significance of differences in secretion weights and symptom scores between groups of subjects was tested using repeated measures of analyses of variance (ANOVA). A one-factor analysis of

variance was performed using either secretion weight or symptom score as the dependent variable and group as the independent variable. Separate analyses were performed for each side of the nose. A Bartlett test was performed to check that the groups had equal variances. Differences between individual groups were tested using multiple comparisons analysis (Bonferoni method).

## Results

### *Subjects*

When the subjects were classified according to the traditional classification, there were 16 with seasonal allergic rhinitis and 24 with perennial allergic rhinitis. Eleven of the subjects with seasonal allergic rhinitis were also sensitised to perennial allergens (house dust mite), while 10 of the subjects with perennial allergic rhinitis were also sensitised to seasonal allergens (grass pollen). All subjects with seasonal allergic rhinitis participated in the study outside the pollen season, at a time when they were completely asymptomatic.

When classified according to the Allergic Rhinitis and its Impact on Asthma classification, there were 21 subjects with intermittent allergic rhinitis and 19 with persistent allergic rhinitis. Thus, five subjects classified as having perennial allergic rhinitis according to the traditional classification were considered to have intermittent allergic rhinitis according to the Allergic Rhinitis and its Impact on Asthma classification. Of the subjects with intermittent allergic rhinitis, three were sensitised to perennial allergens (house dust mite) only, five were sensitised to seasonal allergens (grass and/or tree pollen) only and 13 had dual sensitisation. All were either asymptomatic or had minimal symptoms at the time of testing. Of the subjects with persistent allergic rhinitis, all were sensitised to perennial allergens (house dust mite), with 15 additionally sensitised to seasonal allergens.

### *Secretion weights*

Mean secretion weights in subjects with seasonal allergic rhinitis and perennial allergic rhinitis are shown in Figure 1. Comparisons between the three groups of subjects (normal, seasonal allergic rhinitis and perennial allergic rhinitis) using repeated measures of ANOVA showed that significant differences in secretion weights were present between the groups after nasal challenge with Hartman's solution ($p < 0.001$ on the ipsilateral side, and $p < 0.01$ on the contralateral side) and with bradykinin ($p < 0.0001$ on the ipsilateral side, and $p < 0.0001$ on the contralateral side). Significant differences were also present in the increases in bradykinin-induced secretion weights compared with those induced by Hartman's solution on the ipsilateral ($p < 0.01$) and contralateral ($p < 0.01$) sides. Subgroup analysis showed significant differences to be present in all cases between subjects with perennial allergic rhinitis and those with seasonal allergic rhinitis, and between subjects with perennial allergic rhinitis and normal subjects. Significant differences were not present between subjects with seasonal allergic rhinitis and normal subjects.

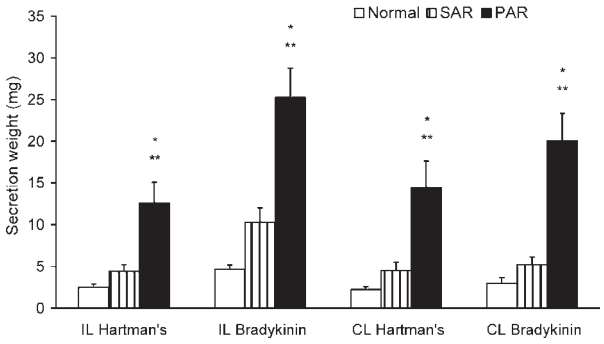


FIG. 1

Secretory response to Hartman's solution and bradykinin on the ipsilateral (IL) and contralateral (CL) sides of the nose in normal subjects and those with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). *Significant difference compared with normal subjects; **significant difference between subjects with seasonal compared with perennial allergic rhinitis.

Mean secretion weights for subjects with intermittent and persistent allergic rhinitis are shown in Figure 2. Comparisons were again made between the three groups of subjects (normal, intermittent allergic rhinitis and persistent allergic rhinitis) using repeated measures of ANOVA. Once again, significant differences between the groups were found for secretion weights after nasal challenge with Hartman's solution ($p < 0.01$ on the ipsilateral side, and $p < 0.01$ on the contralateral side) and bradykinin ($p < 0.0001$ on the ipsilateral side, and $p < 0.0001$ on the contralateral side). Significant differences were also present in the increases in bradykinin-induced secretion weights compared with those induced by Hartman's solution on the ipsilateral ($p < 0.01$) and contralateral ($p < 0.01$) sides. Subgroup analysis showed significant differences to be present in all cases between subjects with persistent allergic rhinitis and those with intermittent allergic rhinitis,

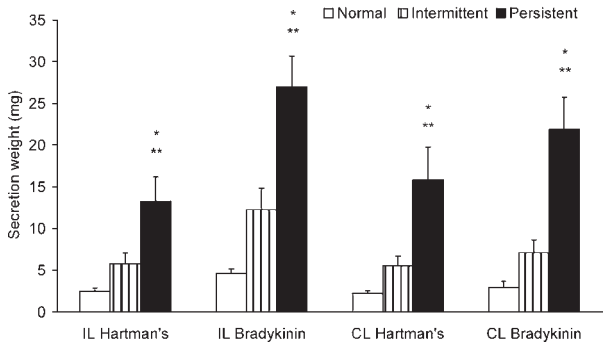


FIG. 2

Secretory response to Hartman's solution and bradykinin on the ipsilateral (IL) and contralateral (CL) sides of the nose in normal subjects and those with intermittent allergic rhinitis and persistent allergic rhinitis. *Significant difference compared with normal subjects; **significant difference between subjects with intermittent compared with persistent allergic rhinitis.

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and between subjects with persistent allergic rhinitis and normal subjects. Significant differences were not present between subjects with intermittent allergic rhinitis and normal subjects.

*Symptom scores*

Mean symptom score in subjects with seasonal allergic rhinitis and perennial allergic rhinitis are shown in Figure 3. There were significant differences in ipsilateral symptom scores between the three groups (normal, seasonal allergic rhinitis and perennial allergic rhinitis) after nasal challenge with Hartman's solution ($p = 0.04$) and with bradykinin ($p < 0.01$). However, multiple comparisons analysis showed no significant differences to be present between the individual subgroups after Hartman's solution challenge. After bradykinin challenge, significant differences were present only between normal subjects and those with perennial allergic rhinitis; there were no significant differences between subjects with seasonal allergic rhinitis and those with perennial allergic rhinitis, or between subjects with seasonal allergic rhinitis and normal subjects.

There were significant differences between the three groups in contralateral symptom scores after challenge with Hartman's solution ($p < 0.001$) and bradykinin ($p < 0.001$). Significant differences were present between normal and perennial allergic rhinitis subjects after both Hartman's solution and bradykinin challenge. Significant differences were present between seasonal allergic rhinitis and perennial allergic rhinitis subjects after Hartman's solution challenge, but not after bradykinin challenge. No significant differences in symptom scores were present between normal and seasonal allergic rhinitis subjects.

There were no significant differences between the groups in the increase in bradykinin-induced symptoms compared with those induced by Hartman's solution.

Figure 4 shows the mean symptom scores in normal subjects and in subjects with intermittent allergic rhinitis and persistent allergic rhinitis. There were significant differences in ipsilateral symptom scores between the three groups of subjects after challenge with both Hartman's solution ($p < 0.01$) and bradykinin ($p < 0.001$). In both cases, significant differences were present between normal subjects and those with persistent allergic rhinitis, and between subjects with persistent allergic rhinitis and those with intermittent allergic rhinitis. There were no significant differences between normal subjects and those with intermittent allergic rhinitis. Significant differences were also present in contralateral symptom scores between the three groups of subjects ($p = 0.0001$ after Hartman's solution, and $p < 0.00001$ after bradykinin). Once again, multiple comparisons demonstrated significant differences to be present between normal subjects and those with persistent allergic rhinitis, and between subjects with persistent allergic rhinitis and those with intermittent allergic rhinitis. No significant differences were present between subjects with intermittent allergic rhinitis and normal subjects.

There were no significant differences between the groups in the increase in bradykinin-induced symptoms compared with those induced by Hartman's solution.

## Discussion

The main purpose of the present study was to investigate whether allergic rhinitis classified according to the Allergic Rhinitis and its Impact on Asthma system corresponded well with the state of nasal responsiveness. Good correspondence was plainly demonstrated by the finding of clear-cut differences in both ipsilateral and contralateral secretory responses to bradykinin, as well as in symptom scores, comparing subjects with intermittent and persistent allergic rhinitis. In fact, the Allergic Rhinitis and its Impact on Asthma classification may have some advantages over the traditional classification system. This is suggested by the clearer demarcation in nasal symptom scores seen between subjects with

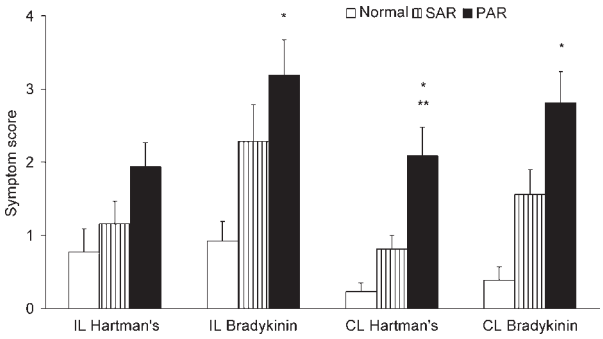


FIG. 3

Symptom scores in response to Hartman's solution and bradykinin on the ipsilateral (IL) and contralateral (CL) sides of the nose in normal subjects and those with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). *Significant difference compared with normal subjects; **significant difference between subjects with seasonal compared with perennial allergic rhinitis.

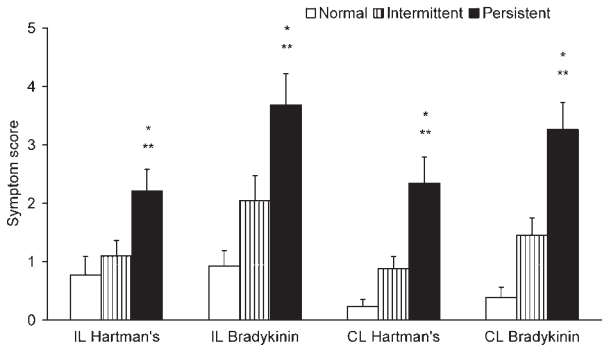


FIG. 4

Symptom scores in response to Hartman's solution and bradykinin on the ipsilateral (IL) and contralateral (CL) sides of the nose in normal subjects and those with intermittent allergic rhinitis and persistent allergic rhinitis. *Significant difference compared with normal subjects; **significant difference between subjects with intermittent compared with persistent allergic rhinitis.

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intermittent and persistent allergic rhinitis. In contrast, subjects with seasonal and perennial allergic rhinitis were less well demarcated by symptom scores.

The Allergic Rhinitis and its Impact on Asthma classification of allergic rhinitis has other important advantages over the traditional classification (i.e. into seasonal and perennial allergic rhinitis). One of the main advantages of the former classification system is its ease of use. In contrast, when using the traditional classification, difficulties may arise owing to such factors as: difficulty in distinguishing between seasonal and perennial symptoms; the presence of dual sensitisation; the presence of long-standing exposure to seasonal allergens; and inconsistent exposure to perennial allergens.[3]

- **The recently proposed Allergic Rhinitis and its Impact on Asthma classification of allergic rhinitis is easier to use and more inclusive of commonly encountered patients than the traditional classification into seasonal and perennial forms**
- **The symptomatic and secretory responses of subjects with allergic rhinitis correlates well with the Allergic Rhinitis and its Impact on Asthma classification**
- **The use of the Allergic Rhinitis and its Impact on Asthma classification should be recommended in future studies regarding allergic rhinitis**

A further important advantage of the Allergic Rhinitis and its Impact on Asthma classification relates to the treatment of subjects with seasonal symptoms but sensitisation to both seasonal and perennial allergens. These subjects are neatly classified, without regard to their pattern of sensitisation, by the Allergic Rhinitis and its Impact on Asthma system. On the other hand, it is unclear how these subjects should be classified according to the traditional classification. In experimental studies, one answer to this problem would be to exclude these subjects and to include only those sensitised exclusively to seasonal allergens.[2] However, most patients with allergic rhinitis are sensitised to both seasonal and perennial allergens, so excluding these subjects would mean excluding the group most representative of the actual patient population. In the present study, these subjects were classified as having seasonal allergic rhinitis. These subjects' secretory responsiveness to bradykinin outside the pollen season did not differ significantly from that of normal subjects, and was significantly less than that of subjects with perennial symptoms (i.e. perennial allergic rhinitis). However, even outside the pollen season, these subjects' degree of symptomatic responsiveness did not differ significantly from that of perennial allergic rhinitis subjects. This contrasts with the Allergic Rhinitis and its Impact on Asthma classification, in which significant differences in symptomatic responses were seen between those subjects with intermittent and persistent allergic rhinitis.

## Conclusion

The findings of the present study support the suggestion that the Allergic Rhinitis and its Impact on Asthma classification of allergic rhinitis correlates well with the underlying disease activity and degree of nasal responsiveness. This new classification is appropriate for future research studies on allergic rhinitis.

## Acknowledgements

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Mr P Sheahan takes responsibility for the integrity of the content of the paper.
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