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Late allergic airway response to segmental bronchopulmonary provocation in allergic subjects is related to peripheral blood basophil histamine release

Nizar N. Jarjour, MD [[MEDLINE LOOKUP](#)]

Julie B. Sedgwick, PhD [[MEDLINE LOOKUP](#)]

Cheri A. Swensen, BS [[MEDLINE LOOKUP](#)]

William W. Busse, MD [[MEDLINE LOOKUP](#)]

- *Madison, Wis.*

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Abstract

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Background: Basophil histamine release has been found to correlate with the presence and severity of allergic disease. However, it remains to be established whether airway response to antigen is related to basophil involvement and its release of histamine.

Objective: The purpose of this study was to investigate whether the intensity of airway response to an inhaled antigen challenge in allergic subjects is related to IgE-dependent peripheral blood

basophil histamine release.

Methods: The response to segmental bronchoprovocation with antigen was examined in 34 subjects with allergic rhinitis. Bronchoalveolar lavage samples were obtained 5 minutes (immediate response) and 48 hours (late response) after allergen challenge. Peripheral blood maximal basophil histamine release (MBHR) in response to in vitro antigen stimulation was determined in each subject before segmental bronchoprovocation.

Results: Bronchoalveolar lavage samples obtained during immediate response showed an increase in histamine, whereas the late response was noted for a marked enhancement in airway cells, particularly eosinophils. Interestingly, a significant correlation ($r = 0.73$, $p < 0.0001$, Spearman Rank test) was noted between MBHR and intensity of bronchoalveolar lavage eosinophilia at 48 hours. Furthermore, subjects with high ($\geq 20\%$) MBHR had significantly higher total cells and eosinophils in bronchoalveolar lavage fluid 48 hours after antigen segmental bronchoprovocation when compared with subjects with low ($< 20\%$) MBHR.

Conclusion: Our data suggest that the intensity of airway eosinophilia in response to antigen challenge is correlated with the magnitude of basophil mediator release in allergic subjects. (J Allergy Clin Immunol 1997;99:87-93.)

APD₂₀ Antigen provocative dose leading to a 20% fall in FEV₁

BAL Bronchoalveolar lavage

CBU Cumulative breath units

MBHR Maximal basophil histamine release

PNU Protein nitrogen units

SBP Segmental bronchoprovocation

(Click on a term to search this journal for other articles containing that term.)

Key Words: [Basophil](#), [histamine release](#), [allergen bronchoprovocation](#), [bronchoalveolar lavage](#), [eosinophils](#)

To establish the characteristics of the airway response to antigen, we and others have used bronchoscopy with segmental antigen bronchoprovocation (SBP) to measure the immediate and later reactions.¹⁻⁵ With this procedure, antigen is instilled into a bronchopulmonary segment; analysis of bronchoalveolar lavage (BAL) fluid obtained minutes later characterizes the immediate airway response. Bronchoscopy and lavage can be repeated later to determine features associated with the later airway response. When allergic subjects undergo SBP with antigen, there is an immediate increase in mast cell mediators in BAL fluid, and samples obtained 48 hours later show significant eosinophilia.³ Because SBP with antigen does not always result in airway eosinophilia at 48 hours even when the antigen is selected on the basis of the patient's history and positive skin test (or inhaled bronchial challenge) response, it would be helpful to have a simple, minimally invasive predictor of the late response.

Previous studies have shown that in vitro basophil histamine release is increased in atopic individuals⁶ and that the clinical severity of some atopic conditions correlates with this increase.⁷ Likewise, airway eosinophilia is an important feature of bronchial asthma and a marker for asthma severity,⁸ and it is possible that recruitment of eosinophils to the lungs in allergic subjects correlates with basophil histamine release. The purpose of this study was twofold. The first objective was to determine whether there is an in vitro response that can be used to predict and select subjects who will have "late phase" eosinophilia in response to antigen. The second objective was to determine whether, if such an in vitro evaluation can be found, the results provide insight into the development of the late allergic reaction. This report describes the value of peripheral blood basophil histamine release for the prediction of airway responses to antigen.

Methods

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Subjects

Thirty-four subjects with allergic rhinitis underwent antigen SBP and BAL and were included in this analysis. The subjects ranged in age from 19 to 51 years. All had a clinical history of allergic rhinitis. Atopy was defined as a positive immediate skin prick test response to at least one aeroallergen (see below). At the time of study, all subjects were clinically stable and had FEV₁ values of 75% of predicted value or higher. No subject had a respiratory tract infection for the month preceding the study. Furthermore, none of the subjects had smoked in the previous 5 years or had a smoking history of more than 5 pack-years. These studies were approved by the University of Wisconsin Committee for Human Subjects. All participants gave informed consent at the time of entry into the study, and the consent was reconfirmed before each bronchoscopy.

Study design

Each subject underwent a medical history, physical examination, and pulmonary function testing by spirometry. Prick puncture skin testing with common aeroallergens was performed with aqueous extracts of ragweed, grass, trees, house dust mite, *Alternaria* spp., cat, and dog (Greer Laboratories, Lenoir, N.C.). The responses to saline and histamine solutions were used as negative and positive controls. Selected subjects had positive ragweed skin reactions and were studied out of season. Phlebotomy was performed to obtain blood samples for basophil histamine release assay before antigen bronchoprovocation and bronchoscopy. Inhalation bronchoprovocation with ragweed antigen was performed in each participant, and the dose required to decrease FEV₁ by 20% (antigen PD₂₀ [APD₂₀]) was calculated.⁹ Each subject underwent two bronchoscopies. At the initial bronchoscopy (day 1), a pulmonary segment was challenged with antigen, and BAL was performed 5 minutes after SBP; a second bronchoscopy and BAL were repeated on the same segment 48 hours later (day 2).

Spirometry and bronchoprovocation

Pulmonary functions were calculated from a flow-volume loop (Med-Graphic, St. Paul, Minn.). The best of three acceptable trials was used to obtain the FEV₁ and forced vital capacity. Antigen bronchoprovocation was performed as previously described.⁹ Briefly, spirometry was performed to

obtain a baseline value, then repeated 5 minutes after 5 breaths of the diluent fluid had been inhaled. If no significant response to diluent occurred (FEV_1 within 10% of baseline), 5 breaths of the least concentrated ragweed antigen solution (0.5 protein nitrogen units (PNU)/ml) were given, and spirometry was repeated 10 minutes later. Consecutively higher antigen doses were then given until the FEV_1 fell by 20% or more from the postdiluent value. APD_{20} was calculated by linear interpolation of the dose-response curve with a computer program (PD20; Madison Scientific Software, Wexford, Pa.) and expressed in cumulative breath units (CBU) for ragweed or the maximum delivered dose for other antigens. Subjects who did not show a 20% drop in FEV_1 after the challenge with the most concentrated ragweed antigen solution used (10,000 PNU/ml), meaning that a PD_{20} was higher than 1666.7 CBU, were assigned an APD_{20} of 2000 CBU. Twenty-six of these subjects also underwent a histamine bronchoprovocation to identify the level of bronchial responsiveness by calculating histamine PD_{20} with a protocol similar to antigen challenge.⁹ Subjects who did not show a 20% drop in FEV_1 after histamine challenge, meaning that PD_{20} was higher than 150 CBU, were assigned a histamine PD_{20} of 200 CBU.

Bronchoscopy, SBP, and BAL

Bronchoscopy

Bronchoscopy was performed as previously described^{10 11} and in accordance with published guidelines for bronchoscopy in patients with asthma.^{12 13} Premedications included intramuscular atropine sulfate (0.6 mg) and midazolam (1.5 mg). Heart rate and oxygen saturation were monitored by continuous pulse oximetry (model 504; Criticare Corp., Milwaukee, Wis.). Low flow supplemental oxygen was given to maintain oxygen saturation above 90% throughout the procedure. A fiberoptic bronchoscope (P20D; Olympus Corporation of America, New Hyde Park, N.Y.) was introduced transnasally and passed into the bronchial tree; a segment was identified for SBP and BAL. Minimal quantities of 1% lidocaine were used for airway anesthesia.

SBP and BAL

Antigen SBP was performed at the time of the first bronchoscopy. The antigen dose was diluted in 10 ml of sterile 0.9% NaCl, which was instilled in a pulmonary segment and followed by a flush of 5 ml of air. The scope was maintained in a wedged position for a dwell time of 5 minutes; lavage was then performed with four 60 ml aliquots of warm, sterile 0.9% NaCl (total injected volume, 240 ml). At the second bronchoscopy, 48 hours later, the previously challenged segment was identified, and lavage (60 ml of sterile 0.9% NaCl $\times 4$) was performed. The dose of ragweed antigen used in SBP was based on the response to inhaled antigen bronchoprovocation. Subjects who did not show a 20% fall in FEV_1 in response to inhaled challenge received a higher dose (median antigen dose of 1000 PNU) of antigen compared with the group that responded to inhaled antigen challenge with a fall in FEV_1 of 20% or more (median antigen dose of 150 PNU).

Processing of BAL fluid

The lavage fluid returns from each segment were pooled and centrifuged (400 *g* for 10 minutes) to sediment BAL cells. Each cell pellet was washed once in phosphate-buffered saline, suspended in

Hanks' balanced salt solution (Life Technologies, Grand Island, N.Y.), and kept on ice. Total BAL cell count was obtained by using a hemocytometer and adjusted to a final concentration of 2×10^6 cells/ml. Cytocentrifuge preparations were air-dried, fixed in methanol, and stained (Diff-Quik; Scientific Products; Chicago, Ill.). For differential cell counts, 300 cells were enumerated; each cell was identified as lymphocyte, neutrophil, eosinophil, macrophage, or epithelial cell.

Basophil histamine release assays

Basophil-enriched peripheral blood leukocytes were obtained by Ficoll-Hypaque (Pharmacia, Uppsala, Sweden) centrifugation and incubated with 1×10^{-2} to 3×10^{-4} μg of ragweed antigen/ml at 37°C for 20 minutes. In our laboratory these concentrations allow for a full dose response. Because they include concentrations that are considered supraoptimal for release, they typically permit the location of the peak or optimal release of histamine by basophils. The reactions were stopped by centrifugation, and the supernates were collected for analysis by an automated fluorometric technique (Technicon Auto Analyzer II; Penstrop Analytical Inc., Silver Spring, Md.), which uses the organic extraction of histamine and its linkage to o-phthaldialdehyde.¹⁴ The lower level of detectability of the assay is 5 ng/ml. Total histamine content was determined after lysis with 3% perchloric acid. Spontaneous histamine release (approximately 5% in our laboratory) was subtracted when maximal basophil histamine release (MBHR) was calculated. MBHR was calculated as (maximum antigen stimulated histamine release - spontaneous release) $\div$ (total histamine concentration - spontaneous release). Basophils from all subjects released histamine in a dose-dependent fashion; peak basophil histamine release was used for data analysis.

Determination of BAL histamine

BAL fluid was assayed for histamine content by a radioenzymatic assay as previously described.¹⁵ Histamine N-methyltransferase and S-adenosyl-C[³H-methyl] methionine were used to convert histamine to [³H]tele-methylhistamine, which was then isolated from other radiolabeled material and quantitated by liquid scintillation. Standard curves were prepared for each experiment with histamine concentrations from 15 to 5000 pg/ml (linear coefficient of correlation equal to 0.99) and used to calculate the histamine concentration. Analysis of variance demonstrated a lower limit of sensitivity of 30 pg/ml.

Data and statistical analysis

Most of the lavage and airway responsiveness data were not normally distributed. Thus they are presented as medians and (25% to 75%) interquartiles and compared by using the Wilcoxon or Mann-Whitney U test for paired and unpaired data, respectively. Correlation was done by using Spearman Rank test. Normally distributed data (Kolmogorov-Smirnov normality test) were expressed as mean $\pm$ SEM and analyzed by using Student's *t* test. A *p* value of less than 0.05 was considered significant.

Pulmonary physiology and subject characteristics

Before the first bronchoscopy, all subjects had normal pulmonary function with a mean FEV₁ value of 4.4 ± 0.17 L ($104\% \pm 2\%$ predicted value). Before the second bronchoscopy, the FEV₁ values had not changed (4.22 ± 0.16 L, [$101\% \pm 3\%$ predicted value]). The group as a whole had an MBHR of $44.8\% \pm 5.0\%$. In seven subjects MBHR was not distinguishable from spontaneous basophil histamine release ($n = 5$) or minimally increased over spontaneous release (5% to 10%, $n = 2$). Because the usual standard deviation of peak histamine release in our allergic volunteers is around 20% and because these seven subjects clearly had nonresponsive or minimally responsive basophils, we divided our subjects into two groups “high release group” (MBHR $\geq 20\%$) and “low release group” (MBHR $< 20\%$). The group with low histamine release ($n = 7$) had an MBHR of $2.1\% \pm 1.5\%$, whereas the group with high release ($n = 27$) had an MBHR of $55.8\% \pm 4.1\%$. Subjects from the high and low histamine basophil release groups were similar in age, baseline pulmonary functions, airway responsiveness to histamine, and number of positive skin test reactions to common aeroallergens (Table I).

Table I. Subject characteristics

	Low release ($n = 7$)	High release ($n = 27$)
Age (yr)	26 ± 1	27 ± 1
Skin test (no.) of positive reactions)*	5.6 ± 1.2	4.9 ± 0.4
Histamine release (%)	2.1 ± 1.5	55.8 ± 4.1
FEV ₁ (% predicted)	95 ± 7	107 ± 3
Histamine PD ₂₀ (CBU)†	76 (11-123)	65 (18-200)
Antigen PD ₂₀ (cumulative units)	2000 (2000-2000)	1091 (128-2000)‡
Antigen dose used in SBP	1000 (625-1000)	150 (20-475)‡

Results are shown as means $\pm$ SEM for normally distributed data and medians with (25% to 75%) interquartiles for nonnormally distributed data.

*A total of 12 prick skin tests were performed.

†Results are based on data from five subjects in the low release group and 21 subjects in the high release group.

‡ $P < 0.01$ high versus low release groups Mann-Whitney U test.

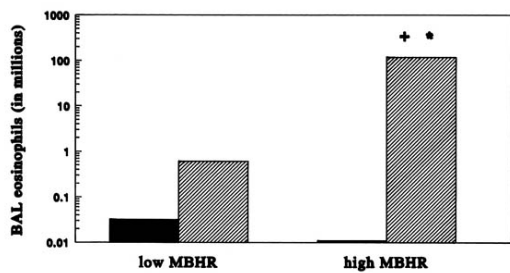
Median ragweed APD₂₀ for the two groups with high and low MBHR were 1091 and 2000 PNU, respectively ($p < 0.05$, Mann-Whitney U test). The median dose of ragweed used in SBP was 1000 PNU in the group with low MBHR and 150 PNU in the group with high MBHR ($p < 0.05$, Mann-Whitney U test).

BAL analysis

Segmental antigen challenge was associated with significant increase in BAL eosinophils (numbers and percentage of total cells) 48 hours later. Importantly, there was a significant correlation between MBHR and the numbers (and percentage) of eosinophils recruited to the airway at 48 hours ($r =$

0.73 for eosinophil numbers, $r = 0.67$ for eosinophil percentages, $p < 0.0001$ for both correlations; Spearman Rank test) (Fig. 1).

Fig. 1. Absolute eosinophil numbers (medians) in BAL fluid in groups with low and high basophil histamine release at 5 minutes (*solid bars*) and 48 hours (*hatched bars*) after antigen SBP. Both groups showed an increase in eosinophils at 48 hours compared with 5 minutes. In the group with high basophil histamine, this increase was dramatic and statistically significant, whereas in the group with low histamine release the increase was modest and only marginally significant ($p = 0.06$, Wilcoxon test). $*p < 0.05$, high release versus low release at 48 hours (Mann-Whitney test). $p < 0.05$, day 1 versus day 2 (Wilcoxon signed-rank test).



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There was a clear difference in this cellular and eosinophilic response between the groups with high and low MBHR (Table II), with nearly 200 times more eosinophils at 48 hours in the group with high MBHR (Fig. 2).

Table II. BAL characteristics

	<u>5 minutes</u>		<u>48 hours</u>	
	Low	High	Low	High
Volume	180 (159-185)	167 (151-179)	166 (159-183)	171 (163-185)
Cells	20.2 (10.6-31.0)	16.1 (10.7-22.4)	34.5 (24.7-41.2)	198.4 (69.3-341.0) ^{†*}
AM%	94.0 (91.6-96.1)	92.7 (85.8-97.2)	93.0 (66.8-95.4)	32.7 (21.5-70.3) ^{†*}
EOS%	0.3 (0.0-0.6)	0.0 (0.0-1.7)	3.0 (0.3-6.0)	61.0 (20.1-76.0) ^{†*}

PMN%	0.0 (0.0-0.3)	0.3 (0.0-0.7)	2.7 (0.4-3.7)	1.0 (0.3-1.9)†
LYM%	3.7 (3.4-6.8)	4.7 (1.4-9.3)	0.3 (0.0-4.2)	0.7 (0.0-4.2)†
EPI%	0.3 (0.1-1.2)	1.3 (0.0-2.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)†
Histamine level (pg/ml)	155 (55-492)	686 (30-6147)	50 (31-299)	156 (30-5081)

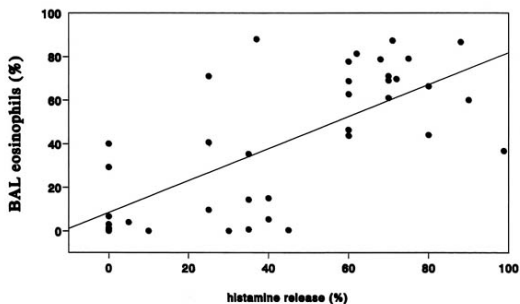
Data are expressed as medians and (25% to 75%) interquartiles. Volume: BAL fluid volume return in ml (240 ml injected). Cells: Total BAL cell return in millions.

AM%, EOS%, PMN%, LYM%, EPI%: percentages of alveolar macrophages, eosinophils, neutrophils, lymphocytes and epithelial cells in BAL fluid.

* $p < 0.05$, high vs low histamine release (Mann-Whitney U test).

† $p < 0.05$, 5 minutes versus 48 hours (Wilcoxon test).

Fig. 2. Correlation between histamine release and proportion of eosinophils in BAL fluid obtained 48 hours after antigen SBP ($r = 0.67$, $p < 0.0001$, $n = 34$, Spearman Rank test).



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We also compared changes in BAL cells between 5 minutes and 48 hours after SBP within each group (Table II ■). In the group with high MBHR, there was a significant increase in the percentages of eosinophils and neutrophils and a decrease in the percentages of alveolar macrophages, lymphocytes, and epithelial cells. On the other hand, the group with low MBHR had marginal increases in total cells ($p = 0.05$), eosinophils ($p = 0.06$), and neutrophils ($p = 0.06$) and no changes in lymphocytes, alveolar macrophages, or epithelial cells ($0.08 < p < 0.2$). This minimal “late phase” cellular response was probably not related to lower antigen dose or lesser intensity of mast cell mediator release during the “immediate phase response,” because the antigen dose used in SBP was actually higher in the group with low MBHR (Table I ■), and the histamine levels in BAL fluid obtained at 5 minutes were not statistically different between the two groups (Table II ■).

To determine whether the subjects with low MBHR did not show significant eosinophilia simply because they did not receive an adequate antigen dose to cause an immediate response and to evaluate whether MBHR is a useful predictor of the magnitude of the late phase in patients with similar early-phase responses, we analyzed the late response in the subgroup with comparable BAL histamine levels 5 minutes after antigen SBP. In the group as a whole, BAL histamine levels were 493 pg/ml (range, 30 to 3214 pg/ml). Thus we grouped together subjects whose BAL

histamine levels at 5 minutes were lower than the median (<493 pg/ml) and evaluated the effect of histamine release on late lavage eosinophilia. In these 17 subjects with a minimal early-phase histamine response to antigen, there was a clearly greater late-phase response as reflected by higher BAL eosinophilia ($p < 0.05$) in the subjects with high MBHR compared with those with low MBHR (Table III).

Table III. Percentage of eosinophils in BAL fluid 48 hours after antigen SBP

Group (n)	Low MBHR	High MBHR
Entire group, (n = 34)	3.0 (0.3-6.0), n= 7	61.0 (20.1-76.0),* n= 27
Subjects with BAL histamine <493 pg/ml after Ag-SBP (n = 17)	1.3 (0.0-3.9), n = 5	53.2 (7.8-69.3),* n = 12
Subjects with APD ₂₀ = 2000 CBU(n = 19)	3.0 (0.3-6.0), n = 7	50.3 (7.5-65.7),* n = 12

Data are shown as medians with (25% to 75%) interquartiles. Ag, Antigen. In the entire group, as well as in each of the two subgroups, high MBHR was associated with significantly enhanced BAL eosinophilia 48 hours after antigen SBP. * $p < 0.05$ high versus low MGHR (Mann-Whitney U test).

Furthermore, in the group as a whole (n = 34), there was no correlation between BAL histamine level at 5 minutes after SBP and the percentage or numbers of eosinophils in BAL fluid at 48 hours ($r = 0.3$, $p > 0.08$ for both correlations, Spearman Rank test).

Because the physiologic response to inhaled antigen can be an important determinant of lower airway cellular changes in response to antigen, we sought to evaluate the importance of MBHR in subjects who did not show a significant early airway obstruction (assigned an APD₂₀ of 2000) in response to antigen challenge. In the 19 subjects who fulfilled this criterion, the group with high MBHR (n = 12) had a greater BAL eosinophilia than those with low MBHR (n = 7) (Table III ■). This could not be explained by differences in antigen dose used in SBP, because the doses were similar in the two groups (850 vs 619 PNU in the low and high MBHR groups, respectively).

Discussion

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In this study we demonstrated a significant correlation between MBHR in response to antigen and the recruitment of eosinophils to the airway in response to antigen SBP in subjects with allergic rhinitis. The group with high basophil histamine release in response to antigen had nearly a 200-fold greater number of eosinophils in BAL fluid 48 hours after antigen SBP compared with the group with low histamine release. This difference was still significant even within the subgroup that showed no significant physiologic response to inhaled antigen or the subgroup with minimal increase in BAL histamine at 5 minutes after antigen SBP. These findings suggest that basophil histamine release can be used to predict the magnitude of the eosinophilic airway response to antigen. Furthermore, our data suggest that the late allergic airway response to segmental antigen challenge can be elicited in subjects with minimal mast cell activation during the early phase as measured by BAL

histamine levels. Finally, our observations add indirect support to the hypothesis that mast cells and/or basophils play a role in the pathogenesis of the late phase as previously shown in other studies.^{4 16}

Previous studies demonstrated that atopic subjects have increased histamine release compared with normal subjects.⁶ In patients with atopic dermatitis, those with more severe clinical disease had higher basophil histamine release.⁷ Furthermore, in patients with atopic asthma a significant correlation was found between IgE levels and basophil histamine release.¹⁷ In our studies we detected a significant correlation between MBHR and airway eosinophilia in response to a segmental antigen challenge.

The exact mechanism by which increased basophil histamine relates to enhanced eosinophilic influx to antigen is not known or established in our study; however, there are several possible explanations. First, mast cells and basophils are present in the lungs and are presumed to be activated during the early-phase response to antigen and to secrete histamine and other mediators. Because the subjects with increased basophil histamine release showed a trend toward higher levels of BAL histamine immediately after SBP, it is possible that they also had increased release of other mediators including those that are capable of recruiting eosinophils. Second, differences in disease severity are unlikely to account for these findings, because the subjects in the two groups were equivalent in age, pulmonary function, number and relative intensity of positive skin test responses to common aeroallergens, and airway responsiveness to histamine; thus, the difference in the late-phase eosinophilia could not be simply attributed to increased severity of “allergies” in the group with high MBHR. Third, even airway responsiveness to inhaled antigen was not a strong predictor of eosinophilic airway inflammation in response to antigen challenge. The proportion of eosinophils in BAL was 32% in those who did not respond to inhaled antigen ($n = 19$) and 55% in those who responded ($n = 15$), whereas there was a dramatic difference in eosinophils between the two groups with high and low MBHR (Table II[■]). Fourth, there was no correlation between the intensity of immediate mast cell response to antigen SBP and eosinophil recruitment during the late phase: thus, the events of early- and late-phase responses may not be linked, at least when the early phase is assessed on the basis of BAL histamine levels. Finally, the correlation between basophil response and eosinophil response to antigen may be related to the common lineage of these two cells, which leads them to have a similar response to the effects of mediators released during antigen provocation of the airway (e.g., cytokines). From a practical point of view, because the majority of subjects with MBHR of 20% or greater had a significant BAL eosinophilic response, this test can be used prospectively to recruit subjects with higher likelihood of demonstrating significant eosinophilic airway inflammation in response to antigen challenge, which is of particular value in clinical research studies.

In summary, this study has shown that basophil histamine release is a good predictor of the intensity of airway inflammatory response to antigen challenge in subjects with allergic rhinitis and suggests that basophils might be involved in directing the late-phase reaction and airway inflammation in allergic subjects.

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- *From Sections of Pulmonary and Critical Care Medicine, Allergy and Immunology, Department of Medicine, University of Wisconsin School of Medicine, Madison.*
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- *Reprint requests: Nizar N. Jarjour, MD, Pulmonary Medicine Section, 600 Highland Ave., (H6/380 CSC), Madison, WI 53792.*
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