

Extrathoracic and intrathoracic airway responsiveness in sinusitis

Caterina Bucca, MD, Giovanni Rolla, MD, Ermanno Scappaticci, MD, Fabrizia Chiampo, MD, Massimiliano Bugiani, MD, Mauro Magnano, MD, and Micaela D'Alberto, MD *Torino, Italy*

Background: Asthma associated with sinusitis is supposed to be sustained by bronchoconstrictive reflexes originating in extrathoracic airway (EA) receptors.

Objective: The study was designed to evaluate the relationship between EA responsiveness and bronchial responsiveness in sinusitis.

Methods: We performed histamine inhalation challenge in 106 patients with chronic sinusitis, during disease exacerbation and after treatment with antimicrobials and nasal flunisolide (100 µg daily) for 2 weeks. Forced expiratory volume in 1 second (FEV₁) and maximal mid-inspiratory flow (MIF₅₀) were the respective indexes of bronchial and EA narrowing; the histamine concentrations causing a 20% fall in FEV₁ (PC₂₀) and 25% drop in MIF₅₀ (PC₂₅MIF₅₀) were used as thresholds of bronchial and EA responsiveness. Thresholds of 8 mg/ml or less were assumed to indicate bronchial hyperresponsiveness (B-HR) or EA hyperresponsiveness (EA-HR).

Results: During sinusitis exacerbation 76 patients had EA-HR, which in 46 was associated with B-HR. The values of PC₂₀ were closely related with those of PC₂₅MIF₅₀ ($p < 0.001$). EA-HR and B-HR were strongly associated with pharyngitis. After treatment, mean PC₂₅MIF₅₀ and PC₂₀ were significantly increased ($p < 0.001$). The improvement of PC₂₅MIF₅₀ was closely related to that of PC₂₀ ($p < 0.001$) and to the decrease in neutrophils in nasal lavage ($p < 0.05$). EA-HR reversed in 58 patients and improved in 10; B-HR reversed in 29 and improved in 12.

Conclusions: Our findings suggest that in sinusitis, B-HR may be sustained by constrictive reflexes originating in pharyngeal receptors, made hypersensitive by seeding of the inflammatory process. (*J ALLERGY CLIN IMMUNOL* 1995;95:52-9.)

Key words: Sinusitis, bronchial hyperresponsiveness, extrathoracic airway hyperresponsiveness, pharyngitis, pharyngobronchial reflex

Although the association between sinusitis and asthma is well recognized,¹⁻⁵ whether the two diseases are linked by a cause-and-effect relationship or are the result of a pathogenetic event affecting the whole respiratory tract is still controversial. The hypothesis that asthma is triggered by sinusitis is supported by the results of clinical investigations showing that sterilization and drainage of paranasal sinuses results in improvement of asthma.⁶⁻¹¹ According to this hypothesis, inflammatory mediators produced in paranasal sinuses elicit broncho-

Abbreviations used

B-HR:	Bronchial hyperresponsiveness
EA:	Extrathoracic airway
EA-HR:	Extrathoracic airway hyperresponsiveness
FEV ₁ :	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
MEF ₅₀ :	Mid-expiratory flow
MIF ₅₀ :	Mid-inspiratory flow
PC ₂₀ :	Provocative concentration causing a 20% fall in FEV ₁
PC ₂₅ MIF ₅₀ :	Provocative concentration causing a 25% fall in MIF ₅₀
TLC:	Total lung capacity

From the Department of Biomedical Sciences and Human Oncology, University of Torino.

Supported by a grant from the Italian Ministry of Scientific Research.

Received for publication Dec. 13, 1993; revised June 13, 1994; accepted for publication June 21, 1994.

Reprint requests: Caterina Bucca, MD, Dipartimento di Scienze Biomediche, Sezione Clinica, via Genova 3, 10126 Torino, Italy.

Copyright © 1995 by Mosby-Year Book, Inc.

0091-6749/95 \$3.00 + 0 1/1/58628

constriction either by stimulating neural receptors in the nose, sinuses, or pharynx or by dripping into the lower airway. To explore this hypothesis Irvin¹² performed an elegant series of experiments with an

TABLE 1. Data obtained at the first examination during exacerbation of sinusitis

Variable	No.	%
Number of patients	106	
Women	55	52
Smokers	22	21
Increased total or specific IgE	36	34
Allergic rhinitis	14	13
Postnasal drip	89	84
Cough	84	79
Pharyngitis	49	46
Wheeze	42	40
Sinusitis type:		
Maxillary	55	52
Frontal	22	21
Ethmoidal	12	11
Pansinusitis	17	16
Hyperplasia of turbinates	50	48
Polypoid changes	15	14
Nasal lavage		
Neutrophil score mean (SEM)	3.04 (1.47)	
Nasal eosinophilia	36	34
Histamine responsiveness		
EA-HR	76	72
EA-HR + B-HR	46	43

animal model of sinusitis.¹² Their findings indicate that nonspecific bronchial hyperresponsiveness (B-HR) is sustained by activation of a pharyngobronchial reflex, rather than by a nasobronchial reflex or by seeding of the inflammatory process into the lower airway.

On the basis of physiologic studies showing that inspiratory flows are sensitive indicators of extrathoracic airway (EA) narrowing, either fixed or variable in nature,¹³⁻¹⁵ we commonly record the flow-volume loop, in addition to the forced expiratory volume in 1 second (FEV₁), during bronchial challenge to explore EA responsiveness. Using this method, we previously found that patients with asthmatic symptoms¹⁶ showed three different patterns of response to histamine inhalation challenge: one third had a decrease in FEV₁, consistent with predominant B-HR, one third had only a marked dose-dependent decrease in inspiratory flows, consistent with predominant EA hyperresponsiveness (EA-HR), and one third had both B-HR and EA-HR. Fibroscopic examination, performed in a few of these patients before and after the challenge, actually showed that the drop in inspiratory flows after histamine corresponded to reddening, edema, and hypersecretion of pharyngolaryngeal mucosa and to paradoxical adduction

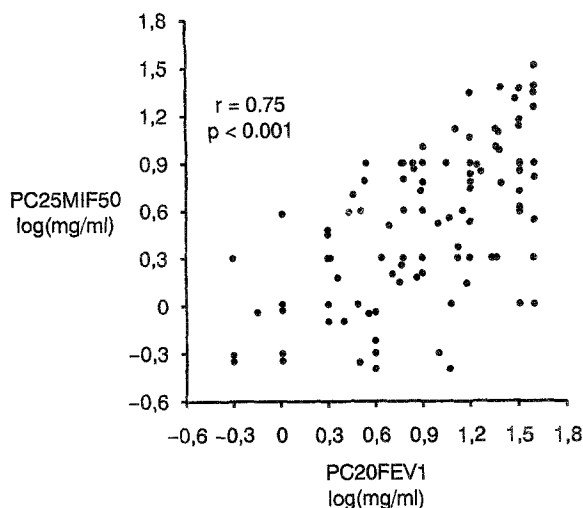


FIG. 1. Relationship between bronchial and EA responsiveness during exacerbation of sinusitis.

of the vocal cords during forced inspiration.¹⁶ Interestingly, this abnormal response pattern was strongly associated with upper respiratory tract diseases, such as postnasal drip, pharyngitis, and sinusitis. These findings indicated that EA-HR may be sustained by a local inflammatory process.

The aim of this study was to investigate whether hypersensitivity of EA receptors might represent the link between sinusitis and bronchial hyperresponsiveness. To investigate this matter we evaluated the relationship between extra- and intrathoracic airway responsiveness to inhaled histamine in patients with chronic sinusitis. The patients were examined during exacerbation of the disease and after treatment with topical flunisolide and antibiotics for 2 weeks.

METHODS

One hundred six subjects who had exacerbation of chronic sinusitis were selected from the outpatients of an ear, nose, and throat clinic. Exacerbation of chronic sinusitis was defined on the basis of: (1) purulent discharge from the nose, (2) postnasal drip, (3) tenderness over any of the paranasal sinuses, (4) radiologic evidence of opacification or mucoperiosteal thickening or air fluid level in one or more paranasal sinuses, (5) prevalence of neutrophils in nasal swab greater than 10% of enumerated cells, and (6) documented recurrence of acute purulent infection in the last 12 months. The selection criteria were: (1) normal lung function test results, with no evidence of EA obstruction in the inspiratory flow/volume curve¹³⁻¹⁵; (2) no documented history of asthma, cystic fibrosis, chronic bronchitis, bronchiectasis, immunodeficiency state, or diabetes; (3) no reported viral airway infection and no contact with subjects affected by

TABLE II. Factors affecting EA and bronchial responsiveness

	B	SEM of B	t	p Value
PC ₂₅ MIF ₅₀				
Constant	0.982			
Female sex	-0.196	0.068	2.882	0.01
Cough	-0.208	0.085	2.447	0.02
Pharyngitis	-0.140	0.067	2.089	0.05
Multiple <i>r</i> = 0.509				<0.001
PC ₂₀ FEV ₁				
Constant	1.390			
Wheeze	-0.384	0.106	3.597	<0.001
Pharyngitis	-0.279	0.093	2.988	0.004
Female sex	-0.260	0.097	2.676	0.009
Nasal eosinophils	-0.252	0.106	2.367	0.02
Multiple <i>r</i> = 0.653				<0.001

B, Coefficient B; t, t test.

"common cold" or the "flu syndrome" in the 6 weeks preceding the study; (4) no use of antimicrobials in the past 4 weeks, (5) no need for bronchodilators, corticosteroids, disodium chromoglycate, or antihistaminics in the last 3 months.

The protocol of the study was approved by a local ethical committee, and informed consent was obtained from all the patients. Patients were examined during exacerbation of sinusitis and after treatment with antimicrobials and topical flunisolide for 2 weeks.

First examination

During exacerbation of the disease, the subjects underwent the following procedures.

Recording of symptoms. Symptom recording was based on the American Thoracic Society questionnaire,¹⁷ which included detailed questions on upper airway symptoms. Pharyngitis was defined in patients with sore or burning sensation in the throat, in whom the ear, nose, and throat consultant had found reddening, edema, and exudation of the pharyngeal mucosa.

Sinus x-ray films. Upright, posteroanterior, and lateral views were taken.

Serum IgE measurement. Total serum IgE levels were titrated by the Phadebas PRIST (Pharmacia Diagnostics AB, Uppsala, Sweden), and serum-specific IgE levels for the most common aeroallergens were determined by the Phadebas RAST (Pharmacia). Subjects with levels of specific IgE over 3 UI/ml or total IgE counts over 180 kU/L, the upper normal value in our laboratory, were designated as atopic.

Nasal swabs. A nasal secretion sample was taken from both nasal cavities by wiping the surface of the inferior turbinate with a cotton-tipped applicator. The sample was smeared over a standard glass slide, fixed, stained, and immediately examined to confirm the predominance of neutrophils over other cell types.

TABLE III. Effect of treatment on prechallenge lung function, bronchial and EA responsiveness, and neutrophil score in nasal lavage

Variable	Before treatment (mean ± SEM)	After treatment (mean ± SEM)
FEV ₁ (L)	3.25 ± 0.09	3.26 ± 0.09
MEF ₅₀ (L/sec)	4.36 ± 0.14	4.54 ± 0.15
MIF ₅₀ (L/sec)	5.14 ± 0.15	5.60 ± 0.16
PC ₂₀ (mg/ml)*	7.94 ± 1.12	15.8 ± 1.10†
B-HR (n)	46 (52%)	17 (19%)†
PC ₂₅ MIF ₅₀ (mg/ml)*	3.24 ± 1.12	16.2 ± 1.10†
EA-HR (n)	76 (86%)	18 (20%)†
Neutrophil score (n)	3.08 ± 0.17	0.68 ± 0.84†

*Geometric mean.

†*p* < 0.001.

Nasal lavage. Five milliliters of saline solution was inserted in each nostril, with the patient's head bent backwards, during closure of the soft palate. After 10 seconds, the patient flexed his neck and expelled the liquid into a plastic tube. The volume of returned fluid was then measured, and the total number of cells was counted in a Bürker chamber (Assistant, Sondheim/Rhön, Germany). Samples containing more than 10⁴ cells were processed according to the method suggested by Bascom et al.¹⁸ Briefly, the liquid was centrifuged and then incubated with 8% N-acetylcysteine for 45 minutes to dissolve mucus. Cytospin slides were then prepared and stained for differential counts of epithelial cells, neutrophils, and eosinophils. Percentage of neutrophils was expressed as a score from 1 (10% of total cell count) to 6 (60% or greater). Nasal eosinophilia was diagnosed when more than 5% of enumerated cells were eosinophils.

Measurement of lung volumes and flow-volume loop. A computerized water-sealed spirometer (BAIRES Biomedin, Padova, Italy) was used to measure lung volumes and flow-volume loop. The flow-volume loop was recorded by instructing the subjects to perform a maximal expiratory effort from total lung capacity (TLC) to residual volume and, immediately after, a maximal inspiratory effort from residual volume to TLC. The test was repeated until 5 reproducible curves were obtained, that is, with forced vital capacity (FVC) that did not differ by more than 5% from its greatest value. To avoid the effects of deep inspiration, the tests were performed at intervals of at least 2 minutes. FVC, FEV₁, maximal mid-expiratory flow (MEF₅₀), and mid-inspiratory flow (MIF₅₀) were calculated from the best curve. Reference values were obtained from the study by Quanjer.¹⁹

Histamine inhalation challenge with assessment of bronchial and EA responsiveness. Histamine inhalation challenge was carried out according to the guidelines of the American Academy of Allergy and Immunology.²⁰ His-

TABLE IV. Patients' characteristics by response to treatment

Variable	B-HR			χ^2	EA-HR			χ^2
	No B-HR (n = 42)	responders (n = 29)	nonresponders (n = 17)		No EA-HR (n = 12)	responders (n = 58)	nonresponders (n = 18)	
Female (%)	40.5	62.7	85.7	9.51* (B)	8.3	56.9	86.7	16.73† (A, B)
Atopy (%)	33.3	27.6	58.8	4.84	33.3	31.0	55.6	3.62
Smokers (%)	33.3	17.2	5.9	5.93	16.7	25.0	12.5	4.52
Pharyngitis (%)	30.9	62.1	52.9	7.17‡ (A)	8.3	50.0	55.6	7.89§ (A, B)
Cough (%)	76.2	75.9	100.0	5.04	58.3	81.0	94.4	6.04‡ (B)
Runny nose (%)	31.0	24.1	47.1	2.62	50.0	24.1	44.4	4.73
Wheeze (%)	11.9	48.3	88.2	18.46† (A, B, C)	16.7	27.6	88.9	24.68† (B, C)
Nasal eosino- phils (%)	25.0	29.6	69.2	8.69§ (B, C)	33.3	28.0	57.1	4.13

A, Significant difference between No(B or EA)-HR and (B or EA)-HR/responders; B, significant difference between No(B or EA)-HR and (B or EA)-HR/nonresponders; C, significant difference between (B or EA)-HR+/responders and (B or EA)-HR/nonresponders.

* $p < 0.01$.

† $p < 0.001$.

‡ $p < 0.05$.

§ $p < 0.02$.

tamine was delivered in doubling concentrations from 0.5 to 32 mg/ml, by a compressed air nebulizer, controlled by a breath-actuated dosimeter (MEFAR MB3, Markos, Monza, Italy). The dosimeter was set to nebulize for 0.7 second (output = 0.09 ml); the mass median diameter of particles was 1.65 μ m (geometric standard deviation = 3.3). Each dose of histamine was inhaled through a mouthpiece by taking 5 slow vital capacity breaths from the nebulizer. Two minutes after each set of inhalations, 3 flow-volume loops were recorded 1 minute apart. The interval between one dose and the next was about 5 minutes. FEV₁ was used as the index of bronchial response, and MIF₅₀ as the arbitrary index of EA narrowing. To account for changes in FVC, the MIF₅₀ was calculated by matching the curves at TLC. This was justified by the observation that TLC does not change by more than 5% after acute induced bronchoconstriction.²¹ The challenge was stopped when FEV₁ dropped by 20% or when the highest histamine concentration was reached. The histamine provocative concentration causing a 20% fall in FEV₁ from baseline (PC₂₀) was used as threshold of bronchial responsiveness; B-HR was diagnosed when PC₂₀ was less than or equal to 8 mg/ml.²²⁻²³ The histamine provocative concentration causing a 25% fall in MIF₅₀ (PC₂₅MIF₅₀) was used as an arbitrary threshold of EA responsiveness; EA-HR was diagnosed when PC₂₅MIF₅₀ was less than or equal to 8 mg/ml, because we previously found that this cutoff may discriminate presence from absence of EA diseases.²⁴

Each patient was then treated with oral antimicrobials combined with topical flunisolide (25 μ g in each nostril twice daily) for 2 weeks. The choice of the antimicrobial

was based on the information available in the literature about the organisms commonly isolated from infected sinuses.^{3, 6, 9, 25-29} The first-choice antibiotic was a combination of amoxicillin (875 mg) plus clavulanic acid (125 mg) twice daily, which was expected to be effective even against an ampicillin-resistant strain of *Haemophilus influenzae*. Patients with history of allergy or adverse reactions to penicillins were given the second-choice antibiotic, which was trimethoprim (160 mg)-sulfamethoxazole (800 mg) twice daily. The third-choice antimicrobial was erythromycin (1 gm) twice daily. After 1 week, patients were required, by phone, to give a subjective evaluation of treatment efficacy. Sixteen patients who had no symptomatic improvement, underwent sinus puncture and were treated according to the result of bacteriologic culture.

Second examination

The patients were invited to attend the laboratory at the end of treatment at the same time of day. At the return appointment the subjects underwent the following procedures: (1) recording of interval history and subjective evaluation of treatment efficacy, (2) nasal lavage for cytologic examination, and (3) measurement of lung function tests and of EA and bronchial responsiveness to inhaled histamine.

Statistical analysis

Data were analyzed with a general linear model analysis system.³⁰ Descriptive analysis was used to evaluate the general characteristics of the sample. Student's

TABLE V. Mean values and SEM of baseline parametric data by response to treatment

Variable	No B-HR (n = 42)	B-HR responders (n = 29)	B-HR nonresponders (n = 17)	F
Sinusitis duration (yr)	3.00 ± 0.56	3.71 ± 0.76	6.92 ± 0.90	7.53* (B, C)
FEV ₁ (% pred)	103.2 ± 1.79	95.76 ± 2.06	97.53 ± 2.77	3.89† (A)
MEF ₅₀ (% pred)	92.21 ± 3.03	82.55 ± 4.19	74.47 ± 5.21	4.61† (A, B)
PC ₂₀ (mg/ml)‡	21.9 ± 1.07	3.89 ± 1.17	2.18 ± 1.17	103.4* (A, B, C)
PC ₂₅ MIF ₅₀ (mg/ml)‡	5.37 ± 1.17	2.57 ± 1.20	1.29 ± 1.20	20.6* (A, B)

A, Significant difference between No(B or EA)-HR and (B or EA)-HR/responders; B, significant difference between No(B or EA)-HR and (B or EA)-HR/nonresponders; C, significant difference between (B or EA)-HR/responders and (B or EA)-HR/nonresponders.

* $p < 0.001$.

† $p < 0.02$.

‡Geometric mean.

t test for unpaired data was used to compare the patients who completed the study with the dropouts. Linear regression analysis was used to assess the relationship between PC₂₀ and PC₂₅MIF₅₀ before and after treatment. Factors influencing the degree of bronchial and EA responsiveness were evaluated by multiple linear regression analysis, having as dependent variable the values of PC₂₀ or PC₂₅MIF₅₀ and as independent variables sex, atopy, smoking habits, duration of chronic sinusitis, type of sinus involved (maxillary, frontal, ethmoidal, pansinusitis), symptoms (cough, rhinorrhea, pharyngitis, postnasal drip, wheezing), nasal eosinophilia, and neutrophil score in nasal lavage.

Response to treatment

Analysis of variance was used to compare the values of PC₂₀ and PC₂₅MIF₅₀ during exacerbation of sinusitis with values observed after treatment. Patients with B-HR and/or EA-HR during exacerbation of sinusitis were classified as "responders" or "nonresponders" to treatment whether or not their PC₂₀ and/or PC₂₅MIF₅₀ at the second examination were increased over 8 mg/ml. The nonresponders were considered improved if the increase in PC₂₀ and/or PC₂₅MIF₅₀ was greater than 1 histamine dose step, the limit of PC₂₀ reproducibility.²² The characteristics of responders, nonresponders, and those who had no airway hyperresponsiveness even during exacerbation of sinusitis were compared with the chi square test for nonparametric data and the analysis of variance for parametric data (i.e., anthropometric data, sinusitis duration, prechallenge lung function tests, PC₂₀ and PC₂₅MIF₅₀).

For each test, a *p* value of 0.05 or less was considered statistically significant.

RESULTS

First examination

The characteristics of the 106 patients admitted to the study are reported in Table I. Sinusitis most frequently affected the maxillary sinuses. During exacerbation of sinusitis most of the patients complained of cough, about half had clinical evidence of pharyngitis, and one third had increased total or specific serum IgE levels, which in less than half were associated with allergic rhinitis.

Nasal lavage cells. A readable cytocentrifuge slide was obtained in 87 patients (82%). All the patients had nasal neutrophilia, which in 36 was combined with eosinophilia. Nasal eosinophilia was associated with wheezing ($r = 0.27$, $p < 0.05$) but not with atopy, rhinitis, or increased serum IgE levels.

Histamine inhalation challenge. During sinusitis exacerbation 76 of the 106 patients had EA-HR, which in 30 was the predominant abnormality and in 46 was associated with B-HR. The values of PC₂₀ were closely related to those of PC₂₅MIF₅₀ ($r = 0.75$, $p < 0.001$) (Fig. 1). In patients with predominant EA-HR the course of EA constriction could be followed up to the highest histamine concentration. The analysis of the dose-response curve showed that MIF₅₀ decrease was dose-dependent up to a 50% fall from baseline, and then showed a plateau.

The study was completed in 88 patients; seven patients were excluded because of poor compliance with treatment, and 11 were lost to follow-up.

No EA-HR (n = 12)	EA-HR responders (n = 58)	EA-HR nonresponders (n = 18)	F
2.25 ± 0.45	3.55 ± 0.54	6.67 ± 0.85	7.88* (B, C)
107.2 ± 3.18	99.55 ± 1.59	95.00 ± 2.09	3.97† (A, B)
98.17 ± 5.38	86.41 ± 2.79	74.61 ± 5.23	4.48† (B, C)
28.2 ± 1.10	6.46 ± 1.15	6.30 ± 1.26	9.69* (A, B)
16.6 ± 1.10	2.24 ± 1.12	6.17 ± 1.12	29.74* (A, B, C)

The 18 patients who were excluded from the study had characteristics very similar to those of patients who completed the study, apart from a significantly higher PC₂₀ (geometric mean, 15.14 ± 1.26 mg/ml vs 7.94 ± 1.12 mg/ml, $t = 2.168$, $p < 0.05$).

Any further analysis was performed on the data from the patients who completed the study. The results of multiple linear regression analysis on factors influencing the degree of bronchial or EA responsiveness during sinusitis exacerbation are shown in Table II. PC₂₅MIF₅₀ was significantly lowered by female sex and presence of cough and pharyngitis, PC₂₀ by presence of wheeze and pharyngitis, female sex, and eosinophilia in nasal lavage. No other factor had significant influence on bronchial or EA responsiveness.

Second examination

Most of the patients reported an improvement in symptoms after treatment. The mean values of FEV₁, MEF₅₀, MIF₅₀, PC₂₀, and PC₂₅MIF₅₀ and the mean values of neutrophil score in nasal lavage, during exacerbation of sinusitis and after treatment, are reported in Table III. After treatment, there was a significant improvement in both EA and bronchial responsiveness and a significant decrease in nasal neutrophilia, whereas prechallenge lung function test results were nearly unchanged. The improvement in PC₂₅MIF₅₀ was closely related with that of PC₂₀ ($r = 0.36$, $p < 0.001$) and with the decrease in neutrophil score in nasal lavage ($r = 0.25$, $p < 0.05$).

The analysis of individual values of PC₂₅MIF₅₀ showed that 12 patients had no EA-HR either before or after treatment, 58 of the 76 patients with EA-HR during exacerbation of sinusitis were responders (i.e., had a PC₂₅MIF₅₀ over 8 mg/ml, the arbitrary cutoff for defining EA-HR), and 16 of the 18 nonresponders were improved (i.e., had a

PC₂₅MIF₅₀ increase greater than 1 doubling dose). The analysis of individual values of PC₂₀ showed that 42 patients had no B-HR either before or after treatment. Twenty-nine of the 46 patients with B-HR at the first examination were responders, and 12 of the 17 nonresponders were improved. The comparisons among responders, nonresponders, and nonhyperresponsive subjects are shown in Table IV for nonparametric data and in Table V for parametric data. Among patients with B-HR, nonresponders, as compared with responders, had significantly greater prevalence of wheezing and nasal eosinophilia, longer duration of sinusitis, and lower PC₂₀ values (but similar PC₂₅MIF₅₀ values) during exacerbation of sinusitis. Among patients with EA-HR, nonresponders had significantly greater prevalence of wheezing and longer duration of sinusitis, lower MIF₅₀ values, and higher PC₂₅MIF₅₀ values (but similar PC₂₀ values) than responders.

No significant difference in age, smoking habits, prevalence of atopy, nasal polyposis, or type of sinusitis was found between the two groups.

DISCUSSION

In this study we examined the relationship between EA and bronchial responsiveness in patients with chronic sinusitis, during exacerbation of the disease and after treatment with oral antibiotics and nasal flunisolide. We used MIF₅₀ as an arbitrary index of EA responsiveness because maximal inspiratory flows are known to be much more sensitive than FEV₁ in detecting constriction of the EA,¹⁹⁻²¹ and we defined as hyperresponsive (EA-HR) those patients who showed a marked decrease in MIF₅₀ (after the very first histamine inhalation) at low histamine concentrations.

The main findings of the study are that during exacerbation of sinusitis most of the patients

(86%) had EA-HR, which in two thirds of them was combined with B-HR; both B-HR and EA-HR were strongly associated with presence of pharyngitis and were reversed in most of the patients after treatment with antibiotics and nasal flunisolide. Bronchial threshold was closely related to EA threshold, both before and after treatment.

In patients in whom EA-HR was not associated with significant bronchoconstriction, according to the challenge protocol, the course of EA narrowing could be followed up to the highest histamine concentration. This allowed us to verify that MIF_{50} , the arbitrary index of EA response, decreased in a dose-dependent fashion up to a 50% drop from baseline and then reached a plateau. Because a further decrease in EA caliber would have produced serious respiratory difficulty, it is plausible that counterbalancing mechanisms were activated at this point.

The close relationship between $PC_{25}MIF_{50}$ and PC_{20} , found either during exacerbation of sinusitis or after treatment, suggests an interdependence between bronchial and EA thresholds. Several arguments arise from our findings in favor of the hypothesis that B-HR was the effect rather than the cause of EA dysfunction. First, the drop in MIF_{50} during the histamine inhalation challenge was generally earlier and greater than that of FEV_1 . Second, during exacerbation of sinusitis B-HR had a prevalence much lower than EA-HR (43% vs 72%) and was invariably associated with EA-HR. Third, both EA-HR and B-HR were strongly associated with clinical evidence of pharyngitis. This suggests that airway hyperresponsiveness in sinusitis might depend on pharyngobronchial reflexes triggered by seeding of the inflammatory process into the pharynx, through postnasal drip of mediators and infected material from affected sinuses. This hypothesis is supported by the observation of Irvin,¹² in experimental sinusitis, that blocking postnasal drip prevented the development of B-HR. The finding that treatment of sinusitis reversed B-HR, as well as EA-HR, in most of the patients and that the increase in PC_{20} was closely related to that in $PC_{25}MIF_{50}$, further supports the cause-and-effect relationship between EA and bronchial responsiveness. In fact, it seems unlikely that a low dose of a poorly absorbable corticosteroid inhaled through the nose could have had a therapeutic effect in the bronchi. On the other hand, the analysis of bronchoalveolar lavage fluid and lung histologic features in an animal model of sinusitis failed to demonstrate any consistent bronchial inflammation.¹² It seems more plausible that

treatment decreased pharyngeal inflammation by decreasing the quantity of inflammatory mediators leaked from the sinuses and/or by postnasal dripping of flunisolide into the pharynx. These considerations suggest that the increase in bronchial threshold after treatment of sinusitis might depend on attenuation of the pharyngobronchial reflex.

Although the mechanisms through which pharyngeal inflammation triggers reflex bronchoconstriction have not been clarified, experimental observations indicate the involvement of activated neutrophils.³¹ The close relationship between the improvement of $PC_{25}MIF_{50}$ and the decrease of neutrophils in nasal lavage found in our study is in agreement with this hypothesis.

Despite the sharp increase in the mean values of PC_{20} and $PC_{25}MIF_{50}$ observed after treatment, about 20% of the patients were still hyperresponsive to histamine. Although subjects with documented history of asthma, chronic bronchitis, bronchiectasis, and a recently reported episode of the common cold or flu syndrome had not been admitted to the study, we cannot exclude that in these patients, conditions known to increase airway responsiveness coexisted with sinusitis. For example, in the absence of specific viral diagnostic tests, a viral infection of the upper respiratory tract sustaining both EA-HR and B-HR and triggering an exacerbation of sinusitis cannot be excluded with certainty, particularly if we consider that virus-induced B-HR usually requires more than 2 weeks to resolve.³²

An even more plausible explanation is that nonresponders had subclinical asthma. This possibility is supported by the finding that B-HR nonresponders as compared with B-HR responders, had a significantly higher prevalence of wheeze and nasal eosinophilia and lower PC_{20} values during exacerbation of sinusitis. Whether these abnormalities were the expression of a pathogenetic event involving the whole respiratory tract or the consequence of sinusitis cannot be ascertained. The second hypothesis is supported by the finding that nonresponders had significantly longer duration of sinusitis, which suggests that in long-standing sinusitis B-HR may be sustained by mechanisms more complex than the pharyngobronchial reflex, which might ultimately lead to clinical asthma.

In conclusion, the results of this study indicate that B-HR in sinusitis is strongly associated with EA dysfunction and may be sustained by constrictive reflexes originating in pharyngeal receptors made hypersensitive by local seeding of the inflammatory process. However, the role of pharyngo-

bronchial reflexes in sinusitis should be confirmed by physiologic studies examining the effect produced by isolated EA stimulation or of EA deafferentation on bronchial patency. Moreover, long-term follow-up studies are needed to determine whether B-HR represents the preclinical stage of the sinusitis-asthma complex and whether the development of asthma may be prevented by proper and early treatment of sinusitis.

REFERENCES

- Berman SZ, Mathison DA, Stevgenson DD, Usselman JA, Shore S, Tan EM. Maxillary sinusitis and bronchial asthma: correlation of roentgenograms, cultures and thermograms. *J ALLERGY CLIN IMMUNOL* 1974;53:311-7.
- Slavin RG. Relationship of nasal disease and sinusitis to bronchial asthma. *Ann Allergy* 1982;49:76-80.
- Rachelefsky GS, Katz RM, Siegel SCS. Chronic sinus disease with associated reactive airway disease in children. *Pediatrics* 1984;73:526-9.
- McFadden ER. Nasal-sinus-pulmonary reflexes and bronchial asthma. *J ALLERGY CLIN IMMUNOL* 1986;78:1-3.
- Adinoff AD, Irvin CG. Upper respiratory tract disease and asthma. *Semin Respir Med* 1987;8:308-14.
- Rachelefsky GS, Katz RM, Siegel SCS. Chronic sinusitis in children with respiratory allergy: the role of antimicrobials. *J ALLERGY CLIN IMMUNOL* 1982;69:382-7.
- Friedman R, Ackerman M, Wald ER, Cassellrant M, Friday G, Fireman P. Asthma and bacterial sinusitis in children. *J ALLERGY CLIN IMMUNOL* 1984;74:185-9.
- Cummings NP, Wood RN, Lere JL, Adinoff AD. Effect of treatment of rhinitis/sinusitis on asthma: results of a double blind study [Abstract]. *Pediatr Res* 1983;17:373.
- Slavin RG, Cannon RE, Friedman WH, Palitang E, Sundaram M. Sinusitis and bronchial asthma. *J ALLERGY CLIN IMMUNOL* 1980;66:250-7.
- Juntunen K, Tarkkanen J, Makinen J. Caldwell-luc operation in the treatment of childhood bronchial asthma. *Laryngoscope* 1984;94:249-51.
- Phipatanakul CS, Slavin RG. Bronchial asthma produced by paranasal sinusitis. *Arch Otolaryngol* 1974;100:109-12.
- Irvin CG. Sinusitis and asthma: an animal model. *J ALLERGY CLIN IMMUNOL* 1992;90:521-33.
- Miller D, Hyatt E. Evaluation of obstructing lesions of the trachea and larynx by flow-volume loops. *Am Rev Respir Dis* 1973;108:475-81.
- Shim C, Corro P, Park SS, Williams MH Jr. Pulmonary function studies in patients with upper airway obstruction. *Am Rev Respir Dis* 1972;106:233-8.
- Acres JC, Kryger MH. Upper airway obstruction. *Chest* 1981;80:207-11.
- Bucca C, Rolla G, Scappaticci E, Baldi S, Caria E, Oliva A. Histamine hyperresponsiveness of the extrathoracic airway in patients with asthmatic symptoms. *Allergy* 1991;46:147-53.
- Ferris BG. Epidemiology standardization project. *Am Rev Respir Dis* 1978;118 (part 2):1-88.
- Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late response to antigen challenge. *Am Rev Respir Dis* 1988;138:406-12.
- Quanjer PH, ed. Standardized lung function testing. *Bull Eur Physiopathol Respir* 1983;19(Suppl. 5):1-91.
- Chai H, Farr RS, Froelich LA, et al. Standardization of bronchial inhalation challenge procedures. *J ALLERGY CLIN IMMUNOL* 1975;56:323-7.
- Habib MP, Pare' PD, Engel LA. Variability of airway responses to inhaled histamine in normal subjects. *J Appl Physiol* 1979;47:51-8.
- Hargreave FE, Ramsdale EH, Dolovich J. Measurement of airway responsiveness in clinical practice. In: Hargreave FE, Woolcock AJ, eds. *Airway responsiveness measurements and interpretation*. Mississauga, Ontario, Canada: Astra, 1985:122-6.
- Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977;7:235-43.
- Bucca C, Rolla G, Bugiani M, Oliva A, Scappaticci E, Brussino L. Accuracy of the MIF50 histamine dose-response curve to assess extrathoracic airway hyperresponsiveness (EA-HR) [Abstract]. *Am Rev Respir Dis* 1990;141:A730.
- Jousimies-Somer HR, Savolainen S, Ylikoski JS. Comparison of the nasal bacterial floras in two groups of healthy subjects and in patients with acute maxillary sinusitis. *J Clin Microbiol* 1989;27:2736-43.
- Jousimies-Somer HR, Savolainen S, Ylikoski JS. Bacteriological findings of acute maxillary sinusitis in young adults. *J Clin Microbiol* 1988;26:1919-25.
- Wald ER, Chiponis D, Ledesma-Medina J. Comparative effectiveness of amoxicillin and amoxicillin-clavulanate potassium in acute paranasal sinus infection in children: a double-blind, placebo-controlled trial. *Pediatrics* 1986;77:795-800.
- Friday GA, Fireman P. Sinusitis and asthma: clinical and pathogenetic relationships. *Clin Chest Med* 1988;9:557-65.
- Gwaltney JM Jr, Scheld WM, Sande MA, Sydnor A. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a fifteen-year experience at the University of Virginia and review of other selected studies. *J ALLERGY CLIN IMMUNOL* 1992;90:457-62.
- Aitkin M, Anderson D, Francis B, Hinde J. *Statistical modelling in GLIM*. Oxford: Oxford Scientific Publications, Clarendon Press, 1979:119-213.
- Corren J, Honour J, Irvin CG. Activated neutrophils are crucial for the development of airway hyperresponsiveness in sinusitis [Abstract]. *Am Rev Respir Dis* 1990;141:A177.
- Busse WW. Infections. In: Barnes PJ, Rodger IW, Thomson NC, eds. *Asthma: basic mechanisms and clinical management*. London: Academic Press, 1989:483-502.