

Histamine hyperresponsiveness of the extrathoracic airway in patients with asthmatic symptoms

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Functional abnormalities of the extrathoracic airway (EA) may produce symptoms mimicking bronchial asthma. We assessed the bronchial (B) and EA responsiveness to inhaled histamine in 40 patients with asthmatic symptoms and in nine asymptomatic controls. FEV₁ and maximal mid-inspiratory flow (MIF₅₀) were used as index of bronchial and EA narrowing. Hyperresponsiveness of the intra-(BHR) or extra-(EA-HR) thoracic airway was diagnosed when the provocative concentrations of histamine (PC₂₀FEV₁ or PC₂₅MIF₅₀) were < 8 mg/ml. Fiberoptic laryngoscopy was performed in nine patients and three controls. The glottal region was measured at mid-volume of maximal inspiration (AgMI) and expiration (AgME) before and after histamine. Predominant EA-HR was found in 13 patients, predominant BHR in 12, equivalent BHR and EA-HR in another 12; no significant airway narrowing was observed in three patients and in the nine controls. EA-HR was significantly associated with female sex, sinusitis, post-nasal drip, dysphonia; BHR with atopy, wheezing and lower MEF₅₀. The percent change in AgMI after histamine was closely related to the PC₂₅MIF₅₀ ($r = 0.87$, $P < 0.001$), that of AgME to the PC₂₀FEV₁ ($r = 0.78$, $P < 0.01$). These findings suggest that the assessment of EA responsiveness may be useful in the evaluation of asthmatic symptoms, especially in patients with no BHR.

Key words: asthmatic symptoms; bronchial provocation tests; extrathoracic airway hyperresponsiveness.

CLINICAL ASPECTS

We investigated whether assessment of the responsiveness of the extrathoracic airway (EA) would help in the evaluation of patients with asthmatic symptoms. To this aim, we recorded the flow-volume loop, in addition to the FEV₁, during histamine challenge, and used the mid-inspiratory flow (MIF₅₀) as an arbitrary index of EA responsiveness. We examined 40 patients who had complained of episodic dyspnea combined with wheezing and/or cough for at least 2 months and had no previous medical diagnosis of bronchial asthma. All except three patients had airway hyperresponsiveness that in 13 was limited to the EA, in 12 to the bronchi and in 12 involved both intra- and extrathoracic airways. EA hyperresponsiveness was strongly associated with symptoms and diseases of the upper respiratory tract, such as post-nasal drip, dysphonia and sinusitis. Bronchial hyperresponsiveness was strongly associated with wheezing, atopy and lower MEF₅₀. In three subjects the symptoms were not associated with any airway hyperresponsiveness. Our findings suggest that EA hyperresponsiveness is a distinct pathologic entity that may produce symptoms mimicking bronchial asthma. This abnormality seems to be sustained by chronic inflammatory diseases of the upper respiratory tract. Further studies are needed to confirm our results and to assess whether proper treatment of the underlying disease would result in relief of symptoms and of airway hyperresponsiveness.

In the absence of lung function abnormalities and a documented history of bronchial asthma, non-specific bronchial challenges are widely employed to evaluate patients who complain of

asthmatic symptoms. Prior investigations demonstrated a strong association between chronic symptoms, such as cough, episodic wheezing and dyspnea, and bronchial hyperresponsiveness (BHR) (2, 11, 21, 23, 27). However, as this association is far from certain, the symptom etiology remains unexplained in a great many patients. We wondered whether in these cases symptoms could originate from an increased responsiveness of the extrathoracic airway (EA). Our hypothesis was supported by several reports on patients in whom functional abnormalities in the EA produced symptoms mimicking bronchial asthma in the absence of BHR (6, 7, 10, 22, 24). Unfortunately, the responsiveness of the extrathoracic airway had not been investigated as the FEV₁, commonly used to assess airway response during conventional challenge tests, is not as sensitive as the inspiratory flow-volume curve for detecting EA narrowing (1, 12, 17, 18, 25). By recording the flow-volume loop during histamine challenge, Zach (30) found that children with pseudocroup had a marked fall in inspiratory flow, which he interpreted as suggestive of hyperresponsiveness of the extrathoracic airway (EA-HR).

We investigated whether recording the inspiratory flow-volume curve as well as the FEV₁ during histamine inhalation challenge, could help in the evaluation of patients with asthmatic symptoms. To this aim, we examined 40 patients who had had episodic dyspnea associated with cough and/or wheezing for at least 2 months, but had normal lung function and no previous medical diagnosis of asthma. Nine asymptomatic healthy subjects served as controls.

We performed fiberoptic laryngoscopy in a subgroup of nine patients and three controls, to verify whether the changes in inspiratory flow induced by histamine corresponded to changes in the glottal region.

METHODS

Forty subjects (20 women and 20 men) with a 2-month history of episodic dyspnea associated with wheezing and/or cough were selected for examination by the following criteria: a) base-

line lung volume and airflow within the normal range, no evidence of EA obstruction on the flow/volume loop (18) and mid-inspiratory/mid-expiratory flow ratio (MIF/MEF) > 0.95, b) no previous medical diagnosis of asthma, no acute airway infection in the last 2 months, c) no reaction to inhalation of buffered saline, and d) no treatment with anti-histaminic drugs, DSCG or corticosteroids in the last 2 months. Inhaled beta₂-adrenergic agonists were withdrawn 2 days before the challenge. Nine asymptomatic, non-smoking, non-atopic normal subjects (5 women and 4 men) in the same age range, served as controls.

A detailed questionnaire about symptoms and diseases of the upper and lower respiratory tract was administered to all the patients, and skin prick testing for the most common aeroallergens was performed.

Lung volumes and airflow rates were measured in patients and controls using a computerized water-sealed spirometer (BAIRES Biomedin, Padova, Italy). FVC, FEV₁, MIF₅₀, MEF₅₀ and MIF/MEF were calculated from the best of five reproducible curves. Reference values were obtained from Quanjer (20) for FVC and FEV₁ and from Knudson et al. (16) for MEF₅₀. Five reproducible flow-volume loops (with an FVC which did not differ > 5% from its highest value) were obtained before the aerosol challenge, to establish the 95% confidence limits of control MIF₅₀ for each subject. The coefficient of variation ranged from 5.4 to 9.2%.

Each subject underwent a multistep histamine inhalation challenge, using the ATS procedure (5). Histamine was delivered in doubling concentrations from 0.25 to 32 mg/ml, by a compressed air nebulizer controlled by a breath actuated dosimeter (MEFAR MB3, Brescia, Italy). The dosimeter was set to nebulize for 0.6 s; the mass median diameter of dried particles was 1.65 µm (GSD 3.3). Each dose of histamine was inhaled by taking five slow vital capacity breaths from the nebulizer. Two min after each inhalation, three consecutive measurements of FEV₁ and flow-volume loop were obtained; the interval between one dose and the next was about 5 min. The test was stopped

when FEV_1 had dropped by 20% or the highest concentration was reached. FEV_1 was used as an index of bronchial narrowing, MIF_{50} of EA narrowing. To account for changes in FVC, MIF_{50} was calculated by matching the flow/volume loops at total lung capacity. This is justified by the observation that TLC does not change by more than 5% after acute induced bronchoconstriction (13). The responses of FEV_1 and MIF_{50} were expressed as the percent fall from baseline and were plotted against log-dose of histamine. The histamine provocative concentration for EA was arbitrarily established as the dose associated with a 25% fall in MIF_{50} ($PC_{25}MIF_{50}$), that for intrathoracic airways as the dose causing a 20% fall in FEV_1 ($PC_{20}FEV_1$). EA-HR and BHR were diagnosed when $PC_{25}MIF_{50}$ or $PC_{20}FEV_1$ were 8 mg/ml or lower.

Fiberoptic laryngoscopy was performed within 1 month in three controls and nine patients, who gave their informed consent. The day before the examination, histamine challenge was repeated to assess the reproducibility of $PC_{25}MIF_{50}$. The fibroscope was passed through the nostrils and positioned 2 cm above the vocal cords. The mucosa of nose and pharynx, but not of larynx, were anesthetized with topical 2% lignocaine. The glottal movements were video recorded. To relate glottal size to the

respiratory cycle, subjects breathed through a mouthpiece in a pneumotacograph. After 5 min of quiet breathing the subjects performed a forced expiration from TLC to residual volume followed by a forced inspiration to TLC. The maneuver was repeated at least 3 times. The glottal region was measured during quiet breathing and at mid-volume of maximal expiration (AgME) and inspiration (AgMI) applying the formula used by Collett et al. (9), which accounts for the variations in the distance between the glottis and the tip of the fibroscope: $real\ AG = screen\ AG \times real\ antero-posterior\ diameter\ (APg)^2 / screen\ APg^2$.

The real APg corresponded to the height of the triangular air space between the vocal cords, measured in baseline at mid-volume of a forced inspiration with the fibroscope 2 cm above the cords. The same protocol was repeated after 5 deep breaths of nebulized histamine at the concentration corresponding to the $PC_{25}MIF_{50}$ or to the $PC_{20}FEV_1$, depending on the type of response previously assessed; the three controls inhaled 32 mg/ml.

Statistical analysis: Student's *t* test for unpaired data was used to evaluate the differences in lung function tests, $PC_{20}FEV_1$ and $PC_{25}MIF_{50}$. The chi-square test was used to evaluate the association of the type of histamine response and dis-

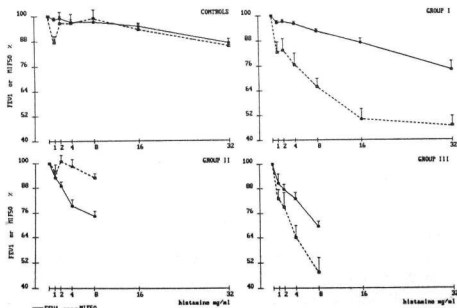


Fig. 1. Histamine dose-response curves for FEV_1 (solid line) and MIF_{50} (dashed line) in controls and in the 3 groups of patients.

Table 1.

Mean values and (SEM) of age and lung function tests and geometric means of $PC_{20}FEV_1$ and $PC_{25}MIF_{50}$ in control subjects and in the three groups of patients

	Controls <i>n</i> = 9	Group 1 <i>n</i> = 13	Group 2 <i>n</i> = 12	Group 3 <i>n</i> = 12
Age (years)	32.6 (2.9)	36.5 (3.0)	32.8 (4.0)	37.9 (3.5)
VC % pred.	105 (4.0)	103 (3.2)	97 (4.2)	98 (3.0)
FEV ₁ % pred.	104 (3.5)	99 (1.8)	92 (3.6)	96 (3.0)
MEF ₅₀ % pred.	97 ^{b,c} (5.7)	96 ^{b,c} (4.0)	71 (8.0)	78 (6.6)
MIF/MEF baseline	1.00 ^b (0.08)	0.98 ^b (0.07)	1.57 (0.20)	1.10 (0.17)
histamine	1.10 ^{a,b} (0.10)	0.70 ^{b,c} (0.06)	3.57 ^c (0.61)	1.16 (0.16)
$PC_{20}FEV_1$ mg/ml	NR	NR	4.17 (1.17)	2.40 (1.38)
$PC_{25}MIF_{50}$ mg/ml	NR	3.39 (1.38)	NR	1.58 (1.29)

% pred. = percent of predicted value. NR = no significant response. ^aSignificantly different from Group 1. ^bSignificantly different from Group 2. ^cSignificantly different from Group 3.

tribution of symptoms and diseases. The linear regression analysis was used to assess the reproducibility of $PC_{25}MIF_{50}$ on 2 separate days and to evaluate the relationship between the changes (as percent of baseline) in AgME and AgMI after histamine and the $PC_{20}FEV_1$ or $PC_{25}MIF_{50}$, respectively. For all the tests, a *P* value < 0.05 was considered to be statistically significant.

RESULTS

The dose-response curves relative to FEV₁ and MIF₅₀ showed three different patterns of histamine hyperresponsiveness which are shown in Fig. 1. Based on these findings the patients were arbitrarily divided into three groups:

Group 1 (13 patients) with predominant EA-HR, characterized by a significant decrease in MIF₅₀ and MIF/MEF ratio, but not in FEV₁.

Group 2 (12 patients) with predominant BHR, characterized by a significant decrease in FEV₁ but not in MIF₅₀ and by an increase in MIF/MEF ratio. In seven subjects bronchoconstriction was associated with increased MIF₅₀.

Group 3 (12 patients) with equivalent EA-HR and BHR, characterized by a parallel decrease in MIF₅₀ and FEV₁.

In three patients and in the nine controls no significant change in FEV₁ and MIF₅₀ was produced by histamine.

In patients with BHR (Groups 1 and 3), the challenge was stopped within the histamine concentration of 8 mg/ml.

Age range and mean values of baseline lung function tests, MIF/MEF ratio before and after histamine, and the geometric means of $PC_{20}FEV_1$ and $PC_{25}MIF_{50}$ observed in controls and in three groups of patients are shown in Table 1.

The distribution of symptoms and diseases in the three groups of patients were significantly different, see Table 2. EA-HR was strongly associated with chronic sinusitis, post-nasal drip, dysphonia and female sex, whereas BHR was associated with lower MEF₅₀, higher MIF/MEF ratio, atopy, wheezing and male sex. Apart from episodic dyspnea, cough was the most frequently reported symptom and had a slightly lower prevalence in Group 2. The highest prevalence of abnormalities was found in patients with combined BHR and EA-HR. Among patients with neither BHR nor EA-HR, none was a smoker or atopic or suffered from sinusitis; all three complained of dyspnea and cough, one had wheezing, one post-nasal drip. The reproducibility of PC₂₅MIF₅₀ over 2 different days, assessed in 12 subjects, was very good ($r = 0.953$, $P < 0.0001$).

Fiberoptic laryngoscopy was done in four patients of Group 1, two of Group 2, three of Group 3 and in three controls. In baseline conditions, no abnormality in structure and motility of the vocal cords was observed in patients and controls.

After histamine, the seven patients with EA-HR (Groups 1 and 2), showed marked mucosal edema, pharyngoconstriction and adduction of the vocal cords during the forced inspiratory maneuver. This reaction was often accompanied by a stridor. No significant change in the AgMI was observed in patients of Group 2 and

in controls. The expiratory glottal region after histamine decreased only in the five patients with BHR. In the majority of subjects the change in AgMI was closely related to PC₂₅MIF₅₀ ($r = 0.87$, $P < 0.001$), that of AgME to PC₂₀FEV₁ ($r = 0.78$, $P < 0.01$), (Fig. 2).

DISCUSSION

Respiratory physicians are often faced with patients who complain of asthmatic symptoms in the absence of a spontaneous or induced bronchoconstriction. We investigated whether in these cases the symptoms might originate from receptors in the extrathoracic airway. To this aim we assessed the bronchial and EA responsiveness to inhaled histamine (using the maximal mid-inspiratory flow as an index of EA narrowing) in 40 patients who suffered from accessional dyspnea associated with cough and/or wheezing. We observed three types of response: 13 patients (Group 1) had a dose-dependent decrease in MIF₅₀ with no bronchoconstriction, suggestive of hyperresponsiveness limited to the extrathoracic airway, 12 patients (Group 2) had a decrease in FEV₁ with no change in MIF₅₀, suggestive of isolated bronchial hyperresponsiveness, and 12 patients (Group 3) had a decrease of MIF₅₀ and FEV₁, suggesting hyperresponsiveness of the intra- and

Table 2.

General characteristics and symptom distribution in the three groups of patients

Per cent	Group 1 (EA-HR)	Group 2 (BHR)	Group 3 (EA-HR + BHR)
Females	77	17 ^{a,c}	67
Smokers	23	17	25
Atopy	23 ^{b,c}	50	50
Cough	85	75	92 ^b
Phlegm	23	33	92 ^{a,b}
Dysphonia	85	33 ^{a,c}	92
Postnasal drip	62	33 ^{a,c}	83 ^a
Sinusitis	46	17 ^{a,c}	92 ^{a,b}
Wheezing	23 ^{b,c}	75	92 ^b

^a Significantly different from Group 1. ^b Significantly different from Group 2. ^c Significantly different from Group 3.

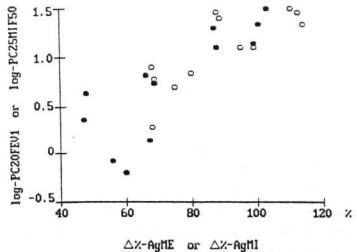


Fig. 2. Relationship between the percent change in mid-inspiratory glottal region after histamine (%-AgMI) and log-PC₂₅MIF₅₀ (open circles) and between the change in mid-expiratory glottal region (%-AgME) and log-PC₂₀FEV₁ (closed circles).

extrathoracic airways. In only three patients were the symptoms not associated with any airway hyperresponsiveness. Interestingly, each type of response was characterized by a definite cluster of features. In agreement with the literature, bronchial hyperresponsiveness was strongly associated with lower baseline expiratory flow (8, 27), wheezing (21, 23, 27) and positive allergy prick tests (4, 29). In contrast, EA hyperresponsiveness was strongly associated with diseases and symptoms of the extrathoracic airway, such as sinusitis, post-nasal drip and dysphonia. The highest prevalence of symptoms was found in Group 3, with combined BHR and EA-HR. These patients had characteristics very similar to those of the children with recurrent croup described by Zach (30).

EA hyperresponsiveness was much more frequent in women. The tendency of women to have constrictive reactions in the EA has already been indicated in reports on patients with severe paroxysmic glottal closure (6, 7, 10, 22, 24) and has been attributed to a psychosomatic illness (24). This does not appear so in our patients as their EA-HR had never presented as a medical emergency, was often associated with extrathoracic airway disease and was combined with BHR in half of the cases.

Indeed, the use of $PC_{25}MIF_{50}$ as an index of EA responsiveness is totally arbitrary, and further studies are needed to better estimate its accuracy in relation with symptoms. However, in the subgroup of patients who underwent laryngoscopy, we could demonstrate that its reproducibility over several days was fairly good. Moreover, the close relationship between the $PC_{25}MIF_{50}$ and the change in the inspiratory glottal region induced by histamine suggests that the test is sensitive enough to detect EA responsiveness.

Although the pathogenesis of extrathoracic airway hyperresponsiveness is presently unknown, our findings suggest that chronic inflammation, through mediator release and mucosal damage, may be the underlying trigger, as is supposed for asthma associated with nasal diseases (15, 26). The marked edema and constriction of the pharynx and glottis seen at laryngoscopy after histamine in patients with

EA hyperresponsiveness suggest the activation of local reflexes having nervous receptors as the afferent pathway, and skeletal muscles, glands and blood vessels as the effector tissues. A reflex constriction of the larynx (28) and bronchi (19, 28) has been demonstrated after laryngeal stimulation, as well as after induced bronchoconstriction (9, 14).

In conclusion, our results suggest that the hyperresponsiveness of the extrathoracic airway is a distinct pathological entity that may produce symptoms mimicking bronchial asthma. The high prevalence of chronic diseases of the upper airways found in patients with EA-HR suggests that inflammation may be the triggering factor for this functional abnormality. The finding that in about one third of the patients it was combined with bronchial hyperresponsiveness suggests that EA-HR may have an important role in the pathogenesis of asthma associated with nasal disease (26). Further studies are needed to confirm this hypothesis and to assess whether a proper treatment of the underlying EA disease may result in relief of symptoms and airway hyperresponsiveness.

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