Clinical Significance of Nonspecific Bronchial Hyperresponsiveness in Asthma*

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Measurement of nonspecific bronchial hyperresponsiveness remains largely a research tool in asthma, and its usefulness in the assessment and management of asthma is poorly defined. We studied the relationship of bronchial hyperresponsiveness to the clinical severity of asthma in 54 asthmatic subjects. In order to find out whether measurement of bronchial hyperresponsiveness could be used to predict future symptomatic status and requirements for drugs, ten patients were followed for three months. We found that there was no correlation between the clinical severity of asthma and the degree of bronchial hyperresponsiveness and, also, that the latter could not be used as a prognostic indicator of future symptomatic status and drug requirements. Measurement of nonspecific bronchial hyperresponsiveness, therefore, adds little to the assessment and management of asthma.

(Chest 1989; 96:596-600)

Measurement of nonspecific bronchial hyperresponsiveness is a well-accepted and widely applied tool in research on asthma today; however, the value of this measurement in the day-to-day management of asthma is poorly defined. Its correlation with the clinical severity of the disease is not well established. While some workers have suggested that subjects with a greater degree of nonspecific bronchial responsiveness had more severe asthma, others have disagreed. Debate also exists over the prognostic value of bronchial hyperresponsiveness (as defined during bronchoprovocation tests), as to whether it can be used to determine future requirements for treatment. The present study was performed to determine whether bronchial hyperresponsiveness reflected the clinical severity of asthma retrospectively and whether its measurement could be used as an objective prognostic indicator of future symptoms and requirements for drugs.

MATERIALS AND METHODS

Fifty-four asthmatic subjects, diagnosed by history, physical examination, and demonstration of reversibility of airway obstruction were included in the study. Their ages ranged from 12 to 57 years. These were 30 male and 24 female subjects. All of the patients had chronic perennial intrinsic asthma. The duration of the disease varied from 1 to 22 years. Drugs required to control their symptoms included albuterol (salbutamol; oral or inhaled) and theophylline. A few patients had been receiving corticosteroids for most of the year. Many others required occasional to several short courses of corticosteroids to control acute exacerbations of asthma.

Based on Mansmann's method, Rubinfeld and Pain developed a scoring system for the assessment of the severity of asthma. We adopted the latter system, with some modification, to assess the severity of asthma over the past one year. The score took into account of the following factors (with maximal scores in brackets): (1) frequency and severity of wheezing (200); (2) impairment of daily activities (100); (3) absenteeism from school or work (100); (4) sleep disturbance (100); and (5) requirements for medication (200). Thus, the minimum possible score was zero, and the maximum was 700. The severity of asthma was defined as mild (total score less than 233), moderate (234-467), and severe (467-700). The number of subjects in each group was 17, 19, and 18, respectively.

Specific airway conductance was measured in a constant-volume body plethysmograph using a quiet-breathing technique. This technique is highly reproducible, is easy to perform, and gives the 

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The histamine scores required. The daily intake of drugs (inhaled or oral albuterol, theophylline, and corticosteroids) was also scored according to the amount required. At the end of the three-month period of study, the percentage of asymptomatic days, symptom scores, and drug intake scores were calculated from the patients' records.

For statistical analysis, logarithmic transformation of values for histamine PD_{35} Gaw/VL was done. The geometric means (±SD) in the three groups (namely, mild, moderate, and severe asthma) were compared by analysis of variance. The scores for the severity of asthma in the three groups were compared with the Kruskal-Wallis nonparametric test. Correlations of histamine PD_{35} Gaw/VL with percentage of asymptomatic days, symptom scores, and drug scores were determined by the method of least-squares regression.

RESULTS

Figure 1 shows the geometric mean (GM) of the values for histamine PD_{35} Gaw/VL (in milligrams per milliliter) in the three groups (severity of asthma: mild, moderate, and severe). The GM ± SD was, respectively, 0.189 ± 0.28 mg/ml, 0.153 ± 0.3 mg/ml, and 0.192 ± 0.39 mg/ml. Analysis of variance did not reveal any significant differences among these (p<0.05).

The range of values for histamine PD_{35} Gaw/VL in the three groups was as follows: mild, 0.04 to 0.92 mg/ml; moderate, 0.03 to 1.05 mg/ml; and severe, 0.03 to 3.3 mg/ml. The individual values in the three groups are shown in Figure 2. The correlations between histamine PD_{35} Gaw/VL and the percentage of asymptomatic days (Fig 3; r = −0.091), the asthma symptom scores (Fig 4; r = 0.163), and the drug intake scores (Fig 5; r = −0.271) were not significant (p>0.05) for each correlation.

The Gaw/VL (mean ± SD) in the three groups (mild, moderate, and severe asthma) was, respectively, 0.16±0.04, 0.12±0.04, and 0.09±0.3, with the difference being statistically significant by analysis of

![Figure 1. Geometric means of values for histamine PD_{35} Gaw/VL in three groups.](image1)

![Figure 2. Distribution of values for histamine PD_{35} Gaw/VL in three groups.](image2)

![Figure 3. Correlation between histamine PD_{35} Gaw/VL and percentage of asymptomatic days.](image3)
variance ($p<0.01$). The Gaw/VL in the severe group was significantly less compared to the mild ($p<0.01$) and moderate groups ($p<0.002$). The difference between the mild and moderate group was also significant ($p<0.01$). No significant correlation was found between baseline Gaw/VL and the values for $PD_{35}$ Gaw/VL ($n=54$; $r=0.21$; $p>0.05$). The mean ($\pm SD$) scores of asthma severity in the mild, moderate, and severe groups were, respectively, $143.65\pm44.68$, $382.42\pm61.52$, and $622.56\pm66.40$, with the difference between the groups being highly significant ($p<0.001$). Intergroup comparisons revealed that the severe group had significantly higher scores compared to the moderate ($p<0.001$) and mild ($p<0.001$) groups, while the scores in the moderate group were significantly higher compared to the mild group ($p<0.001$).

**DISCUSSION**

The results of the present study show that patients with most marked bronchial hyperresponsiveness do not necessarily have the most severe asthma clinically. The range of bronchial hyperreactivity in the three groups (mild, moderate, and severe asthma) was broad and overlapped, so that the means were not significantly different. Bronchial hyperreactivity was also not found to correlate with future symptomatic status and requirements for drugs.

Makino et al. found a significant correlation between the clinical severity of asthma over the preceding year and the provocation dose of acetylcholine but not of histamine; however, the correlation was lacking when the severity over the immediately preceding two weeks was considered. Townley et al. found that subjects with a greater degree of nonspecific bronchial responsiveness tended to have more severe asthma than those with a lesser degree of bronchial responsiveness; however, in Kiviloog's study, the seasonal increase in the severity of asthma did not correlate with an increase in sensitivity to methacholine. Quantifying bronchial reactivity by response to exercise, Anderson et al. reported its lack of a significant relationship with the severity of asthma. Rubinfeld and Pain et al. also failed to find a correlation between the severity of asthma and bronchial responsiveness to methacholine; however, more recently, Murray et al. have reported a significant correlation between bronchial responsiveness to histamine and the severity of asthma. Our failure to find any relationship between the severity of asthma and bronchial responsiveness to histamine is in agreement with several earlier studies but at variance with some others. The reasons for the conflicting results among the studies reviewed are not obvious but may relate to differences in the population studied and the method of assessing the clinical severity of asthma.

Cockcroft et al. observed a positive correlation between bronchial responsiveness to histamine and previous requirements for drugs. Later, in a prospective study, Juniper et al. raised the possibility that measurement of bronchial hyperresponsiveness may be useful in substantiating or questioning the medication requirements of a patient; however, in a subsequent review by the same group of workers, it was noted that in view of the scatter of bronchial responsiveness in each category of disease severity, its measurement could not be used to determine require-
ments for treatment. Our finding of a lack of correlation of bronchial hyperreactivity with drug intake scores implies the same. In addition, the lack of any significant correlation with the percentage of asymptomatic days and symptom scores indicate that it cannot be used as a prognostic indicator of future symptomatic status. Thus, our results confirm and extend the conclusions of other workers.¹⁰

The degree of bronchial hyperresponsiveness reflects the ease with which bronchospasm may be provoked; however, if a patient with marked bronchial hyperresponsiveness can avoid stimuli (such as antigen exposure, exercise, or cold air) which precipitate his asthma, he may not develop any symptoms and thus not require any medication. Moreover, the perception of obstruction and tolerance are other major factors which would determine the actual symptoms in a patient. The severity and expression of the symptoms of asthma and the patients' perceived therapeutic needs have multiple determinants which are poorly understood. Bronchial hyperresponsiveness is perhaps only one of these. Therefore, the failure to demonstrate its correlation with the severity of asthma is not surprising. It must be emphasized that the mere presence of bronchial hyperresponsiveness is not enough to produce asthmatic symptoms because it has been documented in other conditions such as rhinitis¹⁵ and tropical pulmonary eosinophilia.¹⁶

The overall severity of asthma is assessed by history, while the severity of obstruction of the airways at any point in time is assessed by physical examination and usually spirometry. These methods are not entirely satisfactory. Airway obstruction may be perceived imperfectly,¹⁷ and its correlation with physical signs is poor,¹⁸ however, in view of our results and similar observations by other workers (as pointed out earlier), the measurement of bronchial responsiveness also apparently does not permit a more objective way to grade the clinical severity of asthma.

An important observation was the lack of a significant correlation between the baseline airway caliber and bronchial hyperresponsiveness. Benson¹⁹ had suggested that this characteristic feature of asthma was simply the result of a reduced baseline airway caliber. The reasoning was that because resistance is inversely proportional to the fourth power of the radius, narrowing of an already constricted airway causes a disproportionate increase in resistance. Prior narrowing may exaggerate the effect of the test stimulus on the measured response; however, while changes in baseline caliber may affect the measured response, these cannot be the sole cause of bronchial hyperresponsiveness. Increased bronchial responsiveness is also present in asthmatic subjects with a normal airway caliber. Our finding of a lack of any significant correlation between bronchial hyperresponsiveness and baseline airway caliber agrees with those of several other workers.⁶,²⁰,²¹

The systems adopted by us to score the severity of asthma retrospectively and the symptoms and drug requirements prospectively are open to criticism in that they depend largely on subjective criteria; however, it was our endeavor to include only those patients who were good perceivers of asthma. They understood the purpose behind the study and were instructed properly. In addition, they attended our clinic every two weeks, where their records were checked to see if compliance was proper.

In summary, the degree of bronchial responsiveness, as assessed by the histamine bronchoprovocation test, does not reflect the clinical severity of asthma. It is also not a reliable prognostic indicator of future symptomatic status and therapeutic needs. Therefore, its measurement adds very little to the assessment and everyday management of asthma. We find little support for the statement that measuring bronchial responsiveness is as essential to the diagnosis and management of asthma as the glucose tolerance test is to diabetes mellitus.²²

ACKNOWLEDGMENTS: We are grateful to Dr. K. P. Agrawal for providing laboratory facilities, Mr. D. R. Patil for technical assistance, and Mr. K. Gopalakrishnan for secretarial assistance.

REFERENCES

2 Makino S. Clinical significance of bronchial sensitivity to acetylcholine and histamine in bronchial asthma. J Allergy 1966; 38:127-42
3 Townley RG, Blyo UV, Kolotkin BM, Kang B. Bronchial sensitivity to methacholine in current and former asthmatic and allergic rhinitis patients and control subjects. J Allergy Clin Immunol 1975; 56:429-42
4 Kiviloog J. Variability of bronchial reactivity to exercise and methacholine in bronchial asthma. Scand J Respir Dis 1973; 54:359-66
9 Juniper EF, Frith PA, Hargreave FE. Airway responsiveness to histamine and methacholine: relationship to minimum treatment to control symptoms of asthma. Thorax 1981; 36:575-79
14 Chhabra SK. Modulation of airway reactivity in bronchial asthma by theophylline, disodium cromoglycate and lipotropic factor choline, M.D. (Tuberculosis and Respiratory Diseases) thesis. University of Delhi, Delhi, India, 1985
17 Rubinfeld AR, Pain MCF. Perception of asthma. Lancet 1976; 1:882-84
21 Galver RA, McLaughlin FJ, Levison H. The relationship between airway obstruction and bronchial hyperreactivity in childhood asthma. Ann Allergy 1987; 58:45-7