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Sensitivity and specificity of the histamine challenge test for the diagnosis of asthma in an unselected sample of children and adolescents

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ABSTRACT: The purpose of this investigation was to study factors of importance for the degree of bronchial responsiveness and, furthermore, to evaluate the sensitivity, specificity and predictive value of a bronchial challenge test with histamine for the diagnosis of asthma in 495 randomly selected children and adolescents, aged 7–16 yrs, from Copenhagen, Rigshospitalet. Detailed history about allergic symptoms, physical examination and bronchial histamine challenge tests were performed at the out-patient clinic.

Asthma, atopic disease and height were found to be of great importance for the degree of bronchial responsiveness, whereas the age, sex and smoking habits were of no significance. The percentage of asthmatics with bronchial hyperresponsiveness, *i.e.* sensitivity to the test, increased towards 100% on inhaling increasing concentrations of histamine, but this was accompanied by a decrease in specificity and predictive values of positive test in regard to the diagnosis of asthma. However, lower concentrations of histamine may be preferable in order to distinguish between asthma and non-asthma in population samples, as inhalation of 2.4 mg·ml^{-1} and provocative concentration producing a 20% fall in forced expiratory volume in one second (FEV_1) (PC_{20}) provided an acceptable sensitivity (57%), specificity (98%), and predictive value of a positive test (60%).

We conclude that as regards the diagnosis of asthma, a low predictive value confirms that the bronchial challenge test plays only a supplementary, but valuable, role in detecting the disease in population samples.

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Airway responsiveness is usually measured by inhalation of pharmacological agents [1–4]. It is influenced by various factors such as asthma, atopy, family background of allergic diseases, age and smoking [5–8].

Bronchial hyperresponsiveness (BHR), *e.g.* to inhaled histamine, has been cited as the "gold standard" in separating asthma from healthy subjects or other respiratory diseases [1, 2]. However, differentiating between asthma and non-asthma by the level of responsiveness has proved rather disappointing [9, 10]; and, therefore, the significance of BHR has been questioned [11]. However, the absence of a generally accepted definition of clinical asthma makes the diagnostic value of inhalation challenge tests in population samples very important and the separation between normal responsiveness and hyperresponsiveness necessary.

The purpose of this investigation was to study factors of importance for BHR and to evaluate the sensitivity, specificity and predictive value of the bronchial challenge test with histamine for the diagnosis of asthma, in order to establish an appropriate index for distinguishing between non-asthmatic and asthmatic children and adolescents in population samples.

Material

Subjects

A random sample of 983 children and adolescents aged 7–16 yrs living in the area surrounding the State University Hospital, Rigshospitalet, in Copenhagen was drawn from the civil registration list and invited to participate in the study. Five hundred and twenty seven (54%) unselected children and adolescents accepted the invitation and were examined. However, 27 subjects refused the histamine challenge test when visiting the laboratory, and five were excluded because of systemic disease (n=4) or a forced expiratory volume in one second (FEV_1) less than 1.0 *l* (n=l). The median age of the 495 subjects (250 boys, 245 girls), in whom a histamine challenge test was performed (94%), was 12 yrs (range 7–16 yrs).

A sample of 100 non-responders (families who did not respond when contacted by letter) was contacted by telephone. The families of these non-responding children answered the same questionnaire as the children examined. No differences in sex, age, or disposition to allergic symptoms were observed between the 527 responders and the 100 non-responders, but there were significantly fewer children with allergic symptoms in the group of non-responders compared with the responders. Twelve children and adolescents claimed to have allergic symptoms, of whom two had asthma, seven had rhinitis and/or atopic eczema and three subjects had urticaria. Furthermore, four subjects had respiratory symptoms, not defined as asthma.

All participants and their parents were interviewed by one of the authors (VB); the participants then completed a questionnaire about asthmatic symptoms [12] and other allergic symptoms, *i.e.* rhinitis (sneezing, running or blocked nose, not associated with colds) and atopic dermatitis (an itchy dry rash on face, arms or legs) as regards themselves, their siblings and their parents [13].

The material of 495 children and adolescents was divided into two groups.

Group 1: asthmatic children and adolescents (n=28). The questionnaire and criteria for asthma used were those of Hopp *et al.* [12]. The questions were as follows: 1) Have you ever had asthma diagnosed? 2) Have you ever had wheezy or dry cough? 3) Do you have attacks of shortness of breath with wheezing? 4) Have you ever been hospitalized and/or been treated for asthma by a doctor? 5) Have you ever received medication for your asthma? 6) Did the medication help? and 7) Do exertion, stress, cold air, damp weather or allergen exposure give you pulmonary symptoms?

Twenty children had definite asthma, *i.e.* positive response to questions 1–6; none had probable asthma, *i.e.* positive responses to questions 1–4 and 5 or 6; whereas, eight had questionable asthmatic symptoms, *i.e.* positive response to any two of question 1–3 and any one of questions 4–7. All of the asthmatic subjects had current asthma and none of the non-asthmatic children had ever had asthmatic symptoms. Nineteen of the 28 subjects with asthma had positive allergen skin prick tests, and nine reacted negatively to the skin prick test.

Group 2: non-asthmatic children and adolescents (n=467). Among the 467 non-asthmatic subjects, 88 were found to have atopic symptoms, *i.e.* subjects who had rhinitis (n=43), eczema (n=31), or asymptomatic positive skin prick test (n=14). Fifty of the 88 subjects (57%) had no family background of atopic diseases. Eighty two subjects (16%) claimed doubtful respiratory symptoms (doubtful asthma), whereas 417 individuals had no respiratory symptoms, whatsoever. Seventy five of the 82 subjects had occasional cough, six had experienced shortness of breath and one subject had experienced wheezing on one occasion. The overall number of children and adolescents with family histories of allergic diseases in their first degree relatives was 183 subjects (39%), whereas 234 subjects (50%) had no allergic symptoms themselves, and no positive skin prick test or allergic symptoms in their near relatives.

Methods

All subjects were asked not to smoke for two hours before the tests and to avoid anti-asthmatic medication. All participating persons were subjected to a allergen skin prick test with nine common allergens [14], baseline lung function, *i.e.* forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) (Vitalograph®), six minute exercise test and histamine challenge test. In addition, measurement of serum immunoglobulin E (IgE) and of antibodies (IgM and IgG) to six common respiratory viruses (parainfluenza 1 and 2, influenza A and B, adenovirus and respiratory syncytial virus (RSV)) was performed. In cases with recent respiratory infection, all tests were postponed for at least six weeks.

Predicted values based on the height of the subjects were calculated according to Zapletal *et al.* [15]. Bronchial responsiveness to histamine was measured according to the method described by Cockcroft *et al.* [1]. Histamine aerosol was generated by a Wright nebulizer® with an output of 0.14±0.015 $ml \cdot min^{-1}$. Nine concentrations of histamine were used: from 0 (saline) to 8.00 $mg \cdot ml^{-1}$. Testing was terminated when the maximum concentration had been reached, or when a decrease of at least 20% of FEV_1 was observed. The threshold value of BHR was PC_{20} of 8 $mg \cdot ml^{-1}$. The percentage reduction in FEV_1 per micromole of the last inhaled concentration of histamine, *i.e* the dose-response slope (DRS) was recorded and used in the analysis [16]. The protocol was evaluated and approved by the local Ethical Committee and informed consent was obtained from all participating subjects and their parents.

The differences in degree of bronchial responsiveness, FEV_1 and FVC between the two groups were analysed by the Mann-Whitney rank test. An univariate linear regression analysis and a multiple regression analysis were performed for each of the involved background variables. The non-significant variables were deleted by retrograde (backward) elimination to determine those associated with the dose-response slope.

The ability of the bronchial provocation test for diagnosis of bronchial asthma was assessed by calculating sensitivity, specificity and the predictive values of the positive and negative test (PV+ and PV-) as follows:

$$\text{Sensitivity} = \frac{\text{Asthmatic subjects with positive test}}{\text{Total number of asthmatic subjects}}$$

$$\text{Specificity} = \frac{\text{Non-asthmatic subjects with negative test}}{\text{Total number of non-asthmatic subjects}}$$

$$\text{PV+} = \frac{\text{Asthmatic subjects with positive test}}{\text{Total number of subjects with positive test}}$$

$$\text{PV-} = \frac{\text{Non-asthmatic subjects with negative test}}{\text{Total number of subjects with negative test}}$$

The receiver operating characteristic (ROC) curve was constructed as the relationship between true positive rate (sensitivity) and false positive-rate (1-specificity) and was calculated for each percentage of reduction in FEV_1 from 1% to 20% after every inhalation of histamine.

The change in percentage fall in FEV_1 during the challenge was analysed by the Friedmann two-way rank sum analysis of variance. The Spearmann rank correlation test was used for correlation analysis. The variance of FEV_1 was analysed using the variance-ratio distribution, *i.e.* the F-distribution.

Results

Baseline FEV_1 values were slightly significantly lower in the asthmatic subjects (median FEV_1 98%pred) than in the non-asthmatic subjects (median FEV_1 106%pred) ($p=0.03$, table 1). There were no significant differences between asthmatic and non-asthmatic subjects regarding FVC. Furthermore, no differences in lung function (%pred) were found between the participating boys and girls.

The asthmatic subjects in the present study had a concentration-related decrease in FEV_1 for the entire range of concentrations tested (fig. 1, $p<0.001$). The non-asthmatic subjects had no significant bronchial response to the first six histamine concentrations with a median change in FEV_1 which increased from +0.08% (saline) to -0.48% (1.2 $mg \cdot ml^{-1}$) (data not shown), but at higher concentrations an increasing reduction of FEV_1 was found (median change of -0.74% at 2.4 $mg \cdot ml^{-1}$ to 3.42% at 8 $mg \cdot ml^{-1}$, $p<0.001$). The overlap with regard to reduction in FEV_1 between asthmatic and non-asthmatic subjects to concentrations of 4.8 and 8.0 $mg \cdot ml^{-1}$ was negligible (fig. 1) .

As shown in table 2, asthma, bronchial response to exercise (BRE), FEV_1, a positive skin prick test, height and age of the subjects seems to be important

Table 1. – Baseline FEV_1 in % of predicted by age and sex in 495 randomly selected children and adolescents

Age yrs	Initial FEV_1% pred					
	Boys			Girls		
	n	Median	Interquartile range	n	Median	Interquartile range
7	11	106	97–122	16	104	97–116
8	33	104	97–112	20	108	101–118
9	15	103	97–109	19	106	96–109
10	35	103	94–107	31	106	97–113
11	32	101	95–108	23	100	94–105
12	27	97	92–107	19	101	92–111
13	17	103	98–109	30	115	105–125
14	20	102	95–112	32	113	108–129
15	34	105	96–114	23	118	106–129
16	26	116	108–124	32	112	97–113
all	250	103	96–113	245	107	100–118
Asthmatic	17	93	84–105	11	112	97–130
Non-asthmatic	233	104	97–113	234	107	100–118

Values adjusted to body temperature and pressure, saturated (BTPS). FEV_1: forced expiratory volume in one second.

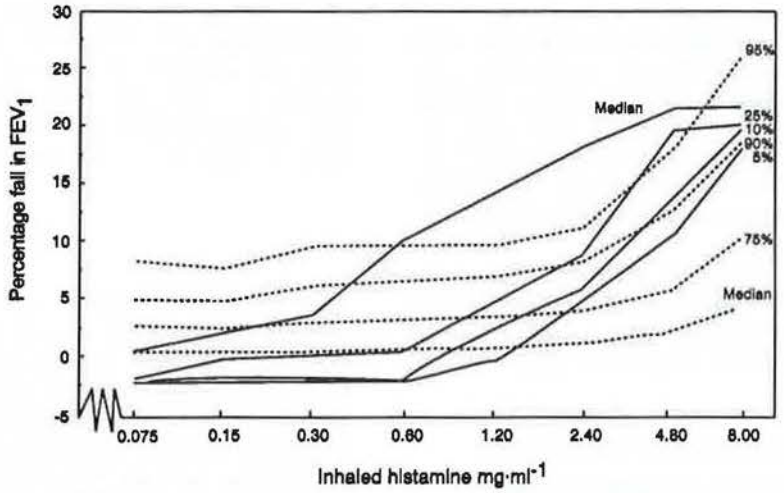

Fig. 1. – Changes in post-saline FEV_1 values for asthmatic (solid lines) and non-asthmatic subjects (punctuated lines) after challenge with eight different histamine concentrations. For non-asthmatic subjects medians and 75–95 percentiles have been drawn, and medians and 5–25 percentiles for asthmatic subjects. FEV_1: forced expiratory volume in one second.

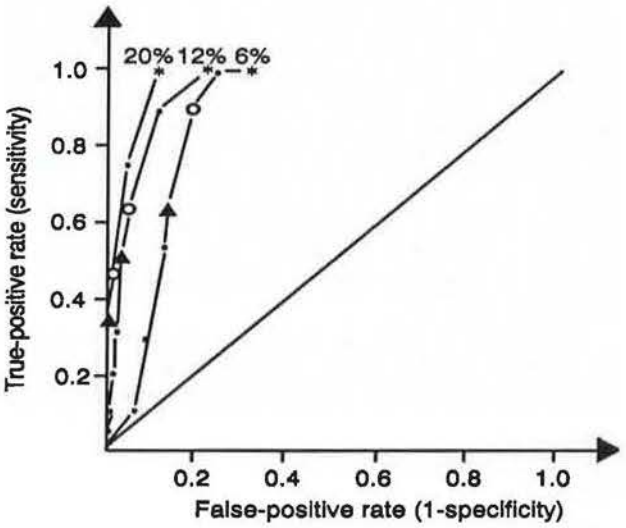

Fig. 2. – ROC curves for 495 children and adolescents tested with histamine challenge test using 20%, 12% and 6% fall in post-saline FEV_1 as cut-off. Value at concentration of 1.2 (▲), 2.4 (○) and 8.0 (✱) $mg \cdot ml^{-1}$ are illustrated on the curves. The heavily drawn line (45°) indicates the state where the diagnostic test provides no more than chance information. FEV_1: forced expiratory volume in one second.

factors, whereas smoking had no influence on the degree of bronchial responsiveness. However, the final multiple regression model demonstrated that only respiratory symptoms, airflow variability to exercise and atopic disease is important, whereas the age of the subjects were of no significance (table 3).

The ROC curves for distinguishing asthmatic from non-asthmatic children by the level of bronchial responsiveness are shown in figure 2. The curves for 6, 12 and 20% decrease in FEV_1, *i.e.* PC_6, PC_{12} and PC_{20}, after inhalation of increasing concentrations of histamine were selected for illustration. The sensitivity increased towards 100% with increasing concentrations of histamine, however, a high sensitivity was followed by a decrease in specificity.

Table 2. – Univariate regression analyses with log dose-response slope (DRS) as dependent variable and the listed variables as background variable

Background variable	Regression coefficient β (SD)	T-ratio	Significance level
Sex	0.023 (0.024)	0.98	0.3
Body height cm	-0.002 (0.001)	-2.80	<0.01
Age	-0.012 (0.004)	-2.94	<0.01
Family background	0.046 (0.018)	2.52	<0.05
Asthma	0.675 (0.042)	16.06	<0.001
Other atopic symptoms	0.002 (0.016)	0.15	0.9
Doubtful asthma	0.011 (0.034)	0.36	0.7
FEV_1 absolute value	-0.047 (0.014)	-3.44	<0.001
FEV_1 %pred	-0.003 (0.001)	-2.84	0.01
FEV_1/VC	-0.003 (0.002)	-1.17	0.2
BRE	0.014 (0.002)	9.66	<0.001
Tobacco - adults	-0.001 (0.001)	-0.63	0.5
Tobacco - participants	-0.004 (0.005)	-0.87	0.4
Serum IgG-RSV respiratory viruses	-0.004 (0.023)	-0.19	0.8
Serum IgM respiratory viruses	-0.018 (0.037)	-0.48	0.6
Month for examination	-0.005 (0.004)	-1.34	0.2
Results of skin prick test	0.072 (0.010)	7.21	0.001
IgE $kU \cdot l^{-1}$	0.073 (0.017)	4.37	<0.001

FEV_1: forced expiratory volume in one second; VC: vital capacity; BRE: bronchial response to exercise; IgG, IgM and IgE: immunoglobulin G, M and E, respectively; RSV: respiratory syncytial virus.

Table 3. – Final multiple regression model of background variables to log dose-response slope

Background variable	Regression coefficient β (SD)	T-ratio	Significance level
Body height cm	-0.0019 (0.001)	-3.07	0.002
Age	-0.0057 (0.004)	-1.38	0.17
Family background	-0.0544 (0.022)	-2.52	0.012
Asthma	0.2919 (0.025)	11.56	<0.0001
Doubtful asthma	0.0717 (0.029)	2.45	0.02
BRE	0.0050 (0.002)	3.20	0.002
Results of skin prick test	0.0367 (0.010)	3.86	<0.001

The intercept of the final regression equation was 0.45±0.1 (SD). SD=0.21; R-sq=40%. BRE: bronchial response to exercise.

Table 4. – The sensitivity, specificity and predicted value of a positive test (PV+) and predicted value of a negative test (PV-) to distinguish asthma from non-asthma at two different concentrations of histamine (2.4 mg·ml^{-1} and 8.0 mg·ml^{-1}) among 495 subjects

% fall in FEV_1	Sensitivity	Specificity	PV+	PV-
Cut-off at 2.4 mg·ml^{-1}				
PC_6	100	74	19	100
PC_{12}	75	93	40	98
PC_{20}	57	98	59	97
Cut-off at 8.0 mg·ml^{-1}				
PC_6	100	46	10	100
PC_{12}	100	73	18	100
PC_{20}	100	89	35	100

FEV_1: forced expiratory volume in one second, PC_6, PC_{12} and PC_{20}: provocative concentration producing a 6, 12 and 20% fall in FEV_1, respectively.

Predictive value of a positive test increased when inhaling low concentrations of histamine in a population sample, *i.e.* all those who respond significantly to the challenge test really have clinical asthma (table 4). However, the best diagnostic cut-off point, in the clinical situation, was obtained at a 20% reduction in FEV_1 for a histamine concentration of 8.0 mg·ml^{-1}, because of a high sensitivity and specificity, although PV+ is rather low. Conversely, to distinguishing between asthma and non-asthma in population samples the best diagnostic cut-off point would be achieved by inhalation of weaker concentrations, *e.g.* 2.4 mg·ml^{-1} with a PC_{20}, because that would result in an enhanced PV+ of 60%. Not all of the subjects with respiratory symptoms were classified as asthmatics. However, if all 110 subjects with respiratory symptoms were defined as having asthma, both those with confirmed asthma (n=28) and the 82 non-asthmatic subjects who claimed to have respiratory symptoms, the sensitivity, specificity, PV+ and PV- at PC_{20} and histamine of 8 mg·ml^{-1} were 36, 90, 49 and 83%, respectively, for the diagnosis of asthma.

The variance of changes in FEV_1 in asthmatic subjects following inhalation of saline (range -3.6% +11.6%) was significantly different from that of non-asthmatic subjects (range -3.8% to +7.6%) ($p<0.05$), whereas mean change in FEV_1 after inhalation of saline was similar in the two groups.

Discussion

We have performed an investigation concerning respiratory symptoms, allergic manifestations, atopic diseases (*i.e.* allergen skin reactivity), pulmonary function, bronchial response to exercise and the degree of BHR in 495 randomly selected children and adolescents. We used DRS when we examined the different factors of importance. The major advantage of DRS is that a value can be calculated for the entire population [16, 17].

The asthmatic subjects in the present study were found to have a shift to the left of the dose-response curves as compared with the non-asthmatic subjects, and the asthmatics were found to have significant dose-response for the entire range of histamine concentrations used; an observation which is in accordance with other studies [18, 19]. We found a negligible overlap in bronchial response between asthmatic and non-asthmatic subjects when inhaling histamine concentrations above 5 $mg \cdot ml^{-1}$, which is similar to findings by others [5]. At the weaker end of the challenge test, a difference between the asthmatic and non-asthmatic was also found, as the asthmatic subjects showed significantly greater scatter of the bronchial response to saline inhalation compared with the non-asthmatic subjects, which was probably due to greater spontaneous changes in airway resistance in asthmatic subjects than in normal subjects [20].

Four factors examined were found to be markedly related to the degree of bronchial responsiveness to histamine: clinical asthma, bronchial responsiveness to exercise, atopic diseases and body height. For three of these four factors, close association is in accordance with other studies [1, 5, 21–24]; whereas, we were unable to find a relationship between BHR and age of the children as was found by HOPP *et al.* [6]. However, a strong correlation between body height and BHR could equalate with the findings by HOPP *et al.* [6]; the height may even be more relevant than the age as such. Height seems to be related to the bronchial diameter in children, and reduced bronchial diameter causes both relatively greater airway deposition of histamine [25] and a relatively greater effect of airway contraction [26].

We showed that smoking and previous respiratory viral infections, *e.g.* with RSV, were found to be of no relevance for the degree of bronchial responsiveness, an observation which is different from findings in selected groups of subject with BHR [7, 27]

Although a marked relationship between asthma and BHR was found [1, 2, 5] and all asthmatic subjects had BHR, *i.e.* a sensitivity of the test of 100%, the present study shows that only in approximately 40% of those with BHR had asthma been diagnosed clinically. If a less restrictive definition of asthma had been used [12], a decrease in sensitivity, fewer misclassifications (false positives), and a minor improvement in symptomatic hyperresponsiveness (*i.e.* PV+) would have been achieved. These findings are in accordance with other studies [9, 10].

PATTEMORE *et al.* [9] found, in a population study of children, that 60% of those with clinical asthma had BHR, when inhaling lower concentrations of histamine than in the present study, whereas all subjects with clinical asthma in the present study had BHR independent of cut-off point (PC_6 to PC_{20}) when inhaling high concentrations of histamine. However, inhalation of lower concentration of histamine, *e.g.* 2.4 $mg \cdot ml^{-1}$ revealed fewer asthmatic subjects, in the present study, who had BHR (75% (PC_{12}) and 57% (PC_{20})). These findings could explain some of the dissimilarities between the different studies. Furthermore, we found that the misclassification of subjects without respiratory symptoms as asthmatics decreased when high concentration of agent and greater reduction in lung function were used to distinguish between asthma and non-asthma, *e.g.* 20% instead of 6%.

Although PC_{20} at 8 $mg \cdot ml^{-1}$ may be the best criterion for asthma in clinical practice [1], as the sensitivity, specificity and predictive value of a negative test for the diagnosis of asthma had the highest values, PV+ is disappointingly low. A low PV+ is the reason why PC_{20} at 8 $mg \cdot ml^{-1}$ in population studies may not always be the best. A low PV+ suggests that bronchial challenges are inadequate in epidemiological studies to differentiate between asthma and non-asthma. In general, PV+ are found to be low in population samples [5, 10, 12, 21–23] and the differences in PV+ between the studies are small. If, however, a cut-off limit of 12% (PC_{12}) to 20% (PC_{20}) had been used after inhalation of *e.g.* 2.4 $mg \cdot ml^{-1}$, a gain in clinical diagnostic value was obtained. We found that a greater number of those with increased bronchial responsiveness have symptoms of asthma as PV+ increased from 40 to 59%, and only with some expense of sensitivity (75 to 57%). Therefore, this study indicates that an attractive definition between asthma and non-asthma, in regards to histamine challenge test, in population studies may be 12% (PC_{12}), as suggested by other studies [28–30]. Although bronchial challenge tests are only valuable in population samples to some degree, bronchial responsiveness remains useful in the clinical situation; because many persons with symptoms of asthma have BHR, and BHR correlates closely with the degree of airway obstruction, the severity of asthmatic symptoms and the need for anti-asthmatic medication [1, 2, 5]. Furthermore, COCKCROFT and HARGREAVE *et al.* [11] suggested that challenge tests should be used in selected groups of asthmatics, whereas BHR is insufficient to discriminate between asthma and non-asthma in population samples.

Bronchial responsiveness and asthma were found to be closely associated, although it is well known that BHR and asthma are not identical [5, 12, 21, 32]. Differentiation between BHR and normal bronchial responsiveness is arbitrary [9, 33, 34], and follow-up studies of population samples in the future might reveal whether increased degree of bronchial responsiveness increases the future risk of developing respiratory symptoms with time.

A limitation of the present study is, that not all invited subjects participated and the conclusions might therefore not be completely satisfactory, although the error seems to be of minor consequence.

In conclusion, this study shows that asthma, atopy and body height are strongly associated with the degree of bronchial responsiveness. Although there was a marked relationship between asthma and BHR, the histamine challenge tests must not be used as "diagnostic criteria" for asthma. With respect to the diagnosis of asthma, a low predictive value confirms that the bronchial challenge test has only a supplementary, but valuable, role in detecting the disease in population samples.

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Sensibilité et spécificité du test de provocation à l'histamine pour le diagnostic de l'asthme, dans un échantillon non sélectionné d'enfants et d'adolescents. V. Backer, S. Groth, A. Dirksen, N. Bach-Mortensen, K.K. Hansen, E.M. Laursen, D. Wendelboe.

RÉSUMÉ: Le but de cette investigation fut l'étude des facteurs intervenant dans le degré de réactivité bronchique, et d'autre part d'évaleur la sensibilité, la spécificité et la valeur prédictive d'un test de provocation bronchique à l'histamine, pour le diagnostic de l'asthme chez 495 enfants et adolescents sélectionnés au hasard, âgés de 7 à 16 ans, et provenant du Rigs-hospitalet à Copenhague. Une anamnèse détaillée concernant les symptômes allergiques, un examen physique, et des test de provocation bronchique à l'histamine, ont été menés à la polyclinique.

L'asthme, les maladies atopiques et la taille, se sont avérés importants pour le degré de réactivité bronchique, alors que l'âge, le sexe et les habitudes tabagiques ne furent pas significatifs. Le pourcentage d'asthmatiques avec hyperréactivité bronchique, des c'est-à-dire la sensibilité tests, a augmenté vers 100% par l'inhalation de concentrations croissantes d'histamine, mais ceci s'accompagna d'une diminution de la spécificité et des valeurs prédictives des tests positifs en ce qui concerne le diagnostic de l'asthme. Toutefois, de plus faibles concentrations d'histamine pourraient être préférables pour distinguer entre l'asthme et le non-asthme dans les échantillons de population, puisque l'inhalation de 2.4 mg/ml d'histamine et le PC_{20} ont fait preuve d'une sensibilité (57%), d'une spécificité (98%) et d'une valeur prédictive d'un test positif (60%) tout à fait acceptables.

Nous concluons qu'en ce qui concerne le diagnostic de l'asthme, une valeur prédictive basse confirme que le test de provocation bronchique ne joue qu'un rôle complémentaire, quoique valable, pour le détection de la maladie dans les échantillons de population.

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