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Non-specific bronchial airway hyperreactivity and the diagnosis of asthma

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Summary

In very mild and atypical cases of asthma, highly discriminative tests are needed to make the diagnosis. To demonstrate this, measurement of non-specific bronchial airway hyperreactivity by means of standardized bronchial inhalation challenge tests with histamine and methacholine were performed in 10 very mild asthmatic and nine normal control subjects; both groups included Nigerians who were temporarily resident in London at the time of the study. Bronchial reactivity was expressed as the provocative concentration of the agents causing a 20% fall in forced expiratory volume in 1 sec ($PC_{20}FEV_1$); higher values indicating lower levels of non-specific bronchial reactivity.

The level of non-specific bronchial reactivity in these very mild asthmatics, whose baseline physiological data were not different from those in normals, was found to be 18–29 times higher than the normal control subjects.

These tests very effectively discriminated between asthmatic and normal control subjects. With available resources it should be possible to study a large number of Nigerians in their own environment.

Résumé

Lorsqu'il s'agit des cas très bénins et atypiques de l'asthme, des tests hautement discriminatoires s'avèrent nécessaires pour réussir le diagnostic. Pour démontrer ceci, des mesures de l'hyperréactivité du couloir d'air non-spécifique des bronches au moyen des tests d'évaluation standardisés de l'inhalation bronchique à l'aide de l'histamine et de la métacholine ont été effectuées auprès de 10 cas d'asthme très bénins et de neuf cas normaux servant de contrôle, les deux groupes comprenant des Nigérians domiciliés à titre temporaire à Londres à l'époque de la recherche. La réactivité bronchique s'est exprimée en la concentration provocatrice de l'agent, résultant en une chute de 20% du volume d'air expiré de force par seconde ($PC_{20}FEV_1$); alors que des mesures plus élevées étaient indicatrices des degrés moindres de réactivité bronchique non-spécifique.

L'on a découvert que le niveau de réactivité bronchique non-spécifique chez ces asthmatiques très bénins, dont les données physiologiques de base n'étaient pas différentes de celles des normaux, était de 18–29 fois plus élevé que chez des sujets normaux servant de contrôle.

Ces tests avaient donc discriminé, de facon très efficace, entre les sujets asthmatiques et les normaux de contrôle. Il devrait être possible, à l'aide des ressources disponibles, de mener une recherche sur un grand nombre de Nigérians dans leur propre environnement.

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Introduction

Bronchial airway hyperreactivity is a phenomenon used to describe the increased sensitivity of the airway smooth muscle in asthmatic individuals to a wide range of stimuli which may be specific (allergens), or non-specific. This airway hyperreactivity is thought to be the basic defect in asthma [1,2]. The non-specific stimuli include histamine, cholinergic drugs such as methacholine, cold air, dust and exercise.

Bronchial asthma can be diagnosed by em-

ploying the standard criteria of history, physical examination, and the demonstration of reversible airway obstruction according to the American Thoracic Society [3]. In some mild cases of asthma the diagnosis is suspected from the history, but the physical examination is normal and spirometry may not show airway obstruction at the time of the evaluation. In many of such cases, the diagnosis cannot be made with certainty; consequently, a more discriminative test is needed. Application of non-specific bronchial airway hypersensitivity for this purpose, using bronchial inhalation challenge tests, has been advocated and considerably developed in the technologically developed countries within the past decade [4,5]. There are no reports of the application of these techniques in Africa. This communication is based on inhalation challenge tests on Caucasians and some Nigerians temporarily resident in Britain at the time of the study.

Subjects and methods

Subjects

About 80 adults, including four Nigerians, with characteristic clinical history of asthma were under the follow-up list of one of the authors (P.O.O) at the Asthma Clinic of the King's College Hospital, London, at the time of the study. Only 10 of these, including two Nigerians, satisfied the inclusion criteria of a forced expiratory vital capacity in the first second (FEV_1) that is greater than 80% of the predicted normal value indicative of very mild asthma, absence of current or previous history of smoking, and ability to withhold medication for 24 h without symptoms. History, physical examination and chest X-ray examination excluded the presence of other respiratory diseases in these patients.

Nine adult non-asthmatic, non-smoking subjects including four Nigerians were recruited from hospital staff as normal controls. None had recurrent or previous episodic dyspnoea, chest tightness, wheezing, chronic cough or any symptoms suggestive of other respiratory disease. They were all non-atopic as indicated by absent weal-and-flare responses to skin-prick tests with 10 common allergens, and none had a positive family history of asthma.

At the time of the study, all the subjects had been free of symptoms of respiratory infection for at least 6 weeks. Symptoms of asthma in the asthmatic subjects were all carefully controlled, with no exacerbations during the previous 6 weeks. Medication with methylxanthines and steroid inhaler was withheld for at least 72 h, while sympathomimetics were withheld for at least 72 h, prior to the test on each of the study days in accordance with standard recommendations [4].

Informed consent was obtained from the subjects and the approval of the Hospital Ethics Committee was obtained for the study. The predicted values for FEV_1 for the Nigerians were derived from the equation of Patrick and Femi-Pearse [6] while that for Caucasians were obtained from the nomogram of Cotes [7].

Inhalation challenge tests

Histamine and methacholine inhalation tests were performed by the slightly modified tidal breathing method described by Cockcroft *et al.* [5]. The details of this method have been published elsewhere [8,9]. Bronchial reactivity to histamine (H) and methacholine (M) were expressed at the provocative concentration of the agents causing a 20% fall in FEV_1; $PC_{20}FEV_1H$ and $PC_{20}FEV_1M$ respectively. Higher values of $PC_{20}FEV_1$ indicated lower levels of non-specific bronchial reactivity.

The inhalation tests with histamine and methacholine were performed in a random order with the subjects attending the laboratory on two different days, at the same time of the day, within a 2-week period.

At the completion of each challenge, asthmatic subjects with any residual bronchospasm received 200 μg of salbutamol aerosols which alleviated the transient discomfort.

Analysis of results

Student's *t*-test for unpaired observations was used to evaluate the statistical significance of the differences between normal and asthmatic subjects in relation to bronchial reactivity. *P* values less than 0.05 were considered significant.

Results

The anthropometric and baseline physiological data for the asthmatic and control groups are summarized in Table 1. The asthmatics com-

Table 1. Anthropometric and baseline physiological data of the subjects

		Sex		Age		Height (m)		Weight (kg)		FEV_1					
										Pred.		Obs.		% Pred.	
Subjects	No.	Male	Female	$\bar{x}$	±s.d.	$\bar{x}$	±s.d.	$\bar{x}$	±s.d.	$\bar{x}$	±s.d.	$\bar{x}$	±s.d.	$\bar{x}$	±s.d.
Asthmatics	10	5	5	33.5	13.0	1.70	0.10	69.6	11.60	3.32	0.75	3.28	0.93	98.0	8.0
Controls	9	5	4	25.9	5.21	1.70	0.10	64.9	9.21	3.36	0.72	3.33	0.65	99.5	4.3

FEV_1 = forced expiratory volume in the first second.
Pred. = predicted value.
Obs. = observed value.
% Pred. = percentage of predicted normal value.

prised five males and five females while the controls comprised five males and four females. Even though the asthmatics were significantly older than the normal subjects ($P < 0.01$), the mean of baseline FEV_1 values of subjects with asthma (expressed as percentage of predicted normal values) of 98.0 ± 8.0 did not differ from the control value of 99.5 ± 4.3 ($P > 0.5$). The predicted value is a function of the observed value of FEV_1, the age, sex, and height of the individual.

Table 2 shows the non-specific bronchial reactivity to histamine and methacholine in asthmatic and control subjects. The asthmatics proved to be far more sensitive than the controls to both histamine and methacholine. The mean $PC_{20}FEV_1H$ for controls was 9.53 ± 2.05 mg/ml and for asthmatic subjects, 0.54 ± 0.68 mg/ml; the difference was highly significant ($P < 0.001$). The mean $PC_{20}FEV_1M$ values for controls and asthmatics were 12.29 ± 3.09 mg/ml and 0.42 ± 0.54 mg/ml, respectively, with a highly significant difference between them ($P < 0.001$). The level of bronchial reactivity was thus 18–29 times higher in the asthmatics than in the controls. Figure 1 compares these results in the control and asthmatic subjects and shows that both methacholine and histamine inhalation tests clearly separate normal controls from very mild asthmatics.

Table 3 summarizes the bronchial reactivity of the Caucasian and Nigerian control subjects

Table 2. Inhalation challenge tests in asthmatics and controls

Subjects	Histamine challenge PC_{20} FEV_1H (mg/ml)	Methacholine challenge PC_{20} FEV_1M (mg/ml)
Asthmatics		
KG	0.440	0.510
AP	0.112	0.185
SJ	1.150	0.580
JE	2.200	1.825
EG*	0.137	0.130
TB	0.198	0.083
GR	0.070	0.088
JL	0.780	0.560
MH*	0.190	0.095
PH	0.165	0.103
mean	0.54	0.42
s.d.	0.68	0.54
n	10	10
Controls		
FW	10.75	10.50
HD*	10.25	10.50
NO*	9.60	10.50
PO*	8.00	10.25
JC	11.00	16.00
GU*	10.50	16.00
NB	6.30	8.91
JL	12.50	16.00
JK	6.90	8.95
mean	9.53	12.29
s.d.	2.05	3.09
n	9	9

* = Nigerians studying or working in London, U.K.

$PC_{20}FEV_1H$, $PC_{20}FEV_1M$ = provocative concentration of histamine and methacholine required to reduce the FEV_1 by 20%.

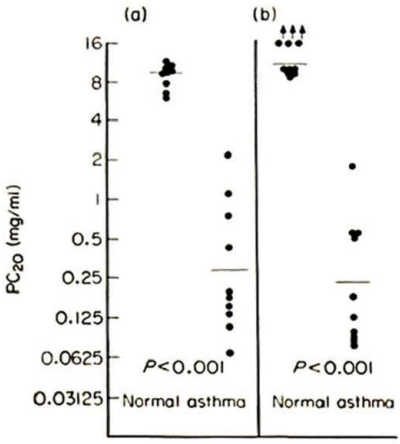

Fig. 1. Histamine (a) and methacholine (b) challenge in normal control and asthmatic subjects. PC_{20} = the provocative concentration of agonist producing a 20% fall in FEV_1, ↑ = concentration exceeding this value, and horizontal bars indicate the geometric mean.

separately. There is no significant difference between the groups either in respect of histamine or methacholine challenge ($P > 0.5$).

Discussion

Observations of exaggerated bronchoconstrictor response to parenteral and inhaled pharmacological bronchoconstrictor agents in patients with asthma have long been reported [10,11]. In addition, a number of recent studies have also shown that systematic inhalation challenge tests with histamine and methacholine are very reliable means of measuring airway hyperreactivity in bronchial asthma [12,13]. The use of these tests in normal and asthmatic subjects in more recent studies have demonstrated that 100% of symptomatic asthmatics have increased non-specific bronchial reactivity [5,14,15].

Our results in Caucasian and Nigerian subjects are in agreement with results from a large number of studies involving Caucasian subjects only [13–16]. In addition, both methacholine and histamine challenge tests have been shown to be quite effective in distinguishing very mild asthmatics from non-asthmatics. The $PC_{20}FEV_1$ shows no overlap between the asthmatic and non-asthmatic groups to either methacholine or histamine. These data suggest that, for diagnostic purposes, the response to inhaled methacholine and histamine may be used to identify clearly patients with asthma even when they are largely asymptomatic and their spirometric characteristics are no different from those of non-asthmatics. The observation that there was no difference in the bronchial reactivity of Caucasian and Nigerian controls to histamine and methacholine not only emphasizes the homogenous nature of this control population but also suggests that there is no racial difference in bronchial reactivity to these agents; at least when assessed in individuals of different racial groups living in the same environment.

While a low level of non-specific bronchial reactivity virtually excludes asthma, a high level is not necessarily diagnostic of asthma, as

Table 3. Inhalation challenge tests in Causasian and Nigerian controls compared

	Histamine challenge $PC_{20}FEV_1H$ (mg/ml)		Methacholine challenge $PC_{20}FEV_1M$ (mg/ml)	
	Caucasians	Nigerians	Caucasians	Nigerians
mean	9.49	9.59	12.07	11.81
s.d.	2.73	1.12	3.64	2.79
n	5	4	5	4

$PC_{20}FEV_1H$, $PC_{20}FEV_1M$ = provocative concentration of histamine and methacholine required to reduce the FEV_1 by 20%.

up to 3% of normal individuals and up to 50% of individuals with a history of hay fever without asthma can have abnormally high reactivity [17]. The diagnostic usefulness of these tests therefore, lies mainly in the demonstration of an increased non-specific bronchial reactivity in an individual with a history suggestive of asthma but who has no evidence of airway obstruction. The demonstration of an increased reactivity may be the only means of making a diagnosis of asthma in cases where the history is atypical such as in the situation of asthma presenting solely with exertional dyspnoea as described by McFadden [18], and as chronic cough as described by Carrao *et al.* [19]. The demonstration of an increased non-specific bronchial reactivity is also of diagnostic significance in suspected cases of occupational asthma [20], especially in situations where the facilities for the specific tests are not available as in the developing countries.

The equipment for the simple histamine and methacholine challenge tests are inexpensive and should be available in some centres in developing countries such as Nigeria. With available resources, it should be possible to study a large number of Nigerians in their own environment. It would be interesting to see whether adverse climatic conditions, such as a combination of high humidity and high ambient temperature as found in this region at the end of the rainy seasons, has any influence on non-specific bronchial reactivity.

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