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Airway responses to hypertonic saline, exercise and histamine challenges in bronchial asthma

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Airway responses to hypertonic saline, exercise and histamine challenges in bronchial asthma. N.G. Belcher, T.H. Lee, P.J. Rees
ABSTRACT: The airway responses to histamine, exercise and ultrasonically nebulized hypertonic saline have been compared in ten asthmatic patients. The responses to hypertonic saline were not significantly different when the same volume of aerosol was given in a single dose or in 10 *l* aliquots, suggesting that the challenge is cumulative. The variability of the response to hypertonic saline challenge was not significantly different from that of exercise challenge. Response to hypertonic saline correlated significantly with exercise (r=0.68, p<0.05) and with histamine response (r=0.74, p<0.02), but the correlation between exercise and histamine was not statistically significant (r=0.15, p>0.1). These findings suggest that exercise-induced asthma has a closer relationship to bronchial responsiveness to hypertonic saline aerosol than it does to non-specific reactivity demonstrated by histamine challenge.
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An enhanced bronchoconstrictor response to a wide variety of stimuli is a characteristic feature of asthma. This feature is often termed non-specific bronchial hyperreactivity or airway hyperreactivity and can be measured in a number of ways. The methods most commonly used to assess reactivity include challenges with methacholine and histamine inhalation [1], exercise [2], isocapnic hyperventilation [3], and inhalation of ultrasonically nebulized solutions of hypo- and hypertonic aerosols [4].

Smith *et al.* have shown a correlation between bronchial responsiveness to methacholine and nebulized hypertonic saline [5].

It has been suggested that respiratory water loss during exercise may initiate exercise-induced asthma (EIA) by inducing a transient hyperosmolarity of the respiratory epithelium [6–8].

We reasoned that if hyperosmolarity of the airway mucosa is an important initiating factor in EIA, there should be a close relationship between responses to inhaled hyperosmolar aerosols and exercise. We have, therefore, compared airway responses to hypertonic, exercise and histamine challenges in a group of ten asthmatic subjects. We have also examined the reproducibility of hypertonic aerosol challenge and compared it to the reproducibility of exercises challenges in a separate group of eleven asthmatic subjects.

Methods

Patients

Group A. The reproducibility and the cumulative nature of hypertonic challenge were assessed, in eleven perennial, atopic, asthmatic subjects (six males, five females, mean age 23 yrs, range 16–33 yrs) known to have EIA, under laboratory conditions using our current methods. Seven of the subjects used inhaled beclomethasone dipropionate and salbutamol as regular therapy, three used regular inhaled salbutamol alone and one used intermittent inhaled salbutamol. No subject had taken oral corticosteroids or methylxanthines in the preceding six months.

Group B. The bronchial responses to ultrasonically nebulized hypertonic saline, histamine and exercise were compared in a further group of ten perennial, allergic, asthmatic subjects. Although all subjects gave a history suggestive of EIA at some time in the past, their response to exercise under laboratory conditions using our methods was not known at the time of recruitment. Six subjects used inhaled beclomethasone dipropionate and salbutamol as regular therapy, two used regular inhaled salbutamol alone and two used intermittent inhaled salbutamol. No subject had taken oral corticosteroids or methylxanthines in the preceding six months.

All subjects in both groups gave informed consent and the study was approved by the Hospital's Ethical Committee.

Protocol

Group A. All eleven subjects performed two identical exercise tasks and three hypertonic saline (HS) challenges. After an initial exercise task, all subjects underwent a hypertonic saline challenge which was administered in a dose-dependent manner with 10 *l* aliquots of aerosol (HS_{DR}). The challenge was discontinued when the decrease in forced expiratory volume in one second (FEV_1) was similar to that observed after the exercise test. Each individual then underwent, in random order, a further exercise test and two hypertonic saline challenges, in which the total volume of hypertonic saline aerosol given in the HS_{DR} challenge was administered as a single dose (HS_C). Each challenge was separated by about one week.

Group B. All ten subjects had their bronchial responsiveness measured to an exercise task, histamine inhalation and inhaled ultrasonically nebulized hypertonic saline. The three challenges were undertaken in random order and each challenge was separated by about one week.

Challenges

All medication was witheld for 12 h before each study day. No subject had a history of respiratory infection or had received oral corticosteroid treatment in the preceding six months. All challenges were performed at the same time of day for each individual. After arrival in the laboratory subjects rested for 10 min before baseline FEV_1 was recorded on a dry bellows spirometer (Vitalograph, UK). Two FEV_1 measurements were recorded on each occasion and the best value was used in the analysis. Baseline FEV_1 was within 10% on each study day for each individual. The ambient temperature varied between 16–22°C and relative humidity ranged from 38–50%.

Exercise challenge (groups A and B)

Subjects wore a noseclip and performed 8 min exercise on a static braked bicycle ergometer at 50–75 W (Bodyguard 990, Oglaend, Sandes, Norway) to achieve 80% of maximal predicted oxygen uptake according to pulse rate. FEV_1 was measured before and immediately after challenge and 5, 10, 15, 30 and 60 min later.

Hypertonic saline aerosol challenge

Hypertonic saline (3.6%) aerosol was generated using a DeVilbiss 65 ultrasonic nebulizer (DeVilbiss UK Ltd, Feltham, Middlesex, UK). This produces particles with a mass median diameter of 4.7 μm [9]. Subjects wore a noseclip and inhaled the mist from a tube 1.4 m long and 2.8 cm diameter, through a mouthpiece attached to a low resistance two-way valve (P. K. Morgan, Chatham, Kent, UK). The volume of expired air was measured using a Wright's respirometer (Medishield, Harlow, Essex, UK). Each 10 *l* of hypertonic saline aerosol delivers 1.6±0.06 g of saline solution (mean±SEM) to the subject at the mouthpiece. Before each challenge baseline FEV_1 was measured, then each subject inhaled room air through the circuit whilst tidal breathing for one minute. The ultrasonic nebulizer was then connected to the circuit and the challenge performed.

Group A. For the hypertonic saline challenge which was administered in a dose response manner (HS_{DR}), 10 *l* of hypertonic saline aerosol was administered during tidal breathing and FEV_1 was recorded 30 s later. If the fall in FEV_1 did not reach the required level, a further 10 *l* was administered and the FEV_1 measured again. This procedure was repeated until a fall in FEV_1 which was similar to that observed following exercise was obtained. The dose needed to produce the required fall in FEV_1 was calculated from the log dose-response curve by linear interpolation from the last two points [4]. This calculated dose was used as a single challenge (HS_C) in subsequent studies and FEV_1 was measured 5, 10, 15, 30 and 60 min later.

Group B. These subjects underwent a single challenge with hypertonic saline aerosol in a dose-response manner (HS_{DR}) identical to group A until a 20% fall from baseline FEV_1 was achieved. The volume of hypertonic saline producing a 20% fall from baseline FEV_1 ($PD_{20}HS$) was determined by linear interpolation of the log cumulative dose-response curve.

Histamine challenge

Histamine acid phosphate in isotonic phosphate buffered saline was delivered from a Wright's nebulizer driven by compressed air at a flow of 8 $l \cdot min^{-1}$ [10]. The concentration of histamine producing a 20% fall in FEV_1 from baseline (PC_{20}) was determined by linear interpolation of the log cumulative dose response curve.

Statistics

The reproducibility of exercise and hypertonic challenges and the comparison of the falls in FEV_1 following HS_{DR} and HS_C were studied by analysis of variance. Subjects were ranked according to their responses to each challenge and correlations between the maximal fall in FEV_1 following exercise challenge, the PC_{20} histamine and the PD_{20} hypertonic saline ($PD_{20}HS$) were examined by Spearman's rank correlation.

Results

Group A. Comparison of the variability of the fall in FEV_1 following the two HS_C challenges and the two exercise tests showed that the variance of the HS_C challenges was 0.151 and that the variance of the exercise challenges was 0.118, giving a variance ratio test (F) of 1.28. Comparison with probability tables of the F-distribution showed that there was no significant difference between the variability of fall in FEV_1 following HS_C or exercise (p=0.7).

Table 1. – Baseline FEV_1 and maximal percentage decreases in FEV_1 following challenge with hypertonic aerosol given in dose dependent manner (HS_{DR}), when total dose was administered as a single challenge on each of two occasions (HS_{C1} and HS_{C2}) and following two identical exercise tasks in eleven subjects (group A)

Subject	HS_{DR} Baseline FEV_1	HS_{DR} % pred	HS_{DR} % Fall	HS_{C1} Baseline FEV_1	HS_{C1} % pred	HS_{C1} % Fall	HS_{C2} Baseline FEV_1	HS_{C2} % pred	HS_{C2} % fall	$Exercise_1$ Baseline FEV_1	$Exercise_1$ % pred	$Exercise_1$ % Fall	$Exercise_2$ Baseline FEV_1	$Exercise_2$ % pred	$Exercise_2$ % fall
1	5.3	112	19	5.3	112	20	5.3	112	14	5.4	114	15	5.0	105	15
2	5.0	112	14	5.4	121	17	5.5	124	14	5.1	115	15	5.5	124	16
3	2.5	88	18	2.5	88	22	2.5	88	24	2.6	91	16	2.5	88	18
4	3.1	75	16	3.0	72	30	3.0	72	40	3.3	80	20	3.1	75	16
5	3.8	107	58	4.1	115	37	3.7	104	58	4.0	113	58	4.0	113	36
6	3.0	98	20	2.8	92	22	3.0	98	17	3.0	98	24	3.0	98	33
7	3.5	86	34	3.5	86	35	3.4	84	54	3.5	86	34	3.5	86	37
8	1.6	57	39	1.6	57	37	1.7	61	22	1.6	57	25	1.6	57	18
9	2.8	70	38	2.7	68	56	2.8	70	46	2.8	70	46	2.7	68	37
10	2.6	75	45	2.8	81	47	2.7	78	31	2.7	78	44	2.7	78	54
11	1.7	57	41	1.7	57	32	1.7	57	44	1.8	60	29	1.8	60	27
Mean	3.2	85	31	3.2	86	32	3.2	86	33	3.3	87	30	3.2	87	28
SEM	0.4	6	4	0.4	7	4	0.4	6	5	0.4	6	4	0.4	7	4

FEV_1: forced expiratory volume in one second in litres; MS_{DR}: hypertonic aerosol given in dose dependent manner; HS_{C1}, HS_{C2}: total hypertonic aerosol dose given as single challenge on two occasions; $Exercise_1$, $Exercise_2$: two identical exercise tasks

The mean of the fall in FEV_1 following challenge with HS_{DR} was not significantly different from the mean of the fall following the two HS_C challenges (HS_{DR} and HS_{C1}, p=0.86; HS_{DR} and HS_{C2}, p=0.89; HS_{C1} and HS_{C2} p=0.84). The difference in the means was 0.036 *l* (95% confidence intervals -0.164–0. 236 *l*) (table 1).

Group B. There was a statistically significant correlation between the fall in FEV_1 following exercise and $PD_{20}HS$, by Spearman's rank correlation (r=0.68, p<0.05) (table 2 and fig. 1). There was also a statistically significant correlation between the $PD_{20}HS$ and

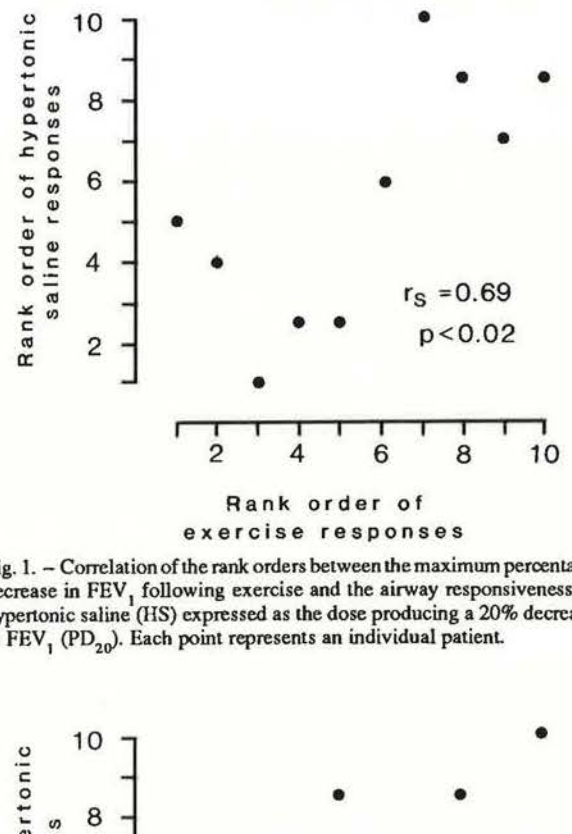

Fig. 1. – Correlation of the rank orders between the maximum percentage decrease in FEV_1 following exercise and the airway responsiveness to hypertonic saline (HS) expressed as the dose producing a 20% decrease in FEV_1 (PD_{20}). Each point represents an individual patient.

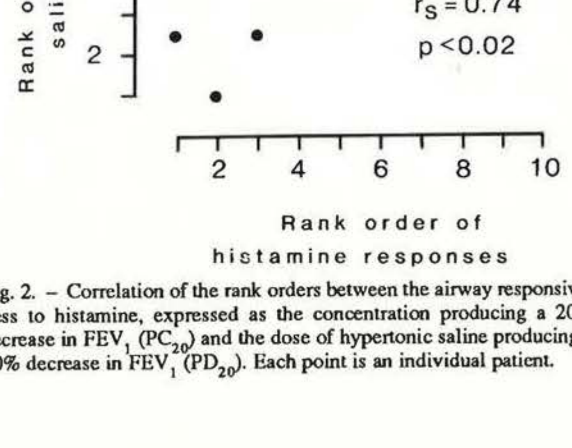

Fig. 2. – Correlation of the rank orders between the airway responsiveness to histamine, expressed as the concentration producing a 20% decrease in FEV_1 (PC_{20}) and the dose of hypertonic saline producing a 20% decrease in FEV_1 (PD_{20}). Each point is an individual patient.

Table 2. – Baseline FEV_1 and airway responses to hypertonic saline, exercise and histamine in ten asthmatic patients (group B)

Subject	Baseline FEV_1	% pred	$PD_{20}HS$ *l*	Baseline FEV_1 *l*	% pred	Maximum % fall in FEV_1 after exercise	Baseline FEV_1	% pred	PC_{20} histamine $mg \cdot ml^{-1}$
12	3.7	84	9	3.4	77	36	3.4	77	0.21
13	2.7	77	12.5	2.7	77	26	2.7	77	0.72
14	2.8	70	12.5	2.8	70	20	2.7	68	0.03
15	2.5	88	14	2.5	88	39	2.6	84	2.3
16	2.5	82	15	2.5	82	54	2.4	79	3.5
17	5.0	111	23	5.1	113	16	5.3	118	1.5
18	3.8	105	35	4.0	111	7	3.7	103	2.3
19	1.7	52	60	1.7	52	14	1.7	52	1.6
20	3.1	75	60	3.3	80	26	3.3	82	3.1
21	5.3	112	75	5.3	112	18	5.4	114	3.6
Mean	3.3	86	33	3.3	86	24	3.3	85	1.89
SEM	0.4	6	8.5	0.4	6	5	0.4	6	0.41

FEV_1: forced expiratory volume in one second in litres; $PD_{20}HS$: volume hypertonic saline producing a 20% fall in baseline FEV_1; PC_{20}: concentration of histamine producing a 20 % fall in baseline FEV_1.

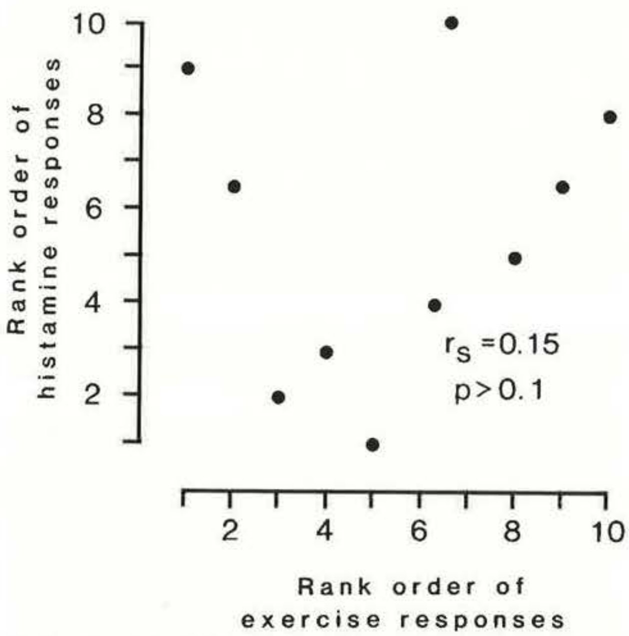

Fig. 3. – Correlation of the rank orders between the maximum percentage decrease in FEV_1 following exercise and the airway responsiveness to histamine expressed as the concentration producing a 20% decrease in FEV_1 (PC_{20}). Each point is an individual patient.

PC_{20} histamine, (r=0.74, p<0.02) (table 2 and fig. 2). However, the correlation between the fall in FEV_1 following exercise and PC_{20} histamine (r=0.15, p>0.1) (table 2 and fig. 3) was not statistically significant.

Discussion

Our present experiments show that challenge with intermittent doses of hypertonic aerosol, as given in this study, produces the same bronchoconstriction as that seen when the whole cumulative dose is given as a single challenge. In this respect, the challenge is similar to the bronchoconstriction which is produced by inhaled histamine but not by inhaled methacholine [11]. The reproducibility of challenge with hypertonic saline aerosol was found to be similar to the reproducibility of exercise challenge in the same subjects.

Some of the previous studies which have examined the relationship between histamine bronchial reactivity and exercise challenge have documented a correlation between EIA and histamine reactivity [12, 13]. This supports the concept that EIA is an expression of bronchial hyperresponsiveness [14]. However, Mellis *et al.* [13] did not provide sufficient data to enable calculation of the strength of the relationship, and another study on 29 children [2] found only a very weak correlation (r=0.38) between EIA and the histamine index. Anderton *et al.* [12] found a good correlation between the severity of EIA and histamine responsiveness, when the response to exercise was expressed in terms of lability. If their results were expressed as a percentage fall in FEV_1 from baseline values as in this study, the correlation would not have been significant (r=0.41, n=19, p=0.08). There is a good correlation between bronchial reactivity as assessed by histamine and methacholine challenge [11] and several groups have reported a correlation between EIA and methacholine bronchial reactivity [15–17]. However, Foresi *et al.* [18] did not find a correlation between methacholine responsiveness and EIA. Thus, there is discordance between different studies on the relationship between the severity of EIA and histamine and methacholine bronchial reactivity. Smith *et al.* [5] have recently reported a close correlation between bronchial reactivity as measured by nebulized hypertonic saline and methacholine inhalation.

We have previously shown that there are similarities between asthma induced by exercise and by hypertonic aerosol challenge, in that they appear to share a final common pathway [19], and that both are associated with the release of a high molecular weight neutrophil chemotactic activating factor (NCA) [20, 21].

In this study we have compared EIA, hypertonic and histamine responsiveness in the same ten individuals. There was a significant correlation between bronchial responsiveness to histamine and hypertonic saline aerosol, and there was a significant correlation between EIA and bronchial reactivity to hypertonic saline challenge. However, there was no significant correlation between EIA and bronchial responsiveness to histamine. Although it is possible that such a relationship might have been detected if patients with lower histamine reactivity had been studied, our data suggest that the relationship between EIA and bronchial responsiveness to hypertonic saline aerosol is closer than that between EIA and histamine response.

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Réponses des voies aériennes à la solution saline hypertonique à l'effort et aux provocations à l'histamine dans l'asthme bronchique. N. Belcher, T. Lee, P. Rees.

RÉSUMÉ: Les réponses des voies aériennes à l'histamine, à l'effort et à une solution saline hypertonique nébulisée au moyen d'un aéroliseur ultrasonique, ont été comparées chez 10 patients asthmatiques. Les réponses à la solution saline hypertonique n'ont pas été significativement différentes lorsque le même volume d'aérosol était donné en une dose unique ou en 10 aliquots/litre, suggérant que la provocation est cumulative. La variabilité de la réponse à la provocation au moyen de solution saline hypertonique n'est pas significativement différente de celle de la provocation par l'effort. La réponse à la solution saline hypertonique est en corrélation significative avec l'effort ($r=0.68$, $p<0.05$) et avec la réponse à l'histamine ($r=0.74$, $p<0.02$), mais la corrélation entre l'effort et l'histamine n'est pas statistiquement significative ($r=0.15$, $p>0.1$). Ces observations suggèrent que l'asthme induit par l'effort a une relation plus étroite avec l'hyperréactivité bronchique à l'aérosol de solution saline hypertonique, qu'il ne l'a avec une réactivité non spécifique démontrée par une provocation à l'histamine.

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