Histamine reactivity during the refractory period after exercise induced asthma

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ABSTRACT An episode of exercise induced asthma will usually be followed by a period during which further exercise will not induce asthma. Postulated mechanisms include persistence of catecholamines released during exercise, development of tolerance to released mediators, and mediator depletion. To investigate the underlying mechanism further eight asthmatic men underwent three experimental protocols as follows: two treadmill runs of eight minutes; two incremental challenges with histamine inhalation; and a treadmill run of eight minutes followed by an incremental challenge with histamine inhalation. In each case the two challenges began 40 minutes apart. Patients performed the paired exercise trial first. Refractoriness to bronchoconstriction was shown in the repeated exercise studies but did not occur with repeated histamine challenge. The geometric mean histamine concentrations required to produce a 20% fall in forced expiratory volume in one second (FEV_1) were 1·53 mg/ml and 0·93 mg/ml for the first and second challenges respectively (NS) and 1·4 mg/ml (NS) for the histamine challenge after exercise. It is concluded that refractoriness to exercise induced asthma is not explained by the development of smooth muscle tolerance to repeated histamine exposure or by the persistence of catecholamines released during exercise. The data are consistent with the theory of mediator depletion as the cause of refractoriness.

After an attack of exercise induced asthma, many asthmatic patients show a refractory period characterised by a substantially diminished bronchoconstrictive response to further exercise challenge.[1-3] For any individual the duration of this period appears to be directly proportional to the severity of the initial asthmatic episode and, in some cases, may exceed two hours.[3]

The existence of the refractory period after exercise induced asthma has generally been attributed to depletion of mediators stored in airway mast cells.[2-4] An alternative suggestion is that there may be increased sympathoadrenal effects with repeated exercise.[5] We reasoned that, if the first hypothesis were true, the sensitivity of subjects to inhaled his-

tamine should remain unchanged during the refractory period. If refractoriness is due to accumulation of bronchodilating catecholamines persistence of these substances after an initial exercise test should afford some protection from the effects of histamine challenge. We therefore compared the response to inhaled histamine during the refractory period with the response in the absence of preceding exercise. We also examined the effect of repeated histamine provocation to exclude the development of smooth muscle tolerance to histamine as the mechanism of refractoriness.

Methods

Eight men (mean (SD) age 30·6 (9) years) gave their informed consent. All had a history of exercise induced asthma and showed a reduction of more than 15% in forced expiratory volume during the

first second of exhalation (FEV_1) in response to a preliminary exercise test.

PAIRED EXERCISE TEST

Each subject initially performed two treadmill runs of eight minutes each separated by a recovery period of 32 minutes, the times being in keeping with the work of Schoeffel *et al*.[4] The running speed was that which during preliminary tests produced a heart rate of 80–85% of the age predicted maximum.[6] During exercise subjects breathed dry medical air from a Keogel Y valve connected to a balloon reservoir. The air was first cooled to below −20°C by passage through a copper coil immersed in alcohol and dry ice, ensuring a moisture content of less than 1·07 mg/l.[7] Rewarming of the air before inhalation produced a mean (SD) inspiratory temperature of 11·7° (2·9°)C. In no subject did this temperature vary by more than 2°C between tests. Minute ventilation rates were recorded by a Hewlett Packard pneumotachograph in the inspiratory line. Expired air was passed through a 5 l mixing box, from which samples were drawn during the final two minutes of each treadmill run. The samples were analysed for oxygen and carbon dioxide content (Morgan oxygen analyser model OA-500 and Morgan carbon dioxide analyser model 901-MK2), and oxygen uptakes were computed.

Temperatures of inspired and expired air were measured by standard thermistor probes (Yellow Springs Instruments, series 409-A) positioned 3·5 cm upstream and downstream from the oral cavity and connected to telethermometers (Yellow Springs Instruments, model 46 TUC). Respiratory heat exchange values were estimated for each minute of exercise using the formula of Deal *et al*.[8] Dryness of the inspirate and full saturation of the expirate were assumed.

FEV_1 was measured one minute before the start of the first of the paired exercise tests and immediately after its completion. Further measurements were taken after five, 10, 15, 20, 28, and 31 minutes' recovery, the last recording representing the pre-exercise value for the second treadmill challenge. After the second challenge FEV_1 was measured at the same intervals except that observation was stopped after 20 minutes' recovery. All measurements were made with a Minato Autospirometer Model AS-700. Subjects were considered to have shown refractoriness if the percentage reduction in FEV_1 from the immediate pre-exercise value was less than half as great for the second run as for the first.[4]

DUAL HISTAMINE CHALLENGE

On another day subjects underwent two challenges with histamine inhalation, each requiring adminis-

tration of histamine in increasing concentrations (0·03, 0·06, 0·125, 0·25, 0·5, 1·0, 2·0, 4·0, 8·0, and 16·0 mg/ml) until FEV_1 fell by 20% from the preinhalation baseline. The second challenge began 40 minutes after the first. Histamine aerosols were generated by means of a Hudson nebuliser attached to a cylinder of medical air set at a flow rate of 8 l/min. Subjects inhaled five inspiratory capacities of each concentration with 75 seconds between successive dosages. FEV_1 was measured immediately before challenge and one minute after administration of each histamine dosage.

ADMINISTRATION OF HISTAMINE AFTER EXERCISE

On a separate occasion subjects completed an eight minute treadmill run followed 40 minutes later by a histamine inhalational challenge. Both challenges followed the protocols outlined above.

STATISTICAL ANALYSIS

The concentration of histamine causing a 20% fall in FEV_1 (PC_{20}) was obtained from individual dose response curves, and geometric mean values were calculated. Baseline and subsequent FEV_1 values were compared by repeated measures analysis of variance followed where necessary by paired *t* tests. The same techniques were used to compare oxygen uptake, minute ventilation, and respiratory heat loss during exercise. One way repeated measures analysis of variance was applied to the natural logarithms of PC_{20} values.

Results

FACTORS INFLUENCING REPRODUCIBILITY OF CHALLENGES

Mean FEV_1 values recorded on arrival at the laboratory did not differ significantly between the three experimental protocols (p > 0·05). The two exercise tests constituting the first challenges of their respective paired sequences did not differ significantly (p > 0·05) in terms of oxygen uptake, minute ventilation, or respiratory heat loss (table 1). The tests evoked very similar changes in FEV_1, with maximum percentage falls virtually identical in seven of the eight subjects (mean (SD) values 43·2 (12·7)% and 42·7 (10·7)%. The coefficient of variation[9] was 6·6%. Recovery was more rapid from histamine provocation than from exercise. Baseline FEV_1 scores before the second of the paired provocations with histamine were therefore significantly higher than those for the challenge after exercise (p < 0·05; table 2).

Table 1 *Mean values of oxygen uptake, total ventilation, and total respiratory heat loss for the three exercise challenges. (Differences did not reach significance (p = 0·05) on any occasion*

		Run 1: paired exercise test	*Run 2: paired exercise test*	*Run before histamine challenge*
Oxygen uptake (l/min)	Mean	2·33	2·41	2·37
	SD	0·54	0·56	0·60
Total ventilation (1 BTPS)	Mean	473·9	473·0	456·0
	SD	139·6	121·1	121·2
Total respiratory heat loss (kJ)	Mean	41·8	41·5	39·7
	SD	13·8	11·8	11·4

Conversion: SI to traditional units—Heat loss: 1 kJ ≈ 0·24 kCal. BTPS—body temperature, pressure and saturation.

PAIRED EXERCISE CHALLENGE

Maximum fall in FEV_1 averaged 43·2 (12·7)% for the first run and 15·7 (9·0)% for the second (figure). According to the criterion employed, all eight subjects showed refractoriness. Mean pre-exercise FEV_1 was significantly lower for the second treadmill run (1·85 (0·47) l) than for the first (2·65 (0·55) l; $p < 0·001$). The immediate postexercise scores, however, were not significantly different ($p > 0·05$), and the second run was associated with significantly higher values at five, 10, 15 ($p < 0·05$ in each case), and 20 ($p < 0·01$) minutes of recovery (figure). This was despite close similarity of the two runs in terms of minute ventilation, respiratory heat loss, and oxygen uptake (table 1; $p > 0·05$) by Student's t test in each case).

DUAL HISTAMINE CHALLENGE

Table 2 shows the PC_{20} values for each subject. The geometric mean PC_{20} was 1·53 mg/ml for the first challenge and 0·93 mg/ml for the second. The difference was not significant ($p > 0·05$). Of the eight subjects, five showed increased sensitivity to histamine in the second trial, two were less responsive, and one showed little change. Mean (SD) baseline FEV_1 was slightly higher for the first challenge (2·50 (0·49) l) than for the second (2·33 (0·44) l), but the difference was not significant ($p > 0·05$).

HISTAMINE CHALLENGE AFTER EXERCISE

For the histamine challenge after exercise the geometric mean PC_{20} was 1·4 mg/ml. This was not significantly different from the corresponding values for the first and second stages of the dual histamine challenge ($p > 0·05$; table 2).
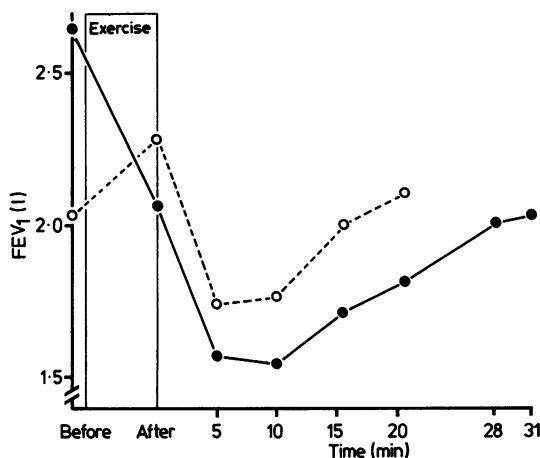
Mean forced expiratory volumes in one second (FEV_1) in eight men with refractory asthma during a paired exercise test with two treadmill runs of eight minutes separated by an interval of 32 minutes. Figures on the horizontal axis indicate time after the end of exercise. ——— Exercise 1; – – – exercise 2.

Table 2 *Prechallenge forced expiratory volumes in one second (FEV$_1$) and histamine concentrations required to produce 20% fall in FEV$_1$ (PC$_{20}$) for the various challenges with histamine*

Case No	Dual histamine challenge I		Dual histamine challenge II		Histamine challenge after exercise	
	Baseline FEV$_1$ (l)	*PC$_{20}$ (mg/ml)*	*Baseline FEV$_1$ (l)*	*PC$_{20}$ (mg/ml)*	*Baseline FEV$_1$ (l)*	*PC$_{20}$ (mg/ml)*
1	1·86	8·17	1·98	2·80	1·31	7·39
2	2·10	1·22	2·08	0·46	1·65	1·08
3	2·50	1·12	1·75	5·47	1·86	1·72
4	2·40	3·16	2·20	0·82	1·30	0·24
5	2·32	2·32	2·47	0·82	2·57	0·76
6	3·21	0·22	2·81	0·35	2·60	0·41
7	2·37	0·83	2·25	0·07	2·49	2·27
8	3·25	1·97	3·10	4·86	2·34	6·36
Mean	2·50		2·33		2·02	
(SD)	(0·49)		(0·44)		(0·55)	
Geometric mean		1·53		0·93		1·40

Discussion

Previous research has indicated clearly that there are some asthmatic patients who do not show refractoriness after exercise induced asthma.[1 4] The eight subjects in the present study were selected on the basis of their refractory responses to the paired exercise challenge. This refractoriness was apparently not due to increased tolerance of airway smooth muscle resulting simply from the effects of repeated exposure to histamine as successive challenges with exogenous histamine produced no overall diminution in pulmonary responsiveness. This finding contradicts the work of Schoeffel *et al*, who reported a significant reduction in bronchial hyperreactivity to histamine with repeated challenges.[4] They, however, administered histamine in progressively increasing concentrations in the case of the initial challenge and as a single large dose in subsequent trials. The actual histamine concentrations in the airways may therefore have differed between challenges. In our study histamine was always administered in gradually increasing dosage. Furthermore, Schoeffel *et al* allowed a clear interval of 40 minutes between successive histamine trials.[4] We allowed an interval of this duration between the starts of the two challenges so that the period between the end of the first challenge and the beginning of the second was about 30 minutes. This earlier rechallenge may have limited opportunity for repolarisation of airway smooth muscle cells.

It is conceivable that persistence of catecholamines after exercise could produce changes in airway smooth muscle that might protect from the influence of subsequent mediator exposure.[5] The available evidence indicates, however, that plasma adrenaline concentration either does not rise in asthmatic patients in response to exercise[10] or shows a rapid return to resting concentrations after stopping exercise.[11] Furthermore, if the effects of catecholamines did persist, reduced histamine sensitivity might be expected during the refractory period, but this was not seen. The question arises of whether the unchanged PC_{20} in the presence of a significantly reduced baseline FEV_1 (table 2) indicates a real decrease in histamine reactivity. The crucial comparison in the present context concerns the exercise and histamine provocations carried out during the refractory period after initial exercise challenge. The mean baseline FEV_1 scores for these provocations were very similar. The histamine challenge produced a percentage fall in FEV_1 similar to that seen under control conditions, whereas the exercise challenge (by definition) did not. These findings indicate that during the period of diminished sensitivity to exercise there is no equivalent change in responsiveness to histamine. The suggestion that refractoriness is due to persistence of bronchodilating catecholamines after initial exercise[5] is therefore not supported.

The refractory period after exercise induced asthma has been widely ascribed to depletion of mediators stored in airway mast cells.[2–4] The duration of the refractory period is believed to correspond to the time required for complete mediator resynthesis.[3] This view is supported by evidence clearly suggesting mast cell roles in at least a substantial proportion of cases of exercise induced asthma. Lee *et al* reported increased plasma concentrations of neutrophil chemotactic factor in association with development of exercise induced asthma and also showed that no such increase occurs in response to exercise performed with warm humid inspirate to prevent asthmatic attack.[12] Anderson *et al* have observed raised arterial histamine concentrations during acute exacerbations of asthma provoked by exertion.[13] Pre-exercise inhalation of disodium cromoglycate, a substance capable of inhibiting mast cell degranulation, can prevent or ameliorate exercise induced asthma in most patients.[14 15] A similar finding has been reported with H_1 receptor antagonists.[16]

Our data are compatible with the theory of mediator depletion. Reduced percentage fall in FEV_1 with exercise at a time of unchanged PC_{20} for histamine certainly suggests the possibility of considerably decreased mediator release. The extent of mediator depletion that would be necessary to explain this result is debatable. In the early stages of exercise asthmatic patients typically bronchodilate.[17] In the second of the paired exercise tests the initial bronchodilating influence may have caused rapid repolarisation of airway smooth muscle after initial exercise induced asthma. Accordingly, the underlying state of airways at the time of mediator release in the second test may have been better than suggested by the pre-exercise FEV_1. Use of the pre-exercise reading as a baseline for calculating maximum reduction in FEV_1 may therefore have led to overestimation of the degree of refractoriness displayed by our subjects.

Arguments against mediator depletion as the mechanism of refractoriness are based partly on the report of Ben-Dov *et al* that exercise with hot humid inspirate (which produces little or no asthma) is often followed by a refractory period.[18] This report, however, is in conflict with the findings of Anderson *et al*[19] and with unpublished data from our laboratory. Repeated brief treadmill runs can cause refractoriness without provoking asthma,[20] but this may be due to release of mediators over an extended period at a rate insufficient to affect airways calibre. We

believe that, on the current evidence, mediator depletion remains the most likely explanation for the refractory period after exercise induced asthma.

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