

Influence of Relative Humidity and Repeated Exercise on Exercise-Induced Bronchoconstriction

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The relationship between previous exercise-induced bronchoconstriction (EIB) of different magnitude and the pulmonary response to exercise 1 h later was examined in asthmatic children. After acclimatization they performed repeated, paired exercise tests in a clean-air climatic chamber at 23°C. The first test of each pair was carried out in 15%, 50% and 85% relative humidity (RH), respectively, to produce different degrees of EIB. All second tests were performed in 50% RH. Changes in pulmonary function were assessed by measuring PEF and FEV₁.

Bronchodilatation during exercise was not influenced by RH, whereas dry air increased and humid air decreased the bronchoconstrictive response to exercise. When both tests were performed in 50% RH, the second test caused significantly less EIB than did the first test. However, no differences were found between the three second test responses.

This suggests that the relative refractoriness after an episode of EIB is not related to the severity of previous bronchoconstriction, but could be associated with exercise as such or other mechanisms in EIB.

Key words: bronchial asthma; climatic chamber; exercise-induced asthma; refractory period; relative humidity.

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In recent years several reports have demonstrated a decreasing bronchospastic response to exercise with increasing humidity of inhaled air (2, 5, 27). These results indicate that cooling of the bronchial mucosa during exercise is the initiating stimulus for exercise-induced bronchoconstriction (EIB). Despite these developments in the understanding of EIB, the fundamental mechanism underlying this phenomenon is still not clearly defined. It has been suggested that EIB is the result of released, mast-cell derived mediators. This conception has been supported by the prophylactic effect of sodium cromoglycate on EIB (1, 12, 13), and the relative refractoriness seen after an episode of EIB has been considered due to depletion of

stored mediators, which takes time to regenerate (4, 11, 18). Few studies have been designed to evaluate the refractory period, and the effect of exercise as such in repeated EIB is not known.

The aim of the present study was further to investigate how post-exertional bronchoconstriction of different magnitude influences the severity of the response in a following exercise test. This was attained by keeping the individual work loads constant during the study and by modulating the bronchospastic responses by the effect of relative humidity on EIB. This method also gave the possibility to examine, whether humidity influences the bronchodilatation during exercise.

SUBJECTS AND METHODS

Climate chamber

The study was carried out in the climate chamber at the Institute of Hygiene, University of Aarhus. This chamber has a floor area of $5.55 \text{ m} \times 5.45 \text{ m} = 30 \text{ m}^2$ and a volume of 76 m^3 . Walls, ceiling and floor in the chamber are made of stainless steel with a temperature controlling tube-system built in between the steel plates and insulation layer behind the surfaces. The air flow in the chamber is adjustable and was set to a volumetric flow of 500 m^3 per hour equal to an air change rate of 6.5 per hour, and a ventilation rate of 23 liters per person and second when the chamber was occupied by a maximum of six individuals. The air supplied to the chamber was outdoor air purified in the air conditioning system of the chamber by passing a prefilter unit type HI-FLO 3P-45, an Absolute filter type 1D-1000-11, a carbonfilter type Camcarb-1000, and an additional filter type HI-FLO 3P-45. Relative humidity of the room air was continuously controlled by a hygrostatic Lithium Chloride Sensor in the chamber. When needed, air was humidified by steam injection made by an Armstrong AMPH32DM-1 humidifier, and dehumidified when needed in two steps: the first step by water vapour condensation in cooling coils of the air conditioning system, and the second step by passing a Munters type MA-1000-20-22E rotating adsorption/dryer unit.

Subjects

Fourteen asymptomatic children, 9–15 years old (mean age 11.4 years), with a history of EIB were studied with the approval of their parents. The selection criterion for EIB was a fall in *peak expiratory flow* (PEF) of 15% or more after submaximal exercise. Eleven children completed the study. They were all considered atopic as demonstrated by clinical histories and skin prick tests with common allergens. All had perennial bronchial asthma and, in addition, six subjects had allergic rhinitis. Eight subjects used inhaled salbutamol and/or sodium cromoglycate daily

for control of symptoms, three were free from medicine. Medication was withheld for at least 12 h prior to all experiments.

Study design

All tests were started at the same time of day after 1 hour's rest in the climate chamber. Each subject performed two exercise tests daily on 3 consecutive days. All conditions were kept constant except relative air humidity (RH). The first test of each pair was, in random order, carried out in 15%, 50% and 85% RH, respectively at 23°C . After 1 hour's rest the test was repeated in 50% RH. Change in RH was initiated 20 min after the first test, and was fulfilled not later than 15 min before the second test.

Exercise testing

Exercise tests were performed on a mechanically braked ergometercycle (Monark, Sweden) and consisted of 6 min continuous pedalling (70 rounds/min) with a constant work load adjusted to 80–85% of the maximal working capacity. Each child undertook the same work load during the study. Loads were determined a few days prior to the study and ranged from 1.2 to 3.0 Watts per kg body weight (mean $\pm$ 1 SD, 2.6 ± 0.3 Watts). Immediately before exercise the children were provided with a nose-clip to ensure identical respiration in separate tests.

During the last minute of exercise the heart rate was monitored by radiotelemetry (Danica, Denmark) and displayed on a recorder.

Pulmonary function

To assess pulmonary function, *peak expiratory flow* (PEF) was measured with Wright's Peak Flowmeter (Airmed, England) on entry to the chamber, immediately before exercise, after 2, 4, and 6 min of exercise and 3, 5, 10, 15 and 20 min after exercise. *Forced expired volume in 1 s* (FEV_1 , BTPS) was measured before exercise and 5, 10, and 20 min after exercise. FEV_1 was calculated from a spirogram (Vitalograph, England) and was always measured immediately after peak flow. In all measurements the best of

three efforts was used. All values were calculated to percent of expected normal values (14, 15).

The data were analyzed by two-factor analysis of variance and Student's t-test for paired comparisons. Correlation coefficients (*r*) between parameters were calculated from the individual values by the method of linear least squares.

RESULTS

Eleven children, six boys and five girls, completed the study. Their resting percent expected FEV₁ at start of the study was 82 ± 10% (mean ± SD) indicating mild bronchoconstriction. Three children were excluded, one because of poor co-operation, two because of too excessive changes in resting pulmonary function on separate days.

Mean room temperature during the study was 22.5 ± 0.4°C (SD). Control-readings of relative humidity in the first tests were 15 ± 2%, 50 ± 0% and 83 ± 2%, respectively, and in the second tests 49 ± 0% (means ± SD).

Mean percent expected PEF at rest, the highest observed mean PEF during exercise, and mean heart rate (HR) during the last min of

exercise are shown in Table 1. An analysis of variance showed no significant within- or between-day differences in resting PEF, either initial to acclimatization (*F* = 1.04, 3.20 df, NS) or pre-exercise (*F* = 0.66, 5.50 df, NS), and t-tests showed no significant changes in PEF in the acclimatization period. Similarly, no significant differences were found in HR between studies (*F* = 2.21, 5.50 df, NS). During exercise, there was a significant improvement in PEF (percent expected, 94 ± 1%) compared to the mean resting value (78 ± 2%, *P* < 0.001, t-test). Bronchodilatation was negatively correlated to pre-exercise PEF (*r* = -0.45, *P* < 0.001). On an individual basis, the upper level of PEF during exercise showed no significant changes between studies (*F* = 0.09, 5.50 df, NS), indicating independence of previous exercise and relative humidity.

Fig. 1 illustrates the mean changes in percent of expected PEF during exercise experiments. As seen, PEF increased during exercise and decreased to a minimum 3–5 min after cessation of work. In the first tests with variable humidity, the degree of bronchoconstriction was highly dependent on RH (85% RH vs. 50% RH, *P* < 0.05, 85% RH vs. 15% RH, *P* < 0.001 and 50% RH vs. 15% RH, *P* < 0.01). In the second tests, which were all performed in 50%

Table 1

Mean peak expiratory flow (PEF, percent expected) in 11 asthmatic children before acclimatization (initial), pre-exercise and during exercise (highest observed). The paired tests were performed 1 h apart on 3 consecutive days. Heart rate was recorded during the last min of exercise. All values are mean ± SD

Test No.	Relative air humidity	PEF (% expected)			Heart rate
		Initial	Pre-exercise	During exercise	
1	15	77 ± 10	81 ± 9	94 ± 11	186 ± 8
2	50		77 ± 10	95 ± 12	187 ± 8
1	50	79 ± 10	78 ± 10	93 ± 10	186 ± 7
2	50		76 ± 10	93 ± 13	189 ± 8
1	85	75 ± 10	76 ± 13	94 ± 13	187 ± 7
2	50		79 ± 14	94 ± 16	186 ± 8
F-value		1.04	0.66	0.09	2.21
P-value		N.S.	N.S.	N.S.	N.S.

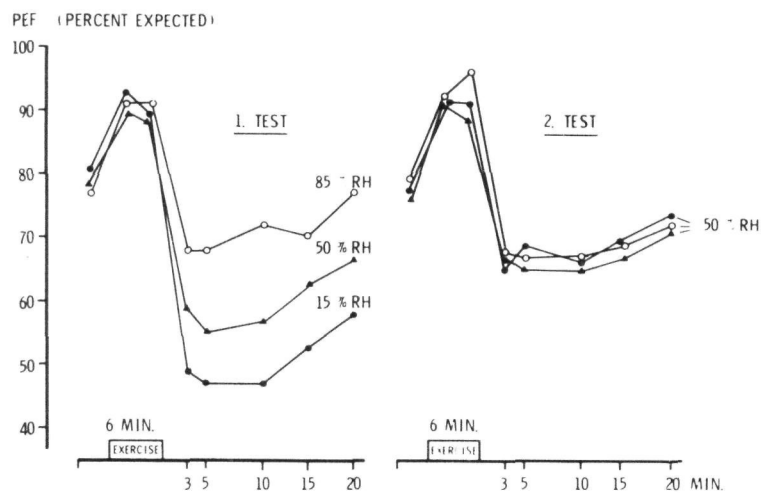


Fig. 1. Mean changes in peak expiratory flow (PEF, percent expected) during and after exercise challenges in 11 asthmatic children. The first tests were performed in variable relative humidity (RH) on 3 consecutive days. The corresponding second test was performed in 50 % RH, 1 h after the first test.

RH, the bronchoconstrictive responses did not differ statistically by t-tests. However, when both the first and the second test were performed in the same condition (50 % RH), the second test caused significantly less EIB than did the first test ($P < 0.02$).

Table 2 shows resting and minimal post-exercise FEV₁ (percent expected) during the

study. Again there were no significant within- or between-day differences in resting values ($F = 0.57$, 5.50 df, NS) though FEV₁ did not recover fully in all subjects after testing in 15% and 50% RH. The changes in FEV₁ following exercise paralleled those in PEF: dry air increased and humid air decreased the broncho-spastic responses in the first tests, whereas the

Table 2
Percent expected FEV₁ in 11 asthmatic children before (pre-exercise) and after (minimum observed) exercise challenges. The first tests were performed in different relative humidity (RH) and *, **, *** denote corresponding tests in the pairs of two tests

Patient	First test						Second test					
	15 % RH*		50 % RH**		85 % RH***		50 % RH*		50 % RH**		50 % RH***	
	Pre-exercise	Mini-mum	Pre-exercise	Mini-mum	Pre-exercise	Mini-mum	Pre-exercise	Mini-mum	Pre-exercise	Mini-mum	Pre-exercise	Mini-mum
1	91	31	96	31	80	29	67	31	64	33	49	31
2	75	32	81	56	86	78	94	75	90	67	103	72
3	59	52	62	64	67	71	67	72	72	71	79	69
4	80	35	74	52	67	57	63	61	61	62	65	54
5	89	67	88	78	92	88	88	80	91	83	92	83
6	71	54	71	53	71	71	81	69	67	55	79	66
7	88	61	84	66	84	80	84	81	81	80	86	82
8	71	52	84	66	69	69	75	71	74	68	68	71
9	83	67	83	79	87	85	83	79	83	73	87	79
10	86	40	90	66	82	60	82	62	90	66	80	60
11	94	22	83	35	96	96	58	63	75	69	98	75
Mean ± SE	81 ± 3	47 ± 5	82 ± 3	59 ± 5	80 ± 3	71 ± 6	77 ± 3	68 ± 4	77 ± 3	66 ± 4	81 ± 5	68 ± 5
		P < 0.001				P < 0.05		NS		NS		
		P < 0.002					NS					
		P < 0.02				P < 0.05		P < 0.05		P < 0.05		

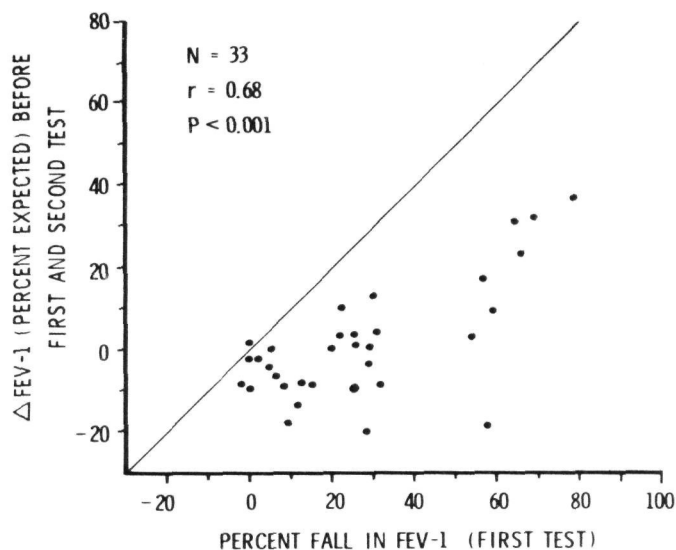


Fig. 2. The relationship between percent fall in FEV_1 (first tests) and the difference in resting percent of expected FEV_1 before the first and the second test (FEV_1). The line of identity is shown.

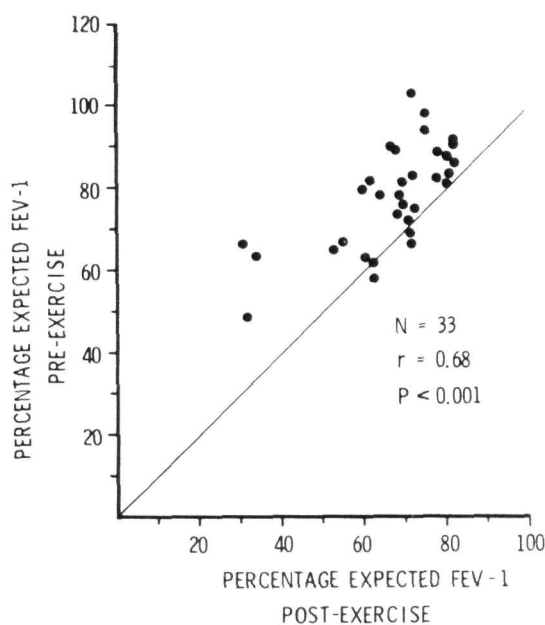


Fig. 3. The relationship between percent expected FEV_1 pre-exercise and minimum post-exercise in all second tests. The line of identity is shown.

responses in the second tests were of the same magnitude ($F = 0.53$, 2.20 df, NS). When comparing the first test performed in 50% RH and the three second tests, they all caused less EIB than did the first test.

When analysing the effect of the first test on the second test, a positive linear correlation between the degree of bronchoconstriction in the first test and the difference in resting FEV_1 before the first and the second tests was found

(Fig. 2). In the second tests a positive correlation between resting FEV_1 and minimal post-exercise FEV_1 (both as percent of expected) was found (Fig. 3).

DISCUSSION

In the present investigation it was essential that individual lung ventilation during exercise was reproduced in successive tests. As we had chosen to study the subjects in a free-breathing system, ventilation was controlled indirectly by measuring heart rate only. However, in sub-maximal exercise testing with constant work load, it has been shown that heart rate and ventilation rise linearly with $\dot{V}O_2$ and reach steady state within 4–6 min (7). The insignificant fluctuations in heart rate together with the observation of a rather constant upper limit of PEF during exercise suggests that the ventilation during exercise was reproduced in the present study.

PEF and FEV_1 were used in preference to other methods for measuring pulmonary function, because these parameters are reproducible and have been well defined. Furthermore, together they have shown to be the most useful in discriminating pulmonary responses of different magnitude (19). One limitation is that PEF and FEV_1 are insensitive to changes in small airways, which have been shown, in some patients at least, to be the predominant site of obstruction in EIB (21). On the other hand, Cropp (8) and Mildon et al. (23) found that the predominant site of obstruction was in the larger, central airways in the majority of patients with EIB, and Biermann (3) noted in a study of theophylline on EIB that the changes in large and small airways paralleled each other.

One of the major problems in comparing exercise responses in asthmatics is the variability in pre-exercise pulmonary level across time. In exercise testing the responses have often been calculated as maximum percentage decrease from pre-exercise resting value (baseline). Using this expression, it has been shown that in individual patients the percent decrease in airway function is independent of the baseline level expressed as percentage of the expected normal

value (26). However, when comparing paired EIB tests under equal conditions it is obvious that the post-exercise fall in airway function will vary depending upon the baseline pulmonary level. In the present study the severity of EIB in the first tests influenced baseline airway function before the second tests. Therefore, we represent the exercise responses as the lowest observed post-exercise pulmonary level in terms of percentage of expected normal values.

The main result of the present investigation was that bronchoconstriction following exercise decreased with increasing relative humidity, and that the considerable differences in these responses were not reflected in the second test responses, which were of the same magnitude. The effect of humidity on EIB confirms the observations by others (2, 5, 27), whereas the lack of relationship between the severity of EIB in the first and second tests is in contrast to the results of Edmunds et al. (11). In a comparable study they found an inverse relationship between the severity of EIB in the first and second tests and suggested that this was due to consumption of stored mediators. The discrepancy between the results from Edmunds et al. and those in the present study might partly be explained by different protocols. They used varying work loads to produce different amounts of EIB in the first tests, and the paired tests were performed with 30 min interval, whereas we used constant work loads and 60 min between the paired tests. In addition, Edmunds et al. based the above conclusions on responses calculated as percent fall from baseline, which in fact did not recover before the second tests, when the first tests were followed by vigorous bronchoconstriction. However, when analyzing their data in terms of the lowest observed post-exercise values in percent of expected, we find no significant difference between the responses in the second tests. From this point of view their results are consistent with ours. So, it seems likely that the response in repeated exercise of short interval is independent of the magnitude of previous exercise. This raises the question, whether mast-cell derived mediators are involved in EIB. There is accumulating evidence suggest-

ing that they are not. The effect of sodium cromoglycate (scg) on EIB has generally been connected to a mast-cell stabilizing action (1, 13), but it has been shown that scg blocks bronchial autonomous nervous reflexes in dogs (16), and it has also been shown to have a phosphodiesterase-inhibiting action (20). In addition, there is the possibility that scg might have a direct activity on smooth muscle. The finding that scg fails on EIB, when given immediately after exercise (25), is no proof of the mediator hypothesis, because scg is not a bronchodilator, and at end of exercise the bronchoconstriction has usually already begun.

Very few studies have been designed to evaluate the refractory period seen after an episode of EIB. Edmunds et al. (11) found that after EIB the ability to constrict fully was recovered within 4 h and associated this period with the time to replenish liberated mediators. Chan-Yeung et al. (4) studied one patient performing three exercise tests with intervals of 2 h and found a decreasing response assigned to depletion of a humoral substance from the body store. James et al. (18) studied asthmatic children at hourly intervals, but the responses were inconstant. Only 6/10 children showed a decreased response in a fourth test compared with the first test. In the present study 9/11 children showed a decreased response in the second test, when both tests were performed under equal conditions. If, in contrast to the above suggestions, the refractoriness in EIB is not due to liberation and consumption of mediators, other factors must be considered. Possibly the refractory period is a parallel to the warm-up phenomenon in angina pectoris. Using paired exercise tests with identical duration and work load, Jaffe & Quinn (17) found that in 34 patients 30 patients had less electrocardiographic evidence of ischemia in the second test than in the first test. In EIB, a 3-min period of warm-up immediately before exercise had no dampening effect on post-exertional bronchoconstriction (24), but other warm-up schedules in EIB have not been studied.

Several other reports lend support to the presumption that factors other than mast-cell derived mediators are involved in EIB. The find-

ing that local anaesthesia of the oropharynx can attenuate EIB suggests that receptors in this part of the airways are involved in the airway response of asthmatic patients (22). Recently, Deal et al. (10) compared the changes in arterial histamine and neutrophil chemotactic activity in asthmatic subjects during bronchoconstriction after isocapnic hyperventilation and after allergen challenge. They found no changes in histamine, but a prolonged release of neutrophil chemotactic activity in relation to antigen provocation only, and suggested that mediators were not involved in EIB. Recently, we have studied the effect of allergen and exercise challenge in 10 asthmatic patients. Only after allergen inhalation was a late asthmatic reaction observed, suggesting that different mechanisms may be responsible for the immediate reaction after allergen and exercise challenge (9). Furthermore, Cockcroft et al. (6) have demonstrated that non-allergic reactivity to inhaled histamine and methacholine increased after allergen-induced asthma in subjects with late allergic responses. A similar effect has never been described in EIB.

The present study confirms that dry air increases and humid air decreases the bronchospastic response to exercise in subjects with EIB, and demonstrates that bronchodilatation during exercise is independent of humidity and previous EIB.

One hour after EIB the subjects as a group were still in relative refractoriness, but the responses in the second tests showed no relationship to the magnitude of EIB in the first tests. These results suggest that EIB is due to other factors than mast-cell derived mediators.

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