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Respiratory heat/water loss alone does not determine the severity of exercise-induced asthma

N. Noviski, E. Bar-Yishay, I. Gur, S. Godfrey

Respiratory heat/water loss alone does not determine the severity of exercise-induced asthma. N. Noviski, E. Bar-Yishay, I. Gur, S. Godfrey.
ABSTRACT: Respiratory heat loss (RHL) or water loss (RWL) have been proposed as possible triggering factors in exercise and hyperventilation-induced asthma (EIA and HIA). It has recently been demonstrated that exercise intensity and climatic factors are both important in determining the severity of EIA. Eight young asthmatics performed both exercise and isocapnic hyperventilation (IHV) manoeuvres under identical climatic conditions, as part of our investigation of these interactive factors which determine the severity of the asthmatic response. It was found that, when challenged at low ventilatory levels, exercise produced a significantly attenuated asthmatic response compared to IHV. The fall in forced expired volume in 1 sec (ΔFEV_1) following exercise was $15 \pm 4\%$ as compared with $27 \pm 3\%$ after IHV ($p < 0.002$). It is concluded that while the hypernoea in exercise may serve as a trigger, exercise *per se* introduces an additional factor which serves to limit the full response seen with IHV. This attenuated response is revealed at low ventilatory levels but is masked at high levels.
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Dept. of Paediatrics and Pulmonary Function Laboratory, Hadassah University Hospital, Mount Scopus, Jerusalem, Israel.

Correspondence address: E. Bar-Yishay, PhD, Pulmonary Function Laboratory, Hadassah University Hospital, Mount Scopus, POB 24305, Jerusalem 91240, Israel.

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Respiratory heat loss (RHL) has been proposed as the triggering factor in exercise-induced asthma (EIA) [7]. More recently, ANDERSON *et al.* carried out a number of studies, which led them to conclude that respiratory water loss (RWL) rather than RHL was the more important factor in determining EIA [11]. These two theories are attractive, since they attempt to unify the mechanisms leading to bronchoconstriction after different types of challenge such as exercise and isocapnic hyperventilation (IHV). Both theories, however, basically concluded that the exercise itself is not essential and serves only as a means to stimulate hypernoea [1, 13]. Remarkable similarity between EIA and hyperventilation-induced asthma (HIA) at relatively high ventilatory levels has also been reported by several investigators [6, 7, 12].

An opposing view has been suggested by some studies, which have described responses unexplained by the RHL and RWL theories [3, 8]. We recently showed an interaction which suggests that exercise intensity determines the severity of EIA whilst climatic conditions act as modifying factors [16]. The aim of this study was to determine whether it is RWL/RHL alone that determines the severity of exercise-induced asthma even at more modest levels of work or ventilation.

Methods

Eight young asthmatics aged 10–17 yr with known EIA took part in the study (table 1). Informed consent was obtained from the subjects and their parents in every case. No bronchodilator medication was taken for at least 8 h prior to any test. Only one of the children was receiving aerosol steroids which were continued at the same dose schedule during both tests.

The study consisted of two tests performed in random sequence. The tests were completed within two days in seven patients and within two weeks for the remaining patient (No. 4). One test consisted of 6 minutes of cycling at a fixed load and the second test consisted of a similar period of IHV. The exercise test was planned in such a way as to achieve roughly 1/3 of predicted maximum oxygen consumption. For those who performed the hyperventilation challenge first the target ventilation was set to a level that would be predicted to develop during exercise at 1/3 of predicted maximum oxygen consumption. At the end of the first test we calculated RWL and the second test was planned in such a way as to achieve the same RWL.

The exercise was performed on an electronically braked ergometer (Lode Inst., N.V., Holland). During the hyperventilation tests end tidal P_{CO_2} was kept at resting level by adding 1–2% carbon dioxide to the inspired air. During both tests, expired gas was passed through a pneumotachograph (Fleish No. 3) to a mixing chamber and gas analysers (P.K. Morgan, England). The data was fed on line to a computer (DEC PDP 11/73, Mass., USA) and a printout of heart rate, ventilation and gas exchange was obtained

Table 1. - Patient data

Subject	Sex	Age yr	Height cm	Weight kg	Regular Treatment
1	M	10.5	140	30	ISB
2	M	14.0	165	41	ISB
3	M	14.5	165	59	ISB
4	M	12.5	154	40	ISB, BDP
5	M	16.0	165	44	ISB
6	F	10.0	136	32	ISB
7	F	17.0	170	60	ISB
8	F	14.0	147	34	ISB

ISB: Intermittent sympathomimetic bronchodilators; BDP: Beclomethasone diproprionate

every 15 s. This information was used to guide the children to cycle or hyperventilate at rates that resulted in minute ventilation levels needed to achieve the same pattern of breathing and the same RWL.

Both tests were performed whilst breathing cold (0 ± 0.5°C), dry air (0 mgH_2O/*l* air), which was supplied to the inspiratory port of the respiratory valve box. It was prepared by passing compressed air through calcium chloride and a copper coil, which was immersed in an iced water bath, and then through a simple refrigeration circuit. The tubing system was thermally insulated and the temperature of the inspired gas was measured 1 cm from the inspiratory port at the valve box with an accurate mercury thermometer. The temperature of the expired gas was recorded during exercise with a high response thermistor (Model 530, Yellow Springs Instrument Co., Ohio, USA). The thermistor tip was suspended at the entrance to the rubber mouth piece in such a way as to be wholly within the mouth, but not touching the sides of the tubing or the tongue. Its 90% response time to a sudden temperature change was found to be 0.51 s. The humidity of the inspired gas was checked by weighing a small canister containing calcium chloride before and after the passage of one litre of the inspired gas. The water content of the expired air was calculated assuming full saturation.

The RWL in g/min was calculated by multiplying the minute ventilation by the difference in water contents between inspired and expired air. The RHL was calculated using the equation of DEAL *et al.* [7]. The severity of the induced asthma is expressed as maximal post challenge fall in FEV_1 as a percentage of the baseline value (ΔFEV_1%) defined as:

$$\Delta FEV_1(\%) = \frac{\text{Baseline } FEV_1 - \text{Lowest post exercise } FEV_1}{\text{Baseline } FEV_1} \times 100$$

Predicted values for FEV_1 and maximum oxygen consumption were calculated from the data of GODFREY [10].

Statistical comparisons were made by means of one way analysis of variance and by paired t-test, with the level of significance being taken as $p < 0.05$.

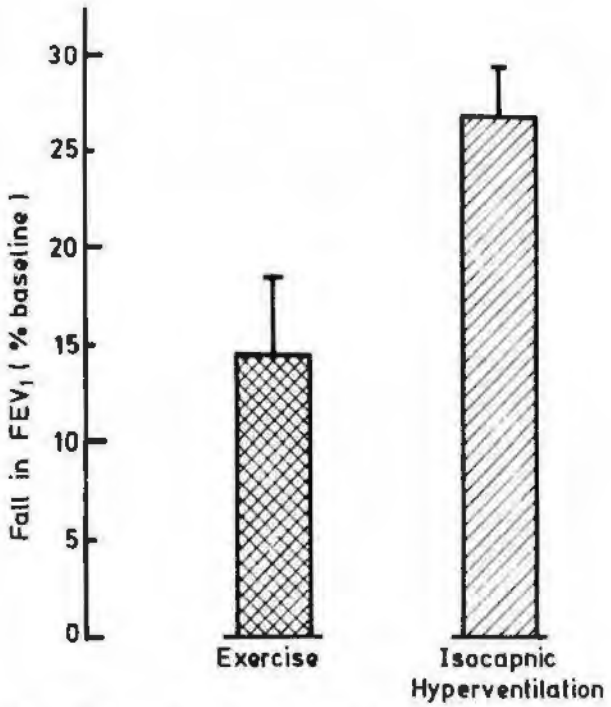

Fig. 1. The severity of exercise and hyperventilation induced asthma. Both tests were performed under the same conditions of respiratory heat loss and respiratory water loss. The mean ± SEM is given for each test.

Results

Mean (±SEM) values of baseline FEV_1 as well as various parameters obtained during the last two minutes of the tests are shown in table 2. The mean oxygen consumption for the exercise test was 20 ± 1 ml/min/kg. The pattern of breathing was similar in both tests with no significant differences in frequency or tidal volume.

Individual values of RHL and RWL during the two challenges are presented in table 3. There was no significant difference in RHL or RWL between the tests. Expired air temperature was found to be slightly, but significantly, lower during exercise but we could

Table 2. - Mean (±SEM) values for various parameters measured during both tests.

	Exercise	Hyperventilation
Baseline FEV_1 % pred	81.00±3	81.00±4
Minute ventilation *l*/min	28.00±3	28.00±3
Frequency of breathing f/min	30.80±5.6	34.20±8.1
Tidal volume *l*	1.00±0.34	1.01±0.42
Expired air temperature °C	31.00±0.2	32.10±0.3

not attribute this difference to any particular parameter. Despite these similarities, the induced asthma was significantly less following exercise ($15 \pm 4\%$) than after hyperventilation ($27 \pm 3\%$; $p < 0.002$). (fig. 1)

Discussion

This study has shown that at mild levels of exercise or IHV and at the same level of RHL and RWL, there is no significant difference between EIA and HIA. This finding contradicts most published reports, including our own [6, 7, 12]. However, most of these studies were performed at high levels of exercise and ventilation. One study that used moderate levels of ventilation was inappropriate, in that the response to the two types of challenge were undertaken in different subjects [7]. To the best of our knowledge, the present study is the only one in which the same subjects were challenged with mild levels of exercise and IHV.

Our results could be said to be due to the fact that the two challenges were not identical in terms of their minute ventilation response profiles. As seen in table 2, the pattern of breathing during the steady state portions of the challenges were similar. It is true that steady state ventilation is normally achieved later in exercise, whilst during IHV challenge, it is usually fully developed from the onset of the manocuvre. We instucted our subjects to increase their ventilation gradually so as to reach the target ventilation level at roughly the same time as in their exercise manoeuvres. Furthermore, since all previous publications at high ventilatory levels have shown the two challenges to result in similar responses, albeit the likely mismatch in ventilatory response profiles, we do not believe that total ventilation envelope during IHV caused the increased asthmatic response.

It is possible that the attenuated response to exercise is due to the release of endogeneous catecholamines, being absent during IHV. However, as no difference in the response to exercise or IHV has previously been observed when the challenges were performed at greater intensities [6, 7, 12], and as the role of catecholamines in EIA and HIA is very controversial [4, 18, 19], we do not believe that the answer lies in this mechanism.

GELB *et al.* [9] and O'BYRNE and JONES [17] suggested a bronchodilating effect of inhibitory prostaglandins during exercise. Since release of these mediators is not believed to occur in IHV, this may contribute to the differences in our study. While this possibility is attractive, the full extent of the interaction of prostaglandins, thromboxanes and other mediators in the pathophysiology of EIA and IHV remains to be clarified. MCFADDEN *et al.* [14] recently demonstrated that the severity of EIA is dependent on the rapidity and magnitude of airway rewarming post challenge. BAILE *et al.* [2] and MCFADDEN and PICHURKO [15] suggested that bronchial and/or pulmonary circulation may be determined by the

Table 3. - Individual values of respiratory heat and water losses and of ΔFEV_1 (%) as measured following both tests.

PATIENT	EXERCISE			HYPERVENTILATION		
no.	RHL kcal/min	RWL gm/min	ΔFEV_1 %	RHL kcal/min	RWL gm/min	ΔFEV_1 %
1	0.58	0.67	4	0.65	0.74	24
2	0.70	0.80	15	0.71	0.81	24
3	1.21	1.38	29	1.24	1.41	25
4	0.68	0.77	34	0.68	0.78	44
5	0.76	0.87	1	0.83	0.95	18
6	0.56	0.67	10	0.56	0.64	25
7	1.18	1.35	11	1.12	1.29	30
8	0.59	0.67	12	0.71	0.83	25
Mean	0.78	0.90	15	0.81	0.93	27
±SEM	0.09	0.11	4	0.09	0.10	3

local thermal needs of the airways. Since cardiac output is increased during exercise, this increase could act to better protect asthmatic subjects during exercise as compared to IHV challenges. Thus, it seems possible to us that the attenuated response observed with exercise relates to the increase in bronchial blood flow, which is effective in providing some protection, but only at low levels of exertion. It should be reemphasized that most published studies have been undertaken at high levels of exercise and of IHV where this attenuated response was not observed. If there were a plateau effect in this protection, the differences between EIA and HIA would not necessarily be apparent at high levels of exercise and hyperventilation.

In conclusion, the results of the present study suggest that whilst it is possible that the increase in ventilation during exercise acts as a trigger, exercise *per se* introduces an additional factor which may act to limit the full response observed following IHV.

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RÉSUMÉ: Il a été suggéré que la perte de chaleur respiratoire (PCR) ou perte d'eau respiratoire (PER) sont des facteurs possibles de déclenchement de l'asthma provoqué par l'exercice et par l'hyperventilation (APE et APH). Il a été démontré récemment que l'intensité de l'exercice ainsi que les facteurs climatiques sont des déterminants importants de la gravité de l'APE. Huit jeunes malades asthmatiques ont chacun fait des exercices et accompli des manoeuvres d'hyperventilation isocapniques (HVI) dans des conditions climatiques identiques dans le cadre de notre enquête sur ces facteurs déterminants interactifs de la gravité de la réponse asthmatique. Nous avons trouvé que, accompli à des niveaux de ventilation peu élevés l'exercice a déclenché une résponse asthmatique nettement plus atténuée que dans le cas de l'HVI. La chute du volume expiré forcé en une seconde (ΔVEF_1) après exercice était de $15 \pm 4\%$ par rapport à $27 \pm 3\%$ après HVI ($p < 0.0002$). L'hyperpnoïa qui accompagne l'exercice pouvant servir de déclencheur, nous en avons conclu que l'exercice lui-même introduit un facteur supplémentaire qui limite la réponse maximum constatée lors de l'HVI. Cette réponse atténuée se manifeste à des niveaux de ventilation bas mais est masquée lorsque ces niveaux sont élevés.