

Original article

Asthma in medium altitude – exercise-induced bronchoconstriction in hypobaric environment in subjects with asthma

Background: Hypoxic gas inhalation has been reported to enhance airway responsiveness and results in bronchoconstriction in animal models and in humans with asthma. However, the data have so far been conflicting. The aim of the present study was to examine the effect of reduced barometric pressure on exercise-induced bronchoconstriction (EIB) in subjects with asthma.

Methods: Twenty subjects (10–45 years old, ♂/♀ = 13/7) with asthma (at least 10% reduction in forced expiratory volume in 1-second postexercise) participated in exercise testing in barometric pressure corresponding to altitudes of 200 (normobaric) and 2500 (hypobaric) m above sea level in random order on separate days. Lung function was measured before and after exercise, as well as after inhalation of salbutamol. Heart rate, oxygen uptake ($\dot{V}O_2$), arterial oxygen saturation (S_pO_2), respiratory gas exchange ratio (RER) and minute ventilation ($\dot{V}_E$) were measured during exercise.

Results: There was no difference in lung function after exercise. The $\dot{V}_{Epeak}$ and HR_{peak} during exercise did not differ. The RER_{peak} was higher ($P = 0.04$) in hypobaric environment. The $\dot{V}O_{2peak}$ decreased 10.1% (7.2–13.0) [mean (95% confidence intervals)] ($P < 0.001$) from normobaric to hypobaric environment. At the same time, S_pO_2 at $\dot{V}O_{2peak}$ decreased from 94.4 (92.2–96.6) to 85.6% (82.8–88.4) ($P < 0.001$).

Conclusions: A barometric pressure corresponding to altitude of 2500 m did not increase EIB in subjects with asthma. The reduction in $\dot{V}O_{2peak}$ is most probably due to the lower S_pO_2 in hypobaric environment.

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Exercise-induced bronchoconstriction (EIB) has been reported to occur in 70–90% of asthmatics who have not received anti-inflammatory treatment (1, 2). The prevalence of EIB among children and adolescents in the general population has been reported to be 16–20% (3, 4). The EIB may limit participation in sports, modern lifestyle activities like skiing and activities of daily living.

Hypoxic gas inhalation enhanced airway responsiveness and resulted in bronchoconstriction in animal models (5, 6) and asthmatic subjects (7). However, the data on humans have so far been conflicting, and others have found a decrease (8) or no change (9, 10) in methacholine bronchial responsiveness from normal to medium or higher altitudes.

Standardized exercise tests are used to diagnose EIB in asthmatics with a history of shortness of breath during or after exertion. The EIB cannot be diagnosed by methacholine bronchial challenge, and not excluded by negative methacholine challenge (11). To our knowledge, only two groups (12, 13) have studied the effect of reduced barometric pressure on EIB. They found no additional increase in EIB. However, the exercise tests were not satisfactorily standardized (11, 14–17), and not all sub-

jects had a reduction of $\geq 10\%$ in forced expiratory volume in 1 s (FEV_1) after exercise. The main objective of the present study was to examine whether running in a hypobaric environment increases EIB in subjects with asthma, and secondarily to examine the effect of reduced barometric pressure on oxygen uptake ($\dot{V}O_2$), minute ventilation ($\dot{V}_E$), heart rate (HR) and arterial oxygen saturation (S_pO_2) during running.

Materials and methods

Study design

The study had a randomized, crossover design to identify EIB in normobaric (ambient pressure corresponding to 200 m above sea level) and hypobaric environments (ambient pressure corresponding to 2500 m above sea level). On day one, all subjects underwent a standardized EIB test in normobaric environment to see if they satisfied the inclusion criteria (fall in $FEV_1 \geq 10\%$ postexercise). The subjects then participated in exercise testing in normobaric and hypobaric environments in random order on separate days. The study was performed in accordance with the Declaration of Helsinki (18).

Subjects

Twenty subjects with asthma, who were 10–45 years of age, were included in the study. Seventeen subjects were atopic. Exclusion criteria were any other disease, which might influence the results and respiratory tract infection during the last 3 weeks before inclusion in the study, and use of medication, which interfered with the results, according to standard criteria (19). Seven subjects used daily-inhaled steroids, 17 short-acting inhaled β_2 -agonists on demand, 10 long-acting inhaled β_2 -agonists, 1 theophylline, 4 regular antihistamines and 2 subjects used leukotriene antagonists. Nine subjects were without regular asthma medication.

Methods

Lung function was measured outside the pressure chamber by maximum forced expiratory flow–volume curves (Masterlab, Erich Jaeger® GmbH, Germany) (20) with predicted values (21, 22). Lung function [(FEV₁); forced vital capacity (FVC); and forced expiratory flow at 50% of FVC (FEF₅₀)] was measured before, immediately after, 3, 6, 10 and 15 min after exercise, and 15 min after inhalation of salbutamol (5 mg/ml; 0.05 mg/kg).

The skin prick test was performed according to Nordic guidelines (23) with the following prevalent allergens: *Cladosporium herbarum*, *Dermatophagoides pteronyssinus*, dog dander, cat dander, birch, timothy and mugwort pollen, cow's milk, shrimp and egg (Soluprick, ALK, Copenhagen, Denmark).

The EIB was determined by running on a treadmill ('Bodyguard' 2313, Cardionics AB, Sweden) for 6–8 min with sub-maximal workload. The inclination of the treadmill was 5.3% and the speed adjusted during running to achieve a workload of 90–95% of maximum (11). Douglas-bags were used for collecting gas samples of the expired gas every minute during the running (24). The subjects, wearing nose clips, breathed through a mouthpiece (2700 Series; Hans Rudolph Inc., Kansas City, KS), with expiratory gas samples of 30 s. The collected samples were analysed for oxygen and carbon dioxide content (Oxygen analyzer, model S-3A/1 and Carbon dioxide analyzer, model CD-3A; Ametek Inc., Pittsburgh, PA). The volume, temperature and pressure of the expired gas were measured at the time the air was analysed ('Ventilation measuring system', model S-430, KL-Engineering, Northridge, CA). The SpO₂ was recorded during running with a pulse oximeter (Nellcor N-395, Nellcor Puritan Bennett Inc., Pleasanton, CA) with an RS-10 forehead sensor (Nellcor Puritan Bennett Inc.) taped to the skin above arcus superciliaris (25). The heart rate was recorded electronically and registered every minute (Polar Sports tester PE 3000®, Polar Electro OY, Kempele, Finland).

Running was performed in a conditioned pressure chamber (Norwegian Sub diving Techniques A/S, Haugesund, Norway) with temperatures between 19 and 23°C and relative humidity of approximately 40%. The barometric pressures during running were 98.7 (± 1.1) and 75.5 (± 0.2) kPa.

Statistical analysis

Demographics are given as mean values and standard deviation (SD) and results as means with 95% confidence intervals (CI). Differences between the two tests were assessed by Student's paired *t*-test. The bronchoconstrictor response following exercise was measured as the maximum per cent fall in FEV₁ after exercise and the area under the curve (AUC) per cent fall of the preexercise value in FEV₁/time, up to 15-min postexercise, using the trapezoid rule. Identical analysis was made for FEF₅₀. If FEV₁ or FEF₅₀ was greater than baseline values, area was subtracted from the AUC

measurements. Baseline FEV₁, FVC and FEF₅₀ were measured on two consecutive days to calculate the coefficient of repeatability (26). The significance level was set to 5% using two-sided tests. Using preexisting knowledge of the main variable in previous studies monitoring EIB (27, 28), we found that 20 subjects were needed to obtain a power of at least 80% with a significance level of 5%.

Results

Demographics and baseline lung function are given in Table 1. Neither maximum reduction in FEV₁ and FEF₅₀ (per cent of baseline) nor AUC was significantly different after running in hypobaric compared to normobaric environments (Fig. 1). No significant correlation was found between decrease in SpO₂ during exercise in hypobaric environment and maximum drop in FEV₁. The response, 15 min after inhalation of salbutamol, was not significantly different between tests (Fig. 1), but FEV₁ and FEF₅₀ increased significantly ($P < 0.001$) after inhalation of salbutamol compared to baseline values. Baseline FEV₁, FEF₅₀ and FVC did not differ significantly on the two test days.

The $\dot{V}O_{2\text{peak}}$, SpO₂ at $\dot{V}O_{2\text{peak}}$, HR_{peak}, highest recorded oxygen pulse, RER_{peak}, $\dot{V}_{E\text{peak}}$ and highest recorded running speed during treadmill run in normobaric and hypobaric environments are shown in Table 2. The reduction in $\dot{V}O_{2\text{peak}}$ between normobaric and hypobaric conditions was 10.1% (7.2–13.0) ($P < 0.001$). Mean reduction in SpO₂ at $\dot{V}O_{2\text{peak}}$ was 9.3% (7.0–11.6) ($P < 0.001$). The highest recorded oxygen pulse decreased 8.6% (5.9–11.3) ($P < 0.001$) in hypobaric environment (Table 2). On the other hand, the AUC was not different.

Discussion

The present study did not demonstrate an additional reduction in FEV₁ or FEF₅₀ after running in hypobaric environment. The HR_{peak} and $\dot{V}_{E\text{peak}}$ were not higher during running in hypobaric environment. The $\dot{V}O_{2\text{peak}}$ was 10.1% lower in hypobaric environment. Mean reduction in SpO₂ at $\dot{V}O_{2\text{peak}}$ was 9.3% below running in the normobaric environment.

Table 1. Demographic data of the 20 subjects (♂/♀ = 7/13) included in the study

	Mean	SD	Range
Age (years)	24	10.5	10–45
Weight (kg)	67.0	11.1	37–112
Height (cm)	171.5	18.2	147–197
Body mass index (kg/m ²)	22.6	4.7	17.1–37.2
Baseline FEV ₁ (l) (% predicted)	3.7 (101)	0.91 (14.9)	1.9–5.7 (79–126)
Baseline FEF ₅₀ (l) (% predicted)	3.7 (77)	1.40 (22.2)	1.6–6.8 (45–127)
Baseline FVC (l) (% predicted)	4.5 (106)	1.11 (11.7)	2.6–7.2 (84–134)

Data are given as mean, SD and range.

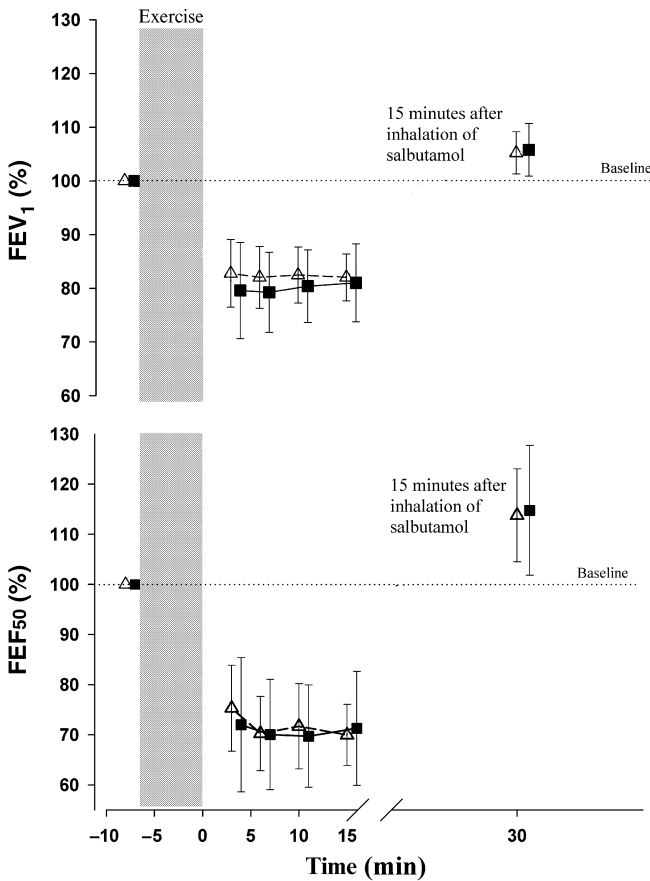


Figure 1. Lung function (FEV₁ and FEF₅₀% of baseline) before and after exercise in normobaric (Δ) and hypobaric (■) environments (*n* = 20). Results are shown as mean values with 95% confidence intervals.

Table 2. Peak oxygen uptake ($\dot{V}O_{2peak}$), S_pO_2 at $\dot{V}O_{2peak}$, peak heart rate (HR_{peak}), oxygen pulse at $\dot{V}O_{2peak}$ ($\dot{V}O_2/HR_{peak}$), peak respiratory exchange ratio (RER_{peak}), peak minute ventilation ($\dot{V}_{Epeak}$) and peak running speed (V_{peak}) during treadmill run in normobaric and hypobaric environment (*n* = 20)

	Normobaric	Hypobaric	Significance
$\dot{V}O_{2peak}$ (ml/kg/min)	47.6 (44.3–50.8)	42.7 (39.7–45.8)	<i>P</i> < 0.001
S_pO_2 at $\dot{V}O_{2peak}$ (%)	94.4 (92.2–96.6)	85.6 (82.8–88.4)	<i>P</i> < 0.001
HR _{peak} (beats/min)	187 (182–192)	185 (180–190)	ns
$\dot{V}O_2/HR_{peak}$ (ml)	17.0 (14.9–19.2)	15.4 (13.6–17.3)	<i>P</i> < 0.001
RER _{peak}	1.03 (1.00–1.07)	1.06 (1.02–1.10)	<i>P</i> = 0.04
$\dot{V}_{Epeak}$ (l/min)	101 (89–114)	105 (92–119)	ns
V_{peak} (km/h)	10.5 (10–11)	9.5 (9.0–10.5)	<i>P</i> < 0.001

Values are given as mean with 95% confidence intervals in parentheses. ns, not significant.

The major factors that determine severity of EIB are the pulmonary ventilation reached and sustained during exercise and water content and temperature of the inspired air. The stimulus by which exercise causes the airways to narrow is respiratory water and heat loss (29, 30). This is thought to stimulate the release of inflammatory mediators

such as histamine and leukotrienes. The EIB in hypobaric environment may be due to the same mechanisms, even though some have speculated whether inhalation of hypoxic gas could enhance airway responsiveness (6) and result in bronchoconstriction (31). Exercise in medium or high altitudes is usually associated with increased ventilation due to hypoxic conditions (32). In addition, the temperature and water content of the air at these altitudes are substantially lower than at sea level. The present study was, however, conducted in a low-pressure chamber enabling control of air temperature and relative humidity. Except for the barometric pressure, the climatic conditions were equal. Reduced $\dot{V}O_{2peak}$ and running speed during exercise in hypobaric environment could partly explain why the subjects did not increase their $\dot{V}O_{Epeak}$. The reduction in $\dot{V}O_{2peak}$ is most probably due to the lower S_pO_2 . Since the temperature and water content of the inspired air together with $\dot{V}_{Epeak}$ were identical for both conditions, airway cooling and water loss in the airways should be the same. Our findings are in agreement with results from other studies dealing with exercise challenges in hypobaric environment (12, 13). Louie and Paré (12) investigated the effect of various altitudes on EIB during a 2-week trek through the Himalayas (altitudes between 1500 and 3500 m above sea level) in 10 nonasthmatic and 4 asthmatic subjects. The EIB was not an inclusion criterion for the asthmatic subjects. Matsuda et al. (13) tested 20 children with asthma on a bicycle ergometer in a low-pressure chamber. Exercise was performed in 103.1 and 84.5 kPa. The authors in the op. cit. did not find any additional increase in bronchoconstriction in hypobaric environment. However, the number of subjects with EIB was far too low to reach any conclusion, and the exercise protocol was not acceptably standardized (11). Numerous studies have used running on a treadmill for 6–8 min near maximum load to assess EIB both in a clinical setting and in epidemiological studies (14–17).

In conclusion, running in a barometric pressure corresponding to an altitude of 2500 m did not increase EIB in subjects with asthma. The reduction in $\dot{V}O_{2peak}$ is most probably due to the lower S_pO_2 in the hypobaric environment. However, the low temperature and the subsequent reduced water content of the air in the mountainous area can influence both heat loss and dehydration of the airways. The present study suggests that subjects with EIB, like their healthy nonasthmatic peers, can participate in sport activities such as altitude climbing, skiing and tracking in medium high altitudes. The results should, however, be confirmed in a normal altitude setting outside the laboratory.

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