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Response to high-altitude triggers in seasonal asthmatics on and off inhaled corticosteroid treatment

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ABSTRACT

Background: Due to the effects of climate change, winter sport enthusiasts will be increasingly forced to stay at higher altitudes. High altitude (HA) environmental factors such as cold temperature, physical exertion, and hypoxia with subsequent hypocapnia due to hyperventilation have been shown to induce bronchoconstriction. With bronchial asthma being highly prevalent, asthmatics also will be increasingly exposed to HA environment and might experience increasing symptoms.

Methods: We analysed the effects of HA factors at around 2600 m a.s.l. (metres above sea level) on lung function in mild seasonal asthmatics while they were routinely off (January) and on (March, after start of lowland pollen season) low-dose inhaled corticosteroid (ICS) treatment ($n = 10$), and matched healthy controls ($n = 11$).

Results: Without inhaled corticosteroid (ICS) treatment mean FEV1 in asthmatics was 230 ml lower after exercise at HA compared to low altitude (LA, $p < 0.05$), while in healthy controls there was no significant difference. This decrease was mainly induced by cold and exercise at HA. During ICS treatment, this decrease was prevented. Methacholine response was reduced at HA compared to LA.

Conclusions: The decrease of FEV1 in response to a combination of hypoxia, cold, and exercise is prevented by ICS treatment in mild, seasonal asthmatics. However, the FEV1 response to high altitude factors was overall small.

Keywords: Asthma, High altitude, Triggers, Inhaled corticosteroids

INTRODUCTION

Bronchial asthma is highly prevalent worldwide, with allergic asthma being a common phenotype. If the main allergen is a seasonal one, intermittent treatment may be sufficient, with an inhaled corticosteroid (ICS) or a combination of ICS and long-

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acting beta agonist (LABA) during the time of high allergen exposure.[1] With preexisting bronchial hyperreactivity an asthma attack can also be caused by nonspecific triggers. Examples of such nonspecific triggers are cold, dry air, hyperventilation or exercise.

Due to the effects of climate change, winter sport enthusiasts will be increasingly forced to stay at higher altitudes. With the touristic exploitation of the Alps and other mountains, higher altitudes can be reached easily by gondola lift and ski stations and higher altitudes are visited by larger numbers of people because of their snow guarantee. Hence, patients also suffering from bronchial asthma are exposed to and affected by different components of the high altitude environment. The most important factors are cold temperature, physical stress, and hypoxia with subsequent hypocapnia due to hyperventilation. These factors become relevant at altitudes above 1400 m a.s.l. (metres above sea level) and each of these factors alone has been shown to induce bronchoconstriction and airway inflammation.[2]

With increasing altitude, atmospheric pressure and thus oxygen pressure decreases resulting in hypoxemia upon altitude exposure. Patients with asthma who are not treated with corticoids experience increased airway hyperresponsiveness when exposed to hypoxia,[3] whereas methacholine response in hypoxia is unchanged in non-asthmatic subjects.[4]

Hypoxia stimulates hyperventilation which leads to a decrease in partial pressure of carbon dioxide (pCO2). Hypocapnia induces bronchial constriction which can provoke dyspnea.[5] Furthermore, coldness enhances airway hyperreactivity and bronchoconstriction in asthmatic airways[6] by activation of vagal efferences[7] and induction of airway inflammation.[2] This may be aggravated by inspiration of cold and dry air during physical exercise when nasal breathing is switched to mouth breathing. Consequently, there is less warming and less humidification of inspired air and this can lead to bronchoconstriction.[7]

Studies investigating patients with asthma at high altitude have shown that if the asthma is well controlled the risk for exacerbations is low. However, the level of therapy and asthma control of studied individuals is poorly characterized limiting generalizability.[2,8,9] Contrary to the expected increase in bronchial hyperreactivity due to the special climatic conditions, studies have shown a decrease in bronchial hyperreactivity.[10–12] In addition, all of these studies were conducted in the context of high-altitude expeditions, which limited the investigation of the role of individual nonspecific asthma triggers.

From the existing data 2 questions remain unanswered. First, does ICS treatment prevent bronchial hyperreactivity at high altitude conditions? Second, is there a need for preventive ICS treatment in asthmatics without regular ICS use before a high altitude stay?

Therefore, we conducted a study to investigate the effect of high-altitude climate on lung function in subjects with a well-controlled allergic asthma and seasonal ICS usage compared to healthy controls. To address the question on how the non-specific triggers influence lung function a serial setup was chosen. Measurements were conducted during winter when seasonal asthmatics were routinely off ICS treatment and repeated while on their regular ICS treatment during pollen season.

METHODS

Study population

Ten subjects with a mild seasonal and well-controlled bronchial asthma who routinely used seasonal ICS during pollen season, but no ICS off season, were included in the asthma group (5 women and 5 men). Low-dose ICS treatment with budesonide 200 µg dry powder inhalation twice daily was started in spring by the participants during pollen season solely on clinical grounds. As needed salbutamol was available for asthma patients throughout the study. Controls (7 women and 4 men) were matched according to age, gender, body mass index (BMI), health, and physical activity status. The study was approved by the institutional review board (IRB) of the Ludwig-Maximilians-University (LMU) Munich, Germany (Number 327-16) and all participants provided written informed consent.

Study design

Baseline measurements at low altitude (LA) conditions were performed at low altitude around

500 m. High altitude (HA) measurements were performed in early winter at around 2600 m. Ascent was by effortless transport. All measurements were completed within the first 6 h after ascent. Subjects from the control group were measured at 1 timepoint; whereas subjects from the asthma group were measured at 2 different timepoints, while off and on their regular ICS treatment (Fig. 1a). The first HA measurement was performed in January (no/few pollen in lowland, T1), the second in March 4 weeks after initiation of their usual ICS treatment at the beginning of the lowland pollen season (T2).

Asthma control was assessed using the Asthma Control Test (ACT) at LA before ascent to HA at both time points. Blood samples were taken both in LA and HA before the pulmonary function and provocation tests. Pulmonary function tests and

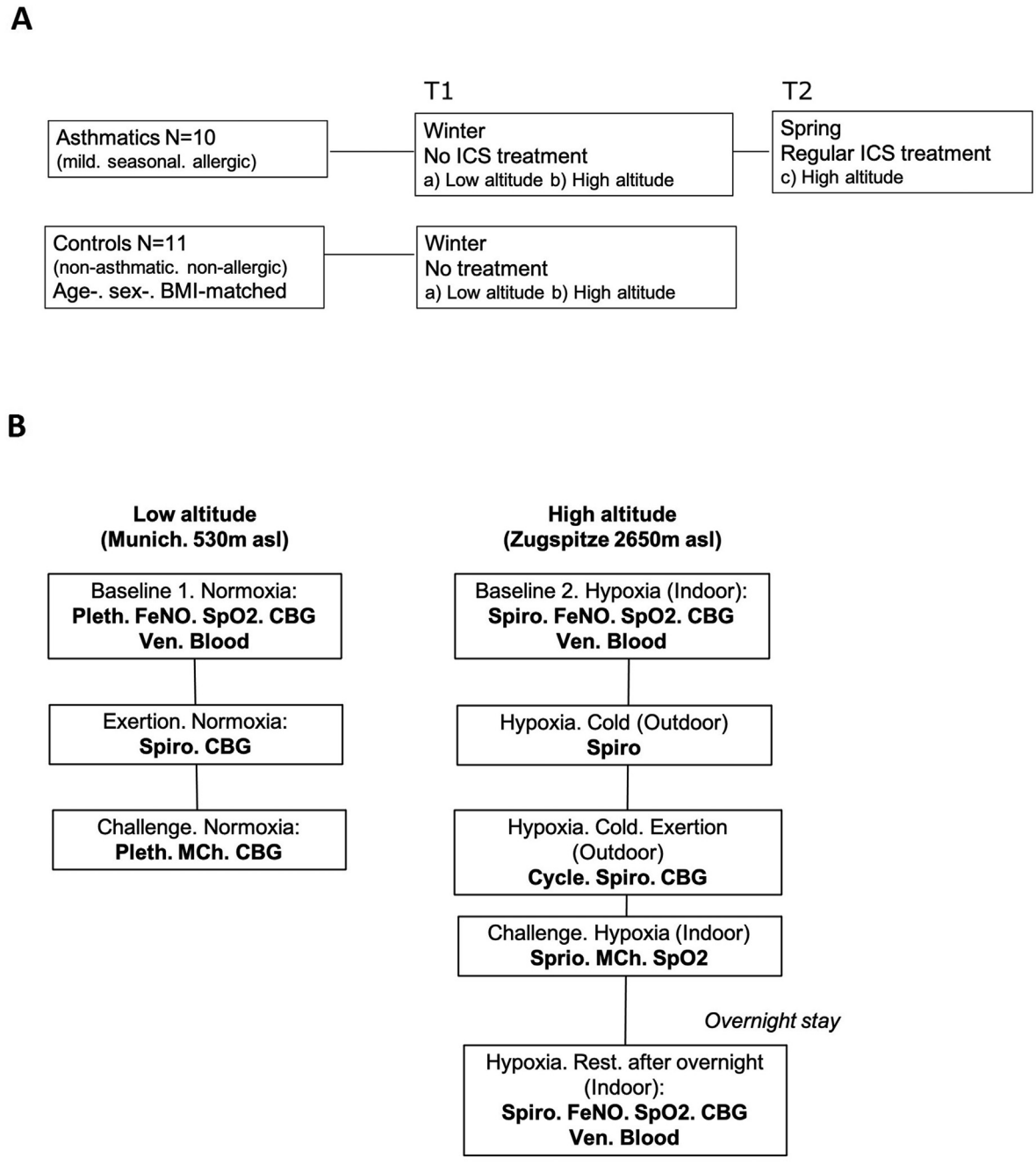

Fig. 1 Study overview A) Study group overview B) Procedure overview

blood gas analyses were performed immediately after the respective provocation test (Fig. 1b).

Measurements & statistics

All measurements at LA and HA were carried out at room temperature (19–22 °C) if not otherwise specified. Cold exposure was between −10 and −4 °C. Baseline measurements at low altitude included venous blood analysis for hemoglobin, IgE, specific-IgE, pulmonary function testing using spirometry, fractional exhaled nitrix oxide (FeNO), asthma control test (ACT), cycle ergometer exercise and arterialized capillary blood gas analysis (aCBG).

HA measurements included pulmonary function testing using spirometry, FeNO, cycle ergometer exercise, methacholine provocation testing and capillary blood gas analysis.

Spirometry was performed using Masterscreen Pneumo (Vyaire, Hoechberg, Germany). FeNO was measured using the NIOX VERO (Circassia, Uppsala, Sweden). Peripheral oxygen saturation (SpO2) was measured at fingertip (Criticare 504-US). BGA was performed from the arterialized earlobe sample using the Rapidpoint 500 (Siemens Healthineers, Erlangen, Germany). Ergometry was performed as bicycle ergometry in sitting position. We used a step-protocol starting 50 W with a 25 W increase every 2 min to a maximum of 150 W. Subjects were monitored during exercise by continuous measurement of heart rate and SpO2. Methacholine provocation testing was performed as described elsewhere.[13] Specific IgE was quantified with ImmunoCap Elisa (Thermo Fisher Scientific, Waltham, USA) following the manufacturer's instructions. Statistical analyses were performed using R[14] and GraphPad Prism. We reported mean ± SD for parametric variables and median (range) for non-parametric variables and applied *t*-test or *U* test respectively. For longitudinal comparisons of subjects within groups we used paired tests, for comparison between asthma and control group unpaired tests. A $p < 0.05$ was considered significant.

RESULTS

The mean age in the asthma group was 41 years and 40 years in the control group; there were no differences regarding baseline characteristics such as BMI or cigarette smoking history (Table 1). As

Baseline characteristics			
	Asthma	Control	*P*-value
Total subject number – n	10	11	
Female – n (%)	5 (50)	7 (64)	
Age - years – mean ± SD	41.4 ± 12.1	39.8 ± 12.0	0.77
BMI - kg/m^2 - mean ± SD	23.8 ± 2.9	22.6 ± 3.4	0.31
Smoking (current/ex/never)	(0/8/2)	(0/8/3)	
Eosinophils/µl -mean ± SD	156 ± 79	82 ± 59	**0.032**
Hb - g/dl -mean (±SD)	13.9 ± 1.5	13.8 ± 1.4	0.85
Total IgE - IU/ml - median (range)	147 (2; 653)	11.7 (3; 66)	**<0.0001***
Specific IgE - number of positives – median (range)	2 (0; 4)	0 (0; 2)	**<0.0001***
FeNO - ppb- median (range)	15 (9; 55)	9 (5; 22)	**0.0228***
ACT score – median (range)		23 (21; 25)	

Table 1. Baseline characteristics in winter at lowland. All comparisons by *t*-test except * by *U* test. $P < 0.05$ was considered significant. *ACT, Asthma control test; BMI, body mass index; Hb, Hemoglobin; IgE, Immunoglobin E; FeNO, fractional exhaled nitric oxide*

Spirometry	Asthma Mean ± SD	Control Mean ± SD	p-value
FEV1 – l	3.59 ± 0.72	3.41 ± 0.76	0.59
FEV1 - % predicted	103.4 ± 14.8	104.8 ± 11.8	0.82
VC – l	4.84 ± 1.01	4.39 ± 0.97	0.31
VC - % predicted	112.9 ± 15.7	111.7 ± 13.8	0.87
FEV1/FVC	0.74 ± 0.7	0.78 ± 0.04	0.22
PEF – l/s	7.41 ± 1.47	7.76 ± 2.29	0.68
PEF - % predicted	91.4 ± 13.0	102.4 ± 19.5	0.15
MEF75 – l/s	6.06 ± 1.64	6.30 ± 1.45	0.72
MEF75 - % predicted	86.4 ± 19.0	96.1 ± 13.9	0.19
MEF50 – l/s	3.86 ± 1.19	3.41 ± 0.87	0.33
MEF50 - % predicted	75.0 ± 22.6	75.4 ± 14.1	0.96
MEF25 – l/s	1.33 ± 0.47	1.33 ± 0.47	0.98
MEF25 – % predicted	64.6 ± 20.4	66.6 ± 17.8	0.81
Arterialized capillary blood gas (aCBG)			
pCO2 – mmHg	36.8 ± 3.3	36.0 ± 2.5	0.55
pO2 – mmHg	82.7 ± 8.1	85.1 ± 6.6	0.46
pH	7.42 ± 0.02	7.43 ± 0.02	0.25
BE – mmol/l	−0.2 ± 1.6	0.05 ± 1.6	0.71
HCO3	24.5 ± 1.2	24.6 ± 1.3	0.96
sO2 - %	97.1 ± 1.0	97.4 ± 0.6	0.48
SpO2 - %	96.3 ± 1.1	96.3 ± 1.2	0.99

Table 2. Spirometry and arterialized capillary blood gases at rest in winter at lowland. *FEV1, forced expiratory volume in 1 sec*

expected baseline (T1) LA mean blood eosinophils (156/µl vs 82/µl, $p = 0.032$), median IgE (147 IE/ml vs 11.7 IE/ml, $p < 0.0001$) and median FeNO (15 ppb vs 9 ppb, $p = 0.0228$) were significantly higher in asthmatics compared to controls (Table 1). Spirometry and aCBG at LA were normal and without significant differences between the two groups (Table 2). Asthmatics were well-controlled with a mean ACT median score of 23 (range 21–25) points before the first HA stay, and 23 points (range 17–25) before the second HA stay.

At low altitude the relative risk (RR) for having a FEV1 drop of ≥20% in the methacholine challenge was 12 times as high for asthmatic subjects compared to the control group. Furthermore, the mean number of dose steps for a positive methacholine challenge was significantly lower in the asthma group with an associated higher mean drop in %FEV1 from the initial FEV1 at cumulative dose of 0.25 mg and at the highest reached cumulative methacholine dose (Table 3).

The comparison of LA and HA aCBG showed respiratory HA adaptions in both groups regarding

		Highest reached provocation step					Stop due to FEV1 drop ≥20%	RR (CI)	mean number of provocations	p-value	mean % reduction	p-value	mean % reduction after step 2	p-value
		1	2	3	4	5								
HA	Asthma	0	0	1	2	7	3	3.30 (0.4,26.8)	4.6	0.22	17.5	0.15	5.0	0.72
	Control	0	0	0	1	10	1		4.9		9.7		3.7	
LA	Asthma	0	1	2	2	5	5	12.0 (0.75, 192.9)	4.1	**0.03**	22.6	**0.01**	6.2	**0.03**
	Control	0	0	0	0	11	0		5.0		9.9		0.8	
Asthma	HA	0	0	1	2	7	3	0.6 (0.19, 1.86)	4.6	0.18	17.5	0.16	5.0	0.48
	LA	0	1	2	2	5	5		4.1		22.6		6.2	
Control	HA	0	0	0	1	10	1	3.0 (0.14,66.5)	4.9	0.34	9.7	0.91	3.7	0.30
	LA	0	0	0	0	11	0		5.0		9.9		0.8	

Table 3. Methacholine provocation. Comparison of Asthmatics vs Controls (upper panel) showed a higher number of asthmatics reaching a drop of FEV1≥20% at LA, while there were no significant differences at HA

hyperventilation and hypoxemia directly after rapid ascent to high altitude as well as after combined cold air exposure and physical activity on a bicycle ergometer (Table 4**)**. ACBG at different conditions did not differ significantly between asthmatics and controls. Median FeNO levels were unchanged in the asthmatics, but rose slightly in the control group at HA (16 ppb) compared to LA **(**9 ppb**;** p = 0.039; Table 4). During both HA stays none of the asthmatic subjects reported an increase of asthma specific symptoms such as dry cough or dyspnea and none needed additional salbutamol inhalation except for the per protocol inhalation at the end of metacholine provocation.

Mean FEV1 in the asthmatics at HA after combined cold air exposure and physical activity on the bicycle ergometer was 230 ml lower than after exercise at low altitude (Fig. 2). In asthmatics, the decrease in FEV1 after methacholine challenge was less pronounced at HA than at LA (Fig. 2), thus at HA methacholine challenge showed no differences between asthma and control group.

The use of ICS treatment starting at the beginning of the pollen season between the first and second HA stay was associated with was a significantly higher FEV1, after combined cold air exposure and physical activity on the bicycle ergometer (+120 ml, p = 0.01; Fig. 2). FEV1 at all other measured points of the study showed no differences during ICS treatment compared to untreated status. During ICS inhalation in spring (T2) eosinophils were significantly lower at HA in the asthma group compared to winter without ICS inhalation (T1) (90/µl ±42 versus 130/µl ±43; p = 0.0023) while median FeNO values did not differ significantly (21.5 vs 17 p = 0.21).

To further analyze the effect of hypoxia on bronchodilatation, the response to salbutamol after methacholine challenge was measured. After 2 puffs of salbutamol, there were no significant differences for asthma and control group between LA and HA measurement (Fig. 2).

DISCUSSION

Our study shows that in mild seasonal allergic asthmatics who were off ICS treatment during winter season, the combination of physical

	1. Baseline (Rest)				p-value HA vs LA		p-value Asthma vs Ctrl	
	High altitude (HA)		Low altitude (LA)					
	Asthma	Control	Asthma	Control	Asthma	Control	HA	LA
pCO2	33.3	32.1	36.8	36.0	**0.02**	**0.001**	0.51	0.56
pO2	65.4	65.5	82.7	85.1	**0.0001**	**<0.0001**	0.96	0.46
pH	7.42	7.44	7.43	7.43	0.92	0.49	0.08	0.25
SpO2	94.5	94.5	96.3	96.3	0.052	**0.002**	0.95	0.99
FeNO	17#	16#	15#	9#	0.50*	**0.039***	0.49*	**0.00228***
	2. after exercise				**p-value HA vs LA**		**p-value Asthma vs Ctrl**	
	High altitude		**Low altitude**					
	Asthma	**Control**	**Asthma**	**Control**	**Asthma**	**Control**	**HA**	**LA**
pCO2	32.5	28.7	35.4	32.8	**0.02**	0.06	0.06	0.25
pO2	55.4	57.9	81.3	86.0	**<0.0001**	**<0.0001**	0.36	0.14
pH	7.40	7.40	7.37	7.38	**0.04**	0.19	0.89	0.94
SpO2	85.6	88.4	95.6	95.8	**<0.0001**	**<0.0001**	0.14	0.60
	3. after overnight stay							
	High altitude	**p-value Asthma vs Ctrl**						
	Asthma	**Control**	**HA**					
pCO2	29.3	30.1	0.60					
pO2	69.0	68.3	0.70					

(continued)

	1. Baseline (Rest)				p-value HA vs LA		p-value Asthma vs Ctrl	
	High altitude (HA)		Low altitude (LA)					
	Asthma	Control	Asthma	Control	Asthma	Control	HA	LA
pH	7.44	7.45	0.32					
SpO2	95.1	95.0	0.88					
FeNO	18[#]	15[#]	0.31*					

Table 4. (Continued) Arterialized capillary blood gased (aCBG) and fractional exhaled nitric oxide (FeNO) in asthmatics and controls under different conditions. Data are presented as mean except for[#] as median, p-values by *t*-test except * by *U* test. Comparison within asthma or control group by paired tests, comparison of asthma versus control by unpaired tests

exercise with cold air exposure at HA lead to a small but significant loss of FEV1 compared to low altitude. HA or cold air exposure alone did not induce a significant drop in FEV1. This loss of FEV1 was prevented by ICS treatment started during allergen season. Airway responsiveness following unspecific provocation with methacholine was reduced at HA compared to LA measurement. There was no difference in the recovery of baseline FEV1 after salbutamol inhalation between high altitude and low altitude.

Even though statistically significant, the exercise-induced loss of FEV1 of 230 ml at HA conditions we found in this population of well-controlled seasonal asthmatics, was small, and therefore of limited clinical relevance. This suggests that in clinically stable asthmatic patients without regular ICS treatment there is probably no need for a preventive ICS inhalation before a high altitude stay. However, as ICS treatment indeed shows protective effects, preventive treatment might be useful in individuals who have previously shown pronounced reactions to high altitude triggers and/or have more severe disease.

High altitude rehabilitation has been shown to reduce asthma specific inflammation, type 2 immune response and improves bronchial hyperresponsiveness in asthmatics.[15,16] These effects may be explained by lower air pollution and a decreasing pollen concentration with increasing altitude.[17,18] Whether a reduction of house dust mites is also a factor responsible for the decrease of asthmatic symptoms in high altitude is part of current scientific discussions.[19]

Our study showed a decrease in bronchial response to methacholine challenge at high altitude confirming findings from other studies. Allegra et al studied the effect of high altitude on bronchial hyperresponsiveness due to hyperosmolar agents in 11 asthmatic subjects at Monte Rosa (4559 m, Italy) and in the Himalayas near Mount Everest base camp (5050 m, Nepal). Compared to sea level the response to nebulized distilled water was significantly less at high altitude with a mean decrease of 6.7% (range 2–11%) and 22.2% (range 15–35%), respectively.[12] Cogo et al showed similar results for methacholine provocation at high altitude.[11] In both studies none of the subjects was on ICS treatment. Interestingly in our study this effect

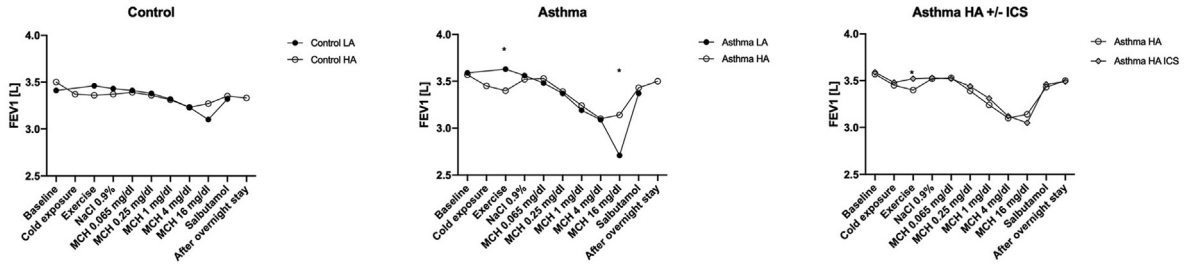

Fig. 2 FEV1 response during different study procedures and conditions. Comparison of control subjects at low altitude (LA) and high altitude (HA) (left panel), comparison of asthmatic subjects off ICS at LA and HA (middle panel), comparison of asthmatic subjects at HA on and off ICS (right panel). *$p < 0.05$ by *t*-test

occurred quite fast after ascent, as methacholine provocation was performed within the first 6 h after ascent.

We show that ICS treatment prevents a cold, exercise, and hypoxia induced loss of FEV1 at high altitude. The induction of bronchospasm by exercise and cold air was described in healthy athletes at lowland and at high-altitude conditions.[20,21] Freezer et al showed in a pediatric asthma cohort that ICS treatment has a protective effect on exercise-induced bronchial hyperresponsiveness.[22] ICS inhalation in spring in the asthma group resulted in a small but significant decrease in blood eosinophils compared to winter without ICS; whereas FeNO was unchanged. Whether the observed decrease in bronchial hyperresponsiveness at high altitude during ICS therapy was due to the decrease in blood eosinophils, or other effects such as decrease in the vulnerability of the bronchial epithelium, cannot be resolved from our data.

There is only a small number of studies investigating the effect of high altitude in asthmatic subjects and most of them were conducted in the context of high-altitude expeditions. Seys et al showed in 18 asthmatic subjects that both normobaric hypoxia (FiO2 11%) and 24-h cold air exposure led to a significant loss of FEV1. They also showed that during and after high altitude expedition to Aconcagua (5963 m) there was a significant loss of FEV1, and a slight increase of symptoms measured by the ACT. During baseline and expedition 72% respectively 89% of participants were on ICS treatment.[2]

Another study in 24 asthmatics and 7 healthy controls climbing to 6410 m at Mount Everest showed significant differences between both groups only for FVC% at 4310 m and 6410 m, but not for FEV1. Within the groups there was a significant loss of FEV1% and FVC%, but no change for FEV1%/FVC%. The loss of FEV1% following ascent in both groups was not clinically relevant with values still around 100%. Of note in this study 88% of asthmatics used ICS at baseline and up to 50% increased their ICS dose during the expedition. Interestingly, the change of FEV1% in the asthma group was, even if not statistically significant, smaller than in the control group, suggesting a protective effect of increased ICS use. Two subjects in the asthmatic group experienced an exacerbation.[8]

In a prospective study Golan et al found that frequent use of bronchodilators in the year before travel and extensive exercise as independent risk factors for asthmatics traveling a high altitude. Of 203 evaluated travelers with asthma, of whom 147 were engaged in high altitude trekking, only 23% used ICS at baseline evaluation.[23] The small number of patients on ICS therapy and the frequent use of bronchodilators suggest that the patients studied already had inadequately controlled asthma at study inclusion and thus before the high altitude stay.

In 18 subjects with well-controlled mild to moderate asthma with only two of them using ICS there were no significant differences in physiological parameters, peak flow or asthma exacerbations while climbing Mount Kilimanjaro (5895 m).[9]

Most of the studies mentioned included only well-controlled asthmatics, with a high percentage of subjects using ICS regularly at baseline. Hence, only limited conclusions can be drawn from these studies regarding the protective effect of ICS on bronchial response to high altitude triggers. Our study demonstrates in a structured setup that regular ICS inhalation protects against FEV1 loss

induced by exercise, cold and hypoxia. Moreover, we show that the known decline in methacholine response occurs very rapidly after ascent.

This study should be interpreted in light of its strength and limitations. A strength is the well-defined, standardized setup. It allowed us to reproduce the specific triggers in a serial not a parallel manner, and thus led to a better comparability of the different measurements. Limitations include the small number of subjects and the selection of asthmatics with well-controlled seasonal disease. Thus, it remains unclear whether HA triggers would induce larger effects in moderate to severe or uncontrolled disease. A variable that could not be controlled for is the amount and reaction to allergen exposure for each study participant at the start of the pollen season (timepoint that lay in between the 2 measurements). Further, while our data is generally consistent with other studies conducted at higher altitudes than the 2600 m studied here, effects might be stronger at even higher altitudes.

CLINICAL RELEVANCE AND CONCLUSION

Studies available to-date show that patients with well-controlled asthma have a low risk of worsening their asthma during HA exposure as long as they continue their therapy consistently and increase it as needed. Our study adds data for seasonal allergic asthma patients who do not have continuous ICS treatment. As the drop in FEV1 occurring as a result of HA triggers is small, a preventive ICS treatment before a planned HA stay does not seem necessary for most patients with such mild disease. However, as ICS treatment prevented FEV1 decrease in response to hypoxia, cold, and exercise at HA, such treatment may be advisable in patients who had symptoms during a previous HA stay or a history strong response to exercise and cold air.

Abbreviations

aCBG, arterializd capillary blood gases; ACT, asthma control test; BMI, body mass index; FeNO, Fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; HA, high altitude; IRB, institutional review board; ICS, inhaled corticosteroids; LA, low altitude; SpO_2, peripheral oxygen saturation.

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Availability of data materials

Primary data are available from corresponding author upon reasonable request.

Statement of contribution

JG, PM and KM perceived the study., JG, PM, CM, AG, US, RK, NK, KM performed the study measurements and data acquisition. JW performed the statistical analyses. PM, JG, KM, JB and RMH drafted the manuscript. All authors read and critically revised the manuscript.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the 1975 Helsinki Declaration. The study was approved by the ethics committee of the Ludwig-Maximilians-University (LMU) Munich, Germany (Number 327-16). Written Informed Consent was obtained from all participants.

Consent for publication

All authors provided input into the manuscript, reviewed the final draft and provided consent for publication.

Editorial Policy Confirmation and Agreement

None of the material in this manuscript has been published or is under consideration for publication elsewhere.

Declaration of competing interest

All authors declare there are no conflicts of interest.

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