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ORIGINAL ARTICLE

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A positive effect of a short period stay in Alpine environment on lung function in asthmatic children

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Abstract

Lung function is a central issue in diagnosis and determination of asthma severity and asthma control has been previously reported to improve after a stay in mountain environment for at least 2 weeks. No data are available for shorter periods of stay, in particular for small airways during a stay at altitude. The aim of this study is to focus on changes in respiratory function, regarding both the central airways and the peripheral airways in the first 2 weeks of stay in a mountain environment in asthmatic children. In this study, 66 asthmatic children (age: 14 ± 2.8 years) were evaluated through spirometric and oscillometric tests at the time of arrival at the Istituto Pio XII, Misurina (BL), Italy, 1756 m above sea level (T0), after 24 h (T1), and 168 h (T2) of stay. FEV1%, FEF25%–75%, and FEV1/FVC increased significantly from T0 value both at T1 and T2 (respectively, $p = 0.0002$, $p < 0.0001$, $p = 0.0002$). Oscillometry showed a significant improvement in R5, R20, and R5–20 at both T1 and T2 as compared to T0 (respectively, $p = 0.0001$, $p = 0.0002$, and $p = 0.049$). Reactance at 5 Hz (X5) improved significantly at T2 versus T0, $p = 0.0022$. The area under reactance curve between Fres and 5 Hz (AX) was significantly reduced ($p = 0.0001$) both at T1 and T2 as compared to T0. This study shows an improvement in respiratory indices as soon as after 24 h of stay at altitude, persisting in the following week.

KEYWORDS

allergen avoidance, asthma, children, mountain climate

1 | INTRODUCTION

Asthma is a complex disease with a mix of genetic and environmental factors contributing to its development and severity. The prevalence is increasing in many countries, in particular among children, for whom it is the most common chronic disease.[1,2] The relationship between asthma and mountain climate and environment is quite intriguing. In fact, a lower asthma incidence is reported at altitude as compared to sea level; an inverse correlation between residential altitude and the development of asthma, or incidence of exacerbations has been found and the risk of new-onset asthma decreases as altitude increases. However, a clear explanation to motivate this evidence was never reported.[3–5] Similarly, the benefit of a stay at altitude for asthmatics residing at sea level has been known for many years.[6] Mountain climate is characterized by the reduction of the barometric pressure, air density, relative temperature, and humidity; moreover, aeroallergen burden (both pollen and Dermatophagoides) and pollution are also reduced. All these changes can have a positive effect on asthma.[7]

Lung function represents one of the main feature for the diagnosis and the determination of asthma severity and asthma control,[2] and its improvement has been previously reported after a stay at altitude of at least 2 weeks.[8] On the other hand, to the best of our knowledge, no information is currently available in the literature about changes in respiratory function in the first week as well as no data is available for this frame of time about small airways' evaluation during a stay at altitude, even though peripheral airways impairment, as determined by oscillometry, is common also in children with well-controlled asthma. The aim of this study is to focus on changes in respiratory function, regarding both the central airways and the peripheral airways, during the first week of stay at altitude at the Istituto Pio XII Misurina (BL), Italy, 1756 m.asl (above sea level).

2 | METHODS

2.1 | Patients and study design

This is an analysis of a single-center on children asthmatic community-treated patients, consecutively recruited between July and September 2020. The study was approved by the Ethics Committee of Province of Treviso and Belluno (May 26, 2020, n. 838). Written informed consensus was obtained from parents or legal representatives. Sixty-six patients were evaluated. All were born and lived below 600 m asl. Regarding the severity of asthma, 49 patients (74.5%) had moderate asthma, 3 patients (4.5%) had severe asthma, and 14 (21%) mild asthma. At the time of admission, asthma was not controlled in 21 patients (35%), while in the remaining 45 (65%) it was controlled. Forty-seven patients (71%) were allergic to both grasses and mites, four were allergic only to mites, nine only to grass, and six were not allergic. Most of the patients (56) suffered also from allergic rhinitis, 1 had chronic hepatitis, 1 rheumatoid arthritis, 1 gastroesophageal reflux, 1 bronchiectasis, 4 atopic dermatitis, and 1 tachycardia.

Respiratory function was evaluated at the time of arrival at the Istituto Pio XII, Misurina (BL), Italy, 1756 m.asl (T0), after 24 h (T1), and 168 h (T2) of stay. All the evaluations were performed at the same time of the day to avoid circadian modifications. Prestudy controll treatment was unchanged throughout the study period.

2.2 | Oscillometry measurements

The respiratory resistance and reactance were measured before spirometry using impulse oscillometry (IOS) with Sentry Suite (VyAire Medical) and following the European Respiratory Society (ERS) technical standards for respiratory oscillometry.[9] The IOS system was calibrated daily, as suggested by the manufacturer. Measurements were performed using a mouthpiece and a bacterial/viral filter during tidal breathing, and subjects were asked to wear a nose clip and exert a slight manual compression on their faces to reduce the influence of cheek compliance and air leak. IOS values were measured in real-time as a function of flow volume and pressure for approximately 20 s. Respiratory resistance at 5 Hz (R5) and 20 Hz (R20), the difference between R5 and R20 (R5–R20), reactance at 5 Hz (X5), resonant frequency (Fres), and the area under reactance curve between Fres and 5 Hz (AX) were measured. The mean values of at least three adequate trials (with a coefficient of variability for R5 ≤ 15%) were graphically displayed and used for the analysis.[9]

2.3 | Spirometry measurements

Spirometry was performed by Masterscreen IOS/Sentry Suite, VyAire Medical according to the American Thoracic Society (ATS)/ERS guidelines.[10] Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), maximum mid-expiratory flow (FEF25%–75%) and FEV1/FVC ratio were considered for the analysis. System was calibrated daily with a 3-L syringe (Hans Rudolph Inc) to test the accuracy of the volume measurement and to check the ambient temperature and humidity. To evaluate bronchial reversibility, four separate doses 100 µg salbutamol (total dose, 400 µg) through a metered-dose inhaler was administered through spacer and spirometry was repeated after 15 min. For BR was positive if the improvement of FEV1 ≥12% and/or 200 ml compared with baseline values before inhalation. Spirometry tests were performed according to guidelines and the check of FEV1 and FVC repeatability criteria were applied to acceptable FVC and FEV1 values.[10]

2.4 | Statistical analysis

The analysis had exploratory, and hypothesis-generating aims. A 10% statistical significance threshold was set for primary endpoint which was considered FEV1.

Data were examined for normality of distribution, when appropriated. Categorical data were summarized as percentages. Continuous variables were expressed as median and interquartile range or as means (±standard deviation), depending on normality demonstrated by Kolmogorov–Smirnov test. Repeated measurement ANOVA, to remove effect of potential confounders (age, sex, and, Body Mass Index [BMI]), was applied to assess differences across the three study visits. All the analyses were performed using GraphPad Prism for Windows. A p value <0.05 was considered as a nominal statistical significance.

3 | RESULTS

Sixty-six children completed the study. Patient personal characteristics are reported in Table 1.

FEV1% of predicted, FEF25–75% of predicted and FEV1/FVC increased significantly from T0 value both at T1 and T2 as reported in Table 2. Statistics for spirometric values is summarized in Table 3.

Oscillometry showed a significant improvement in R5, R20, and R5–20 at both T1 and T2 as compared to T0 (Table 5). Reactance at 5 Hz (X5) improved significantly at T2 versus T0.

The area under reactance curve between Fres and 5 Hz (AX) was significantly reduced both at T1 and T2 as compared to T0. Statistics for oscillometric values is summarized in Tables 4 and 5.

No significant correlation was found between respiratory functional changes and age, sex, BMI, asthma severity.

TABLE 1 Patient characteristics

Subjects, *n*	66
Male, *n* (%)	39 (59.1)
Female, *n* (%)	27 (40.9)
Age, years, mean (SD)	14 (2.8)
Age range (years)	8–19
Weight, kg (SD)	57.1 (18.7)
Height, m (SD)	1.6 (12.4)
BMI (SD)	21.6 (4.9)

Note: All values are shown as means and standard deviations (SD). Categorical variables are shown as percentage.

TABLE 2 Spirometry values at the different times of the study; mean and standard deviation (SD) are expressed as percentage of predicted

	T0	T1	T2	*p* value
FEV1	94.84 (11.65)	97.67 (11.05)	97.88 (11.34)	0.0002
FEF 25–75	86.32 (29.44)	93.88 (28.08)	95.19 (25.47)	<0.0001
FEV1/FVC	83.23 (9.39)	85.68 (8.11)	86.19 (7.76)	0.0002
FVC	99.23 (10.67)	99.28 (11.33)	99.00 (13.15)	NS

Abbreviations: FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

TABLE 3 Statistics for spirometric values at the different times of the study

	Timing	*p* value	Timing	*p* value
FEV1	T0–T1–T2	0.0002	T0–T1	0.0011
			T0–T2	0.014
FEF 25/75	T0–T1–T2	0.0002	T0–T1	<0.0001
			T0–T2	<0.0001
FEV1/FVC	T0–T1–T2	<0.0001	T0–T1	<0.0001
			T0–T2	<0.0001
FVC	T0–T1–T2	NS	T0–T1	NS
			T0–T2	NS

Abbreviations: FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

4 | DISCUSSION

In the present study we demonstrated that in asthmatic children lung function parameters (measured through spirometry and impulse oscillometry) show a significant improvement at moderate altitude (1756 m), already detectable 24 h upon arrival.

As for spirometry, we found that, after 24 h, FEV1 increased from 94% to 97% of predicted values, an improvement statistically significant but of poor clinical relevance. Likewise a significant improvement was found in FEF25–75 after 24 h, with a further rise in the mean value after 1 week, while no change was found in FVC.

These results are in keeping with previous studies that described a general improvement in lung function parameters during a stay at altitude for a period ranging from 2 weeks to 12 months.[8,11–13] Nonetheless, a systematic review of the studies which evaluated the effects on asthmatic subjects' respiratory function of a period at moderate altitude reported a trend toward improvement but with an overall small effect. The authors concluded suggesting the need for further, qualitatively strong research, including larger sample sizes and controlled trial design.[14]

Our study expands these previous results showing that also a short-term stay at altitude significantly affects lung function. Though the underlying mechanisms driving these changes are not explained by the results of the present study we are tempted to speculate that environmental characteristics may be involved.

It is likely, in fact, that in asthmatic children the improvement in lung function also mirrors the effects of breathing in a cleaner environment, that is, less polluted and with lower levels of allergens. A lower exposure to environmental allergens, in fact, results in a reduction of peripheral blood T-lymphocyte activation, eosinophil counts and markers of eosinophil activation.[15–17] Similarly, the relocation in a less polluted environment is associated with a rapid

TABLE 4 Oscillometry values at the different times of the study; mean and standard deviation (SD) are expressed as percentage of predicted

	T0	T1	T2	*p* value
R5	101.0 (83.00–109.0)	88.0 (73.00–107.5)	85.0 (71.00–107.5)	0.0001
R20	97.0 (80.5–106.5)	85.0 (76.0–103.5)	83.0 (73.00–105)	0.0002
X5	109.0 (76.5–153)	98.0 (74.5–130.0)	97.00(80.00–131.5)	0.049
AX	0.80 (0.49–1.49)	0.66 (0.45–1.15)	0.71 (0.45–1.01)	0.0001
R5%–20%	18.13 (9.61–30.64)	15.88 (9.15–26.74)	18.97 (9.93–25.69)	0.054
R5–20	0.07 (0.035–0.14)	0.06 (0.03–0.11)	0.07 (0.03–0.11)	0.02

reduction of airway inflammation in allergic asthmatic children as shown by a rapid decline in nasal eosinophils and fractional exhaled nitric oxide after 7 days.[18,19] The beneficial effects on asthma have been recently confirmed by Quignon et al.[20] in a group of asthmatic children monitored over the course of an entire school year at altitude. These children showed a significant improvement in asthma control and a decrease in the levels of expired NO and interleukin (IL)-13 and IL-10, with a tendency toward a worsening of these parameters upon returning home for Christmas holidays.

Noteworthy exposure to an environment polluted and rich in allergens leads to effects specular but opposite in sign are. In fact, it has been recently demonstrated that short term pollution and pollen exposure have a synergistic detrimental effect of children's lung function, particularly in asthmatic children.[21] Moreover, the close correlation between pollution and respiratory function, even in the short-term, has been shown in both asthmatic and healthy children.[22,23]

According to what has been said so far, these results can have implications for clinical practice. In fact, the rapid improvement of reactance and area of reactance highlights the importance of avoiding the factors triggering bronchial inflammation. On the other hand, it is known that peripheral airways impairment can precede asthma worsening and can predict the probability of asthma exacerbations. Carefully avoiding exposure to triggers can reduce the risk of exacerbations and can be relevant for the subsequent clinical evolution of asthma.

We believe that especially the significant improvement of AX and X5 are of clinical importance.[24,25]

In fact, peripheral airways impairment can be present early, even during symptom-free period and has been suggested to predict the probability of asthma exacerbations.

The fact that avoidance of trigger of airways inflammation improves small airways disfunction is important for clinical practice. In fact, it probably reduces the risk of exacerbations and is relevant for the subsequent clinical evolution of asthma.

The novelty of our study lies not only in the evaluation of the short-term effect of altitude on spirometric parameters, but also in the assessment of the effects on airway resistance and reactance.

To our knowledge, this is the first study applying impulse oscillometry in the assessment of altitude effects on lung function in asthmatic children followed-up in a mountain environment.

TABLE 5 Statistics for oscillometric values at the different times of the study

	Timing	*p* value	Timing	*p* value
R5	T0–T1–T2	0.0001	T0–T1	0.0004
			T0–T2	<0.0001
R20	T0–T1–T2	0.0002	T0–T1	0.0001
			T0–T2	0.0003
R5-20	T0–T1–T2	0.0199	T0–T1	0.0018
			T0–T2	0.0088
X5	T0–T1–T2	0.0485	T0–T1	NS
			T0–T2	0.0022
AX	T0–T1–T2	0.0001	T0–T1	<0.0001
			T0–T2	0.0003

In 1997 Valletta et al.[13] demonstrated that FEF25–75 improved significantly after 12 weeks of stay in Alpine environment. Nowadays FEF25–75 is no longer considered the gold standard for small airway assessment due to its high variability[26] while impulse oscillometry performs better in identifying peripheral airway impairment.[27,28]

Impulse oscillometry is an effort independent pulmonary function measurement requiring minimal patient cooperation and giving valuable information on different aspects of lung function as compared to spirometry. Since spirometry and IOS assess different aspects of lung function, IOS is now considered a useful supplement to spirometry, mainly in children[29,30] and there is mounting evidence that support the inclusion of small airway measures in routine asthma testing.

In the present study, we observed an improvement in resistence and in reactance area, reflecting changes in the degree of small airways patency. IOS parameters, in particular AX, can be used as an early marker of lung function improvement after starting a controller therapy.[31] Moreover, recent studies have suggested that peripheral airway impairment, evaluated by oscillometry, can characterize children with a greater risk of losing asthma control over the following months.[32,33] We, therefore, believe that the rapid improvement during the stay at altitude observed in this study could be relevant from a clinical standpoint.

However, the issue of how long the effect lasts, after returning home remains open. Although in adults a decrease in exacerbations and sustained improvement in asthma control has been reported up to 12 months after an altitude stay[34] there is currently no information on children. This topic should be the subject of future research.

A limit of our study is the lack of a group of control, due to fact that only asthmatic children are hosted at the Istituto Pio XII in Misurina.

In conclusion, the present study shows that an improvement in respiratory parameters can be detected after only 24 h of stay at altitude. This new evidence contributes to the understanding of the effects of stay at moderate altitude for asthmatic children, suggesting a measurable benefit as early as 24 h after arriving in the Alpine environment.

4.1 | Limitations of the study

This study has several limitations. First of all, the lack of a control group, due to fact that only asthmatic children are hosted at the Istituto Pio XII in Misurina. Second, the study design did not include biological or environmental measurement to correlate with functional data. As far as environmental pollution is concerned, however, we would like to underline that all the measurements performed by the Regional Agency for the Environment (ARPA-Veneto) show a clear reduction of pollutants in Misurina, compared to the areas from which asthmatic children come (Po Valley and neighboring areas) (https://www.arpa.veneto.it).

Another limit of our study is that we have no sea level measurement and considered as baseline the lung function measured on arrival at altitude.

AUTHOR CONTRIBUTION

Annalisa Cogo: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review & editing. Michele Piazza: (equal); Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); software (equal); validation (equal); writing – original draft (equal); writing – review & editing. Silvia Costella: (equal); Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); validation. Massimiliano Appodia: (equal); Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); validation. Raffaele Aralla: (equal); Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); validation. Stefania Zanconato: (equal); Supervision (equal); validation (equal); vsualization (equal); writing – original draft (equal); writing – review & editing. Silvia Carraro: (equal); Supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review & editing. Giorgio Piacentini: (equal); Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review & editing.

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CONFLICT OF INTEREST

The Authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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