Original Article

Nasal Function Changes at High Altitude

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Abstract

Background: An ever-increasing number of people are involved in sport activities at high altitude.

Objective: This study aimed to evaluate the pulmonary and nasal functions, including nasal cytology, in healthy volunteers moving for 1 week from an altitude of 2000 m to another of 3400 m.

Methods: Peak nasal inspiratory flow (PNIF), pulmonary function, including peak expiratory flow (PEF), mucociliary transport time (MCTt), nasal cytology, and oxygen saturation (O_2 sat) were studied in 5 different occasions—T1: at base camp (2000 m); T2: at the mountain refuge (3400 m); T3: after 7 days at 3400 m; T4: after the return at the base camp (2000 m); and T5: at the base camp (2000 m) after 15 days.

Results: With respect to T1, PEF values decreased at T2 ($P = .004$), T3 ($P = .004$), T4 ($P = .000$), and T5 ($P = .001$). Forced expiratory volume in the first second and forced vital capacity did not differ among the 5 different times of measurements. In regard to T1, PNIF values increased at T2 ($P = .003$) and T3 ($P = .001$). MCTt and O_2 sat showed similar but opposite changes with MCTt increased at T2 and T3 in respect to T1 ($P = .000$ for both), while O_2 sat decreased at T2 and T3 in respect to T1 ($P = .000$ for both). At nasal cytology, the number of neutrophils increased at T2 in respect to T1 ($P = .008$). At multivariate analysis, PNIF changed with altitude from T1 to T4 even accounting for the effect of all the other variables (T1 vs T2 PNIF, $P = .009$; T1 vs T3 PNIF, $P = .007$; T1 vs T4 PNIF, $P = .021$).

Conclusions: Although the study has some limitations, being conducted on a small cohort and at no controlled environmental conditions, data seem to support the utility of MCTt for studying nasal mucosa damage induced by high altitude. Nasal cytology seems to be able to identify the inflammation of the nasal mucosa exposed to hypoxia. Further investigations on larger series and possibly conducted in hypobaric chamber at controlled standardized conditions are necessary in order to confirm these results and, most importantly, the improvement of PNIF at high altitude.

Keywords

high altitude, PNIF, PEF, O_2 sat, spirometry, FEV1, FVC, MCTt, nasal cytology, neutrophils

Introduction

Physical activity is recognized as an effective health promotion habit.[1] All over the world, an increasing number of people living at low altitude enjoy sport activities in the mountainous areas at altitudes higher than 2000 m.[2,3]

It has been demonstrated that during altitude exposure, the airways adapt by activating a number of acute and chronic mechanisms aimed at optimizing oxygen availability. In particular, high-altitude trips (defined as higher than 2700 m above sea level)[4] may cause nasal congestion, impaired nasal mucociliary transport

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rate, and increased nasal resistances due to decreased partial oxygen pressure and dry air.[5–7]

Even though nasal cytology has been recognized as a useful diagnostic tool in rhinology for more than 100 years, only recently the interest in this field has increased. Nasal cytology is indeed relatively simple and very useful in clinical follow-up,[8,9] and in the last years, many authors have tried to investigate rhinopathies also from a cytological point of view.[10,11] However, to the best of our knowledge, no studies have evaluated nasal cytology modifications induced by high-altitude exposure.

The aim of this prospective study was to investigate some pulmonary and nasal function parameters, including nasal cytology, in a group of healthy volunteers moving from an altitude of 2000 m to another of 3400 m in a 1-week journey.

Materials and Methods

The present investigation was a prospective study approved by the scientific committee of the Otolaryngology Section, University of Padova and was conducted in accordance with the 1996 Helsinki Declaration. All subjects gave their written informed consent for the inclusion in the study and for the clinical publication of the data. Data were examined in agreement with the Italian privacy and sensible data laws (D.Lgs 196/03).

For this study, healthy volunteers involved in a high-altitude skiing vacation lasting 1 week were recruited. All participants were evaluated after at least 20 minutes of rest in 5 different occasions. The first evaluation (T1) was performed at the base camp (2000 m of altitude), before starting the vacation. The second evaluation (T2) was performed on the same day, once arrived at the mountain refuge at 3400 m of altitude (all volunteers went up by cable car; the lifts lasted 30 min). The third evaluation (T3) was taken at the mountain refuge (3400 m of altitude) 7 days after the arrival, just before leaving. The fourth evaluation (T4) was performed on the same day at the base camp, once the volunteers arrived by cable car. Finally, another (and last) evaluation (T5) was performed at the base camp 15 days after the vacation's end. At each evaluation, all volunteers were assessed by means of peak nasal inspiratory flow (PNIF), pulmonary peak expiratory flow (PEF), basal saturation of oxygen (O_2 sat), heart rate, spirometry, nasal cytology, and mucociliary transport time (MCTt). At the beginning of the study (T1), the volunteers also completed a Sinonasal Outcome Test-22 questionnaire[12] (SNOT-22) to record their nasal symptoms.

A portable Youlten peak flow meter (Clement Clark International, Harlow, UK) was used to measure PNIF. Volunteers were encouraged to inhale as hard and fast as they could through the nose with their mouth tightly closed and the mask placed firmly over the face, starting from the end of a full expiration. All subjects were seated during the test. As in previous experiences, 3 satisfactory maximal inspirations were obtained for each subject, and the highest value was considered as the basal PNIF value.[13] All PNIF measurements have been done by the same operator (E. N.).

PEF was measured with a portable peak flow meter (Clement Clark International, Harlow, UK). Volunteers were encouraged to exhale through the mouth as hard and fast as they could into the mouthpiece of the instrument, starting from the end of a full inspiration. Three satisfactory maximal expirations were obtained and the highest value was considered as the basal PEF value.[14] All PEF measurements have been done by the same operator (E. N.).

Spirometry was performed with a portable Cosmed Pony Grapic® device; basal O_2 sat, heart rate, forced expiratory volume in the first second (FEV1), and forced vital capacity (FVC) were detected. Spirometry has been performed by the same operator (M. D. P.).

Nasal cytology was performed by anterior rhinoscopy, using a nasal speculum. The collection technique consisted of scrapings from the middle portion of the inferior turbinate, using a Rhino-Probe (Arlington Scientific Inc., Springville, Utah) nasal curette. The specimens were fixed in 100% alcohol and underwent May–Grunwald–Giemsa staining. All specimens were examined under the light microscope by the same operator (G. O.), who was unaware of which visit the specimen was related to. The cytologic variables considered were the total number of ciliated cells, with and without hyperchromatic supranuclear stria, and the total number of inflammatory cells (neutrophil granulocytes and eosinophil granulocytes) counted for each specimen in 5 separate high-power fields (original magnification $\times 100$).[15]

The MCTt was established by positioning charcoal powder on the medial surface of the inferior nasal turbinate,[16] 1 cm from the anterior end, to avoid the squamous epithelium.[13] Charcoal powder transit from the nasal fossa to the post nasal space was evaluated by means of direct pharyngoscopy.[17] The participants were asked not to blow their nose or sniff during the test.

Statistical Analysis

To evaluate the mean difference for the considered experimental conditions, we relied on pairwise *t* tests, where family-wise error rate was adjusted via the sequential procedure described by Holm.[18] In addition, to investigate if changes in PNIF values had any correlation with the other measured variables, a random effect model was estimated, including a random intercept for

each of the subjects to account for repeated measure, and relying on Satterthwaite's approximation for P values.[19] Finally, to measure the correlation occurring between O_2 sat, MCTt, and neutrophils, a Pearson correlation test was applied for each considered altitude.

The R: a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses. In particular, the lme4 and lmerTest packages were used to estimate the random effect model.

Results

Eighteen Caucasian healthy volunteers (14 males and 4 females; mean age 30.2 ± 10.0 years; mean height 176.6 ± 6.6 cm) were enrolled for this study. Among them, 5 were smokers, while 2 were allergic. One smoker had also allergic rhinitis. None of the volunteers had a history of previous sinonasal surgery, and 3 of them were taking medications (1 female was taking estroprogestin pill and 2 males were taking proton pump inhibitors). Finally, 3 of them suffered from mountain sickness. SNOT-22 at the beginning of the study was 20.5 ± 11.5. Neither epistaxis nor crusts were observed in the subjects during the study period. Table 1 shows the main characteristics of the population studied.

Although PEF showed a significant decrease at T2, T3, T4, and T5 when compared to the values measured at T1 ($P = .004$, $P = .004$, $P = .000$, and $P = .001$, respectively; Table 2), PNIF showed a significant increase at T2 and T3, if compared to the values measured at T1 ($P = .003$ and $P = .001$, respectively; Table 2, Figure 1). FEV1 and FVC did not differ among the 5 different occasions of measurement (Table 2).

Table 1. Clinical and Demographic Variables of the Cohort of Volunteers.

	Subjects (n = 18)
Age, mean ± SD (range), years	30.2 ± 10.1 (20–48)
Sex, n (%)	
Female	4 (22.2%)
Male	14 (77.8%)
Height, mean ± SD (range), m	1.76 ± 0.07 (1.64–1.85)
BMI, mean ± SD (range), kg/m^2	24.3 ± 3.2 (20.0–32.1)
SNOT-22, mean ± SD (range)	20.5 ± 11.5 (6–55)
Smokers, n (%)	5 (27.8%)
Allergic rhinitis, n (%)	2 (11.1%)
Previous sinonasal surgery, n (%)	0 (0%)
Medications, n (%)	
Estroprogestin pill	1 (5.6%)
Proton pump inhibitor	2 (11.1%)
History of mountain sickness, n (%)	3 (16.7%)

Abbreviations: BMI, body mass index; SNOT-22, Sinonasal Outcome Test-22.

MCTt showed a significant lengthening during the week of vacation. In fact, it significantly increased at T2 and T3 (with both adjusted P values being nearly 0) in respect to T1. At T4, as soon as the subjects arrived at 2000 m, MCTt returned to lower values, although still significantly higher than those found at T1 ($P = .000$). Finally, at the last evaluation (T5), the MCTt appeared to be shorter than T1 ($P = .026$; Figure 2). Similarly, O_2 sat changed in the different evaluations, showing to be significantly lower at T2 and T3 than T1 with both adjusted P values being nearly 0. At T4, O_2 sat increased, but remained significantly lower than T1 ($P = .018$).

Considering nasal cytology, we observed that the number of ciliated cells and eosinophils did not change through the study. The number of neutrophils increased from T1 to T2 ($P = .008$) and decreased passing from T3 to T4 with no significant differences between T1 and neither T4 or T5 (Table 2 and Figure 3).

The multivariate analysis, conducted with a model involving all the available variables to assess their influence on PNIF, showed that MCTt, PEF, FVC, FEV1, O_2 sat, and the number of neutrophils, eosinophils and ciliated cells at nasal cytology did not significantly influence participants' PNIF values. PNIF significantly changed with altitude from T1 to T4 even accounting for the effect of all the other variables (T1 vs T2 PNIF, $P = .009$; T1 vs T3 PNIF, $P = .007$; T1 vs T4 PNIF, $P = .021$; Table 3).

Discussion

In this study, O_2 sat significantly decreased passing from the base camp (T1) to a higher altitude (T2) and remained significantly lower than T1 values during the whole stay at the same altitude (T3).

The exposure to hypoxia could probably be the reason of the prolonged MCTt found in our population when passing from 2000 m (T1) to 3400 m (T2 and T3).[20,21] It is known in fact that the exposure to hypoxia can induce nasal decongestion causing an increase in the MCTt as a consequence.[22] Moreover, it has been demonstrated that the human body produces an increased amount of catecholamines when exposed to high altitude, probably to enable a faster cell regeneration.[23,24] A similar situation occurs during physical exercise when nasal hyperventilation takes place as a result of the active nasal mucosa vasoconstriction due to sympathetic activation.[25] Interestingly, the effects of high altitude on the nasal MCTt seem to be totally transitory and limited to the time of hypoxia exposure, as demonstrated by the fact that T5 MCTt values were shorter than those found at T1. The present result was confirmed at the multivariate analysis, which showed that PNIF changed with altitude independently from the effect of all the other

Table 2. Main Clinical Parameters in the Different Evaluations.

			P Values			
Variables	*t*	Mean ± SD	T1 vs T2	T1 vs T3	T1 vs T4	T1 vs T5
PNIF (l/min)	1	121.7 ± 44.5	**.003**	**.001**	.168	.168
	2	147.8 ± 38.7				
	3	156.7 ± 45.1				
	4	140.6 ± 44.0				
	5	132.2 ± 40.7				
PEF (l/min)	1	607.8 ±108.5	**.004**	**.004**	**.000**	**.001**
	2	580.6 ±103.9				
	3	578.9 ±100.5				
	4	566.7 ± 91.1				
	5	550.6 ± 86.1				
MCTt (min)	1	28.7 ± 5.8	**.000**	**.000**	**.000**	**.026**
	2	53.0 ± 8.8				
	3	64.6 ± 6.2				
	4	34.4 ± 5.3				
	5	25.2 ± 4.9				
Ciliated cells	1	8.5 ± 6.24	1.00	.532	1.00	.532
	2	7.67 ± 7.54				
	3	6.72 ± 5.97				
	4	7.06 ± 9.22				
	5	5.61 ± 4.49				
Neutrophils	1	11.44 ± 9.84	**.008**	.069	.913	.913
	2	26.06 ±14.27				
	3	22.06 ± 19.5				
	4	13.94 ±12.28				
	5	9.77 ± 13.7				
Eosinophils	1	0.5 ± 1.47	.248	.248	.248	.614
	2	1.59 ± 2.87				
	3	1.29 ± 1.72				
	4	2 ± 3.02				
	5	0.77 ± 1.39				
FEV1 (l)	1	3.82 ± 0.79	1.00	1.00	1.00	1.00
	2	3.87 ± 0.64				
	3	3.72 ± 0.66				
	4	3.82 ± 0.55				
	5	3.91 ± 0.53				
FVC (l)	1	4.44 ± 0.99	1.00	1.00	1.00	1.00
	2	4.54 ± 0.88				
	3	4.36 ± 0.88				
	4	4.45 ± 0.71				
	5	4.55 ± 0.71				
O_2 sat (%)	1	96.56 ± 0.98	**.000**	**.000**	**.018**	.067
	2	92.39 ± 2.70				
	3	93.94 ± 1.16				
	4	95.67 ± 1.03				
	5	97.28 ± 1.02				

Abbreviations: FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; MCTt, mucociliary transport time; PEF, peak expiratory flow; PNIF, peak nasal inspiratory flow. Statistically significant values ($P<.05$) are marked in bold.

variables considered in the model (Table 3). Even though PNIF values have been found to decrease with the increase of the altitude,[6] other authors reported no changes of nasal resistances with altitude.[7] Furthermore, a significant increase in PNIF values has been observed when simulating the passage from the sea level to 8000 m in a hypobaric chamber.[26] In our opinion, the increased PNIF values can be considered the result of the nasal decongestion state caused by hypoxia, as already explained above in regard to MCTt.

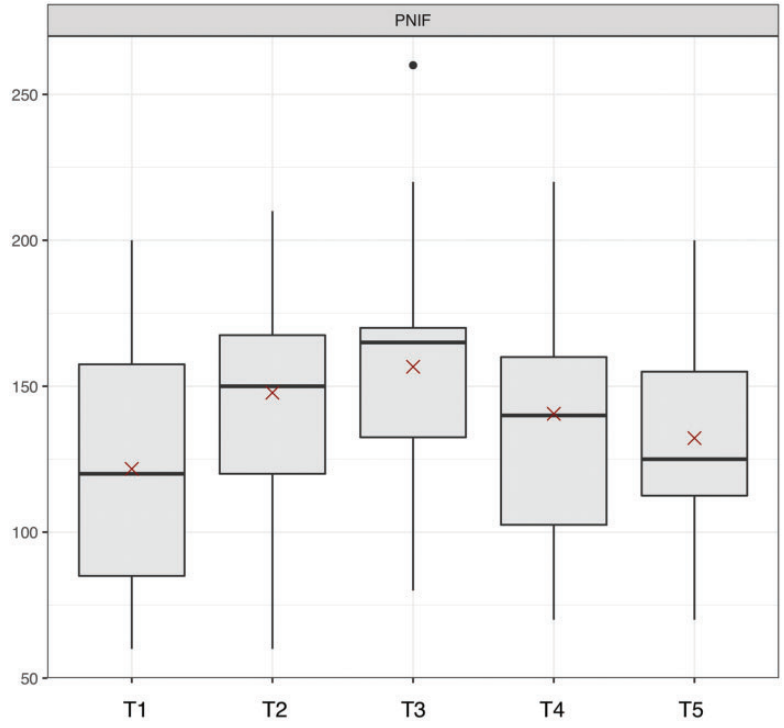

Figure 1. PNIF values (l/min) in the 5 different evaluations (T1: at the base camp [2000 m of altitude]; T2: once arrived at the mountain refuge [3400 m of altitude]; T3: at the mountain refuge [3400 m of altitude] 7 days after the arrival; T4: at the base camp [2000 m of altitude] after the descent from the mountain; T5: at the base camp, 15 days later). PNIF, peak nasal inspiratory flow.

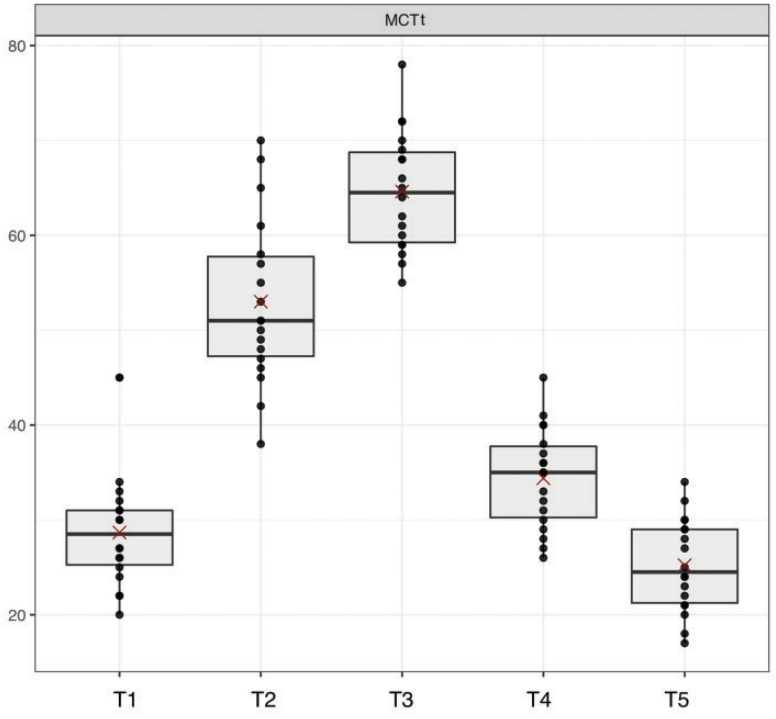

Figure 2. MCTt values (min) in the 5 different evaluations (T1: at the base camp [2000 m of altitude]; T2: once arrived at the mountain refuge [3400 m of altitude]; T3: at the mountain refuge [3400 m of altitude] 7 days after the arrival; T4: at the base camp [2000 m of altitude] after the descent from the mountain; T5: at the base camp, 15 days later). MCTt, mucociliary transport time.

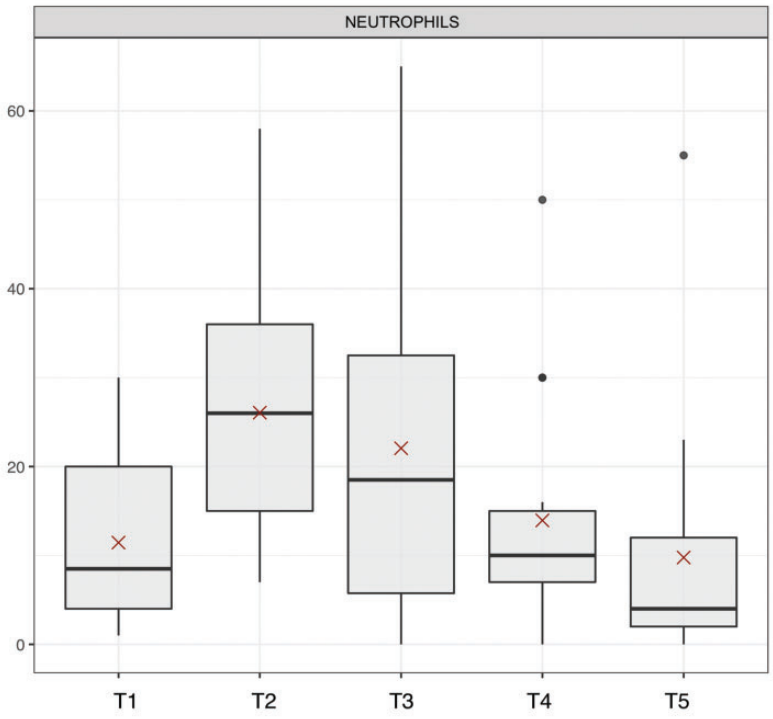

Figure 3. Number of neutrophils at the rhinocytogram in the 5 different evaluations (T1: at the base camp [2000 m of altitude]; T2: once arrived at the mountain refuge [3400 m of altitude]; T3: at the mountain refuge [3400 m of altitude] 7 days after the arrival; T4: at the base camp [2000 m of altitude] after the descent from the mountain; T5: at the base camp, 15 days later).

Table 3. Multivariate Regression Model: Correlations Between PNIF and the Demographic/Clinical Variables Considered.

	Beta	Standard Error	t Value	P
Intercept	−66.2873	240.4324	−0.28	.7836
Sex (male)	41.2475	31.5984	1.31	.2082
BMI	0.2022	3.1178	0.06	.9495
Allergy/asthma	−53.7544	29.5561	−1.82	.0958
Smoke	24.6618	20.7218	1.19	.2602
O_2 sat	2.3088	2.3143	1.00	.3224
Eosinophils	−0.2401	1.6746	−0.14	.8864
Neutrophils	0.2262	0.3272	0.69	.4919
MCTt	−0.7684	0.5984	−1.28	.2036
PEF	−0.0159	0.1031	−0.15	.8783
FVC	12.2191	24.5950	0.50	.6210
FEV1	−26.5575	27.0842	−0.98	.3305
Ciliated cells	0.4194	0.7143	0.59	.5592
T2 vs T1 PNIF	51.7505	19.0667	2.71	**.0086**
T3 vs T1 PNIF	65.1485	23.2847	2.80	**.0068**
T4 vs T1 PNIF	25.1796	10.6160	2.37	**.0206**
T5 vs T1 PNIF	9.1494	11.2096	0.82	.4172

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; MCTt mucociliary transport time; PEF, peak expiratory flow; PNIF, peak nasal inspiratory flow. Statistically significant values ($P<.05$) are marked in bold.

Differently from the study of Barry et al.[26] who reported a significant increase of PEF values passing from a sea-level pressure to a pressure at 8000 m, in our study, PEF values decreased with altitude, which could be related to the decrease in air density.[27] FEV1 and FVC showed a similar behavior, even though they did not reach statistical significance. It has also been proposed that PEF could be not so accurate at high altitude, where fixed orifice devices are preferable.[28] The absence of significant pulmonary function changes at high altitude is in agreement with the study from Pollard et al. who found no FEV1 variations in subjects moving from the sea level to an Everest Base Camp based at 5300 m.[28]

Nasal cytology is a simple and safe diagnostic procedure that allows to assess normal and pathological changes of the nasal mucosa by identifying and counting the cell types and their morphology.[29] It can be used to count the number of inflammatory cells present in the sample (neutrophils, eosinophils, basophils, and mast cells) as an index of the nasal inflammatory status.[13] Moreover, it helps to evaluate the effects of different stimuli on the nasal mucosa.[29]

This study attempted for the first time to assess the changes in nasal cytology after the exposure to different altitudes. In the past, some authors tried to evaluate nasal mucosa changes induced by high altitude in histology. In particular, Rostovshchikov, studying the human mucosa at electron microscopy after exposure to high altitude (3375 m above the sea level) for 2 weeks, observed many changes such as edema, leukocyte infiltration, destructive changes in the cells of tegmental epithelium and their focal desquamation.[30] These histological findings could be the consequence of a barrier dysfunction and increased permeability induced by hypoxia. In fact, Min et al. have demonstrated that hypoxia decreases the expression of either the tight junction protein ZO-1 or the adhesion molecule E-cadherin in the human nasal cells, as well as a drop in the transepithelial resistance.[31] In our study, we found a significant increase of the neutrophil cells passing from T1 to T2. This increase continued during all the vacation at 3400 m (T3), though not quite at the 5% level, demonstrating that high altitude is able to produce nasal inflammation. Interestingly, the number of neutrophils reduced after the vacation (T5) reaching approximately the same level found at the arrival at the base camp (T1). This result seems to demonstrate that the nasal neutrophilic inflammation induced by high altitude is spontaneously reversible. Other authors already observed a transitory increase of leukocyte levels during acute altitude exposure in the peripheral blood,[32,33] suggesting epinephrine and cortisol concentrations as likely candidates, because of their known effects on increasing leukocyte counts in the peripheral blood via demargination from the vascular endothelium and release from the spleen and bone marrow.[34,35] Indeed, the increase of the neutrophil cells found in the nasal samples of the subjects enrolled in the study could be either the expression of a local inflammation or the consequence of the leukocytes increase in the peripheral blood.

We have to acknowledge that the study has some limitations. Due to its design, the study is based on a small cohort. Furthermore, the environmental conditions in which all the tests have been performed were not controlled or standardized. Thus, temperature and humidity could have changed during the different evaluations. Moreover, the presence of 5 smokers and 2 subjects with allergic rhinitis (with one of them being also a smoker) in our cohort can be considered another limitation of the study. However, considering the design of the study and the necessarily small cohort, we preferred to include all the volunteers in the study.

Conclusion

Exposure to high altitude creates a state of local inflammation in the nasal mucosa, and our findings support the hypothesis of a role for nasal cytology in the identification of nasal mucosa inflammation after exposure to hypoxia. Our data seem also to confirm the usefulness of MCTt for studying the nasal mucosa damage caused by high altitude. However, further investigations on larger series are needed in order to confirm these results and, more important, to confirm the improvement of PNIF at high altitude.

Authors' Note

The study was approved by the scientific committee of the Otolaryngology Section, University of Padova and was conducted in accordance with the 1996 Helsinki Declaration. The study data were examined in agreement with the Italian privacy and sensible data laws (D.Lgs 196/03).

Declaration of Conflicting Interests

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