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Influence of Altitude on Pulmonary Function: A Comparative Study on Indian and Kyrgyz Healthy Males

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ABSTRACT

Variation in lung function at high altitude (HA) impacts the working capacity of individuals and may predispose body towards hypoxia induced illness. So, we investigated the changes in pulmonary function of healthy human male volunteers belonging to two different ethnicities i.e. Indian and Kyrgyz. Twenty, age and BMI matched, volunteers (Indian=10 and Kyrgyz=10) were recruited for the study. Measurement for pulmonary functions (FVC, FEV1, FEV1/FVC ratio, PEF, FEF 25-75%, MEF 25%, MEF 50%, MEF 75%, MVV) were performed on each individual at basal (800 m) and high altitude (4,111 m) on day 3,7,14 and 21. Results indicate that Kyrgyz has comparatively higher FVC, FEV1, PEF and MVV values and lower FEV1/FVC ratio upon altitude induction than those of Indian counterparts. Mid expiratory flow FEF25-75% was significantly increased in Kyrgyz upon altitude induction indicate more proficient lung emptying while only moderate increase at day 7 in Indian. MEF25% was significantly increased in Kyrgyz, while no change is observed in Indians at high altitude which indicates that 75% of lung emptying through small airways is better in Kyrgyz. MEF 50% and MEF 75% increased with altitude in both groups. For MVV, the maximum increase was ~17% in Indian at HA14 ($p<0.01$) and in Kyrgyz ~33% ($p<0.001$) at HA14 as compared to basal. Difference in lung function response observed, indicates that Kyrgyz has better pulmonary dynamics during altitude exposure as compared to Indian counterparts. The varied result observed may be due to different ethnic origin of the groups.

Keywords: High altitude hypoxia; Ethnicity; Spirometry; Forced vital capacity; Maximal voluntary ventilation

1. INTRODUCTION

Ascend to high altitude (HA) expose humans to reduced barometric pressure subsequently lowering partial pressure of oxygen in blood[1]. This reduced oxygen in blood is maintained throughout all the stages of oxygen cascade down to the mitochondria. Reduced partial pressure in blood induces central and peripheral responses to improve oxygen delivery and utilisation at altitude. Initial changes are seen in terms of several physiological functions which are related to oxygen delivery[2]. One such change is increased pulmonary ventilation i.e. frequency and depth of breathing because lung is a crossing point between the environment and metabolic mechanism of the body[3-5]. For any given energy expenditure, the ventilation increases proportional with altitude. Hyperventilation is also corroborated with other responses like increased heart rate, erythropoiesis, and redistribution of arterial blood flow to achieve the delivery of oxygen to the cells and tissues[6,7]. Initially the role of lung in the acute exposure to altitude was described by indicating the changes in lung volume and extravascular fluid accumulation in the pulmonary interstitium[8].

The present study was undertaken with an objective to measure the changes in pulmonary function measurement using spirometry, was employed in volunteers from different ethnic origin i.e. Indian and Kyrgyz. Effect of altitude and sojourn on time point basis was analysed and compared in both the groups. Lung function and lung volume capacities are known to exhibit strong ethnic differences. Thus by comparing the two different ethnic groups can enhance the knowledge of the same. Lung mechanics at altitude has been studied by many and indicate changes that could be moderate, immediate or sustained[9-12]. Forced vital capacity, expiratory flows and maximal voluntary ventilation in healthy volunteers in both groups were studied and investigated.

2. MATERIALS AND METHODOLOGY

2.1 Study Volunteers and Protocol

An ethnicity dependant response variation study was performed in Syok Ashu, Kyrgyzstan at an altitude (HA) of 4,111m. Twenty healthy male volunteers matched for age and BMI (Indian=10 and Kyrgyz=10), were enrolled in the study. Care was taken that none of the individual from both the groups had a previous exposure to high altitude for unbiased data. Health related exclusion criteria involve: participants suffering

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from any known respiratory, cardiovascular or neurological disorders, any kind of psychoactive or cardiac related medications, smoker and alcoholic. The basic characteristic of both the groups is summarised in Table 1. Indian volunteers were flown to Bishkek, Kyrgyzstan while Kyrgyz volunteers were local to the study area. Atmospheric temperature was ranging from 10.2 °C to 30.3 °C at Bishkek and -14.6 °C to 13.6 °C at Syok Ashu, whereas inside the rooms, temperature was maintained at 23± 2°C.Study protocol was approved by Defence Institute of Physiology and Allied Sciences Ethics Committee and all the studies were carried out in strict compliance with the approved guidelines and regulations outlined in the Declaration of Helsinki of the World Medical Association. Volunteers were made familiar to the study protocol before obtaining the written informed consent individually.

Table 1. Basic characteristics of the volunteers recruited for the study protocol

Characteristics	Indian group	Kyrgyz group
Number of individuals	10	10
Age (years)		
Mean±SD	24±2.1	22±2.9
Interquartile range	22-25.3	20-23.5
Height (cm)		
Mean±SD	177±4.3	176±4.8
Interquartile range	173.8-180	172.8-179
Weight (Kg)		
Mean±SD	67±5.4	72±4.4
Interquartile range	63.7-70.9	66-74
Other Information		
Previous exposure to high altitude	NO	NO
Smoker/drinker	NO	NO
Mode of induction to high altitude	By road	By road

The protocol of the study involves the measurement at basal (Bishkek), 800 m. Further, volunteers were induced by road to ~3,000 m for acclimatisation, then to high altitude of 4,111 m by road and measurements were done at different time periods HA day3 (HA3), HA day7 (HA7), HA day14 (HA14), and HA day21 (HA21). On arrival to altitude of study, subjects were questioned for the symptoms of headache, nausea, fatigue, cough and sore throat to ensure that these symptoms did not affect the study protocol.

2.2 Acute Mountain Sickness Score Recording

Acute mountain sickness (AMS) was evaluated based on Lake Louise scoring which is a scaling system of 0 to 3 by volunteers where, 0=none, 1=mild, 2=moderate and 3=severs AMS. The scaling involves the occurrence of following symptoms headache, dizziness, gastrointestinal distress (loss of appetite, nausea, or vomiting) and fatigue. AMS scoring was done on first 7 days of high altitude (4,111 m) in both the groups.

2.3 Pulmonary Function Test

Pulmonary function test (PFT) was performed at all-time points in both the groups using a calibrated and portable spirometer (Pony FX, COSMED, Italy). Spirometer is calibrated with a 3 Litres calibration syringe at each time point of study. Temperature of the air in the calibrating 3-L syringe was the same as that of the sensor in the spirometer. All volunteers received training in performance of spirometry and measurements of respiratory muscle strength and endurance. They were encouraged to provide maximal effort by strong verbal encouragement during the performance of the study procedures. It was taken into consideration that test start after at least 2 h of food intake. Using spirometer, forced vital capacity (FVC), forced expiratory volume in 1second (FEV1), FEV1/ FVC ratio, peak expiratory flow (PEF), average mid expiratory flow (FEF25-75%), maximal expiratory flow when 25% of FVC remained to be exhaled (MEF 25%), maximal expiratory flow when 50% of FVC remained to be exhaled (MEF50%), maximal expiratory flow when 75% of FVC remained to be exhaled (MEF 75%), maximal voluntary ventilation (MVV) were measured. Each subject performed three spirometry efforts each lasting for 6 s to obtain ideal flow volume curve for FVC and 12 s for ideal MVV curve. It was assured that out of three manoeuvres obtained at least two meet results repeatability within 5% variation. Acceptability of each manoeuvre was based on criterion:

i. Nose clip is tight to prevent inhalation from nose
ii. No leaks from sides of mouthpiece
iii. No obstruction of mouthpiece from tongue or teeth
iv. Test is performed in upright position during a complete manoeuvre
v. Test must start with full inspiration, and
vi. No evidence that the volunteer take extra breath during expiratory manoeuvre.

2.4 Statistical Analysis

All values were averaged and represented as mean±SEM in the graph and mean±SD in table. The intragroup mean values at each high altitude time point is compared from basal. Intergroup comparison analysis was performed for each time point. The data was analysed using Graph Pad prism v6.0. Two-way repeated measures analysis of variance (2-way ANOVA) was used for multiple comparisons in two groups (i.e. Indian and Kyrgyz) with Bonferroni multiple comparison Post hoc test. Student's t-test was applied in inter comparison analysis. In both the statistics test a p value of less than 0.05 was considered significant.

3. RESULTS

All of the recruited study volunteers accomplished complete study procedure. All volunteers were checked for the preliminary signs of AMS upon exposure to initial altitude days. Mean AMS score remained less than 3 indicating no signs of AMS in both the groups. Changed spirometry measurements in both groups from basal to different time points of high altitude has been recorded and analysed for the different responses. FVC in Indian increased significantly during HA7, 4.7±0.18 L ($p<0.01$) as compared to basal, 4.5±0.12 L and later the mean values started decreasing but remained more than basal. In Kyrgyz the increase was significant on HA21, 5.5±0.17 L ($p<0.001$) as compared to basal, 5.3±0.17 L. Also, at all-time points FVC mean values were significantly ($p<0.05$-0.01) higher in Kyrgyz as compared to Indian. In Indians FEV1 increased upon exposure to altitude but significant ($p<0.01$) increase was seen at HA7, 4.2±0.13 L as compared to basal, 3.9±0.14 L. In Kyrgyz, FEV1 increase was significant at all-time points, with high mean values at HA3 and HA21 4.5±0.13 and 4.6±0.14 respectively ($p<0.001$) as compared to basal, 4.3±0.12 L. In similarity with FVC, higher mean values of FEV1 were obtained in Kyrgyz as compared to Indians at different study time points. There was no significant change in the FEV1/FVC ratio in Indian upon altitude exposure but in Kyrgyz the ratio increased significantly ($p<0.001$) at HA3 85.4±1.72 % and HA7 85.0±2.08 % upon altitude induction. This ratio remained significantly less throughout the study in Kyrgyz when compared to Indians. Upon exposure to altitude the significant increase in PEF was seen in both the groups with higher mean values in Kyrgyz. The highest increase in PEF was ~19% at HA14 ($p<0.001$) in Indians while ~21% increase ($p<0.001$) was observed at HA14 in Kyrgyz as compared to basal (Figs.1.(a-d)).

In Indians FEF25-75% significantly increased upon induction to altitude on day 3 and day 7 with mean value of 5.35±0.35 L/s ($p<0.05$) and 5.28±0.40 L/s ($p<0.05$) respectively as compared to basal 4.9±0.33 L/s. In Kyrgyz, the increase was highest on HA3 with mean values 4.8±0.28 L/s ($p<0.001$) as compared to basal. Also, for rest of the high altitude time points the increase remained significant ($p<0.001$) in Kyrgyz when compared to basal. MEF 25% did not show any significant changes and tend to remain stabilised at high altitude in Indians as compared to basal. In Kyrgyz upon exposure to altitude the increase was significant from HA3 till HA21 with highest mean values at HA3 2.4±0.15 L/s as compared to basal 2.1±0.11 L/s. In MEF 50% the significant increase was seen in Indians at HA3 ($p<0.05$) and HA7 ($p<0.01$) with highest value of 5.9±0.36 L/s at HA3 as compared to basal 5.5±0.36 L/s. The mean values in Kyrgyz group significantly ($p<0.01$-0.001) increased at all-time points in Kyrgyz with mean values of 5.4±0.34 L/s. 5.3±0.37 L/s, 5.1±0.35 L/s, 5.1±0.34 L/s at HA3, HA7, HA14, and HA21 respectively as compared to basal 4.6±0.28 L/s. MEF 75% increased at all high altitude time point exposure in Indians and similarly in Kyrgyz as compared to basal. The highest increase was observed at HA7 with mean value of 9.3±0.39 L/s ($p<0.01$) and in Kyrgyz mean value was 9.3±0.49 L/s ($p<0.001$) at HA3. Maximal voluntary ventilation increased in both the groups with greater increase in Kyrgyz as compared to Indians. The increase was significant at all high altitude time points in both the groups. The maximum increase was ~17% in Indian at HA14 ($p<0.01$) and in Kyrgyz ~33% ($p<0.001$) at HA14 as compared to basal (Figs. 2(a-e)).

4. DISCUSSION

Kyrgyzstan is a small mountainous country, of which ~57% of its total land area is above 2500 m. Recently, the study on pulmonary function test on 17 Indian volunteers in

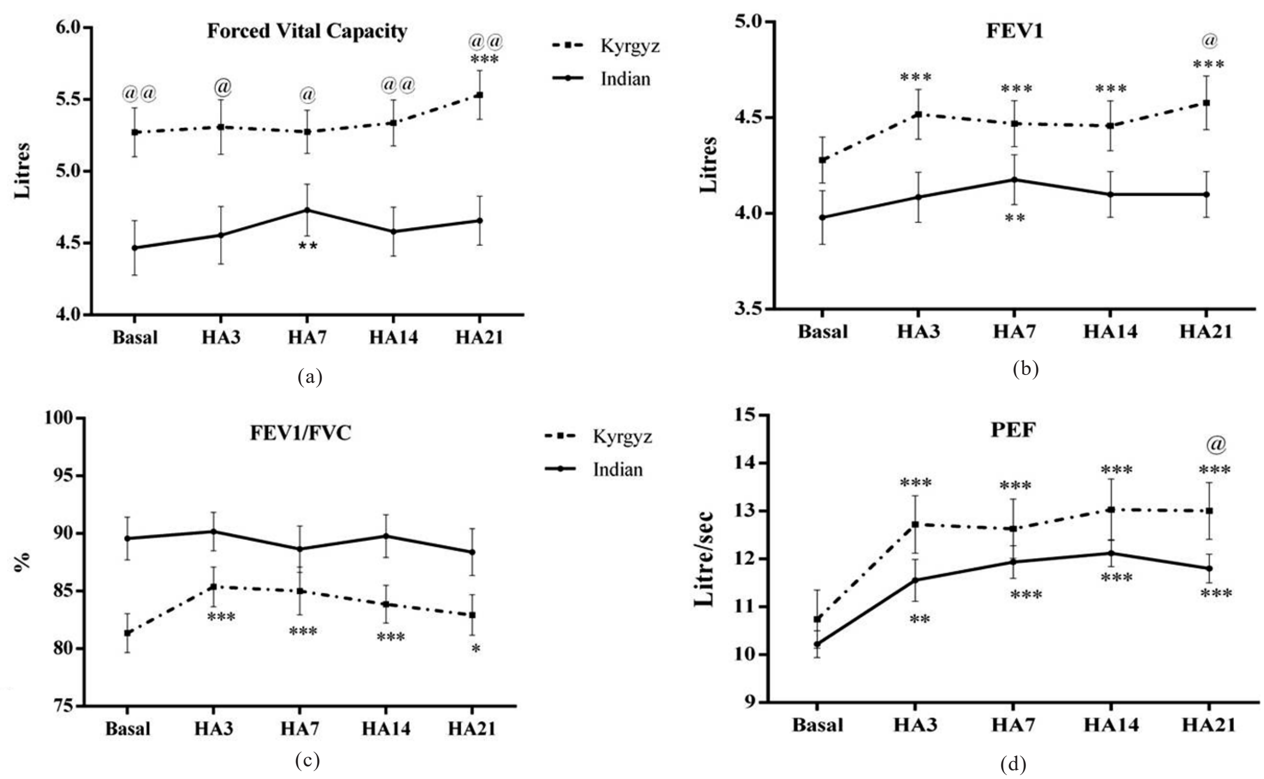

Figure 1. Changes in (a) Forced vital capacity (FVC), (b) FEV1, (c) FEV1/FVC, and, (d) PEF in Indian and Kyrgyz volunteers at basal and different high altitude time points. Each time point in graph is mean±SEM values. Significance depicted as *p<0.05; **p<0.01, ***p<0.001 in Indian and Kyrgyz at high altitude time points in comparison to their respective basal values. $^{@}p<0.05$; $^{@@}p<0.01$ and $^{@@@}p<0.001$ is statistical significance in Kyrgyz as compared to Indians at each time point.

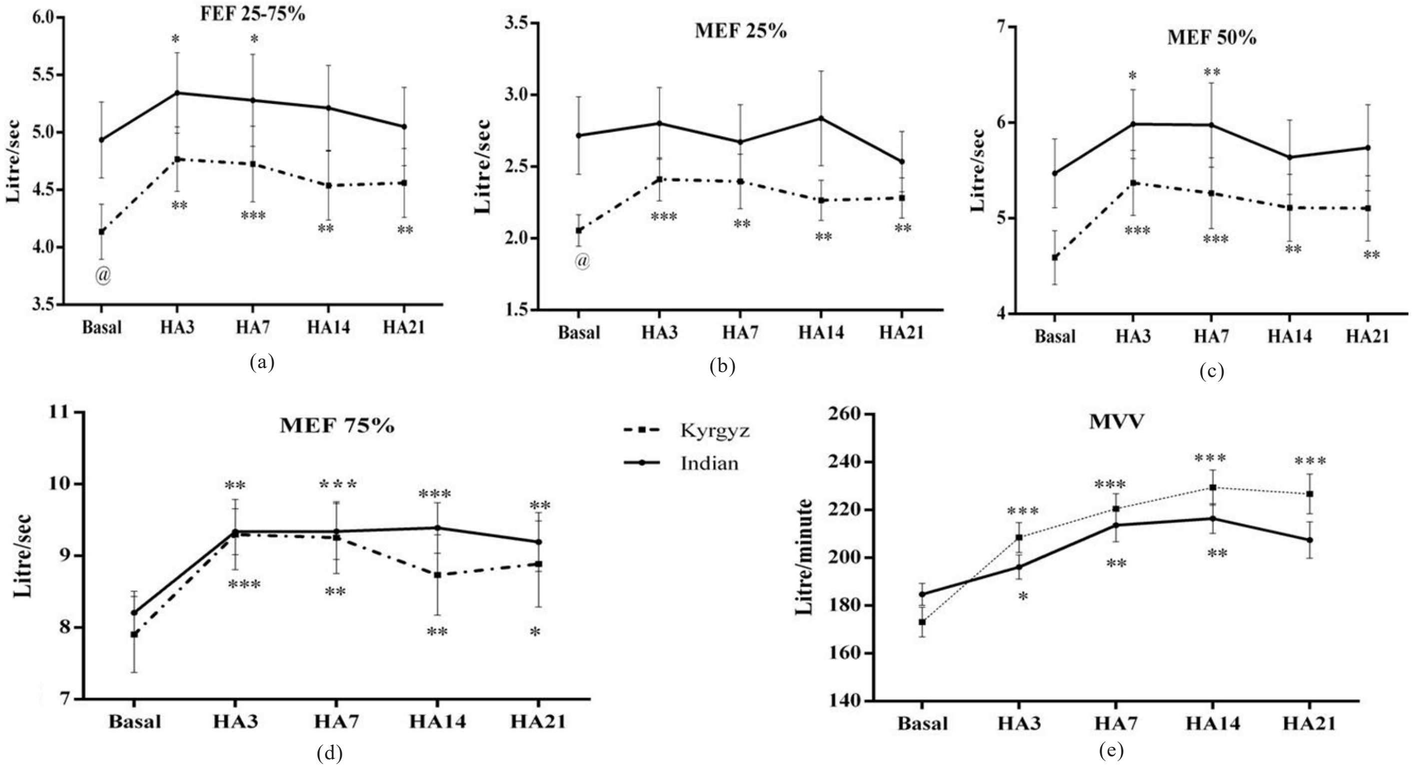

Figure 2. Changes in (a) FEF25-75%, (b) MEF25%, (c) MEF50%, (d) MEF75% and, (e) MVV in Indian and Kyrgyz volunteers at basal and different high altitude time points. Each time point in graph is mean±SEM values. Significance depicted as *p<0.05; **p<0.01, ***p<0.001 in Indian and Kyrgyz at high altitude time points in comparison to their respective basal values. @p<0.05; @@p<0.01 and @@@p<0.001 is statistical significance in Kyrgyz as compared to Indians at each time point.

Tuya Ashu, Kyrgyzstan had been conducted by us at 3,200 m[13]. Previously, study in Tien Shan, Kyrgyzstan indicated the changes in PFT in Indian and Kyrgyz volunteers at high altitude of 3200 m[14]. Taken together, pulmonary physiology has been extensively studied and reviewed by several authors in the past[9-12,15,16]. This is the first study to report changes in pulmonary functions in Indian and Kyrgyz at 4,111m altitude, Syok Ashu, Kyrgyzstan during a long altitude exposure of 21 days and data was collected at different time points. This time point analysis help investigate the pattern of variations in pulmonary function, as a strategy to adapt to altitude. Exposure to hypobaric induces several compensatory mechanisms to ensure increased oxygen supply to cells and tissues[17]. Summarising previous studies it could be said that preliminary response to tolerate extreme altitude is by increased ventilation which can maintain the alveolar partial pressure of oxygen against reduced inspired oxygen concentration[3-5,18,19].

In our study, increased FVC in Kyrgyz and Indian upon altitude induction may be attributed to lower density of air encountered at high altitude which lessens airway resistance and facilitates expiratory airflow and efficient emptying of the lungs[20]. Decreased FVC reported by other studies[9, 21] may be a result of interstitial pulmonary edema development due to lack of acclimatisation[19,22,23], which is not observed in our study subjects. We followed proper acclimatisation protocol and did not perform pulmonary function measurements soon after arrival to altitude. The increased FVC was observed at 3450 m and 5350 m altitude[20] supports our study. During pulmonary function test the maximal exhalation start with a forced exhalation, the force of which is measured by volume of air released in first second i.e. FEV1 after a maximal inspiration. It is indicative of degree of airway obstruction and competence of both large and small airways[24]. Ascent to 5300 m did not change FEV1; also other studies support no change in FEV1 to high altitude[25]. Forte *et al*. described increase in FEV1[26] as observed in our study in both the groups upon ascent to altitude. Kyrgyz had higher mean FVC and FEV1 values at basal and high altitude time points compared to Indian due to different ethnicity[27-30]. FEV1/ FVC ratio determine the pattern of obstructive, restrictive or normal airflow and could be more sensitive index of airflow obstruction[31]. Lower FVC in Indians cause higher FEV1/FVC ratio upon induction to altitude as compared to Kyrgyz. This indicates that Indians are facing restrictive ventilation as compared to Kyrgyz. Overall in both the groups the ratio remained >75% which is normal and 60-75% is the indication of mild obstruction which is not apparent in any of the groups. PEF is reflecting capacity of large airways and the force exerted by the expiratory muscles[24, 32]. In view of this fact FEV1 could be more dependable indicator of airflow limitation than PEF[24,33]. Studies report increased PEF values to 15% at 3600m and 26% at 4559 m[9], and similar results were observed in our study. PEF increased to 19% in Indians and 21% in Kyrgyz upon induction to altitude.

Lung airways has bronchial tube which is further divided into smaller and smaller branches called bronchioles. Further these airways end are divided into air sacs called alveoli from where oxygen moves into the blood. To measure the effectiveness of these small and large airways and efficient emptying of the lungs different expiratory flow rates are measured. FEF 25-75% or mid maximal expiratory flow (MMEF) represents average expired airflow over middle half of FVC manoeuvre which is reflecting the functions of small airways. MEF 75% represents the flow rate at which 25% of the total volume of FVC is exhaled. This indicates the condition of large to medium size bronchi. MEF 50% indicate the flow rate at which the 50% of total FVC exhaled and is indicative of status of medium to small airways. MEF 25% at which 75% of total volume is exhaled indicates the ability of small airways of lungs[34]. Welsch *et.al*. and Basu *et. al.* reported increased mid-range forced expiratory flow at altitude probably due to lessen air density[21,23], also reflected in our results. There was moderate increase in FEF25-75% in Indians at HA7 while there was higher increased mid expiratory flow rates in Kyrgyz. MEF 25%, 50% and 75% increase in Kyrgyz with a greater significance as compared to basal. In Indians though the mean values remained higher than Kyrgyz but there was no significant difference found between both groups at any time point except in basal MEF 25% ($p<0.05$). The results indicate that Indians on reaching to altitude are not able to increase their expiratory flows for proper emptying of the lungs during full exhalation while Kyrgyz have more capacity to perform deep exhalation during altitude exposure. Our study depicting significant increased MEF's in Kyrgyz supports former studies in which there is 11%-15% increase at rise of only 1580m sojourn from sea level[35]. Kyrgyz reflect more efficient lung emptying by increasing their different ranges of expiratory flows as compared to their basal. Our results indicate that Kyrgyz are efficient in emptying lungs, correspondingly higher FVC point out that they might have higher respiratory muscle endurance. It has been reported that MVV is a surrogate for respiratory muscle endurance which is regulated with the FVC, as in, MVV decline with declined FVC[20]. To substantiate it we measured the MVV in 12 sec, the results indicated increased MVV upon induction to altitude in Kyrgyz ~33%. This is also supported by other studies which report improved MVV at high altitude[14, 26.]

Our present study with inter and intra group comparative findings of the pulmonary function measurements in Indian and Kyrgyz at high altitude of 4,111 m for 21 day sojourn reflect that Kyrgyz have higher lung volume function like FVC, FEV1, PEF compared with Indian counterparts. Pulmonary exhalation flow rates for emptying of the lungs was found to be significantly increased at high altitude in Kyrgyz group rather less or moderate changes are observed in Indians. Percent increase in maximal voluntary ventilation in Kyrgyz upon induction to altitude was higher indicates efficient dynamic lung mechanics upon high altitude hypoxic exposure. Difference in response observed, indicates that Kyrgyz has better pulmonary function during altitude exposure as compared to Indian counterparts. The varied result obtained may be due to different ethnic origin of the groups.

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