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**Spirometry findings of chronic lung disease in high-altitude residents of Ladakh
(>11,000 feet above sea level)**

Sonam Spalgais, Siddharth Raj Yadav, Parul Mrigpuri, Raj Kumar

Department of Pulmonary Medicine, Vallabhbhai Patel Chest Institute, University of Delhi,
India

Correspondence: Sonam Spalgais, Department of Pulmonary Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, 110007, India.

Tel.: +91-1127402409.

E-mail: sosolrs@gmail.com

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Abstract

Ladakh is a hilly Himalayan dry desert, situated at an altitude of >11000 feet. Studies have demonstrated that the spirometric values of high-altitude residents are significantly higher than those of low-landers. This is a retrospective observational study that analyzes the spirometry pattern in chronic lung diseases among people from Ladakh. Enrolled subjects were clinic-radiologically diagnosed and had at least one spirometry report. The spirometric parameters were analyzed for normal and abnormal patterns of lung function. The abnormal patterns were further classified into types of ventilator defects and their severity. A total of 122 cases were included, with 67 (55%) men. The mean age was 52.2 ± 15.4 years. The most common diseases were chronic obstructive pulmonary disease (COPD) in 51 cases (41%), and asthma in 41 (33%). The median predicted percentage of forced vital capacity (FVC) was 116% (63-179%) with >100% in 105 (85%) patients. The median predicted percentage of the forced expiratory volume in the 1st second (FEV1) was 113% (99-175%) with >100% in 90 (74%) patients. FVC was reduced in 9 (7%) cases, normal in 62 (51%), and more than normal in 49 (42%), with 11 (9%) cases having >150% of the predicted percentage. FEV1 was reduced in 9 (8%) cases, normal in 67 (55%), and more than normal in 46 (37%) cases, with >150% predicted seen in 10 (8%) cases. Similarly, overall, the predicted percentages of both FVC and FEV1 were >100% in all obstructive airway diseases as well as in the separate COPD and asthma subgroups. FVC and FEV1 amongst chronic lung disease patients from Ladakh were more than normal in the majority. These higher values of spirometry led to incorrect disease severity classifications and disease patterns. We propose that studies should be done to devise local reference equations for spirometry for Himalayan high-altitude residents of India.

Key words: high altitude, spirometry, lung function, Ladakh.

Introduction

India is a diverse country not only in caste, creed, race and food but also in its geographical terrains. India houses population on sea shore, plains and even at high altitudes above 2500 meter (m) above sea level [1]. The Indian Union territory of Ladakh houses a population of nearly 270000 as per 2011 census at the altitude of >3000m [2]. Long term exposure to high altitude has a wide variety of effect on the physiology and disease manifestation. It is well understood that as the altitude increases, there is fall in barometric pressure leading to decrease in partial pressure of oxygen (PO₂) [3]. Inhabiting at high altitudes necessitates anatomical, physiological and gene-molecular adaptation as to overcome chronic hypoxia [4,5]. The changes in anatomy include increase in antero-posteriorly depth and mediolaterally width of thoracic skeleton [6]. Physiological changes include enhanced hypoxemic ventilator response among the highlanders, leading to increased pulmonary ventilation i.e. frequency and depth of breathing [7,8]. It is very interesting to note that highlanders of Himalayan belt have better hypoxic ventilatory responses in comparison to highlanders of north and South America [8]. Studies on Spiro-metric /ventilatory response in this group population is very limited both in healthy and subjects suffering from respiratory ailments.

Spirometry is used as one of the most basic and imperative tool in respiratory disease to classify them as obstructive, restrictive or mixed pattern. Spirometry reference values and equations for various population groups of India are available [9-11]. As per our knowledge no Spirometry reference values or equations have been validated for Indian highlanders of Himalayan region including Ladakhi population which is known for its legendary physical performances [12]. Now many people from Ladakh are referred from remote high altitude terrain to urban metropolitan cities due to improvement in transport and road facilities. It was observed that many patients deemed fit to be classified in disease processes by history and symptoms but cannot be classified on basis of Spirometry values. The study was done with the aim to device local reference equation of spirometry for high Himalayan altitude residents of India.

Materials and Methods

This was a retrospective observational study conducted at one of the tertiary care chest institute of India. The study analyses the spirometry pattern in chronic lung diseases case of people of Ladakh, who reside >11000feet above the sea level. Subjects enrolled were cases of chronic lung diseases including chronic obstructive pulmonary disease (COPD), asthma, Post-TB lung diseases (PTBLD), Interstitial lung disease (ILD), who were clinic-radiologically diagnosed and had at least one spirometry report. The spirometry was done on a dry,

roll-seal spirometer of the Benchmark design lung function machine (P.K. Morgan, Kent, UK) with using the reference prediction equations of north Indian population [10]. Retrospectively analyses of demographic and investigational detail of enrolled cases were done from the file of patients. All the demographic parameters, with copy of investigations and diagnosis are maintained in a record file of registered cases in the institutes as a department protocol.

The spirometric parameters were entered in an excel format and analyses for normal and abnormal pattern of lung function was done for all the cases and sub-analyses separately for done for male and female. The abnormal lung function were further classified to restrictive, obstructive and mixed pattern of defect and in severity of lung function impairment according to percentage predicted of FEV1. The overall FVC and FEV1 were also classified in to normal, below and above normal in percentage of patients. As the majority of enrolled patients was obstructive airway disease (OAD) i.e COPD and asthma. So we further sub-analysed the spirometry parameters of OAD as whole and individually of COPD and asthma for classification of defect and its grading. The lung function abnormality and its grading of impairment were done as per Indian spirometry guideline and GOLD guideline [13].

The diagnosis of chronic lung disease was done as per following in this study.

The diagnosis of COPD was done as per GOLD guideline while the diagnosis of asthma was done as per GINA guideline.

Anthrosilicosis/silicosis: Clinical history suggestive of lung disease with HRCT chest showing nodules with or without progressive massive fibrosis and bronchoscopic finding of anthroctic pigment/anthrofibrosis with compatible histopathology.

PTBLD: Clinical history suggestive of lung disease with history of treatment for pulmonary TB with radiological evidence of post-TB findings after rule out the active pulmonary TB.

ILD: Clinical history suggestive of ILD with CT chest finding consistent with ILD finding and histopathology/cytology of lung/mediastinal lymph node suggestive of ILD.

Data analysis

The extracted data from all chronic lung disease was compiled and analysed using Microsoft Office Excel software. Continuous data is presented as mean and standard deviation or median and inter-quartile range (due to extreme values) and categorical data is presented as number and percentages.

Results

A total of 122 cases were included in the study. The mean age of patient was 52.2 ± 15.4 years with 67(55%) male and 55(45%) female. The most common type of chronic diseases are

COPD in 51(41%), followed by asthma 41(33%), silicosis/anthrosilicosis 13(11%) and PTBLD 8(7%) cases. The most common occupation was homemaker in 40(33%), followed by office worker in 30(24%) and farmer 25(20%). Only 28(23%) had history of smoking with mean pack year of 14.3 ± 9.0 . The mean height was 160 ± 8.6 cm and mean weight was 63.2 ± 12.7 kg. The most common symptoms were breathlessness in 115(94%) and cough 112(92%) cases. The median duration of symptoms was 7.2years (2.2-16.7years)

Overall the median post-bronchodilator FVC was 3.49lts with range from 1.59 to 6.35lts and the median FVC percentage predicted (%pred) was 116% with range from 63 to 179%. The FVC (%pred) was $>100\%$ in 105(85%)patients. The FVC (%pred) was $>120\%$ in 51(41%) and the recorded highest %pred was 179%. Similarly the median post-bronchodilator FEV1 was 2.52lts with range from 0.85 to 5.26lts and the median FEV1 (%pred) was 113% with range from 99 to 175%. The FEV1 (%pred) was $>100\%$ in 90(74%) and $> 120\%$ in 46(37%) with highest recorded %pred was 168%. Overall the FEV1 and FVC were $>100\%$ in 74% and 85% patients respectively. The median FEF_{25-75%} was 1.82 ranges from 0.16 to 6.83. Similarly the median PEF was 5.7lts/s with range from 1.96 to 11.64lts/s. All the parameters were higher in male than female. The detail of all findings are depicted in Table 1.

In overall cases, as per %pred both the pre and post bronchodilator FVC was reduced in only 2-7% cases, normal in 51-60% cases and more than normal in 38-44% cases with 5-9% cases have $>150\%$ of predicted. Similar finding was also found in male and female patients with FVC reduced in 2-3%, normal in 53-61% and more than normal in 34-39% $>150\%$ predicted in 5-11% cases. The detail of FVC findings is depicted in Table 2. Overall study population the FEV1 was reduced in 9(8%) cases only, while it was normal in 67(55%) and more than normal in 46(37%) cases with $>150\%$ predicted seen 10(8%)cases. This classified only 9(8%) cases have moderate to severe lung function impairment and none as very severe impairment. Similar findings also found in male and female patients with FEV1 reduced in 3-6%, normal in 51-60% and more than normal in 29-43% with $>150\%$ predicted in 4-9% cases. This classified only 6(9%) cases have moderate to severe lung function impairment and none as very severe impairment in male population and only 3(6%) cases have moderate lung function impairment and none as severe to very severe grade in female. The detail of FVC findings is depicted in Tables 2 and 3.

As the majority 92 (75%) patients were of obstructive airway disease (OAD) with COPD 51(42%) and bronchial asthma 41(34%). We also analysed the PFT parameters in combined OAD group as well as in COPD and asthma. Overall the %pred of both FVC and FEV1 were $>100\%$ in all OAD as well as in separate COPD and asthma subgroup. The FEV1/FVC was below 80 in both COPD and asthma but not <70 in all groups. This implied that the spirometry with standard prediction reference equation is not correctly classifying the PFT of

high altitudes resident. As in this group the median post bronchodilator FEV1/FVC was 72 in COPD. Similarly the grade of obstructive is not correctly classified as the median percentage predicted of FEV1 was >100% even in both subgroups. This implies that all the patients are having just mild of obstruction. The detail of all the spirometry parameters in all OAD along with separate subgroup of COPD and asthma is depicted in Table 4.

Among the 13 silicoanthracosis patients the mean post bronchodilator FVC was 2.8 ± 0.82 lts with mean %pred of 108.4 ± 17.7 . The FVC (%pred) was <80% in only one patients with >120% in three cases. The mean post bronchodilator FEV1 was 1.8 ± 0.53 lts with mean %pred of 99.1 ± 26.3 . The FVC (%pred) was <80% in only two patients with >120% in three cases. The mean FEV1/FVC was 67.4 ± 12.7 . While on CT chest all cases shoed silicotic nodules involving all the lobes with progressive massive fibrosis in 9(70%) cases.

Discussion

The high altitude has been divided into low, moderate, and high, very high, and extreme. Generally the altitude of >3000m is considered as moderate altitude [14,15]. At this altitude, the inspired PO₂ is reduced to 100mmHg, the alveolar oxygen pressure is estimated to be 70mmHg, which means an arterial oxygen pressure of about 60–63mmHg (hypobaric hypoxia). At altitude of >3000m, many of the physiological responses lead to challenges in the human body like hypoxic ventilator response and hypoxic pulmonary vasoconstriction start develop and it imposes an increased workload on the cardiopulmonary systems [15-17]. Ladakh is a hilly Himalayan, dry desert within an altitude of >11000feet above the sea level. With increasing altitude, there are changes in several physical characteristics such as inspiratory oxygen pressure, air density, barometric pressure, temperature, humidity and ultraviolet radiation. These changes lead to several physiological and immunological adaptation responses [18,19]. The chronic and long term exposure to high altitude induces increase in haemoglobin, capillary density and mitochondrial oxidative capacity. These changes are important for improvement in performance and physical fitness. The native of high altitude are persistently exposure to hypoxia since birth and hence might have such physiological adaptive changes [15,20]. These changes may affects many other physiological changes in people residing at high altitude as home and are crucial for survival at such altitudes, without much difficulty. Here we report the variation in the spirometry parameters of moderately high altitudes people of Ladakh with various chronic lung diseases. Despite the subjects having clinical and radiological diseases, their spirometry parameters are high than expected in most of them. This finding may explained by high altitudes physiology.

There are limited published data on spirometry findings and chronic lung diseases of high altitudes residents. We found that the both median predicted FVC and FEV1 are higher in

most of the cases in this study. India is a country with different geography, altitude, ethnic and culture. The spirometry value also varies with different region. Studies of reference equations showed significant regional difference [9-11,21-23]. It is found that the west and north Indian equations were discordant in 22.1%, and the south and north Indian equations in 12.9% [23]. A significant part of India especially sub-himalayan regions range from Ladakh to Arunachal Pradesh is lies at high altitudes. There is no published data on spirometry findings of these high altitudes residents. The spirometry values may differ for these high altitudes resident due to their physical, environmental and ethnic difference. Saleem S et al in a study from healthy population of Kashmir found that the all the predicted value of spirometry including FVC, FEV1 were higher in their population [24]. Ladakh, Jammu and Kashmir, Himachal Pradesh, Uttarakhand, Sikkim and Arunachal Pradesh are situated at the level of >3000m. So there should be a separate local reference equation of spirometry for better understanding and management in these high altitude residents of Indian population. We found that the predicted percentage of FVC was 116% with >120% in 38% cases. Similarly the predicted percentage of FEV1 was 113% with >120% in 37% cases. A recent study found that the FVC and FEV1 were significantly higher among highlanders of Oyacachi community. They concluded that the higher parameters might be due to a compensatory mechanism towards lower barometric and alveolar PO₂ at high altitude [25]. Wietz CA et al in a study between Han born Chinese with Tibebans residing at high altitudes found, that the FVC and FEV1 values were higher in Tibetans. They postulated that the higher values may be due to accelerated pattern of lung growth that begins during mid-to-late adolescence due to adaptation to high altitude hypoxia. Our findings might be due to similarity of ethnicity, geography and environment of Ladakh and Tibet [26]. In another study from China found that spirometry parameters were higher amongst high altitude residents. They also found that the high altitude lander have larger relative sitting heights, indicating greater thorax lengths and concluded that the higher values is primarily a result of development in a hypoxic environment and adaptive response [27]. Harvyk AP et al in a study of Himalayan high altitude Sherpa found that the FEV1 and FVC were significantly greater than predicted. They concluded that the Sherpa race has significantly larger spirometric values and it is an adaptation in response to chronic hypoxia and high levels of habitual exercise [28]. The above studies demonstrated that the spirometry parameters were significantly greater in the high altitudes residents and much higher with low lander predicted reference equations. So it is important to have a separate reference equation for the high Himalayan residents of our country for better classification of disease state and proper management.

Among healthy adult living at the high altitudes are having higher lung function parameters [26-29]. These findings also relevant in patients of high altitude suffering from chronic lung disease, similar to our findings. The hypobaric hypoxia is the character of high altitude. People living at high altitudes require different physiological, anatomical, genetical, molecular and immunological adaptive mechanisms [29,30]. The physiological response includes change in ventilations rates and improved hypoxic ventilatory responses. While the common anatomical changes includes chest width, chest depth and larger sitting heights, indicating greater thorax lengths [25,27,31,32]. It is also observed that the rate of lung growth with duration and early exposure to hypoxia play an important role for changes in lung function parameters amongst high altitudes residents [25-28]. The recent advancement in medical and transport facilities in our country has leads to increment referral of patients from high altitude to low altitudes for medical ailments including pulmonary diseases. It is prudent to note that not just spirometry but the disease pattern and prevalence is also different at high altitude. So it important to know the high altitude physiology and disease pattern for better management and unnecessary investigations. Likewise the non-occupational silicosis and anthracosis is highly prevalent in high altitude resident of Ladakh and mimicking malignancy leads to unnecessary invasive procedures [33,34]. So it is important for physician to have the knowledge of patients environment for better result in as our country has diverse geographic and environmental variation.

Conclusions

The median predicted percentage of FVC and FEV1 amongst chronic lung diseases from high altitude residents of Ladakh was more than normal in majority of patients. These higher values of spirometry led to incorrect disease severity classification and disease pattern. In accordant to lung function, we advise that a local reference equation of spirometry for high Himalayan altitude residents of our country should be considered for further research, correct classification and better management.

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Table 1. Details of various spirometry parameters in various chronic lung diseases.

Parameters in Median (IQR)	Total patients (n=122)		Male patients (n=67)		Female patients (n=55)	
	Pre-BD	Post-BD	Pre-BD	Post-BD	Pre-BD	Post-BD
FVC(Lts)	3.44(2.75-4.34)	3.49(2.8-4.37)	4.22(3.45-4.77)	4.29(3.57-4.82)	2.79(2.40-3.34)	2.82(2.59-3.34)
FVC Pred%	114(101.2-129.7)	116(105-130)	114(102-128)	115(105.2-129.2)	114(100.5-129.5)	116(104-129.5)
FEV ₁ (Lts)	2.37(1.87-3.13)	2.52(1.97-3.13)	2.84(2.17-3.45)	3.18(2.37-3.57)	1.97(1.53-2.51)	2.16(1.73-2.64)
FEV ₁ Pred%	106(89.2-121)	113(99-126)	106(86-119.5)	111(99.2-122.7)	105(97-125.5)	117(98.5-133)
FEV ₁ /FVC	70.9(60.3-80.2)	74.7(65.7-82.8)	69.3(58.9-80.5)	72(65.7-82.3)	72.4(61.5-79.1)	77.7(65.85-82.45)
FEV ₁ /FVC Pred%	94(78.7-102.5)	98(86-107.5)	91(78-104.2)	94(86-106)	96(84-102)	100.5(91.7-108)
FEF _{25-75%}	1.82(1.02-2.63)	-----	1.09(1.17-2.87)	-----	1.5(0.79-2.3)	-----
FEF _{25-75%} Pred %	76.5(49-120.7)	-----	73(50-117)	-----	79(47.5-121.5)	-----
PEF(L/s)	5.7(4.16-7.11)	-----	6.72(5.12-8.45)	-----	4.65(3.62-5.97)	-----
PEF(L/s) pred%	97.5(73.5-117.7)	-----	92(70.5-113)	-----	100(82.5-125)	-----
FET(sec)	10.4(7.5-14)	-----	10.9(6.8-15.1)	-----	9.8(8.0-12.15)	-----

IQR, interquartile range; BD, bronchodilator.

Table 2. Details of patients according to predicted percentage of forced vital capacity.

FVC%pred	<80%pred	80%-119%pred	120-149%pred	>150%pred
Total (n=122) Pre-BD	3(2%)	73(60%)	40(33%)	6(5%)
Post -BD	9(7%)	62(51%)	40(33%)	11(9%)
Male (n=67) Pre-BD	2(3%)	41(61%)	21(31%)	3(5%)
Post -BD	2(3%)	38(57%)	23(34%)	4(6%)
Female (n=55) Pre-BD	1(2%)	32(58%)	19(34%)	3(6%)
Post-BD	2(3%)	29(53%)	18(33%)	6(11%)

Table 3. Details of patients according to predicted percentage of forced expiratory volume in 1st second.

FEV1%pred	<30%pred	30-49%pred	50-79%pred	80-119%pred	120-149%pred	>150%pred
Total (n=122) Pre	0	2(2%)	20(16%)	67(55%)	27(22%)	6(5%)
Post	0	2(2%)	7(6%)	67(55%)	36(29%)	10(8%)
Male (n=67) Pre	0	2(3%)	11(16%)	37(55%)	14(21%)	3(4%)
Post	0	2(3%)	4(6%)	40(60%)	17(25%)	4(6%)
Female (n=55) Pre	0	1(2%)	8(14%)	30(54%)	13(24%)	3(6%)
Post	0	0	3(6%)	28(51%)	19(34%)	5(9%)

Table 4. Detail of obstructive lung diseases with spirometry parameters.

Parameters in Median (IQR)	OAD(n=92)		COPD(n=51)		Bronchial Asthma(n=41)	
	Pre-BD	Post-BD	Pre-BD	Post-BD	Pre-BD	Post-BD
FVC(Lts)	3.56((2.89-4.35)	3.66(3.1-4.44)	3.39(2.85-4.34)	3.43(2.98-4.43)	3.64(2.98-4.37)	3.77(3.14-4.44)
FVC Pred%	115.5(101.72-131)	117(106.5-133)	114(101-132)	114.5(103-134)	116(108-128)	118(112-126)
FEV ₁ (Lts)	2.49(1.95-3.26)	2.7(2.13-3.37)	2.31(1.77-3.05)	2.4(1.78-3.28)	2.68(2.16-3.32)	2.94(2.37-3.45)
FEV ₁ Pred%	108(95-121)	114(103-126)	108(95-119.5)	113.5(102.3-124)	107(97-125)	116(104-1126)
FEV ₁ /FVC	71.05(61.7-80)	75.5(66.2-82.4)	68.2(58.15-74.8)	70.4(63.1-78.2)	76.7(66.6-82.8)	81.1(73.3-83.8)
FEV ₁ /FVC Pred%	94(81.2-102)	98(87-106)	92(80.5-100.7)	95(86-103)	95.5(84.7-104.2)	99(92-108)
FEF _{25-75%}	1.89(1.11-2.61)	-----	1.41(0.91-2.27)	-----	2.24(1.55-1.77)	-----
FEF _{25-75%} Pred %	83.5(51.7-120.2)	-----	70(51.5-117)	-----	88(54-122)	-----
PEF(L/s)	5.99(4.6-7.34)	-----	5.8(3.7-7.66)	-----	6.08(5.16-6.92)	-----
PEF(L/s) pred%	99.5(81.2-114.7)	-----	102(84.5-118.5)	-----	95(79-122)	-----
FET(sec)	10.4(7.1-14.04)	-----	12.35(7.8-15.5)	-----	9.07(6.4-10.7)	-----