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

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Abstract

Ladakh is a hilly Himalayan dry desert, situated at an altitude of >11,000 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 among chronic lung disease patients from Ladakh were higher 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.

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Introduction

India is a diverse country not only in caste, creed, race, and food but also in its geographical terrains. India houses populations on seashore, plains, and even at high altitudes above 2500 m above sea level [1]. The Indian Union territory of Ladakh houses a population of nearly 270,000 as per the 2011 census at an altitude of >3000 m [2]. Long-term exposure to high altitude has a wide variety of effects on the physiology and disease manifestation. It is well understood that as the altitude increases, there is a fall in barometric pressure leading to a decrease in partial pressure of oxygen (PO_2) [3]. Inhabiting at high altitudes necessitates anatomical, physiological, and gene-molecular adaptation to overcome chronic hypoxia [4,5]. The changes in anatomy include an increase in anteroposterior depth and mediolateral width of the 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 the 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 population are very limit-

ed, both in healthy subjects and subjects suffering from respiratory ailments.

Spirometry is used as one of the most basic and imperative tools 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 the Himalayan region, including the Ladakhi population, which is known for its legendary physical performances [12]. Now, many people from Ladakh are being referred from remote high-altitude terrain to urban metropolitan cities due to the 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 based on spirometry values. The study was done with the aim of devising a 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 institutes of India. The study analyses the spirometry pattern in chronic lung disease cases of people of Ladakh, who reside >11,000 feet above sea level. Subjects enrolled were cases of chronic lung diseases, including chronic obstructive pulmonary disease (COPD), asthma, post-tuberculosis lung diseases (PTBLD), and 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) using the reference prediction equations of the north Indian population [10]. Retrospective analyses of demographic and investigational details of enrolled cases were done from the files of patients. All the demographic parameters, with copies of investigations and diagnoses, 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 patterns of lung function were done for all the cases and sub-analyses separately for done for males and females. The abnormal lung function was further classified into restrictive, obstructive, and mixed pattern of defect, and in severity of lung function impairment according to the percentage predicted of forced expiratory volume in the 1st second (FEV1). The overall forced vital capacity (FVC) and FEV1 were also classified into normal, below, and above normal in percentage of patients. Most enrolled patients had obstructive airway disease (OAD), *i.e.*, COPD and asthma. Therefore, we further sub-analyzed the spirometry parameters of OAD as a whole and individually of COPD and asthma for the classification of defect and its grading. The lung function abnormality and its grading of impairment were done as per the Indian spirometry guidelines and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [13]. The diagnosis of chronic lung disease was done as per the following in this study. The diagnosis of COPD was done following the GOLD guidelines, while the diagnosis of asthma was done following the Global Initiative for Asthma guidelines.

Anthrosilicosis/silicosis: clinical history suggestive of lung disease with high-resolution computed tomography (CT) of the chest showing nodules with or without progressive massive fibrosis and bronchoscopic finding of anthrocotic pigment/anthrofibrosis with compatible histopathology.

PTBLD: clinical history suggestive of lung disease with history of treatment for pulmonary tuberculosis (TB) with radiological evidence of post-TB findings after ruling out 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 diseases was compiled and analyzed 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 patients was 52.2±15.4 years, with 67 (55%) male and 55 (45%) female. The most common type of chronic disease is COPD [51 (41%)], followed by asthma [41 (33%)], silicosis/anthrosilicosis [13 (11%)], and PTBLD [8 (7%)]. The most common occupation was homemaker in 40 (33%) cases, followed by office worker in 30 (24%) and farmer in 25 (20%). Only 28(23%) had a history of smoking with a mean pack year of 14.3±9.0. The mean height was 160±8.6 cm, and the mean weight was 63.2±12.7 kg. The most common symptoms were breathlessness in 115 (94%) and cough in 112 (92%) cases. The median duration of symptoms was 7.2 years (2.2-16.7 years)

Overall, the median post-bronchodilator FVC was 3.49 L with a range from 1.59 to 6.35 L, and the median FVC percentage predicted (%pred) was 116% with a range from 63 to 179%. The FVC (%pred) was >100% in 105 (85%) patients. The FVC (%pred) was >120% in 51 (41%) patients, and the recorded highest %pred was 179%. Similarly, the median post-bronchodilator FEV1 was 2.52 L with a range from 0.85 to 5.26 L, and the median FEV1 (%pred) was 113% with a range from 99 to 175%. The FEV1 (%pred) was >100% in 90 (74%) patients and >120% in 46 (37%), with the highest recorded %pred being 168%. Overall, the FEV1 and FVC were >100% in 74% and 85% of patients, respectively. The median forced expiratory flow 25-75% ($FEF_{25-75\%}$) was 1.82, ranging from 016 to 6.83. Similarly, the median PEF was 5.7 L/s, with a range from 1.96 to 11.64 L/s. All the parameters were higher in males than in females. The details of all findings are depicted in Table 1.

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

moderate lung function impairment, and none as severe to very severe grade in females. The details of FVC findings are depicted in Tables 2 and 3.

The majority [92 (75%)] of patients were of OAD with COPD [51 (42%)] and bronchial asthma [41 (34%)]. We also analyzed the pulmonary function test (PFT) parameters in the 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 subgroups. The FEV1/FVC was below 80 in both COPD and asthma, but not <70 in all groups. This implied that the spirometry with the standard prediction reference equation is not correctly classifying the PFT of high-altitude residents. 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 have just mild obstruction. The details of all the spirometry parameters in all OAD, along with a separate subgroup of COPD and asthma, are depicted in Table 4.

Among the 13 silicoanthracosis patients, the mean post-bronchodilator FVC was 2.8±0.82 L with a mean %pred of 108.4±17.7. The FVC (%pred) was <80% in only one patient, with >120% in three cases. The mean post-bronchodilator FEV1 was 1.8±0.53 L with a 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 showed silicotic nodules involving all the lobes with progressive massive fibrosis in 9 (70%) cases.

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, interquatile range; BD, bronchodilator; FVC, forced vital capacity; pred, predicted; FEV_1, forced expiratory volume in the 1st second; FEF, forced expirstory flow; PEF, peak expiratory flow; FET, forced expiratory time.

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

FVC%pred	<80% pred, n (%)	80-119% pred, n (%)	120-149% pred, n (%)	>150% pred, n (%)
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)

FVC, forced vital capacity; BD, bronchodilator; pred, predicted.

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

FEV_1% pred	<30% pred n (%)	30-49% pred n (%)	50-79% pred n (%)	80-119% pred n (%)	120-149% pred n (%)	>150% pred n (%)
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)

pred, predicted; FEV_1, forced expiratory volume in the 1st second.

Table 4. Details 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 (10172-131)	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)
$FEV1_1$/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)	————

OAD, obstructive airway disease; COPD, chronic obstructive pulmonary disease; IQR, interquatile range; BD, bronchodilator; FVC, forced vital capacity; pred, predicted; FEV_1, forced expiratory volume in the 1st second; FEF, forced expirstory flow; PEF, peak expiratory flow; FET, forced expiratory time.

Discussion

The high altitude has been divided into low, moderate, high, very high, and extreme. Generally, the altitude of >3000 m is considered moderate altitude [14,15]. At this altitude, the inspired PO_2 is reduced to 100 mmHg, the alveolar oxygen pressure is estimated to be 70 mmHg, which means an arterial oxygen pressure of about 60-63 mmHg (hypobaric hypoxia). At an altitude of >3000 m, many of the physiological responses lead to challenges in the human body: hypoxic ventilator response and hypoxic pulmonary vasoconstriction start to develop, and they impose an increased workload on the cardiopulmonary systems [15-17]. Ladakh is a hilly Himalayan dry desert at an altitude of >11,000 feet above 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 an increase in hemoglobin, capillary density, and mitochondrial oxidative capacity. These changes are important for improvement in performance and physical fitness. The natives of high altitude are persistently exposed to hypoxia since birth and hence might have such physiological adaptive changes [15,20]. These changes may affect many other physiological changes in people residing at high altitudes 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 higher than expected in most of them. This finding may be explained by high-altitude physiology.

There are limited published data on spirometry findings and chronic lung diseases of high-altitude residents. We found that both median predicted FVC and FEV1 are higher in most cases in this study. India is a country with different geography, altitudes, ethnic and cultures. The spirometry value also varies with different regions. Studies of reference equations showed significant regional differences [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 from Ladakh to Arunachal Pradesh, lies at high altitudes. There is no published data on the spirometry findings of these high-altitude residents. The spirometry values may differ for these high-altitude residents due to their physical, environmental, and ethnic differences. Saleem *et al*., in a study from a healthy population of Kashmir, found that all the predicted values 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 a level of >3000 m. So, there should be a separate local reference equation of spirometry for better understanding and management in these high-altitude residents of the 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 the Oyacachi community. They concluded that the higher parameters might be due to a compensatory mechanism towards lower barometric and alveolar PO_2 at high altitude [25]. Wietz *et al.*, in a study between Han-born Chinese and Tibetans 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 an 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 the similarity of ethnicity, geography, and environment of Ladakh and Tibet [26]. In another study from China found that spirometry parameters were higher among high-altitude residents. They also found that the high-altitude landers have larger relative sitting heights, indicating greater thorax lengths, and concluded that the higher values are primarily a result of development in a hypoxic environment and adaptive response [27]. Harvyk *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 spirometry values, which 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-altitude residents and much higher than with low landers 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 adults living at high altitudes, there are higher lung function parameters [26-29]. These findings are also relevant

in patients of high altitude suffering from chronic lung disease, similar to our findings. The hypobaric hypoxia is characteristic of high altitude. People living at high altitudes require different physiological, anatomical, genetic, molecular, and immunological adaptive mechanisms [29,30]. The physiological response includes a change in ventilation rates and improved hypoxic ventilatory responses. While the common anatomical changes include 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 in changes in lung function parameters among high-altitude residents [25-28]. The recent advancement in medical and transport facilities in our country has led to increment referrals of patients from high altitudes to low altitudes for medical ailments, including pulmonary diseases. It is prudent to note that not just spirometry, but also the disease pattern and prevalence are different at high altitude. So, it is important to know the high-altitude physiology and disease pattern for better management and unnecessary investigations. Likewise, the non-occupational silicosis and anthracosis are highly prevalent in high-altitude residents of Ladakh, and mimicking malignancy leads to unnecessary invasive procedures [33,34]. So, it is important for physicians to have knowledge of the patient's environment for better results, as our country has diverse geographic and environmental variations.

Conclusions

The median predicted percentage of FVC and FEV1 among chronic lung diseases from high-altitude residents of Ladakh was more than normal in the majority of patients. These higher values of spirometry led to incorrect disease severity classification and disease pattern. In accordance with 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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