

Original Research Article

Study of inspiratory lung function parameters in Indian children

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ABSTRACT

Background: The inspiratory parameters of pulmonary function test commonly used for various purposes in clinical practice including diagnosing airway obstruction. Expiratory portion of the flow volume loop of the pulmonary function test is studied in detail. The prediction equations for expiratory parameters are available for different population. However, the reference equation for inspiratory parameters is not available in Indian context. The current study derived the prediction equation for inspiratory parameters of pulmonary function test.

Methods: The current study was carried out in school going 732 healthy girls and 1377 boys aged 6-15 years in India. The children who meet the inclusion criteria were recruited in the study after detailed medical examination by registered medical practitioner. The lung function parameters were recorded by spirometry. The multivariate regression analysis was done to develop the prediction model.

Results: The prediction equation for predicting inspiratory parameter were developed. This study revealed gender-wise and geographical variation in the inspiratory parameters. Hence this study recommends to derive gender wise prediction equations. The reference equations derived in this study can be used in population with similar background.

Conclusions: Use of these equations for population having similar backgrounds will help for early and accurate diagnosis of the airway abnormalities in children. The inspiratory parameter assessment shall be included in the routine assessment of respiratory patient.

Keywords: Peak inspiratory flow rate, Pulmonary function, Inspiratory volume, Prediction equation, Flow volume loop

INTRODUCTION

Spirometry is one of the reliable tests done for the diagnosis of pulmonary diseases. The routine spirometry test assesses the inspiratory as well expiratory efforts of the patient and gives parameters, graphs for both these efforts.¹ The Peak inspiratory flow rate (PIFR) measured from forced inspiratory maneuver is used for various purposes in clinical practice. PIFR is a good index of a

patient's inspiratory effort as it measures the patient's capacity to generate adequate flow during inspiration. The inhaled drug's effectiveness in chronic obstructive pulmonary disease (COPD) is reduced in patients with PIFR values lower than 60 l/min. Hence, PIFR is a reliable indicator for acceleration in inhalation profile tests.² The forced inspiratory volume in 1 second (FIV₁) which is a parameter of the inspiratory loop of spirometry shows a good bronchodilator response in COPD patients. Accuracy

of diagnosis of COPD can be increased by assessing lung function parameters of inspiratory loop like FIV₁, forced inspiratory vital capacity (FIVC), and forced inspiratory flow at 50% of FIVC (FIF50%)³. Inspiratory portion of the flow volume loop and forced inspiratory maneuver is used to diagnose the various types of extra-thoracic abnormalities of airways.^{4,5} The inspiratory flow-volume loop shape and inspiratory parameters get altered in a variable or fixed extra thoracic obstruction of upper airways.⁶ Expiratory part of the flow-volume loop along with its parameters is studied in detail.

Various researches have established the reference values, prediction equations and diagnostic criteria for expiratory loop parameters.^{7,8} The inspiratory section of flow-volume loop and its parameters are not studied adequately and there is a dearth of literature on reference values, prediction equations in this area.⁹ Hence there was a need to establish reference data for inspiratory parameters of lung function to diagnose inspiratory curve and parameters abnormality. The aim of the study was designed to derive reference values in the form of a prediction equation in Indian children.

METHODS

This study type was observational cross-sectional study. Conducted at VSPM Physiotherapy college and Lata Mangeshkar Hospital, Nagpur, from December 2011 to August 2018.

Inclusion criteria

Patients having normal healthy children living in Maharashtra aged 6-15 years and children with normal BMI (5th percentile to 85th percentile) were included in the study.

Exclusion criteria

Patients having following criteria were excluded from the study- (a) children with spinal/chest wall deformities eg. scoliosis, kyphosis, etc; (b) children diagnosed as childhood asthma; (c) children having family history of respiratory diseases eg. asthma, COPD, cystic fibrosis; (d) children with pleural, parenchymal diseases, congenital heart disease; (e) children underwent pulmonary, cardiac, abdominal surgeries; (f) children with acute infection; (g) children with smoking history or smokers; (h) malnourish or obese child (BMI less than 5th percentile or above 85th percentile); (i) children with delayed milestones/neurological involvement; (j) children with diseases that will affect lung function; and (k) children with metabolic diseases.

A normal child is defined as the one who is free from congenital anomalies, respiratory/cardiac/metabolic diseases without having any of the family histories of bronchial asthma/COPD/bronchiectasis/cystic fibrosis or any other respiratory diseases and having normal BMI (5th

percentile to 85th percentile). The current study was carried out in 2109 school going children aged 6-15 years at eight schools of Beed and Latur districts of the Maharashtra region of India. 732 healthy girls and 1377 boys were selected randomly. A child who was free from cardiac/respiratory/metabolic/ spinal diseases and having a BMI of between fifth to eighty-fifth percentile was defined as a healthy child and was recruited in the study. The written permissions were taken from the authorities of the school to carry out the study. The approval for the study was taken from the ethical committee of institute. The queries of school authorities, parents and subjects were addressed to their satisfaction. A form was designed to acquire the information of the medical and surgical history of the child and it was sent to the home of every child. The written document mentioning the details of the study was sent with the child. On receipt of consent and history form from parents, the examination of the child was done. After a detailed medical examination to rule out cardiac/respiratory/metabolic/spinal diseases and growth abnormalities by registered medical practitioners the subjects were recruited in the study.

Anthropometric parameters of height, body mass index (BMI), body surface area (BSA) weight, and age was measured. The age was measured in years, height in centimetres and weight in kilograms. "Mosteller" formula was used to calculate the BSA.

Recording of PFT

The Helios 401 RMS India, windows based computerized spirometer was used to record the PFT in current study. The technical specification of this instrument was as per American thoracic society (ATS) European respiratory society (ERS) criteria recommendations for Standardization of the spirometer.

Calibration of the instrument

Calibration testing was done every day before recording PFT by clicking the application and 3 liter syringes was used for same. The accuracy of the machine met the European respiratory society and American thoracic society criteria¹⁰.

Position of the child

PFT was performed in sitting position. A standardised plastic chair was used. The subject was made comfortable, the child's trunk and neck were erect during the manoeuvre. The subject was asked to look straight forward during the entire test. The feet were properly supported on the floor. A small stool was used in smaller children who were unable to keep feet on the ground.

Administration of test

After proper positioning and machine preparation the child was instructed to do the FVC manoeuvre. The ATS

recommended standardized instructions were given to each child. The attention was given to the way of the technique carried by each child. The technically acceptable manoeuvre was selected as per ATS guidelines.¹⁰ The child was instructed & encouraged to give forceful maximal effort. The animation cartoon was used to give encouragements. Also, attention was given to check proper mouth seal around mouthpiece, presence of any leakage, confidence/hesitation in doing the manoeuvre. The animation cartoons helped children to improve the forced expiratory manoeuvre performance.

Recognizing correct and incorrect manoeuvres

Identification of the correct pattern of the FVC manoeuvres is the most important in the estimation of the lung function reference values. Hence in this study we have given attention to the quality control of the procedures. ATS-ERS task force within- and between manoeuvre acceptability criteria was used to identify the correct test. Three efforts were taken and the best effort was recorded. The inspiratory parameters FIVC, PIFR, FIV₁, FIF50%, Forced inspiratory flow rate at first 25% of FIVC (FIF 25%), Forced inspiratory flow in the middle half of FIVC (FIF25-75%) were taken for analysis. The disposable mouthpiece was used for every child and used mouthpieces were discarded as per guidelines of local biomedical waste management authorities.

Statistical analysis

The mean, the standard deviation was calculated by descriptive statistics. Multivariate regression analysis was done for PFT parameters and anthropometric parameters to understand the simultaneous effects of all anthropometric parameters on lung function. Gender wise prediction equations were derived. The regression model was derived by enter method. The significance of the model was assessed with a diagnostic F test. Significance of p value was considered if p value was less than 0.05. IBM SPSS package 23 was used for statistical analysis.

RESULTS

The female population had mean age 11.201 years, the mean weight was 33.639 kg, the mean height was 142.022

cm, the mean BMI was 16.490 kg/m² and mean BSA was 1.147 m² whereas mean age of the male population was 11.978 years, mean weight was 35.711 kg, mean height was 146.542 cm, mean BMI was 16.224 kg/m² and mean BSA was 1.289 m² (Table 1). The males have higher values of anthropometric parameters than females. The mean FIVC of girls was 1.535 l, mean PIFR was 2.105 l/s, mean FIV₁ was 2.566 l/s, mean FIF 25% was 1.575 l/s, mean FIF 50% was 1.846 l/s, mean FIF 75% was 1.925 l/s whereas the mean FIVC of boys was 1.7 l, mean PIFR was 2.397 l/s, mean FIV₁ was 2.967, mean FIF 25% was 1.718 l/s, mean FIF 50% was 2.067 l/s, mean FIF 75% was 2.110 l/s (Table 2). The males have higher values of inspiratory parameters than females.

Table 1: Gender wise descriptive statistics for anthropometric parameters.

Parameters	Girls (N=732)		Boys (N=1377)	
	Mean	SD	Mean	SD
Age	11.201	3.087	11.978	2.783
Weight	33.639	8.174	35.711	10.880
Height	142.022	15.621	146.542	16.930
BMI	16.490	1.793	16.224	1.627
BSA	1.147	0.185	1.289	0.218

Table 2: Gender wise comparison of mean values of PFT parameters.

Parameters	Girls		Boys	
	Mean	SD	Mean	SD
FIVC	1.535	0.532	1.700	0.665
PIFR	2.105	0.844	2.397	1.182
FIV ₁	2.566	0.854	2.967	1.201
FIF 25%	1.575	0.969	1.718	1.187
FIF 50%	1.846	0.948	2.067	1.248
FIF 75%	1.925	0.904	2.110	1.179

In females the multiple regression model for predicting FIVC explained 24.1% of the variance in the data whereas the PIFR model explained 29.5%, FIV₁ model explained 42.4%, FIF 25% model explained 25%, FIF 50% model explained 25.6%, FIF 75% model explained 31.4% of the variance in data (Table 3).

Table 3: Regression model summery female.

Model	R	R ²	Adjusted R ²	Std. error of estimate	F	Significance
FIVC	0.496	0.246	0.241	0.46382	47.476	0.000
PIFR	0.547	0.299	0.295	0.70846	62.079	0.000
FIV ₁	0.654	0.428	0.424	0.64806	108.794	0.000
FIF 25%	0.505	0.255	0.250	0.83940	49.820	0.000
FIF 50%	0.511	0.261	0.256	0.81770	51.374	0.000
FIF 75%	0.565	0.319	0.314	0.74848	67.993	0.000

Table 4: Prediction equation of inspiratory parameters for females.

Models		Unstandardized coefficients		Standardized coefficients	t	Significance
		B	Std. error	Beta		
FIVC	Constant	1.412	0.299		4.720	0.000
	Age	0.085	0.030	0.496	2.888	0.004
	Weight	0.031	0.004	0.473	8.134	0.000
	Height	-0.011	0.004	-0.484	-3.069	0.002
	BMI	-0.048	0.015	-0.162	-3.272	0.001
	BSA	0.486	0.261	0.142	1.862	0.063
	FIVC (female)=1.412 (constant)+0.085*age+0.031*weight-0.011*height-0.48*BMI					
PIFR	Constant	1.427	0.457		3.125	0.002
	Age	-0.220	0.045	-0.803	4.857	0.000
	Weight	-0.031	0.006	-0.304	5.419	0.000
	Height	0.020	0.005	0.558	-3.675	0.000
	BMI	-0.004	0.022	-0.008	-0.164	0.870
	BSA	0.099	0.399	0.018	0.249	0.803
	PIFR (female)=1.427 (constant)-0.220*age-0.031*weight+0.020*height					
FIV1	Constant	0.047	0.418		0.112	0.911
	Age	0.042	0.041	0.152	1.017	0.309
	Weight	0.054	0.005	0.513	10.128	0.000
	Height	0.050	0.005	0.028	1.920	0.028
	BMI	0.011	0.020	0.023	0.529	0.597
	BSA	0.206	0.365	0.038	0.566	0.572
	FIV1 (female)=0.47 (constant)+0.054*weight+0.050*height					
FIF 25%	Constant	-1.744	0.541		-3.222	0.001
	Age	-0.011	0.054	-0.036	-0.209	0.834
	Weight	0.037	0.007	0.314	5.432	0.000
	Height	0.011	0.006	0.052	2.331	0.027
	BMI	0.093	0.027	0.172	3.514	0.000
	BSA	0.342	0.473	0.055	0.723	0.470
	FIF 25% (female)=-1.744 (constant)+0.037*weight+0.011*height+0.093*BMI					
FIF 50%	Constant	-1.195	0.527		-2.267	0.024
	Age	0.026	0.052	0.084	0.496	0.620
	Weight	0.034	0.007	0.292	5.076	0.000
	Height	0.030	0.006	0.005	3.030	0.020
	BMI	-0.098	-0.026	0.185	3.788	0.000
	BSA	0.022	0.461	0.004	0.047	0.962
	FIF 50% (female)=-1.195 (constant)+0.034*weight+0.030*height-0.098*BMI					
FIF 75%	Constant	-0.082	0.483		-0.169	0.866
	Age	0.158	0.048	0.539	3.304	0.001
	Weight	0.032	0.006	0.288	5.209	0.000
	Height	0.010	0.006	-0.284	2.895	0.006
	BMI	-0.091	0.024	0.180	3.838	0.000
	BSA	-0.751	0.422	-0.129	-1.782	0.075
	FIF 75% (female)=-0.082(constant)+0.158*age+0.032*weight+0.010*height-0.091*BMI					

Table 5: Regression model summary male.

Model	R	R ²	Adjusted R ²	Std. error of estimate	F	Significance
FIVC	0.727	0.529	0.527	0.45703	308.137	0.000
PIFR	0.659	0.435	0.433	0.89044	210.960	0.000
FIV₁	0.805	0.648	0.646	0.71415	504.295	0.000
FIF 25%	0.444	0.197	0.194	1.06588	67.363	0.000
FIF 50%	0.552	0.305	0.302	1.04275	120.190	0.000
FIF 75%	0.584	0.341	0.338	0.95920	141.581	0.000

Table 6: Prediction equation of inspiratory parameters for males.

Models		Unstandardized coefficients		Standardized coefficients	t	Significance
		B	Std. error	Beta		
FIVC	Constant	0.841	0.166		5.076	0.000
	Age	0.132	0.015	0.552	8.619	0.000
	Weight	0.042	0.002	0.682	20.706	0.000
	Height	-0.013	0.002	-0.520	-8.041	0.000
	BMI	-0.038	0.011	-0.093	-3.360	0.001
	BSA	0.317	0.099	0.104	3.214	0.001
	FIVC (male)=0.841 (constant)+0.132*age+0.042*weight-0.013*height-0.38*BMI+0.317*BSA					
PIFR	Constant	0.137	0.323		0.423	0.672
	Age	0.137	0.323		0.423	0.672
	Weight	0.122	0.030	0.287	4.095	0.000
	Height	-0.062	0.004	0.573	15.880	0.000
	BMI	0.011	0.003	0.239	-3.373	0.001
	BSA	-0.038	0.022	-0.052	-1.731	0.084
	PIFR (male)=0.137 (constant)+0.122*age-0.062*weight+0.011*height+0.642*BSA					
FIV1	Constant	0.872	0.259		3.368	0.001
	Age	0.106	0.024	0.245	4.423	0.000
	Weight	0.090	0.003	0.820	28.756	0.000
	Height	-0.010	0.003	-0.210	-3.749	0.000
	BMI	-0.080	0.018	-0.109	-4.560	0.000
	BSA	0.278	0.154	0.051	1.805	.071
	FIV1 (male)=0.872 (constant)+0.106*age+0.090*weight-0.010*height-0.080*BMI					
FIF 25%	Constant	0.571	0.387		1.478	0.140
	Age	-0.036	0.036	-0.084	-1.008	0.314
	Weight	0.054	0.005	0.495	11.509	0.000
	Height	0.004	0.004	0.063	1.974	0.035
	BMI	-0.066	0.026	-0.090	-2.504	0.012
	BSA	0.219	0.230	0.040	0.952	0.341
	FIF 25% (male)=0.571 (constant)+0.054*weight+0.004*height-0.066*BMI					
FIF 50%	Constant	0.977	0.378		2.584	0.010
	Age	0.031	0.035	0.069	0.888	0.374
	Weight	0.066	0.005	0.575	14.351	0.000
	Height	0.050	0.004	0.037	1.947	0.016
	BMI	-0.126	0.026	-0.164	-4.900	0.000
	BSA	0.522	0.225	0.091	2.321	0.020
	FIF 50% (male)=0.977 (constant)+0.066*weight+0.005*height-0.126*BMI+0.522*BSA					
FIF 75%	Constant	-0.085	0.348		-0.243	0.808
	Age	0.041	0.032	0.097	1.279	0.201
	Weight	-0.059	-0.004	0.545	13.979	0.000
	Height	0.021	0.003	0.143	2.870	0.006
	BMI	-0.029	0.024	-0.040	-1.238	0.216
	BSA	0.811	0.207	0.150	3.919	0.000
	FIF 75% (male)=-0.085 (constant)-0.059*weight+0.021*height+0.811*BSA					

The prediction equations for females were derived (Table 4). In males the multiple regression model for predicting FIVC explained 52.7% of the variance in the data whereas the PIFR model explained 43.3%, FIV₁ model explained 64.6%, FIF 25% model explained 19.4%, FIF 50% model explained 30.2%, FIF 75% model explained 33.8% of the variance in data (Table 5). The diagnostic F test and

ANOVA was significant for all parameters in males and females.

The percent of variance explained by regression models were higher in the male population than the female population. The prediction equations for males were derived (Table 6).

DISCUSSION

The current study was designed to establish reference data for inspiratory lung function parameters in the form of prediction equations. The current study observed gender differences in inspiratory lung function parameters. The male participants have higher values than females. The linear relation was observed between lung function parameters and anthropometric parameters by many researchers.^{11,12}

The mean weight, height BMI BSA in current study was higher in males than females. That might be the reason for observing higher values in males. The PFT maneuver requires forceful inspiratory and expiratory forces. It's also observed that generally males are more muscular than females. Probably that has helped male participant to generate higher volumes and flow rates. This finding of our study is supported by many authors.^{13,14}

The boys of our study had lower PIFR values than boys of the UK and boys of Kerala.^{14,15} The smaller boys of our study (height 120 cm to 140 cm) had lower PIF 25%, PIF 50% PIF 75% than boys of Kerala whereas the boys taller than 140 cm had higher values than boys of Kerala¹⁵. The global differences in lung function parameters can be explained by the differences in cultural, dietary, socioeconomic status, growth pattern, maternal nutrition and environmental differences.¹⁵⁻¹⁹

Limitations

The environmental, socioeconomic factors affecting lung function were not investigated in this study. Effect of passive smoking, smoke inhalation by use of bio fuel and quality of air was not investigated in study. Free fat mass was not calculated and its impact on lung function was not studied in this study. Religion wise and Indian race wise separate analysis was not done. The effect of area of living on lung function was not studied.

CONCLUSION

The pattern of lung growth varies gender-wise. Hence, prediction equations shall be derived for both genders separately. The reference values and equations generated in this study shall be used in a population with a similar background. The geographic variation in lung function exists hence population-specific equations shall be used for the assessment of lung function.

Use of these equations in heterogenous population is not recommended. In such cases, ethnic corrections by use of proper statistical methods has to be carried out. Recording of inspiratory parameters of the flow volume loop shall be an integral part of the assessment of respiratory patients.

The outcome of this study will help in early diagnosis of the pulmonary diseases in children.

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REFERENCES

1. Mahler DA. Peak Inspiratory Flow Rate: An Emerging Biomarker in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2019;199(12):1577-9.
2. Ghosh S, Ohar JA, Drummond MB. Peak Inspiratory Flow Rate in Chronic Obstructive Pulmonary Disease: Implications for Dry Powder Inhalers. *J Aerosol Med Pulm Drug Deliv.* 2017;30(6):381-7.
3. Visser FJ, Ramlal S, Pelzer B, Dekhuijzen PN, Heijdra YF. Random variation of inspiratory lung function parameters in patients with COPD: a diagnostic accuracy study. *BMC Pulm Med.* 2010;10:28.
4. Sterner JB, Morris MJ, Sill JM, Hayes JA. Inspiratory flow-volume curve evaluation for detecting upper airway disease. *Respir Care.* 2009;54(4):461-6.
5. Owens GR, Murphy DM. Spirometric diagnosis of upper airway obstruction. *Arch Intern Med.* 1983;143(7):1331-4.
6. Modrykamien AM, Gudavalli R, Carthy K, Liu X, Stoller JK. Detection of upper airway obstruction with spirometry results and the flow-volume loop: a comparison of quantitative and visual inspection criteria. *Respir Care.* 2009;54(4):474-9.
7. Koopman M, Zanen P, Kruitwagen CL, Ent CK, Arets HG. Reference values for paediatric pulmonary function testing: The Utrecht dataset. *Respir Med.* 2011;105(1):15-23.
8. Kale S, Deshpande M, Chaudhari S. Prediction model for Peak expiratory flow rate in rural Indian girls. *Int J of Pharma and Biomed Sciences.* 2021;12(2):68-72.
9. Viložni D, Efrati O, Barak A, Yahav Y, Augarten A, Bentur L. Forced inspiratory flow volume curve in healthy young children. *Pediatr Pulmonol.* 2009;44(2):105-11.
10. American Thoracic Society. Standardization of Spirometry. *Am J Respir Crit Care Med.* 1995;152(3):1107-36.
11. Schrader PC, Quanjer PH, Zomer BC, Wise ME. Changes in the FEV1-height relationship during pubertal growth. *Bull Eur Physiopathol Respir.* 1984;20(4):381-8.
12. Sliman NA, Dajani BM, Shubair KS. Pulmonary function in normal Jordanian children. *Thorax.* 1982;37(11):854-7.

13. Dickman ML, Schmidt CD, Gardner RM. Spirometric standards for normal children and adolescents (ages 5 years through 18 years). *Am Rev Respir Dis.* 1971;104(5):680-7.
14. Rosenthal M, Bain SH, Cramer D, Helms P, Denison D, Bush A, Warner JO. Lung function in white children aged 4 to 19 years: I-Spirometry. *Thorax.* 1993;48(8):794-802.
15. Nair RH, Kesavachandran C, Sanil R, Sreekumar R, Shashidhar S. Prediction equation for lung functions in South Indian children. *Indian J Physiol Pharmacol.* 1997;41(4):390-6.
16. Quanjer PH, Borsboom GJ, Kivastik J, Merkus PJ, Hankinson JL, Houthuijs D, et al. Cross-sectional and longitudinal spirometry in children and adolescents: interpretative strategies. *Am J Respir Crit Care Med.* 2008;178(12):1262-70.
17. Grivas TB, Burwell RG, Purdue M, Webb JK, Moulton A. A segmental analysis of thoracic shape in chest radiographs of children. Changes related to spinal level, age, sex, side and significance for lung growth and scoliosis. *J Anat.* 1991;178:21-38.
18. Hibbert ME, Couriel JM, Landau LI. Changes in lung, airway, and chest wall function in boys and girls between 8 and 12 year. *J Appl Physiol Respir Environ Exerc Physiol.* 1984;57(2):304-8.
19. Guyton AC, Hau JE. Pulmonary ventilation. *Textbook of medical physiology.* 11th ed. India: WB Saunders Company; 2006:471-448.

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