Reference equation for spirometry interpretation for Eastern India

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ABSTRACT

Introduction: Spirometry measurements are interpreted by comparing with reference values for healthy individuals that have been derived from multiple regression equations from earlier studies. There are only two such studies from Eastern India, both by Chatterjee et al., one each for males and females. These are however single center and approximately two decades old studies. Aims: (1) to formulate a new regression equation for predicting FEV\textsubscript{1} and FVC for eastern India and (2) to compare the results to the previous two studies by Chatterjee et al. Materials and Methods: Healthy nonsmokers were recruited through health camps under the initiative of four large hospitals of Kolkata. Predicted equations were derived for FEV\textsubscript{1}, FVC and FEV\textsubscript{1}/FVC in males and females separately using multiple linear regression, which were then compared with the older equations using Bland-Altman method. Results: The Bland-Altman analyses show that the mean bias for females for FVC was 0.39 L (95% limits of agreement 1.32 to –0.54 L) and for FEV\textsubscript{1} was 0.334 L (95% limits of agreement of 1.08 to –0.41 L). For males the mean bias for FEV\textsubscript{1} was –0.141 L, (95% limits of agreement 0.88 to –1.16 L) while that for FVC was –0.112 L (95% limits of agreement 0.80 to –1.08 L). Conclusion: New updated regression equations are needed for predicting reference values for spirometry interpretation. The regression equations proposed in this study may be considered appropriate for use in current practice for eastern India until further studies are available.

KEY WORDS: Eastern India, reference equation, spirometry

INTRODUCTION

Interpretation of spirometry entails comparing an individual’s measured values to a reference value, which has been calculated from multiple regression analysis equations from studies on healthy individuals. This is because lung function of an individual, unlike most other biological measurements, depends on several factors such as age, gender, height, smoking history, environmental factors, socioeconomic status and ethnicity. Indeed, significant differences are known to exist among the major ethnic groups in the United States.\textsuperscript{[2]} Such changes in lung health over time have been recognized as the “cohort effect” necessitating periodic revision of spirometry prediction equations.\textsuperscript{[2]}

India, being a vast country has a large number of ethnicities and it would be ideal to have separate reference equations for each ethnic group. In fact, despite being limited by methodological differences, there are studies that have proposed different equations for the various regions of India.\textsuperscript{[3–8]} A study that has compared these regression equations has shown that the Eastern Indian population has similar lung functions to Northern India while Western and Southern Indian people had similar but lower spirometry values.\textsuperscript{[9]} Therefore, selection of the correct regression equation is of paramount importance and the use of inappropriate equations may lead to misinterpretation of spirometric data.\textsuperscript{[10]}

So far, eastern India has one study each on males and females that have proposed equations for calculating reference values for forced expiratory volume in
Spirometry was performed in sitting and FVC for eastern India. Values greater than 150 ml were be considered clinically significant difference for 1 second (FEV₁) and forced vital capacity (FVC). These studies are however approximately two decades old and both are single-center studies. Hence, it is likely that these equations may no longer be relevant in the context of changed environmental and socioeconomic conditions in India making a multicenter study necessary in the present socioeconomic and environmental milieu. The objectives of our study were (1) to formulate a new regression equation for predicting FEV₁ and FVC for eastern India and (2) to compare the results to the previous two studies by Chatterjee et al.

MATERIALS AND METHODS

Study participants
Spirometry was performed on healthy males and females aged 15 years and above over a period of 6 months (January to June 2013). The participants were recruited from health camps (1 every 2 months for each hospital, 12 camps in 6 months) held under the initiative of four large hospitals of Kolkata. The four centers were selected such that recruiting from the population attending these hospitals would cover most of the city and adjoining districts. This also ensured that people from a wide socio-economic background and from both urban and rural populations were included. Approval of the institutional review boards of the four participating hospitals was taken. These camps were part of the routine health camps regularly organized by these hospitals. All the camps were held in the concerned hospital. Ethnicity was determined by the ancestral ethnicity. Immigrants from Bangladesh were not excluded. Participants were excluded if (1) they were smokers (current or past); (2) they could not perform spirometry of standards that satisfied ATS guidelines; (3) they had diseases that might affect pulmonary function like subjects with a history of asthma, chronic bronchitis, chronic cough, exposure to any toxic chemicals, or surgery involving the chest wall or spine; (4) they had ongoing respiratory symptoms like that of flu like illness or “common cold” and (5) they did not consent to participate in the study. All the participants provided informed consent before beginning of the study procedure.

Study measurements
All participants were screened by means of a self-administered health questionnaire to exclude cardiopulmonary or other diseases that might affect spirometry results. This is the same questionnaire that was used in the earlier study (Chatterjee et al., Appended). It is in English and was translated by the investigator to Bengali or Hindi as required for persons who did not have knowledge of English. The main aim of the questionnaire was directed at identifying participants with any chest symptoms (such as cough, sputum production, hemoptysis, dyspnea, wheezing, nasal symptoms), evidence of any acute or recent (within 6 weeks) upper or lower chest infection or any chronic chest, cardiac or other systemic disease who would be excluded from the study. An interview cross-checked the results of the questionnaire to eliminate subjects not fulfilling the inclusion criteria. A brief physical examination was subsequently performed by the physician (MD) investigator who conducted the Heath Camp at each center to rule out any acute or chronic respiratory illness.

After the purpose of the study was explained to the participants spirometry was performed by an Indian Chest Society trained personnel using carefully calibrated Jaeger’s computer-based spirometer (MasterScope-PC, pneumotach spirometer with flow sensor). For assuring quality, control spirometers of the same model were used and calibration checks were done daily just before the tests using a 3L syringe according to the manufacturer’s recommendations using the software menu. Linearity checks were performed weekly in all centers. The volumes and flow rates were corrected to body temperature and pressure, saturated with water vapor (BTPS). Maximal expiratory flow volume curves were obtained as per the ATS/ERS 2005 recommendations.[11] Spirometry was performed in sitting position. The spirometry technician under the supervision of a physician (not the conducting respirologist) observed the subject for signs of discomfort or distress and the computer display during the test to ensure a maximal effort with quality control as recommended by the ATS/ERS Task Force.[12] At least three acceptable (free from artifacts, have good starts and have duration of >6 seconds or a plateau in the volume-time curve or if the subject cannot or should not continue to exhale) and two reproducible curves (the difference between the largest and the next largest FVC is ≤0.150 L and the difference between the largest and next largest FEV₁ is ≤ 0.150 L) were obtained in each subject.[12] The highest values of the forced vital capacity (FVC) and forced expiratory volume in the first second (FEV₁) were selected. The Spirograms were also assessed by the respirologist (MD) conducting the health camp in each center.

Age was recorded to the nearest year, height to the nearest centimeter (cm) with the subject standing barefoot, and weight (in light street clothes) to the nearest kilogram. Subjects were weighed on a balanced scale, and height was measured on a stadiometer.

Statistical analysis
Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS version 20.0, Inc. Chicago, USA). Data was expressed as mean (± SD). Multiple linear regression analysis was applied to the observed lung function values (FEV₁, FVC and FEV₁/FVC as dependent variables) with standing height and age as the independent variables. Agreement between the two equations (Chatterjee and present study) for FEV₁ and FVC were assessed using Bland-Altman method. The mean difference between the values obtained by the two equations for a given parameter was plotted against the average of the two values and 95% limits of agreement calculated. Values greater than 150 ml were be considered clinically significant difference for
FVC and FEV$_1$. The minimum sample size recommended for multivariate regression analysis for lung function parameters is 150.$^{[14]}$ We aimed at recruiting as many participants as possible within a time span of 6 months.

### RESULTS

A total of 706 (545 males, 161 females) participants were screened in the four selected centers. Of them, 87 were excluded (66 were respiratory symptoms, 10 could not produce reproducible and acceptable curves and 11 were smokers). All participants who were approached consented to participating in the study.

There were a total of 619 (Centre 1, Centre 2, Centre 3 and Centre 4 recruited 79, 110, 255 and 175 subjects, respectively; Table 1) participants in this study of which 491 were males and 128 were females. The center-wise age distribution of the participants has been tabulated in Table 1. The overall mean (SD) FEV$_1$ for males was 3.09 (0.6) L while that for FVC was 3.71 (0.6) L. For females the mean (SD) FEV$_1$ was 2.37 (0.47) L and FVC was 2.79 (0.55) L.

Figure 1a-f shows the scatter plots of age vs FEV$_1$, FVC and FEV$_1$/FVC ratio and height vs FEV$_1$, FVC and FEV$_1$/FVC ratio for both genders.

The multiple regression equations derived from this study were:

1. For males
   - Predicted FEV$_1$ = $-1.7649 + (-0.0218 \times \text{age}) + (0.0337 \times \text{height})$ (SEE = 0.434; $R^2 = 0.42$)
   - Predicted FVC = $-4.6899 + (-0.0286 \times \text{age}) + (0.0533 \times \text{height})$ (SEE = 0.326; $R^2 = 0.70$)
   - Predicted FEV$_1$/FVC = $0.618 + (-0.0012 \times \text{age}) + (0.0522 \times \text{height})$ (SEE = 0.422; $R^2 = 0.52$)
   - Predicted FEV$_1$/FVC = $1.08994 + (-0.00133 \times \text{age}) + (-0.0012 \times \text{height})$ (SEE = 0.092; $R^2 = 0.34$).

2. For females
   - Predicted FEV$_1$ = $0.3811 + (-0.0197 \times \text{age}) + (0.0196 \times \text{height})$ (SEE = 0.370; $R^2 = 0.41$)
   - Predicted FVC = $-0.902 + (0.025 \times \text{age}) + (0.027 \times \text{height})$ (SEE = 0.465; $R^2 = 0.29$)
   - Predicted FEV$_1$/FVC = $0.9205 + (0.00133 \times \text{age}) + (0.00001 \times \text{height})$ (SEE = 0.076; $R^2 = 0.122$)

Results of Bland-Altman analysis$^{[12]}$ of the predicted FEV$_1$ and forced vital capacities from the four equations are presented in Figure 2a-d. For females, the analyses shows a mean bias of 0.39 L for FVC with very wide 95% limits of agreement (1.32 to –0.54 L) and for FEV$_1$ the mean bias was 0.334 L with the 95% limits of agreement being 1.08 to –0.41 L. For males the mean bias for FEV$_1$ was –0.141 L (95% limits of agreement 0.88 to –1.16 L) while that for FVC was –0.112 L (95% limits of agreement 0.80 to –1.08 L).

### DISCUSSION

This study demonstrates the necessity to work out new regression equations for spirometry interpretation for eastern India. Although the mean bias in the Bland Altman analyses for FEV$_1$ and FVC for males is clinically not significant, the 95% limits of agreement (despite including zero) are wide and clinically significant. Values greater than 150 ml is traditionally considered clinically significant difference for FVC and FEV$_1$. We did not perform post bronchodilator tests. For females, both the mean bias and the 95% limits of agreement for both of FEV$_1$ and FVC are clinically significant. The earlier east Indian studies did not calculate regression equations for FEV$_1$/FVC ratio.$[^{[13,4]}$ Overall, age had a negative relationship and height a positive relationship to all three spirometry parameters except the FEV$_1$/FVC ratio where height had only an extremely small effect. These are consistent with earlier studies in other populations.$[^{[13,4]}$

Differences in predicted spirometry parameters are indeed expected as improvements in socioeconomic and nutritional status result in subjects of greater height who...
Figure 1: (a) Scatter-plot of age vs. FEV₁ and FVC in males showing a linear scatter (b) Scatter-plot of age vs. FEV₁ and FVC in females showing a linear scatter (c) Scatter-plot of height vs. FEV₁ and FVC in males showing a linear spread (d) Scatter-plot of height vs. FEV₁ and FVC in females showing a linear spread (e) Scatter-plot of age vs. FEV₁/FVC and height vs FEV₁/FVC in females showing a good linear spread in age plot. Height has only a small correlation with FEV₁/FVC (f) Scatter-plot of age vs. FEV₁/FVC and height vs FEV₁/FVC in males showing a good linear spread in age plot. Height has only a small correlation with FEV₁/FVC
are then likely to have greater lung flows and capacities. Indeed the two study populations had significant demographic differences especially in mean height and weight. Interestingly for males, the mean FVC and FEV\textsubscript{1} values were similar in both the studies while for females these were significantly higher in the present study as compared to the Chatterjee \textit{et al.} study. Obviously, the improvement in nutritional status also holds good for men making the reason for this difference unclear. The only possible reason was the differences in age distribution between the two populations. Our study had a uniform age distribution while in the study by Chatterjee \textit{et al}, there were proportionately more subjects in the 20‑24 year age group as compared to the older age groups. However, other reasons for this disparity need to be established in future studies.

Another methodological difference between the two studies was in the equipment used. For this study we used a Jaegers spirometer while the Chatterjee \textit{et al} used a modified water‑sealed Toshiwal Expirograph (9 L capacity) with soda lime cannister removed. Such spirometers are not used in clinical work and have also become outdated.

The strength of this study lies in its methodology and careful quality control measures. The study involves four centers across the city of Kolkata unlike the earlier two single centre studies. This gives the study a greater chance of including people from different socioeconomic backgrounds and geographic locations. This was however not looked into systematically. It is the first study after an interval of approximately 20 long years that has explored the applicability of an existing regression equation for predicting spirometry measures. The results of our study clearly show the need for updating predicting regression equations for spirometry at regular time intervals.

The main limitation of this study is that the sample size for females was slightly smaller than that considered adequate for development of regression equations. A minimum sample size of 150 men and 150 women has been recommended.\textsuperscript{[14]} Another limitation of our study is that we considered Kolkata and the surrounding area to be representative of the entire Eastern India which is not necessarily true. Future normative studies should therefore consider having centers in the other Eastern states of India.

CONCLUSION

The predicted equations in this study are different from that of the study by Chatterjee \textit{et al.} implying the need for formulating updated new regression equations. There are however no eastern Indian studies after 1988 for males and 1993 for females that have looked into this or have attempted to formulate new prediction equations using up‑to‑date technology. The regression equations proposed in this study may therefore be considered appropriate for use in current practice. This would be till the time we have a larger study with greater number of participants which looks at all of Eastern India.

APPENDIX A

The lower limits of normal for each spirometric variable can be determined by a 90% confidence interval (CI).

The confidence interval is calculated using the SEE according to the formula:
90% CI = predicted or reference value ± 1.645 * SEE. Thus the lower limits of normal (LLN) = predicted value – (1.645 * SEE.)
For example: The LLN for FEV₁ for males = predicted value – (1.645 * 0.434)
For a 30 yr old male of 165 cm height:
Predicted FEV₁ = –1.7649+ (–0.0218*30) + (0.0337 * 165) = 3.14 L
Therefore, LLN = 3.14 – 0.714 = 2.43 L

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