Original Article

Regression equations of respiratory impedance of Indian adults measured by forced oscillation technique

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ABSTRACT

Background: Forced oscillation technique (FOT) is a technique to measure the mechanical properties of the lung. The present study was aimed to develop regression equations of within- and whole-breath respiratory impedance (Zrs) of healthy Indian adults. **Methods:** Total 323 adults were sequentially screened. Smokers, individuals with respiratory symptoms or diseases, and unable to perform acceptable FOT were excluded. Within- and whole-breath resistance (Rrs) and reactance (Xrs) were measured at 5, 11, and 19 Hz by Resmon Pro® Full device. The regression equations of within- and whole-breath Rrs and Xrs were generated separately for men and women by multiple linear regression models. **Results:** The FOT data of 253 individuals (122 men) aged 18–81 years were included in the analysis. The magnitudes of whole-breath Rrs at 5 Hz (4.53 ± 1.05 $cmH_2O/L/s$ in women vs. 3.26 ± 1.05 $cmH_2O/L/s$ in men; $P = 0.000$) and whole-breath Xrs at 5 Hz (−1.23 ± 0.66 $cmH_2O/L/s$ in women vs. −1.00 ± 0.54 $cmH_2O/L/s$ in men; $P = 0.003$) of women were significantly of higher magnitude as compared to men. The standing height was the best determinant of Zrs, followed by body weight; the effect of age was negligible and was observed in men only. The magnitudes of both Rrs and Xrs decrease with an increase in standing height of both men and women. **Conclusions:** The present study provides regression equations of within- and whole-breath respiratory impedance of Indian adults.

KEY WORDS: Forced oscillation technique, Indian adults, respiratory impedance, regression equation, within-breath analysis

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INTRODUCTION

Forced oscillation technique (FOT) is a noninvasive tool to measure mechanical properties of the respiratory system, i.e., respiratory impedance (Zrs) by superimposing multiple sinusoidal pressure waves on tidal breaths. Zrs is calculated by analyzing the resulting changes in pressure and flow relationships. Zrs is comprised of respiratory system resistance (Rrs) and respiratory system reactance (Xrs). Technically, Rrs measures frictional forces opposing airflow and Xrs measures both elastic and inertial properties of the respiratory system. Physiologically, Rrs at lower frequency, for example, Rrs at 5 Hz (R5) is considered as a representation of total airway resistance, and Xrs at 5 Hz (X5) mostly relates to the functionality of small airways.[1] The advantages of FOT as compared to other lung function tests are easier to perform, require minimal cooperation of individual and no special breathing maneuvers during measurements.

The utility of FOT in adults is gaining clinical importance and its use is also expanding. The sensitivity of FOT to detect airway obstruction is similar or superior to that of spirometry.[2] Studies have shown the potential utility of

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separate measurement of inspiratory and expiratory Zrs, using an approach known as within-breath analysis.[2,3] Within-breath analysis helps to calculate inspiratory and expiratory Rrs and Xrs separately.

For clinical interpretation, observed Rrs and Xrs values are to be compared with reference values generated from a healthy local population. The predicted values of Rrs and Xrs depend on ethnicity, gender, standing height, body weight, and age of the individual.[4] Most of the presently available regression equations of Zrs are derived from Caucasian and Chinese populations.[4] To the best of our knowledge, the reference value for Zrs in healthy Indian adults had never been explored. The present study aimed to develop regression equations of within- and whole-breath respiratory impedance for healthy Indian adults using the forced oscillation technique.

METHODS

Subjects

A prospective cross-sectional study of lung function measurements by FOT and spirometry was carried out in Bhopal, a city located in central India. The study protocol was approved by the Institutional Ethics Committee of the National Institute for Research in Environmental Health, and written informed consent was obtained from each individual.

Study procedure

The study questionnaire was designed by incorporating Hindi Translation of INSEARCH (Indian study on epidemiology of asthma, respiratory symptoms, and chronic bronchitis) questionnaire to identify individuals with respiratory symptoms or disease.[5] In the questionnaire, individuals were asked about history of whistling sound from their chest during the past 12 months, tightness in the chest or breathlessness in the morning; shortness of breath after finishing exercises or at rest; nocturnal awakening due to cough or breathlessness; coughing or expectoration in the morning; past history of ever asthma or asthma attack; and use of any medication for breathlessness. The information on demographic profile, current and past history of smoking, and other diseases including pulmonary tuberculosis were collected. The exclusion criteria were the presence of bronchial asthma; chronic obstructive pulmonary disease (COPD); chronic bronchitis; having any above-mentioned respiratory symptoms; recent respiratory tract infection (<2 weeks); the history of pulmonary tuberculosis; ever-smoker; the history of cardiovascular disease (except hypertension), and unable to perform acceptable FOT. Ever-smoker was defined as those who had smoked more than 1 cigarette or bidi per day.

The age in completed years, gender, and standing height with erect head and without footwear to the nearest centimeter were recorded. Body weight was measured to the nearest 1.0 kg using an electronic scale wearing light clothing and no footwear. Resmon Pro Full device® (Restech Srl, Milan, Italy) was used for FOT. This FOT device is capable to measure both within- and whole-breath Rrs and Xrs at each frequency. Resmon Pro uses a stringent patented breath-reject algorithm to exclude breath with artifacts and nonphysiological breaths.[6] The inspiratory, expiratory, and whole-breath Rrs and Xrs were measured breath-by-breath at 5 Hz, 11 Hz, and 19 Hz, and the results were presented in $cmH_2O/L/s$ as mean (±standard deviation) of all the accepted breaths. The device calibrated daily before use by a reference impedance supplied by the manufacturer. The test procedure was explained to each participant in simple language. The tests were carried out during the morning and early afternoon. The tests were performed in an upright sitting position with the neck slightly flexed and legs uncrossed as per European Respiratory Society recommendation.[1] Participants were asked to breathe normally through a tightly sealed mouthpiece of an antibacterial filter and wearing a nose clip. During the procedure, cheeks were supported by the participant themselves and reinforced by the technician. The impedance of the antibacterial filter was measured before each test by the device and that impedance was adjusted during reporting results. The participants were first allowed to familiarize themselves with the technique by performing a few sham breaths. A minimum of three tests was performed per individual, and each test was continued until 15 accepted breaths were recorded by the device. A test was retained for subsequent analysis only if more than 50% of the breaths were accepted by the device, and within-test coefficient of variation (×100 standard deviation/mean, expressed in percentage) of whole-breath resistance at 5 Hz (R5) was smaller than 30%.[7] Additional spirometry was carried out in agreed individuals as per ATS-ERS recommendation using PowerCube Diffusion+ (GANSHORN Medizin Electronic, Germany).[8]

Statistical analysis

The statistical analyses were performed by IBM SPSS statistics for Window (Version 25.0, Armonk, NY:IBM crop), and data were summarized as a mean ± standard deviation. The study population was further subdivided into four age groups, i.e., 18–30, 31–45 years, 46–60 years, and more than 60 years. One-way ANOVA was used to find significant differences between age groups. The Student's *t*-test was used to compare the sample means of men and women. For all analyses, a two-tailed $P < 0.05$ was considered statistically significant. The relationships of both Rrs and Xrs with independent anthropometric variables were analyzed by Pearson's correlation coefficients. The regression equations for Rrs and Xrs were carried out using a multivariate linear regression model for men and women separately by including independent anthropometric variables (e.g., standing height, body weight, and age) to obtain the best model based on the highest coefficients of determination. Reference equations were presented with coefficients of determination (R^2) and standard errors of estimate.

RESULTS

Study population

From April 2018 to March 2019, 323 adults of age 18 years and more were screened. Out of them, total 253 adults of age 41.8 ± 13.7 years (range: 18–81 years) were included in the present analysis, and causes of rejections are mentioned in Figure 1. Men accounted for 48% (n = 122) of study population. The standing height, body weights, and body mass index of the study population were 161.2 ± 9.9 cm, 65.5 ± 13.3 kg, and 25.1 ± 3.9 kg/m^2, respectively. Men were taller (168.1 ± 8.2 cm) as compared to women (154.8 ± 6.5 cm, P = 0.00). However, body mass index of men (25.3 ± 3.6 kg/m^2) and women was comparable (24.9 ± 4.1 kg/m^2, P = 0.47).

Forced oscillation technique parameters

The inspiratory, expiratory, and whole-breath (R5) Rrs at 5 Hz of the study population were 3.73 ± 1.17 cmH$_2$O/L/s, 4.09 ± 1.37 cmH$_2$O/L/s, and 3.91 ± 1.22 cmH$_2$O/L/s, respectively. Similarly, inspiratory, expiratory, and whole-breath (X5) Xrs at 5 Hz of the study population were −1.13 ± 0.69 cmH$_2$O/Ls, −1.15 ± 0.63 cmH$_2$O/L/s, and −1.12 ± 0.61 cmH$_2$O/L/s, respectively. Both within-breath and whole-breath Rrs at 5 Hz of women <60 years of old were significantly higher as compared to men [Table 1]. The magnitude of within-breath and whole-breath Xrs at 5 Hz of women <60 years old were significantly more negative as compared to men (P < 0.001). In general, more than 60 years older adults had a higher magnitude of Zrs as compared to the corresponding gender and age <60 years, though the difference was statistically nonsignificant. The difference between inspiratory and expiratory Rrs at 5 Hz (ΔR5) of the study population was −0.36 ± 0.75 cmH$_2$O/L/s, and it was statistically not different between men and women (−0.32 ± 0.65 cm H$_2$O/L/s in men vs. −0.40 ± 0.84 cmH$_2$O/L/s in women; P = 0.39). The difference between inspiratory and expiratory Xrs at 5 Hz (ΔX5) of the study population was −0.02 ± 0.64 cmH$_2$O/L/s, and it was also statistically not different between men and women (−0.07 ± 0.61 cm H$_2$O/L/s in men vs. 0.03 ± 0.67 cmH$_2$O/L/s in women; P = 0.19). The difference of Rrs between 5 Hz and 19 Hz (R_{5-19}), i.e., small airway resistance of the study population was 0.53 ± 0.50 cmH$_2$O/L/s. Women had significantly higher R_{5-19} values as compared to men (0.65 ± 0.53 cmH$_2$O/L/s in women vs. 0.39 ± 0.43 cmH$_2$O/L/s in men; P = 0.000).

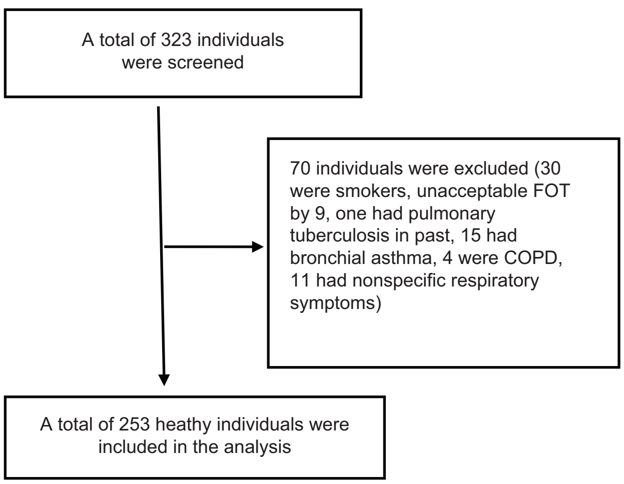

Figure 1: Flowchart of study participant inclusion process

Regression equations of respiratory impedance

The standing height and body weight of the study population showed a significant relationship with R5 and X5. Standing height had a significant negative association with Rrs and a positive association with Xrs. Pearson's correlation coefficient of standing height with Rrs and Xrs was − 0.46 (P = 0.000) and 0.26 (P = 0.000), respectively [Figure 2]. With an increase in body weight, Rrs

Table 1: The comparison of anthropometric parameters and respiratory impedance of study population according to gender in each age group

Variables	18-30 years		31-45 years		46-60 years		>60 years		Total	
	Men (n=30)	Women (n=37)	Men (n=37)	Women (n=45)	Men (n=45)	Women (n=37)	Men (n=10)	Women (n=12)	Men (n=122)	Women (n=131)
Age (years)	24.9±4.0	24.7±3.8	38.9±4.2	38.4±4.5	52.2±4.1	52.7±4.2	67.8±6.2	65.0±5.5	42.7±13.7	40.9±13.7
Height (cm)	170.9±11.1	154.8±5.2#	167.2±6.8	154.9±5.9#	167.5±7.0	154.7±7.0#	166.0±6.1	154.7±10.4#	168.1±8.2	154.8±6.5#
BMI (kg/m^2)	24.0±4.3	22.5±3.9	26.5±2.9	25.2±3.8	24.7±3.3	26.6±3.8*	27.5±1.9	26.4±3.6	25.3±3.6	24.9±4.1
R5 (cmH$_2$O/L/s)										
Inspiratory	2.95±0.89	4.18±0.96#	3.24±0.83	4.38±0.91#	2.94±0.87	4.30±1.29#	3.73±1.34	4.61±1.11	3.09±0.93	4.32±1.05#
Expiratory	3.13±0.86	4.51±1.15#	3.42±0.91	4.82±1.03#	3.35±1.11	4.78±1.32#	4.63±2.55	4.84±1.48	3.42±1.22	4.72±1.19#
Whole-breath	3.04±0.85	4.35±0.99#	3.33±0.84	4.60±0.92#	3.15±0.95	4.56±1.19#	4.21±1.98	4.73±1.25	3.26±1.05	4.53±1.05#
X5 (cmH$_2$O/L/s)										
Inspiratory	−1.03±0.51	−1.29±0.60	−0.92±0.63	−1.21±0.58*	−0.93±0.52	−1.23±0.99	−1.18±0.82	−1.56±0.97	−0.97±0.58	−1.27±0.76#
Expiratory	−0.96±0.35	−1.22±0.53*	−1.02±0.49	−1.31±0.49#	−1.04±0.71	−1.12±0.66	−1.45±1.27	−1.42±0.96	−1.05±0.65	−1.24±0.60*
Whole-breath	−0.99±0.39	−1.25±0.48*	−0.96±0.49	−1.21±0.51*	−0.97±0.54	−1.14±0.84	−1.33±0.97	−1.48±0.94	−1.00±0.54	−1.23±0.66#
R19 (cmH$_2$O/L/s)	2.75±0.72	3.79±0.71#	2.92±0.68	4.04±0.76#	2.74±0.63	3.78±0.89#	3.13±0.81	4.08±0.61#	2.83±0.69	3.89±0.78#
R_{5-19} (cmH$_2$O/L/s)	0.30±0.29	0.62±0.53#	0.44±0.39	0.54±0.39	0.34±0.43	0.76±0.61#	0.77±0.66	0.86±0.69	0.39±0.43	0.65±0.53#
ΔR5 (cmH$_2$O/L/s)	−0.18±0.40	−0.33±0.84	−0.18±0.42	−0.45±0.65*	−0.41±0.66	−0.47±1.05	−0.90±1.33	−0.23±0.78	−0.32±0.65	−0.40±0.84
ΔX5 (cmH$_2$O/L/s)	0.07±0.39	0.06±0.59	−0.10±0.55	0.10±0.68	−0.10±0.69	0.12±0.78	−0.27±0.92	0.14±0.34	−0.07±0.61	0.03±0.67

*P<0.05, #P<0.01. BMI: Body mass index, R5: Respiratory resistance at 5 Hz, X5: Respiratory reactance at 5 Hz, R19: Respiratory resistance at 19 Hz, X19: Respiratory reactance at 19 Hz, R_{5-19}: Difference of resistance between 5 Hz and 19 Hz, ΔR5: Difference between inspiratory and expiratory resistance at 5 Hz, ΔX5: Difference between inspiratory and expiratory reactance at 5 Hz

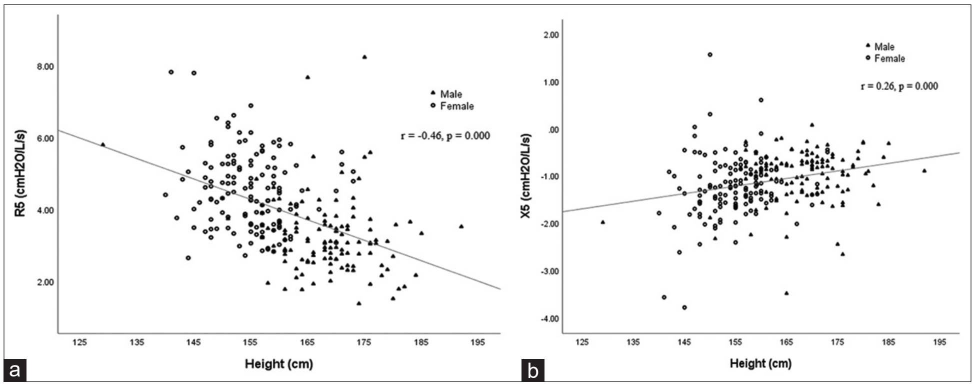

Figure 2: The relationship of standing height with respiratory impedance. (a) Relationship of standing height with whole-breath Rrs at 5 Hz (R5). (b) Relationship of standing height and whole-breath Xrs at 5 Hz (X5)

Table 2: Regression equations of within- and whole-breath respiratory impedance for men and women

Parameters	Equation	$R^{2\dagger}$	SEE
Men			
R5 ($cmH_2O/L/s$)			
Inspiratory	10.498 - (0.056 × ht) + (0.028 × wt)	0.148	0.858
Expiratory	9.931 - (0.060 × ht) +(0.043 × wt) + (0.013 × age)	0.166	1.118
Whole-breath	10.035 - (0.057 × ht) + (0.036 × wt) + (0.008 × age)	0.161	0.961
X5 ($cmH_2O/L/s$)			
Inspiratory	−3.667 + (0.016 × ht)	0.044	0.562
Expiratory	−3.448 + (0.023 × ht) - (0.016 × wt) - (0.007 × age)	0.086	0.620
Whole-breath	−3.334 + (0.018 × ht) - (0.009 × wt) - (0.004 × age)	0.045	0.529
R19 ($cmH_2O/L/s$)	8.077 - (0.040 × ht) + (0.02 × wt)	0.137	0.639
R5-19 ($cmH_2O/L/s$)	2.685 - (0.02 × ht) + (0.012 × wt) + (0.004 × age)	0.122	0.399
Women			
R5 ($cmH_2O/L/s$)			
Inspiratory	9.487 - (0.042 × ht) + (0.022 × wt)	0.058	1.023
Expiratory	9.761 - (0.049 × ht) + (0.042 × wt)	0.126	1.109
Whole-breath	9.697 - (0.046 × ht) + (0.033 × wt)	0.107	0.991
X5 ($cmH_2O/L/s$)			
Inspiratory	−4.545 + (0.019 × ht) + (0.009 × wt) - (0.005 × age)	0.042	0.740
Expiratory	−3.433 + (0.014 × ht)	0.016	0.600
Whole-breath	−4.40 + (0.02 × ht)	0.034	0.646
R19 ($cmH_2O/L/s$)	8.683 - (0.038 × ht) + (0.019 × wt)	0.090	0.745
R_{5-19} ($cmH_2O/L/s$)	2.158 - (0.013 × ht) + (0.009 × wt)	0.022	0.527

†*R*: Adjusted coefficient of determination. SEE: Standard error of the estimate, ht: Standing height (cm), wt: Body weight (kg), age (years)

at both 5 Hz and 19 Hz increases in both men and women. The magnitude of X5 in men increases with an increase in body weight, though X5 of women demonstrated no relationship with body weight. The contribution of aging on predicted Zrs values was negligible and observed in men only. The regression equations of Rrs and Xrs for men and women are presented in Table 2.

The predicted R5 and X5 using the present study regression equations for men and women were compared with predicted equations of Newbury *et al*. and Schulz *et al*. [Figure 3].[9,10] The predicted Zrs were constructed for three different ages (25 years, 45 years, and 60 years) with different standing heights and body weight fixed at 65 kg. The predictive R5 of the Indian population was higher for all age groups, irrespective of gender. The predicted X5 by the present regression equations was also of higher magnitude as compared to the above studies for both the genders and in all ages.

DISCUSSION

In the present study, the regression equations of within- and whole-breath respiratory impedance were derived from never-smoked healthy Indian adults. This study is first in publishing regression equations of respiratory impedance for Indian adults.

As compared to children, fewer studies attempted to develop the regression equations of Zrs for adults, especially within-breath. The within- and whole-breath Rrs and Xrs at 5 Hz of the present study population were very similar to observations by Paredi *et al*.[11] The mean whole-breath R5 and X5 values of Indian adults irrespective of gender were also matched with the values of ECLIPSE study population.[12]

The effect of gender on Zrs of adults had been reported in other ethnicities.[9-13] Australian women had significantly higher values of R5 and lower values of X5 as compared to men.[9] Schulz *et al*. observed significantly higher Rrs and lower Xrs in German women as compared to men in a population of age 45 years and more.[10] Higher Rrs at 4 Hz and lower Xrs at 4 Hz in Brazilian women were also reported by Ribeiro *et al*.[13] In agreement with all these studies, Indian women also had significantly higher magnitudes of R5 and lower magnitudes of X5 as compared to men. It is postulated that smaller lung volumes and smaller airway diameter are responsible for higher Rrs and lower Xrs in women.

The anthropometric parameters of adults influence the regression equations of Zrs, and the relative contribution of each parameter is variable across different ethnicities.[4] Complex regression models of Zrs with anthropometric

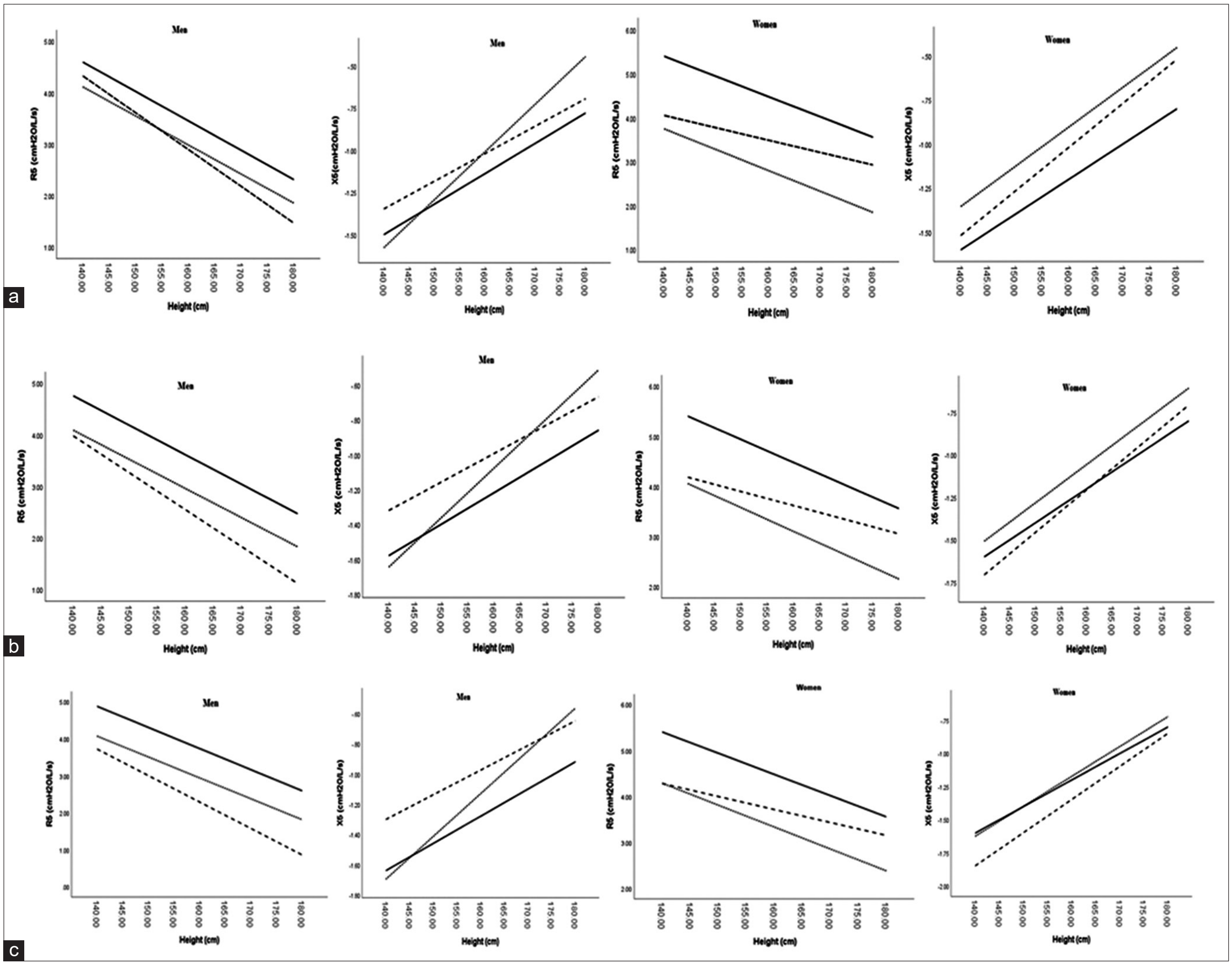

Figure 3: Comparison of whole breath resistance (R5) and reactance (X5) predicted values at 5 Hz for men and women as a function of standing height at different ages and body weight fixed at 65 kg. The values are calculated by the present study equation (continuous line), median values by the equation of Schulz *et al*.[10] (dotted line), and equation by Newbury *et al*.[9] (dashed line). (a) Age 25 years: R5 and X5 for men in upper panel and for women in lower panel; (b) Age 45 years*:* R5 and X5 for men in upper panel and for women in lower panel; (c) Age 60 years: R5 and X5 for men in upper panel and for women in lower panel

parameters were attempted by Schulz *et al*., and they found that liner model was best fitted.[10] Newbury *et al*. found both age and standing height of adults were significant predictors of Zrs. Standing height negatively correlate with Rrs and positively correlate with Xrs, irrespective of genders.[9] Schulz *et al*. observed that both standing height and body weight of individuals were the main predictors of Zrs and body weight had more significant relevance in women than men.[10] However, the effect of age and weight on Rrs and Xrs of their population was variable across genders. Rrs of heathy Caucasians greater dependent on standing height in men and dependent on the body weight of both men and women.[14] In a population of 65 years and older, Guo *et al*. observed that the standing height of an individual was the best predictor of Zrs and the effect of both weight and age was negligible.[15] Therefore, except for standing height, other anthropometric parameters have a considerable variable contribution to regression equations of Zrs across populations. In close agreement with all earlier studies, standing height was the strongest independent predictor of Zrs in Indian adults, followed by body weight. Tramont *et al*. noticed that Xrs decreases with aging due to increased inhomogeneity of ventilation and aging had a negligible effect on Rrs.[16] In the present study, the effect of aging was observed on both Rrs and Xrs values of men only, though the effect was negligible.

Traditionally, the difference between Rrs at lower frequency, for example, R5 and higher frequency, for example, 20 Hz (R_{5-20}) is known as frequency dependence of Rrs, i.e., fall in resistance with increase in oscillating frequency. The presence of a higher magnitude of frequency dependency of Rrs is an indicator of heterogeneous airflow obstruction. Different researchers adopted the difference between different frequencies to demonstrate the frequency dependence of Rrs. Guo *et al*. used the difference of Rrs between 4 and 16 Hz and 4 and 30 Hz.[15] On the other hand, to reduce the effect of harmonic distortion and frequency cross-talk, Resmon Pro employs the difference between Rrs at 5 Hz and 19 Hz (R_{5-19}) to demonstrate frequency dependence of Rrs.[17] In concordance with other studies, the frequency dependence of Rrs was also observed in Indian adults. However, the magnitude of R_{5-19} in Indian adults was less as compared to R_{5-20} values observed by Crim *et al*.[12] Schulz *et al*. observed that R_{5-20} had a significant age dependency in their study population.[10] Whereas, age dependency of R_{5-19} in Indian adults was observed in men only. Both standing heights and body weight of Indian adults are significant predictors of $R_{5-19,}$ irrespective of gender.

The importance of within-breath analysis of respiratory impedance was highlighted by several investigators.[11,18] The difference between inspiratory and expiratory X5 is known as Δ X5. The magnitude of Δ X5 is considered a marker of tidal expiratory flow limitation, i.e., collapsing of airways during the expiration of spontaneous breathing. The Δ X5 values in COPD are higher as compared to both healthy and bronchial asthma patients, and high Δ X5 is considered a hallmark of COPD.[11] The normal value of Δ X5 in the adult population has not studied much. In concordance with observations by Paredi *et al*., ΔX5 of Indian adults was also negligible.

The magnitude of difference between inspiratory and expiratory R5, i.e., ΔR5 in a healthy population has not been much investigated. Paredi *et al*. observed Δ R5 of healthy adults as -0.2 ± 0.1 $cmH_2O/L/s$ and higher Δ R5 in both bronchial asthma and COPD patients.[11] The Δ R5 of the present study population was of little higher magnitude as compared to healthy adults of the above-mentioned study.

Different researchers used different technologies such as impulse oscillometry system (IOS) and FOT to develop regression equations for respiratory impedance. It has been observed that IOS tends to provide bigger values as compared to FOT.[4] Zimmermann *et al.* compared the impedance measured by three commercial FOT devices, and observed measurements of Rrs were similar, but Xrs varies across the devices.[19] Kalchiem-Dekel *et al*. also observed that Zrs values at lower frequencies were independent of measuring device.[4] Therefore, there are possibilities that predictive values generated by different technologies may not be comparable with each other. Both Schulz *et al*. and Newbury *et al*. used IOS in their study. In general, predicted R5 and X5 values by the current study equations are higher magnitudes than those calculated using the equation of Newbury *et al*. and Schultz *et al*.[9,10] The observed difference is either due to ethnicity or due to the use of different technology, i.e., IOS.

The limitation of the present study was that few individuals performed simultaneous spirometry to demonstrate normal spirometry. The numbers of adults more than 60 years were less, and thus, regression equations for more than 60 years must be interpreted cautiously. The signal of 5-11-19 Hz was used in the present study; therefore, two commonly used parameters of FOT, i.e., resonant frequency (Fres) and reactance area (AX) were not measured.

CONCLUSIONS

The regression equations of respiratory impedance for Indian adults were developed for the first time. Indian women had a higher magnitude of both resistance and reactance as compared to men. The standing heights, followed by body weight of Indian adults, are significant determinants of Zrs. The regression equations developed by the present study will be worthwhile for clinical interpretation of FOT results of Indian adults and will encourage the clinicians to use of FOT in their clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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