Reference Values for Lung Volumes in an Iranian Population: Introducing a New Equation Model

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Background: Measurement of lung volumes, especially residual volume and total lung capacity are essential for assessment of restrictive lung disorders. Information regarding normative prediction values for lung volumes as measured by body plethysmography is scarce, and plethysmographic parameters are believed to be poorly reproducible. In this study, we report a comprehensive set of predictive equations for static lung volumes from a general population sample of urban Iranians as measured by body plethysmography.

Methods: Standardized measurements were carried out on 1487 healthy nonsmoking volunteers (845 men and 642 women), aged six to 85 years, living in Isfahan, Iran. Nonlinear multiple regression analysis was used to calculate prediction equations based on subjects' ages and heights for the subdivisions of lung volumes [total lung capacity, functional residual capacity, residual volume, and residual volume/total lung capacity (%)], separately for the two genders. The derived equations were used to calculate prediction values for the subjects. The two sets of predicted and measured values were compared by paired sample t-test.

Results: Prediction equations based on a new nonlinear model, \((\alpha_1 \times \text{age} + \alpha_2 \times \text{age}^2 + \beta \times \text{height} + c)\) which best fitted our data are presented. The measured and predicted values closely resemble and there is no significant difference between the two sets.

Since increments in total lung capacity, functional residual capacity, and residual volume disclose air trapping within the lungs, their upper limits of normal are as important as the lower limits. So, we have presented both for the equations.

Conclusion: Despite the usual beliefs we found rather reproducible prediction equations with high coefficient of determination \((r^2)\) and low standard error of estimate \((\text{SEE})\) in Iranian population.

Keywords: Body plethysmography • Iran • lung volume(s) • prediction equation(s) • reference values

Introduction

Static lung volume (LV) measurements provide valuable information about the overall lung function and performance that can be fundamental in categorizing and staging of pulmonary disorders. Although forced vital capacity (FVC; the amount of air forcefully exhaled after a full inspiration) and static vital capacity (VC) and its components can be readily measured by simple spirometry, residual volume (RV; the volume of air remaining in the lungs after maximal exhalation), by definition, cannot be directly extracted from such a measurement. Measurement of RV allows functional residual capacity (FRC; the amount of air in the lungs at the end-tidal position) and total lung capacity (TLC; the amount of air in the chest after a maximum inspiration) to be derived when combined with the appropriate subdivisions of VC. Unfortunately, these more complex parameters which have greater physiologic and clinical implications than simpler variables are not simply accessible. Therefore, while simple spirometry will continue to be the first choice of pulmonary function study, in order
to compensate for its failure in determining RV and TLC, body plethysmography is used as a complementary method. TLC and its subdivisions are usually measured by body plethysmography and/or gas dilution or nitrogen washout.2

Reference values for pulmonary function tests are rather complex and variable: there are several potential sources of variability, some of which are related to individual characteristics such as sex, age, body size, ethnicity, level of regular physical activity, circadian rhythms, and the others are attributed to environmental factors including socio-economical status, exposures, altitude, smoking history, and technical issues such as posture, instrumentation, and the technique.4–7 Although it seems that much of this variability can be explained by the high degree of multi-collinearity among the mentioned factors, it should be noted that up to 20% of the total variability among populations cannot be explained at all.4,7 In an attempt to reduce this variability and improve accuracy, the use of reference values from a geographically-related population has been strongly recommended.8 Ideally, the population used for developing prediction equations should be asymptomatic general population.4 Unfortunately, to the best of our knowledge, there is no such source of reference values for static LVs obtained from a sample of the general population in Iran. Furthermore, it is usually stressed that values measured by body plethysmography are not exactly reproducible which could reflect technical difficulties with the method.9

The purpose of this communication is to report a comprehensive set of predictive equations for static LVs from a general population sample of urban Iranians as measured by body plethysmography.

**Materials and Methods**

The Institutional Review Board for Medical Ethics at Isfahan Medical School approved the research protocol. During a 16-month period from January 2004 through April 2005, every 20th patient attending a general medical clinic in Isfahan, Iran was invited to bring her/his nonsmoker family members (parents, spouse, and children) for medical evaluation including a meticulous medical history, physical examination made by a general practitioner, and spirometry supplemented by body plethysmography. The exclusion criteria were: respiratory complaints (e.g., chronic or recurrent cough, dyspnea, sputum production, wheezy breathing, etc.), smoking one hundred cigarettes or more during lifetime, any history of hospitalization for pulmonary illness, physical findings suggesting cardiopulmonary disease, and any chest or skeletal deformity. Subjects were included in the study if they did not meet any of the exclusion criteria. Subject’s heights were measured, with bare feet, standing against a wall (buttocks, back, and head against the wall) with their heads erect in the Frankfort horizontal plane. A carpenter's square was placed against the wall and the subject’s head, and the subject was asked to step away from the wall, and the height was measured to the nearest centimeter from the floor to the bottom of the square with a metal ruler attached to the wall (Figure 1).

![Figure 1](image.png)

*Figure 1. Height changes in correlation with age of the subjects in two sexes.*
Age was asked (Figure 2), and in most cases, insurance cards, or identity documents were checked to confirm the accuracy of the stated age. Weight was measured with empty pockets and no shoes on.

Barometric pressures, measured daily by Isfahan Airport, showed a range of 632 to 635 mmHg. Room temperature was monitored using a Brooklyn National Institute of Standards and Technology (NIST) Centigrade thermometer and kept between 21 and 25°C. Spirometry and body plethysmography results were automatically corrected for body temperature pressure saturation (BTPS) conditions by the device software. LVs and subdivision indices were measured, using a body plethysmography machine (ZAN500 Body Box) according to the published standards and criteria.7 The device was calibrated daily by its internal syringe. Spirograms were repeated until three acceptable tests were obtained. Studies were considered acceptable if the largest and second largest values for FVC and FEV1 were within 200 mL of each other. If the first maneuvers were not satisfactory, further maneuvers were used until the reproducibility criteria were satisfied or a maximum of eight maneuvers was reached. After obtaining spirometric measurements, the subject was allowed to rest for five minutes before proceeding to the measurement of lung subdivisions. Briefly, the subject was taught the panting technique while breathing through the mouthpiece of the body plethysmograph. The door was then closed and the measurements, including RV, FRC, and TLC, were made. The results were corrected for BTPS automatically by the Body Box software. All of the measurements were made by a single trained technician. The output report of each subject was scrutinized qualitatively by a pulmonologist (BA) before inclusion for statistical analysis.

**Data analysis**

Data were analyzed using the SPSS for Windows version 13 (SPSS Inc., Chicago, IL). Multiple regression analysis was applied to each of the LV indices and for each sex, separately. The relationship between LVs and anthropometric variables was examined first. Various regression models including quadratic and power functions, log-transformed, and linear relationships were compared.

The usefulness of various predictors of LVs was then compared. Age and standing height were considered as the best potential predictor variables. The dependent LV variables were first regressed individually against the independent variables. Stepwise multiple regression analyses were then used to determine which combination of parameters would fit the model best. Predictor variables were retained in the regression model only if their addition significantly improved the explained variance of the dependent variable. Wherever possible the most parsimonious model was chosen.

Using the derived equations, predicted parameter estimates were calculated for all subjects. Predictions from the new formula were compared with our measured values and also compared with predicted values extracted from previously published prediction equations7 the values predicted by Quanjer et al (Figure 3).3 Paired sample t-test was used to compare measured values versus predicted ones. To adjust for multiple comparisons, the level of statistical significance was set at 0.01.

**Results**

Of the originally invited 1,953 individuals, 1,728 accepted to take part in the study (response rate=88.47%). The main reasons for refusal were: lack of time, negative attitude towards being a medical “research subject”, or being far from the clinic. Of the remaining, 198 were excluded by research criteria, and 146 could not provide satisfactory panting maneuvers. The remaining 1,386 body plethysmography recordings were analyzed to derive prediction equations.

Anthropometric characteristics for both sexes...
are presented in Table 1; height values ranged from 98 to 190 cm (169.54±11.80) in males, and from 104 to 179 cm (157.02±4.92) in females.

In multiple regression approach, age and height were best fitted in all final models.

A nonlinear quadratic model was best fit for all parameters with a general form of:

\[ \alpha_1 \times \text{age} + \alpha_2 \times \text{age}^n + \beta \times \text{height} + c \]

The derived equations for various lung function parameters are presented in Table 2. Ninety Five percent confidence intervals have been used to determine lower limits (LLN) and upper limits of normal (ULN).

As Table 3 shows our predicted values were significantly higher than published predictions.

**Discussion**

In many instances, the use of a widely recommended set of predictive equations for pulmonary function tests induces error. These results demonstrate the necessity of considering, as in most the biologic variables, reference values for LVs which are obtained from a racial, ethnic, and geographically-related population. Also, reference values for pulmonary function tests should derive from studies employing standardized procedures and equipment.

Reported predicted values for static LVs generated with body plethysmography, using either volume-constant or volume-displacement plethysmography, vary markedly. Unfortunately, comparisons among studies are hindered because of some of the following factors: a) Equations for all the subdivisions of static LVs measured in the same group of reference subjects are not provided; b) Subjects with different smoking categories are not analyzed separately; c) The size of the reference population is small; d) A bias in the selection of the sample is present; e) Either the regression model is complex or age is not considered as a covariate. The present study provides a comprehensive description of the static LV values for a healthy, randomly selected sample of the Iranian population.

Age has been consistently related to higher FRC and RV, independent of smoking. The aging process is associated with loss of lung elastance and increase in occlusion volume, both contributing to increased RV, FRC, and RV/TLC ratio. Since age-related changes in LVs are rather complex with an early increment, followed by a trivial flattening, and later decreasing slope of the curve, we used a new regression equation. We assumed that adding an extra age term helps to improve the prediction accuracy. From this one expects that the sign of \( \alpha_1 \) might be positive, whereas \( \alpha_2 \) will be negative, which means that, as the age increases, age contributes progressively less to the predicted value. But despite the fact that the derived equations work perfectly to predict the LV parameters, the signs for \( \alpha_1, \alpha_2, \) and \( n \) were not always the same as we had assumed. Actually
various combinations of parameter signs reflect more complex correlation between the various independent variables with lung parameters.

In opposition to many previous studies,\textsuperscript{3,6,7,11–14} we obtained a rather high coefficient of determination ($r^2$) and low standard error of estimate (SEE) in the LV prediction; however, still a substantial percentage of the LV variance could not be explained by the analyzed variables. These results are not consistent with the traditional notion that “LVs are far less reproducible than spirometric variables”, underlining the need for accurate and representative reference values. Additionally, the use of an adequate lower limit of normality is crucial.

Since increments in some parameters including RV and TLC are usually interpreted as findings in favor of air trapping,\textsuperscript{15} having ULN at hand, might be more important than their lower limits; in this study we are presenting the ULN to cope with this necessity. As much as we could find, this is the first time that ULN is introduced to the literature.

In summary, we have presented what we believe to be the first set of equations for

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|l|}
\hline
\textbf{Parameters} & \textbf{Model summaries for males} & \textbf{SEE for A1} & \textbf{SEE for B} & \textbf{$r^2$} \\
\hline
TLC & $41.228 \times a - 40.872 \times a \times 1.00 + 0.34 \times h - 2.547$ & 0.01 & 0.002 & 0.825 \\
LLN & $41.228 \times a - 40.872 \times a \times 1.00 + 0.030 \times h - 2.547$ & & & \\
ULN & $41.228 \times a - 40.872 \times a \times 1.00 + 0.037 \times h - 2.547$ & & & \\
FRC & $19.494 \times a - 19.258 \times a \times 1.00 + 0.0202 \times h - 2.08$ & 0.002 & 0.001 & 0.863 \\
LLN & $19.494 \times a - 19.258 \times a \times 1.00 + 0.020 \times h - 2.08$ & & & \\
ULN & $19.494 \times a - 19.258 \times a \times 1.00 + 0.024 \times h - 2.08$ & & & \\
RV & $95.09 \times age - 95.05 \times age \times 1.00 + 0.011 \times h - 0.521$ & 0.000 & 0.001 & 0.699 \\
LLN & $95.09 \times age - 95.05 \times age \times 1.00 + 0.010 \times h - 0.521$ & & & \\
ULN & $95.09 \times age - 95.05 \times age \times 1.00 + 0.012 \times h - 0.521$ & & & \\
FRC/TLC & $16.04 \times a - 16.04 \times a \times 1.00 + 0.001 \times h + 0.415$ & 0.001 & 0.000 & 0.203 \\
LLN & $16.04 \times a - 16.05 \times a \times 1.00 + 0.001 \times h + 0.415$ & & & \\
ULN & $16.04 \times a - 16.03 \times a \times 1.00 + 0.001 \times h + 0.415$ & & & \\
RV/TLC ratio & $11.503 \times a - 11.512 \times a \times 1.00 + 0.000 \times h + 0.335$ & 0.000 & 0.000 & 0.240 \\
LLN & $11.503 \times a - 11.512 \times a \times 1.00 - 5.44 \times 10^{-7} \times h + 0.335$ & & & \\
ULN & $11.503 \times a - 11.512 \times a \times 1.00 + 0.000 \times h + 0.335$ & & & \\

\textbf{Model summaries for females} & \textbf{$r^2$} \\
\hline
TLC & $-12.416 \times a - 12.07 \times a \times 1.006 + 0.049 \times h - 5.388$ & 0.005 & 0.002 & 0.929 \\
LLN & $-12.416 \times a - 12.07 \times a \times 1.006 + 0.047 \times h - 5.388$ & & & \\
ULN & $-12.416 \times a - 12.07 \times a \times 1.006 + 0.052 \times h - 5.388$ & & & \\
FRC & $4.265 \times a - 3.916 \times a \times 1.00 + 0.016 \times h - 2.567$ & 0.002 & 0.002 & 0.768 \\
LLN & $4.265 \times a - 3.916 \times a \times 1.00 + 0.013 \times h - 2.567$ & & & \\
ULN & $4.265 \times a - 3.916 \times a \times 1.00 + 0.020 \times h - 2.567$ & & & \\
RV & $-12.64 \times a - 12.821 \times a \times 0.997 + 0.005 \times h - 0.77$ & 0.009 & 0.001 & 0.520 \\
LLN & $-12.64 \times a - 12.821 \times a \times 0.997 + 0.003 \times h - 0.77$ & & & \\
ULN & $-12.64 \times a - 12.821 \times a \times 0.997 + 0.007 \times h - 0.77$ & & & \\
FRC/TLC ratio & $2.387 \times a - 2.35 \times a \times 1.003 - 0.002 \times h + 0.651$ & 0.019 & 0.000 & 0.615 \\
LLN & $2.387 \times a - 2.35 \times a \times 1.003 - 0.003 \times h + 0.651$ & & & \\
ULN & $2.387 \times a - 2.35 \times a \times 1.003 - 0.002 \times h + 0.651$ & & & \\
RV/TLC ratio & $-41.08 \times a - 41.10 \times a \times 1.00 - 0.002 \times h + 0.485$ & 0.002 & 0.000 & 0.210 \\
LLN & $-41.08 \times a - 41.10 \times a \times 1.00 - 0.002 \times h + 0.485$ & & & \\
ULN & $-41.08 \times a - 41.10 \times a \times 1.00 - 0.002 \times h + 0.485$ & & & \\

\textsuperscript{a}=age in years; h=height in centimeters; \textsuperscript{**}=to the power of; \textsuperscript{SEE}=standard error of estimate.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|l|l|l|l|}
\hline
\textbf{Parameters} & \textbf{Measured values (A)} & \textbf{Predicted by new equations (B)} & \textbf{Predicted by Stock's published equations (C)} & \textbf{$P$ value*} (B vs. A) & \textbf{$P$ value*} (B vs. D) \\
\hline
Males & & & & & & & & \\
TLC (L) & 7.62±1.36\textsuperscript{**} & 7.64±1.18 & 7.64±1.18 & 0.93 & 6.15±1.10 & 0.000 \\
FRC (L) & 4.10±0.63 & 5.45±1.13 & 5.45±1.13 & 0.81 & 3.05±0.53 & 0.000 \\
RV (L) & 2.09±0.33 & 2.09±0.30 & 2.09±0.30 & 0.94 & 1.64±0.44 & 0.000 \\
\hline
Females & & & & & & & & \\
TLC (L) & 5.08±0.75 & 5.11±0.57 & 5.11±0.57 & 0.06 & 4.44±0.61 & 0.000 \\
FRC (L) & 2.95±0.58 & 2.94±0.39 & 2.94±0.39 & 0.15 & 2.36±0.37 & 0.000 \\
RV (L) & 1.42±0.32 & 1.41±0.21 & 1.41±0.21 & 0.26 & 2.83±1.56 & 0.000 \\
\hline
\end{tabular}
\caption{Group comparisons.}
\end{table}

\textsuperscript{*}Paired sample \textit{t}-test, \textsuperscript{**}mean±SD.

References

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prediction of static LVs in a random sample of an ethnically heterogeneous population from Iran and the Middle-East. Assuming that these values are at significant and nonparallel variance with a widely recommended set of equations from a North-American-European consensus, the use of equations obtained from foreign subjects with an "adjusting factor" is not advisable. Our results should ideally be applied to clinical and research contexts to evaluate the normalcy of static LV values in subjects aged three to 80 years with heights ranging 155 to 185 cm in males and 145 to 175 cm in females. The accuracy and validity of these equations, however, should be further confirmed in other samples of the Asian population with different ethnic and geographic backgrounds.

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