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Reference values for lung function tests. I. Static volumes

J.A. Neder[1], S. Andreoni[2], A. Castelo-Filho[3] and L.E. Nery[4]

[1]Department of Physiology, St. George's Hospital Medical School, University of London, London, UK
[2]Departamento de Medicina Preventiva e Social,
[3]Grupo Multidisciplinar de Epidemiologia Clínica, and
[4]Disciplina de Pneumologia, Departamento de Medicina, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo SP, Brasil

Abstract

Static lung volume (LV) measurements have a number of clinical and research applications; however, no previous studies have provided reference values for such tests using a healthy sample of the adult Brazilian population. With this as our main purpose, we prospectively evaluated 100 non-smoking subjects (50 males and 50 females), 20 to 80 years old, randomly selected from more than 8,000 individuals. Gender-specific linear prediction equations were developed by multiple regression analysis with total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), RV/TLC ratio and inspiratory capacity (IC) as dependent variables, and with age, height, weight, lean body mass and indexes of physical fitness as independent ones. Simpler demographic and anthropometric variables were as useful as more complex measurements in predicting LV values, independent of gender and age (R^2 values ranging from 0.49 to 0.78, $P<0.001$). Interestingly, prediction equations from North American and European studies overestimated the LV at low volumes and underestimated them at high volumes ($P<0.05$). Our results, therefore, provide a more appropriate frame of reference to evaluate the normalcy of static lung volume values in Brazilian males and females aged 20 to 80 years.

Correspondence
L.E. Nery
Disciplina de Pneumologia
EPM, UNIFESP
Rua Botucatu, 740, 3º andar
04023-062 São Paulo, SP
Brasil
Fax: +55-11-570-2127
E-mail: lenery@pneumo.epm.br

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Introduction

Lung volume (LV) measurements provide useful information about the overall lung function that can be fundamental in categorizing and staging pulmonary diseases (1). Although vital capacity (VC; the amount of air expired or inspired between maximum inspiration and expiration) and its subdivisions can be readily measured with simple spirometry, residual volume (RV; the volume of air remaining in the lungs after maximal expiration), by definition, cannot. 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 by combination with the appropriate subdivisions of VC. Unfortunately, these more complex measurements could have greater physiological and clinical implications than

simpler variables (1-3). For example, although spirometric variables can separate "obstructive" from "restrictive" disturbances, in several circumstances, direct determination of LV is necessary: a generalized restrictive process causes LV to be reduced approximately equally, while obstruction may increase RV with little change in TLC (air trapping) or, alternatively, a higher RV/TLC ratio is associated with an increased TLC (hyperinflation). Moreover, dynamic changes in some components of LV, chiefly the FRC and the end-expiratory lung volume (EELV), either during rest or exercise, have been related to critical mechanical disturbances which affect ventilatory and gas exchange pulmonary properties (1-3).

Reference values for pulmonary function tests are rather complex: there are several potential sources of variability ranging from individual characteristics (gender, age, body size, race, level of regular physical activity, circadian rhythms) to environmental (socioeconomical status, exposures, altitude, smoking history) and technical aspects (posture, instrumentation, technique) (4-7). Although it seems that much of this variability can be explained by the high degree of multi-colinearity among those factors, it is noteworthy 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. Ideally, this should be non-referred (general population) and obtained by some randomization procedure (4). Unfortunately, to the best of our knowledge, there is no such source of reference values for static lung volumes obtained from a sample of the general population in Brazil.

Therefore, the major purpose of this prospective study was to establish, from a randomized sample of urban, adult Brazilians, a comprehensive set of predictive equations for static lung volumes. In addition to the usual demographic and anthropometric measurements which have been associated with LV in humans, this study also evaluated the independent role of some indexes of physical fitness (i.e., level of regular physical activity, maximum aerobic power and peripheral muscular strength) in predicting these variables.

Material and Methods

Study design and experimental subjects

A random sample of non-medical and non-student personnel from the Federal University of São Paulo, São Paulo, Brazil (EPM-UNIFESP) was studied in a controlled, prospective design. This exclusion criterion was set to avoid selection bias of a population with social, anthropometric and nutritional profiles which are different from those of the general population. Part of the older group (61 to 80 years) was obtained from a healthy sedentary general population being followed by the Geriatric Service of EPM-UNIFESP. No voluntary participation was accepted. The study was conducted over an 18-month period.

The subjects were chosen in a random fashion by electronic selection from a total population of 8,226 subjects, who had previously been stratified by gender into six age groups (20-29, 30-39, 40-49, 50-59, 60-69, and 70-80 years); i.e., a total of 12 strata. A total of 100 individuals aged between 20 and 80 years were evaluated. The sample size (N) was estimated according to the relationship between the number of variables (v) entered into the multiple regression analysis (see Data analysis) and the minimum number of observations required: N was higher than both v^2 and 10v (8). Fifty subjects were evaluated in each gender group and the distribution among age groups was as follows: 20-29 years: 9 males (M) and 9 females (F); 30-39 years: 7M/8F; 40-49 years: 7M/7F; 50-59 years: 8M/8F; 60-69 years: 9M/9F

and 70-80 years: 10M/9F.

Subjects who had abnormal EKG tracings, recent febrile illness, medical history or physical findings of cardiac, respiratory or neuromuscular diseases were excluded from the study. No subject had a present or past history of smoking or significant occupational exposure to ambient hazards. Underweight subjects (body mass index (BMI) below 18.5), grade III overweight (BMI >40) (9) or subjects with height values above or below the 95% confidence limits of those predicted for the adult Brazilian population (10) were also excluded. The racial profile of the studied population was heterogeneous: 66 subjects were considered as "white" non-Caucasians (29 males and 37 females), 13 individuals as "browns" (11 males and 2 females), 10 subjects as "blacks" (4 males and 6 females), 5 subjects as "white" Caucasians (3 males and 2 females) and 6 subjects as "yellows" (3 for each sex). There were similar findings with regard to the predominant self-reported ethnic family origin: 40 were Latin, 16 African, 12 North European, 14 South American Indian, 7 Slavic, 4 Japanese, 3 Jewish, 2 Arabic and 2 Chinese: these findings are consistent with the multiracial profile of the urban Southeast Brazilian population. Regarding the place of birth, 48 subjects reported the Southeast region, 26 the Northeast, 13 the South, 8 the North and 5 the Central-West.

Protocol

The subjects were submitted to the protocol in the morning of the same day, and at least 3 h after the last meal and 12 h after significant exertion, following this sequence: a) complete clinical, hematological and cardiorespiratory evaluation at rest; b) evaluation of the regular physical activity pattern by questionnaire (11); c) determination of maximal inspiratory and expiratory pressures and maximal voluntary ventilation (see Ref. 12); d) spirometry and static LV measurements; e) determination of the lung diffusion capacity for carbon monoxide (see Ref. 13); f) cardiopulmonary exercise tests on a cycle ergometer (a square-wave protocol at 25 W for subject familiarization and, after one hour, a maximal ramp-incremental exercise test). On a separate day, g) total and regional body composition were evaluated by dual energy X-ray absorptiometry (DEXA) (14), and h) knee strength measured by isokinetic dynamometry (15).

Before the tests, the procedures, including the known risks, were described in detail and written, informed consent (as approved by the Institutional Medical Ethics Committee) was obtained from all subjects. Subjects were not remunerated.

Clinical evaluation

A comprehensive medical history including previous health information, smoking history, respiratory and sleep-related symptoms was obtained. A complete physical examination was performed by the same physician. Resting 12-lead EKG, complete blood count and blood chemistry were also performed.

Regular physical activity pattern

Information regarding occupation, sports activities and leisure habits were detailed and quantified by the modified Baecke et al. (11) questionnaire for epidemiological studies. Subjects rated their habitual physical activity during the previous two weeks using a scale of one to five (five representing the most active) with eight questions about occupation, four about sport activities and four about habitual leisure habits. Results are reported as sum of scores. On the basis of the questionnaire, 88 subjects were considered to be sedentary with a total score below 8 (of these, 67 subjects had scores between 6 and 8, and 21 had scores below 6). The remaining 12 subjects had scores above 8, being

considered physically more active but still nontrained subjects.

Anthropometry and body composition

Total body mass (kg) was measured using a calibrated balance, and body height was determined to the nearest 0.5 cm using a stadiometer. Both measurements were performed following standard techniques, with the subjects in light clothes and without shoes. For the elderly subjects (above 60 years) an accurate calculation of height was made from the knee-ankle distance using a broad blade caliper.

In a subgroup of individuals (N = 75) representative of the entire population with regard to sex and age, total and regional fat and lean and bone masses were measured using DEXA. In this method, the subjects are scanned with photons produced by an X-ray source at two different energy levels. Bone ash (calcium hydroxyapatite) tissue and soft tissue are separated based on the degree of photon attenuation. The differential absorption within soft tissues is also measured and the ratio of absorbance of the two energy level photons (R_{ST}) has been shown to be linearly related to the percent of fat in these tissues (14). Appendicular skeletal muscle mass is then measured as the total limb mass minus the sum of limb fat and bone mass.

Peripheral muscular strength

Concentric isokinetic knee extensor strength on the dominant side, expressed as peak torque in Newton-meters (the highest torque value seen from all points in the range of motion), was recorded at a speed of 60°/s using the isokinetic dynamometer Cybex 6000 (Lumex Inc., Ronkonkoma, NY, USA). The dominant side was self-reported and confirmed by observing writing skills: in 90 subjects (47 men and 43 women) it was the right side. After stretching, warm-up exercise was done on a cycle ergometer (25 watts, at 60-70 rpm for 10 min). All subjects performed a preliminary test in order to familiarise themselves with the equipment and testing procedure. Positioning and stabilisation of the subjects were standardised. The mechanical axis of rotation of the level arm was aligned to the axis of rotation of the joint being tested. The resistance pad at the end of the level arm was strapped to the most distal part of the tibia. Correction for the effect of gravity was made. The subjects were told to perform "as fast as possible" in both directions and this was verbally reinforced using "high-demand" instructions during the tests (15).

Cardiopulmonary exercise testing

The exercise tests were carried out on a calibrated, electromagnetically braked, cycle ergometer (CPE 2000, Medical Graphics Corp., St. Paul, MN, USA) with gas exchange and ventilatory variables being analyzed breath-by-breath using a digital computer-based exercise system (MGC-CPX System, Medical Graphics Corp.).

The exercise test consisted of: a) 2 min at rest; b) 3 min with real "zero" workload (obtained through an electrical system which moves the ergometer flywheel at 60 rpm); c) during the incremental phase; d) a 4-min recovery period. The power (W) was continuously increased in a linear "ramp" pattern (10 to 25 W/min for females and 15 to 30 W/min for males) so that the duration of the incremental exercise was more than 8 and less than 12 min (16). The subjects were actively encouraged throughout the test to maintain a pedaling rate as constant as possible between 50 and 70 rpm by observing a pedal rate meter. They pedaled to the limit of tolerance with active encouragement from the investigators. The following criteria were used to establish maximum effort: maximum heart rate above 90% of age-predicted (220-age), maximum R above 1.20 or a plateauing

of oxygen uptake ($\dot{V}O_2$) (17). The data were calculated automatically using standard formulae (18) and displayed in descriptive numerical (average of 15 s) and graphical (eight breaths moving average) forms. The average $\dot{V}O_2$ for the last 15 s was considered to be representative of the subject's peak $\dot{V}O_2$.

Spirometry

Spirometric tests were performed using the CPF-System (Medical Graphics Corp.) with flow measurement carried out with a calibrated pneumotachograph (Fleisch No. 3). The subjects completed at least three acceptable maximal forced and "slow" expiratory maneuvers. Technical procedures, acceptability and reproducibility criteria were those recommended by the American Thoracic Society and by the Brazilian Respiratory Society (4,19). The following spirometric variables were recorded and expressed as body temperature, ambient pressure, saturated with water vapor (BTPS) conditions: forced and slow vital capacity (l); forced expiratory volume in 1 s (l) and forced expiratory flow between 25 and 75% of forced vital capacity (l/s). Inspiratory capacity (IC), inspiratory and expiratory reserve volume (IRV and ERV, respectively) values were obtained from the slow vital capacity maneuvers as the largest values of at least three acceptable attempts (4).

Static lung volumes

Functional residual capacity (FRC) was determined by the "breath-by-breath" open-circuit nitrogen wash-out technique, using the PF-DX System (Medical Graphics Corp.) connected to a dedicated microcomputer. Personnel, technique, procedures and calibration were standardized (7,20-22). The reported values are the mean of at least three acceptable determinations which agreed within 10% of the largest value. A minimum of 10 min was allowed to elapse between determinations since this period is considered adequate to restore the normal lung N_2 concentration (20). All tests were performed in the same laboratory at a barometric pressure of 685-699 mmHg, temperature between 22-28°C and altitude of 680 m above sea level (São Paulo, Southeast Brazil).

Central to the underlying theory of the test is the assumption that the lungs are in equilibrium with atmospheric molecular nitrogen (fractional alveolar concentration of nitrogen or F_AN_2 = 0.7093). The subjects start to breath pure O_2 (F_IO_2 = 1) at the FRC in the seated, upright position with a noseclip in position: a continuous display of the tidal volume allows the O_2 switch-on to be synchronized with the EELV. As O_2 replaces N_2 in the alveolar gas, N_2 is washed out gradually until its concentration reaches a nadir (below 1%), usually before 7 min. Using a pneumotachometer to measure flow and an ultra-rapid N_2 analyzer (chromatography), the volume of N_2 washed out can be calculated on a breath-by-breath basis, by integrating flow and N_2 concentration to determine the area under the curve. Therefore, a breath-by-breath plot of log%N_2 x volume of breath is displayed by real-time following. The FRC is then calculated as:

$$V_EN_{2TOTAL} - N_{2TISS}/F_AN_{2INITIAL} \quad \text{(ATPS)}$$

where V_EN_{2TOTAL} is the total expiratory volume of N_2, N_{2TISS} the N_2 removed from blood and tissue reservoirs (0.04 x time of the test), $F_AN_{2INITIAL}$ the initial alveolar fraction of N_2, and ATPS the ambient temperature and pressure, saturated with water vapor.

The following equation is then applied to obtain the FRC under BTPS conditions:

$$FRC\ (BTPS) = FRC\ (ATPS) \times (Pb - PH_2O/Pb - 47) \times (310/273 + T)$$

where Pb is the barometric pressure; PH_2O, the vapor pressure of water at 37°C; 310, the absolute body temperature (°K), and T the actual temperature in degrees Celsius. Addi-

tional corrections were made electronically to account for the changes in gas viscosity as O_2 replaced N_2 in the expired gas and for any non-simultaneity between the O_2 switch-on and the correct EELV (23). Finally, RV is calculated as FRC - ERV, and TLC as FRC + IC.

Data analysis

All data obtained were entered into a personal computer for statistical analysis, using the Statistical Package for the Social Sciences™ - SPSS (24). A descriptive and investigative analysis was first performed to evaluate the distribution of the variables as well as the relationship between them (bivariate regression and Pearson product moment correlational analysis). Means and standard deviations (SD) were obtained for values referring to subjects grouped according to sex and age. Analysis of variance (ANOVA) was used to determine differences among groups. If a significant F-ratio was obtained, then the *post-hoc* comparisons were completed using Neuman-Keuls tests. The sex-grouped descriptive data were compared using the Student *t*-test. The probability of a type I error was established at 0.05 for all tests.

Backward multiple linear regression was done by the technique of least squares minimization with inclusion of lung volume and capacities as dependent variables, and demographic and anthropometric data, and indexes of physical fitness as independent variables. The removal procedure was carried out based on the maximum probability of a P-to-remove value of 0.05. For all data the coefficient of determination (R^2) is reported with the residual standard error (RSE; e.g., the square root of the residual sum of squares/N-2), the equation of the regression line and the partial coefficients (*B*) with their standard errors (SE). After the determination of regression equations, an investigation of possible violations of the normal model was performed with analysis of the studentized residuals (SRED). Linearity and homogeneity of variance were investigated by plotting the SRED against the fitted values and each independent variable, as well as regressing the observed cumulative probability of the SRED values against its expected cumulative probability. Normality was also assessed by verification of the frequency distribution for the residuals of each equation for skewness and kurtosis. Violation of the normal assumptions was also evaluated by examining the partial regression plots for the *i*th independent variable calculating the SRED for y when it was predicted from all minus *i*th variables and by calculating the SRED for *i*th when it was predicted from the other independent variables. The presence of possible influential points was analyzed by comparing the SRED when a suspected case was or was not included in the equation. Finally, multi-colinearity among independent variables was investigated by examining i) the level of tolerance of each variable and the related inflation factor and ii) the eigenvalues of the scaled, uncentered cross-products matrix.

Since the intrinsic dependence of the residuals in a regression equation and the trend to it induces an optimistic estimate of both R^2 and residual standard error (RSE) values, we used the predicted residual sum of squares method (PRESS) because it produces residuals that are independent and, therefore, suitable for cross-validation (25). In this method, a residual is calculated for each subject by developing an equation with the data of all the other individuals and predicting a value for the missed subject; subsequently, the measured value of that subject is subtracted from the predicted value of the equation. Since the R^2 and RSE values after the PRESS method are similar to the previous ones, this suggests that the equations could be used for other similar samples without a significant loss in accuracy (25).

Results

Anthropometric characteristics for both sexes are presented in Table 1; women were shorter and fatter than men for all age decades ($P<0.01$). There was a progressive trend to gain body mass as fat until the 50's for both sexes; after that, a stabilization of % fat was observed (Table 1). BMI and actual body mass values for men ranged from 19.0 to 40 kg/m^2 ($\bar{X} \pm SD = 25.3 \pm 3.9$) and from 51.5 to 105 kg (73.8 ± 10.7), respectively. In the female group, BMI ranged from 19.7 to 40.0 kg/m^2 (24.7 ± 4.0) and actual weight varied from 44.5 to 100.5 kg (62.5 ± 10.8). An even distribution of height was also found in both sexes: in males the values ranged from 155.5 to 185.0 cm (168.4 ± 6.2), and in females from 145.2 to 175.0 cm (157.1 ± 7.1). The main spirometric variables showed a similar pattern, i.e., lower values were found in elderly and female subjects (Table 2). However, all subjects presented spirometric values well above the lower 95% confidence interval of those predicted by adult Brazilians (26).

As expected by the differences in body dimensions, males presented higher TLC values than females in all age groups with the exception of the 50-59 year group where

Table 1 - Anthropometric characteristics for male and female individuals by age group.

BMI = Body mass index. Data are reported as means ± SD. *Measured by dual X-ray absorptiometry (DEXA) (14). +Significant effect among age groups within sex ($P<0.01$); 20-29 age group *vs* 50-59 to 70-80 groups. #Significant effect between sex groups ($P<0.01$); males *vs* females by age-group.

Age (years)	Males (N = 50)				Females (N = 50)			
	Height (cm)	Weight (kg)	BMI (kg/m^2)	% Fat*	Height (cm)	Weight (kg)	BMI (kg/m^2)	% Fat*
20-29	170.0 ± 2.9#	68.9 ± 7.7#	24.1 ± 3.4	19.2 ± 3.3+#	157.7 ± 6.9	61.1 ± 7.8	24.4 ± 4.8	29.7 ± 7.3+
30-39	173.0 ± 5.2#	79.1 ± 10.0#	26.4 ± 3.4	23.3 ± 4.2#	160.5 ± 6.9	64.7 ± 6.7	25.2 ± 5.6	33.7 ± 5.1
40-49	169.8 ± 7.9#	79.5 ± 17.4#	23.4 ± 4.6	27.4 ± 8.0#	155.2 ± 2.0	56.8 ± 6.7	23.6 ± 2.6	34.8 ± 3.3
50-59	163.2 ± 5.6#	76.8 ± 13.9#	29.0 ± 5.9	29.2 ± 3.2#	156.6 ± 7.4	66.3 ± 8.7	27.1 ± 4.2	39.4 ± 4.3
60-69	168.3 ± 7.3#	75.3 ± 5.2#	29.4 ± 5.1	29.4 ± 5.1#	155.9 ± 5.5	62.4 ± 7.7	25.6 ± 3.2	38.4 ± 3.8
70-80	167.3 ± 7.0#	70.0 ± 9.5#	25.1 ± 3.9	27.6 ± 3.5#	154.4 ± 7.6	63.2 ± 9.8	26.5 ± 3.8	38.2 ± 4.8

Table 2 - Main spirometric variables in male and female subjects by age group.

FVC = Forced vital capacity; FEV_1 = forced expiratory volume in 1 s; $FEF_{25-75\%}$ = forced expiratory flow from 25 to 75% of the FVC. Data are reported as means ± SD. *Significant effect among age groups within sex ($P<0.05$); for all variables but FEV_1/FVC, 20-29 age group *vs* 50-59 to 70-80 groups. +Significant effect between sex groups ($P<0.05$); males *vs* females by age-group.

Age (years)	Males (N = 50)				Females (N = 50)			
	FVC (l)	FEV_1 (l)	FEV_1/FVC	$FEF_{25-75\%}$ (l/s)	FVC (l)	FEV_1 (l)	FEV_1/FVC	$FEF_{25-75\%}$ (l/s)
20-29	5.09 ± 0.52*+	4.14 ± 0.48*+	81.6 ± 8.0	4.11 ± 1.0*	3.53 ± 0.47*	3.01 ± 0.38*	85.5 ± 4.6	3.59 ± 0.86*
30-39	5.12 ± 0.69+	4.04 ± 0.51+	79.4 ± 4.5	3.86 ± 0.87	3.76 ± 0.48	3.06 ± 0.34	81.6 ± 3.8	3.21 ± 0.43
40-49	4.61 ± 0.96+	3.55 ± 0.73+	77.2 ± 4.5	3.16 ± 0.79	3.44 ± 0.45	2.76 ± 0.37	80.2 ± 4.2	2.80 ± 0.67
50-59	4.01 ± 0.58+	3.10 ± 0.52+	77.2 ± 3.9	2.82 ± 0.76	3.27 ± 0.45	2.53 ± 0.44	77.4 ± 4.4	2.37 ± 0.93
60-69	3.82 ± 0.73+	3.03 ± 0.50+	79.6 ± 4.3	2.96 ± 0.73+	2.90 ± 0.49	2.19 ± 0.42	75.1 ± 4.6	1.79 ± 0.74
70-80	3.63 ± 0.92+	2.51 ± 0.65+	69.3 ± 5.7+	1.59 ± 0.49	2.62 ± 0.54	1.85 ± 0.29	75.4 ± 3.7	1.60 ± 0.43

the height difference was the lowest (Tables 2 and 3). Similarly, FRC and RV values also tended to be higher in males (Figure 1). Interestingly, age had a less evident effect on the mean values of all LV, but a significant increase in RV, FRC and RV/TLC ratio with age was found in both sexes (Table 3 and Figure 1).

The bivariate correlation analysis (Table 4) showed that height was the strongest predictive factor of TLC (r = 0.84), followed by lean body mass (r = 0.71), weight (r = 0.489) and age (r = -0.24). There was also a strong association between the physical fitness indexes (score of regular physical activity, knee extensor peak torque and aerobic power) and LV (Table 4). This general pattern of relationships was also found with other LV, but age presented a positive relationship with both FRC and RV (Figure 1 and Table 4).

When the correlational analysis was more properly analyzed in a multiple regression approach only age and height remained in all the final models, with the exception of TLC in males, where height was the single predictor (Table 5). Weight presented an independent predictive value only in females: in this group, a positive effect of total body mass on IC and a negative effect on the RV/TLC ratio was found (Table 5). Although maximal aerobic power (peak $\dot{V}O_2$) and other indexes of physical fitness correlated with TLC, their correlations with height and age were also strong (Table 4, Figure 2) and therefore these variables lost their predictive power when considered in the multiple regression analysis (Table 5).

In order to evaluate the predictive power of the most recommended set of prediction equations for LV (ATS/ERS International Consensus, 1995) (7) in our sample, we compared the observed value with that predicted by those equations. As illustrated in Figure 3, there was a non-parallel error in the prediction of LV by the ATS/ERS equations in both sexes, i.e., a systematic bias to overestimate LV values in the lower range and underestimate them at higher values. Finally, in order to perform an internal cross-validation procedure we applied the PRESS method to our original values (see Data analysis). We found that the systematic recalculation of the residuals for each individual from an equation developed without the "missed" subject had only a mild effect on the R^2 and SEE original values (R^2_{PRESS} ranging from 0.018-0.034 units below R^2 and SEE_{PRESS} 0.05-0.10 l above SEE). These results suggest that the reference equations from this study can be used for other similar popula-

Table 3 - Lung volume values for males and females by age group.

TLC = Total lung capacity; RV = residual volume; FRC = functional residual capacity. Data are reported as means ± SD. *Significant effect among age groups within sex (P<0.05); 60-69 and 70-80 age groups *vs* 20-29 to 50-59 groups. $^+$Significant effect between sex groups (P<0.05); males *vs* females by age-group.

Age (years)	Males (N = 50)				Females (N = 50)			
	TLC (l)	RV (l)	FRC	RV/TLC (x100)	TLC (l)	RV (l)	FRC (l)	RV/TLC (x100)
20-29	6.83 ± 0.71$^+$	1.69 ± 0.56$^+$	3.36 ± 0.60$^+$	24.6 ± 7.1*	4.90 ± 0.53	1.33 ± 0.31	2.38 ± 0.34	27.2 ± 4.8
30-39	7.12 ± 1.10$^+$	1.87 ± 0.62$^+$	3.45 ± 0.87$^+$	26.0 ± 5.5	5.25 ± 0.76	1.39 ± 0.62	2.54 ± 0.53	26.0 ± 8.5
40-49	7.07 ± 1.60$^+$	1.75 ± 0.61$^+$	3.50 ± 0.97$^+$	25.0 ± 4.6	5.19 ± 0.55	1.33 ± 0.55	2.49 ± 0.67	24.7 ± 8.7
50-59	5.84 ± 0.95	1.70 ± 0.70$^+$	3.00 ± 0.61$^+$	27.2 ± 9.4	4.95 ± 0.92	1.38 ± 0.58	2.54 ± 0.86	26.7 ± 7.2
60-69	6.14 ± 0.89$^+$	2.12 ± 0.45*$^+$	3.79 ± 0.73*$^+$	32.2 ± 5.5*	5.01 ± 0.64	1.70 ± 0.46*	2.87 ± 0.41*	34.2 ± 8.2*
70-80	6.46 ± 1.20$^+$	2.39 ± 0.60*$^+$	3.88 ± 0.85*$^+$	34.7 ± 7.4*	4.63 ± 0.98	1.88 ± 0.79*	2.99 ± 0.55*	35.8 ± 6.9*

tions without an appreciable loss of accuracy.

Discussion

The present study provides a comprehensive description of the static lung volume values for a healthy, randomly selected sample of the adult Brazilian population. As expected by the determinants of LV in humans, gender, body dimension (height) and age explained 49 to 78% of the variation in the observed values (Table 5). Importantly, the use of a widely recommended set of predictive equations (ATS/ERS International Consensus, 1995) (7) induced a dual error: an overestimation of low LV and an underestimation at higher volumes (Figure 3). These results demonstrate the necessity of considering, as in most of the biological variables, reference values for LV

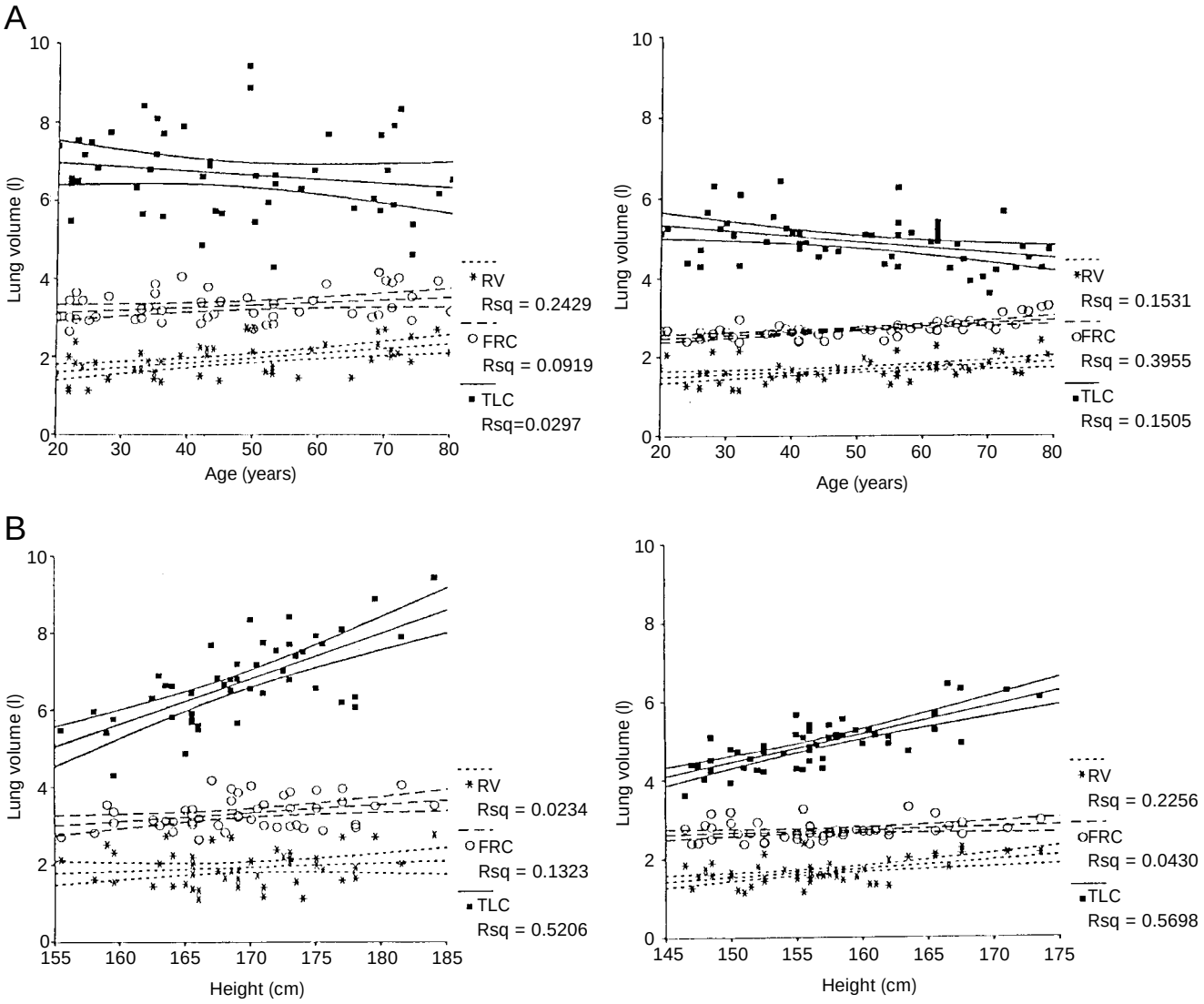

Figure 1 - Lung volumes as a function of age (A) and height (B) for males (left) and females (right). Note that TLC (total lung capacity) values were higher in males and more related to height than age (P<0.05). Age was associated with an increase in RV (residual volume), chiefly in males, and FRC (functional residual capacity), mainly in females (P<0.05). Regression lines are presented with the corresponding 95% confidence limits. Rsq is the coefficient of determination.

Table 4 - Correlation matrix.

LBM = Lean body mass; PAS = physical activity score; $\dot{V}O_2max$ = maximum oxygen uptake; TLC = total lung capacity; FRC = functional residual capacity; RV = residual volume; IC = inspiratory capacity. *P<0.05. **P<0.01.

	Age	Height	Weight	LBM	PAS	$\dot{V}O_2max$	Leg strength	TLC	FRC	RV	IC
Age	1.00										
Height	-0.22*	1.00									
Weight	-0.01	0.54**	1.00								
LBM	-0.24*	0.79**	0.84**	1.00							
PAS	-0.28**	0.38**	0.23*	0.42**	1.00						
$\dot{V}O_2max$	-0.61**	0.67**	0.50**	0.77**	0.58**	1.00					
Leg strength	-0.71**	0.71**	0.46**	0.79**	0.47**	0.86**	1.00				
TLC	-0.24*	0.84**	0.49**	0.74**	0.44*	0.66**	0.71**	1.00			
FRC	0.23*	0.63**	0.31**	0.49**	0.16	0.32*	0.24*	0.63**	1.00		
RV	0.39**	0.40**	0.21*	0.24*	0.23*	0.04	-0.06	0.42**	0.52**	1.00	
IC	-0.38**	0.75**	0.57**	0.77**	0.42**	0.73**	0.79**	0.88**	0.40**	0.15	1.00

Table 5 - Linear prediction equations for static lung volumes of males and females, aged 20 to 80.

Values in the columns represent coefficient estimates followed by standard error of the estimate. M = Males; F = females; TLC = total lung capacity; FRC = functional residual capacity; IC = inspiratory capacity; RV = residual volume; R^2 = coefficient of determination; RSE = residual standard error.

Variable	Sex	Age (years)	Height (m)	Weight (kg)	Constant	R^2	RSE
TLC (l)	M	-	11.8 ± 0.17	-	-13.23 ± 2.82	0.722	0.66
	F	-0.0094 ± 0.003	6.29 ± 0.09	-	-4.48 ± 1.43	0.585	0.39
FRC (l)	M	0.0092 ± 0.003	2.78 ± 0.08	-	-1.83 ± 1.34	0.545	0.34
	F	0.0091 ± 0.001	1.30 ± 0.03	-	0.21 ± 0.55	0.546	0.16
IC (l)	M	-0.011 ± 0.005	6.46 ± 0.02	-	-7.05 ± 2.31	0.672	0.58
	F	-0.012 ± 0.002	1.71 ± 0.07	0.019 ± 0.004	-1.00 ± 1.09	0.781	0.29
RV (l)	M	0.0141 ± 0.003	1.97 ± 0.09	-	-2.08 ± 1.49	0.569	0.37
	F	0.0091 ± 0.002	2.59 ± 0.05	-	-3.15 ± 0.79	0.494	0.21
RV/TLC	M	0.0022 ± 0.001	-0.25 ± 0.01	-	0.61 ± 0.21	0.654	0.05
	F	0.0023 ± 0.001	0.15 ± 0.01	-0.0016 ± 0.001	0.07 ± 0.17	0.681	0.04

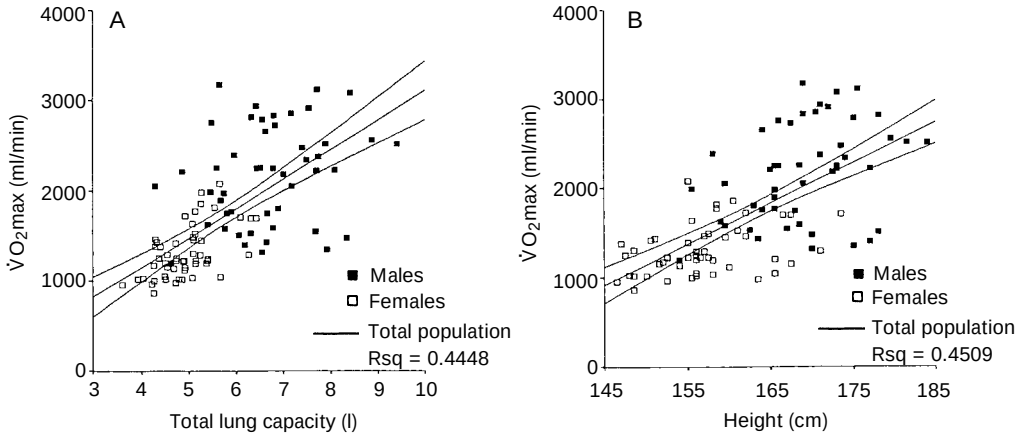

Figure 2 - Maximum oxygen uptake ($\dot{V}O_2max$) as related to total lung capacity (A) and height (B) in males and females, 20 to 80 years old. Regression lines are presented with the corresponding 95% confidence limits. Rsq is the coefficient of determination.

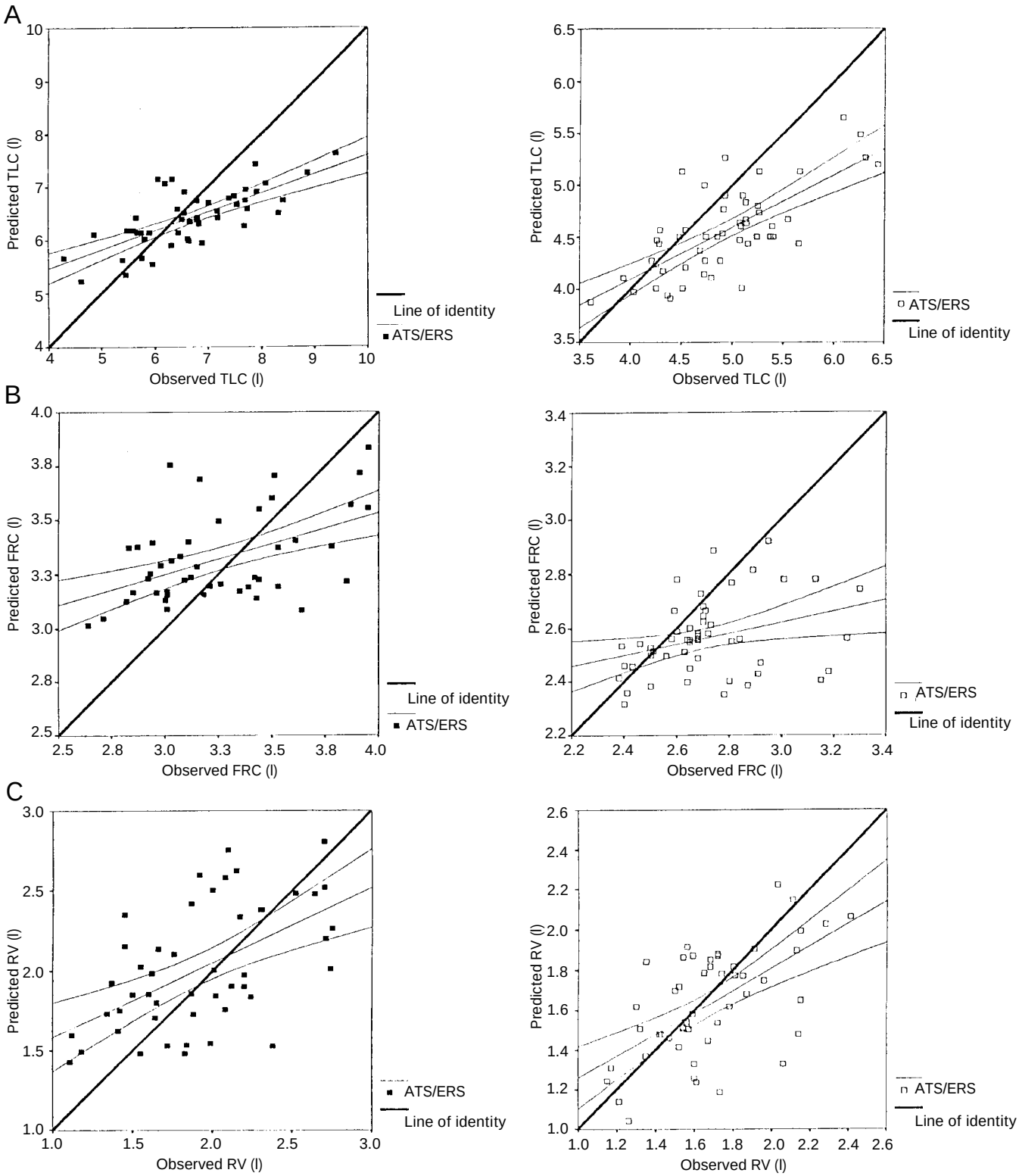

Figure 3 - Comparison between the observed total lung capacity (TLC) (A), functional residual capacity (FRC) (B) and residual volume (RV) (C) values in males (left) and females (right) and the predicted values from the American Thoracic Society (ATS) and European Respiratory Society (ERS) (7). Note that these equations overestimated the observed lung volumes at low values and underestimated them at high values. Regression lines are presented with the corresponding 95% confidence limits. Rsq is the coefficient of determination.

which are obtained from a racial, ethnic and geographically related population (4).

Reference values for pulmonary function tests should derive from studies employing standardized procedures and equipment (4,6,7,22,26). The wide diversity of applications requires particularly accurate reference values: for instance, i) from a clinical viewpoint, these tests are used most commonly to assist in defining a differential diagnosis, to estimate prognosis, follow the course of a disease, estimate the risk of surgical procedures, detect reactions to drugs and assess impairment/disability in occupational settings (27); ii) for the clinical researcher, these results are valuable for excluding or including subjects with specific dysfunctions or degrees of impairment, and finally, iii) for epidemiologists these measurements are crucial to identify the prevalence of adverse responses to environmental exposures or specific causes such as nutrition or aging, and to develop predictors of mortality or disease (5).

To our knowledge, there is only a single published study describing LV in adult Brazilians (26); however, this study presents reference values for dynamic rather than of static LV. There are important conceptual and practical differences between these measurements: static LV are measured by methods based on the completeness of respiratory maneuvers, so that the velocity of those should be adjusted accordingly. On the other hand, dynamic LV are obtained with fast breathing movements assessed during forced expiration, when maximal effort is applied throughout the respiratory maneuver (1). In normal, healthy adults the gas dilution, plethysmographic and roentgenographic methods for measuring static LV are highly comparable (28-30), whereas in patients with gas distribution abnormalities gas dilution methods can underestimate the actual LV (30,31).

A prediction study such as the one presented here could be criticized on the use of a population with a specific ethnic profile, i.e., it would restrict the appropriate use of the prediction data to a small population. However, the ethnic and racial profile of our study population was very broad (see Methods), attributable to the influence of massive internal and external migration into Southeast Brazil. Importantly, we could find no other attempts in the international literature to determine "national" reference values for variables such as the pulmonary function tests: practical, operational and economical limitations are probably the main reason for this absence. However, this could be an important consideration in countries of continental dimensions like Brazil, and therefore additional data from different regions within the country could be useful to address this question.

There is a considerable amount of data concerning the effects of race and ethnicity in LV and pulmonary function testing (32-35), but little is known about the precise underlying physiological mechanisms. Predictive studies for North American and European populations found lower values in "minorities" such as blacks or Hispanics, but their lower socioeconomic and nutritional status are probably important confounding factors (4,7,21). Studies with immigrants suggest that intermarriage can induce LV values which are intermediate between the parents (32,35). Our results are probably influenced by the multiracial profile of the urban Brazilian population, and therefore one would expect intermediate values, for example between Caucasians and blacks. Interestingly, this was not the case: prediction equations derived from predominantly Caucasian samples had a non-parallel error in the prediction of our original data. In this context, it should be noted that although height (the main independent variable) has a quite obvious relationship with the lung base-apex distance, it contains little information about the total chest diameter (7,21); by the same token, little is known about the leg-trunk ratio

of South American populations. These variations could explain the errors found in the ATS/ERS equations in predicting our observed values (7) (Figure 3).

Age has been consistently related to higher FRC and RV, independent of smoking (1,3,36-38). The EELV, which in many circumstances is equal to FRC, is determined by i) the equilibrium between the antagonistic elastic recoils of the chest wall (outward) and that of the lung (inward) and ii) by the volume in which the small airways occlude at the base (occlusion volume). The aging process associates with loss of lung elastance and increase of occlusion volume, both contributing to increased RV, FRC and the RV/TLC ratio (Figure 1, Table 5). Additionally, increases in total body mass are associated with a decline in ERV, and therefore FRC; consistent with the notion that this effect seems to be evident only in severely obese subjects, we were not able to find a negative effect of weight on the LV of males (Table 5). On the other hand, in females, weight was positively related to IC and negatively to RV/TLC (Table 5): the first effect could represent the known positive relation between body mass and PImax (since the inspiratory capacity is closely related to respiratory muscle strength) and the latter effect, a reduction in ERV due to a more central deposition of fat in females (39).

Another variable which has been linked to LV is the level of physical fitness (40). Although it is accepted that there is no true pulmonary/ventilatory limitation of maximal dynamic exercise, at least in non-athlete subjects at sea level, some studies have shown a moderate relationship between LV and indexes of fitness (41,42). Similarly, this feature was also found in the present study (Table 4), but this does not seem to be a cause-effect relationship. Conversely, it is more reasonable to hypothesize that taller, younger and more active subjects present both a higher LV and fitness level. Whether this higher LV could provide an advantage in terms of physical performance has been demonstrated thus far only for competitive athletes and for specific modalities; in sedentary subjects this theoretical handicap seems to be improbable (40).

Consistent with previous studies (3,6,7, 21,36-38,40), we obtained a rather low R^2 and high SEE in the LV prediction, i.e., a substantial percentage of the LV variance could not be explained by the variables analyzed (Table 5). These results are consistent with the traditional notion that LV are far less reproducible than spirometric variables, reinforcing the necessity of using accurate and representative reference values. Additionally, the use of an adequate lower limit of normality is crucial: the high level of homocedasticity found in the residual distribution in our predictive equations precludes the use of a fixed "percentage of predicted" as a limit of normality. For the same reasons, the use of the two-tailed 95% confidence interval (CI) is more adequate (predicted ± 1.96 x SEE). However, one should note that this useful approximation ignores the hyperbolic nature of the CIs around the regression lines, i.e., it tends to be an overoptimistic estimation of the "true" CI (8).

In summary, we have presented what we believe to be the first set of equations for prediction of static lung volumes in a randomized sample of an ethnically heterogeneous population from Brazil. Assuming that these values are at significant and non-parallel variance with a widely recommended set of equations from a North-American-European Consensus (7), 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 lung volume values in subjects aged 20 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 adult Brazil-

ian population with different ethnic and geographic backgrounds.

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