Objective: To derive reference values for healthy white Brazilian adults who have never smoked and to compare the obtained values with reference values derived by Crapo and by Neder. Methods: Reference equations by quantile regressions were derived in 122 men and 122 women, non-obese, living in seven cities in Brazil. Age ranged from 21 to 92 years in women and from 25 to 88 years in men. Lung function tests were performed using SensorMedics automated body plethysmographies according ATS/ERS recommendations. Lower and upper limits were derived by specific equations for 5 and 95 percentiles. The results were compared to those suggested by Crapo in 1982, and Neder in 1999. Results: Median values for total lung capacity (TLC) were influenced only by stature in men, and by stature and age in women. Residual volume was influenced by age and stature in both genders. Weight was directly related to inspiratory capacity and inversely with functional residual capacity and expiratory reserve volume in both genders. A comparison of observed TLC data with values predicted by Neder equations showed significant lower values by the present data. Mean values were similar between data from present study and those derived by Crapo. Conclusion: New predicted values for lung volumes were obtained in a sample of white Brazilians. The values differ from those derived by Neder, but are similar to those derived by Crapo. Keywords: Pulmonary volumes; Pulmonary function tests; Reference values; Pulmonary plethysmography.

ABSTRACT

INTRODUCTION

The measurements of static pulmonary volumes in practice refer to the measurement of the several lung capacities and volumes. Capacities include: Functional Residual Capacity (FRC) - the volume of air present in the lungs at the end of Tidal Volume (TV) expiration; Total Lung Capacity (TLC) - total volume of air in the lungs at the end of a maximal inspiration; Vital Capacity (VC) - Total expired air volume after maximum inspiration or maximum inspiration after maximum expiration; Inspiratory Capacity (IC) – volume of air inspired from the end of a normal expiration. These four capacities can be divided into volumes, with particular interest in the Expiratory Reserve Volume (ERV), the maximum volume of gas that can be exhaled from the FRC, and the residual volume (RV) which is the volume of gas remaining in the lungs after maximal expiration. The measurement of pulmonary volumes has several clinical applications. The TLC reduction establishes the presence of restriction. Apparent restriction on spirometry (reduction of FVC and FEV1, with FEV1 / FVC in the expected range) in many cases it is not confirmed by reduced TLC. This combination is called nonspecific pattern and is commonly observed in obstructive diseases with

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airway closure, obesity and neuromuscular diseases.(2) In patients with reduced TLC, a disproportionately reduced FVC (TLC-%FVC expected > 10%), recently termed “complex restrictive pattern”, points to clinical entities that result in impaired pulmonary emptying, such as neuromuscular diseases, obstruction and chest wall disease.(3) Elevated pulmonary volumes, particularly the increase in RV and RV / TLC ratio are common in airflow limitation and may be the only finding abnormal.(4,5) Air trapping is important in evaluating the severity of obstructive diseases and in response to treatment. In many cases, the reduction of RV is observed to a greater degree than the changes observed in spirometry.(6) The FRC reduced at the expense of ERV reduction is a characteristic of obesity.(7) Increase in ERV in obese patients is associated with reduced dyspnea after bariatric surgery.(8) The FRC increases with the degree of airflow obstruction, which results in IC decrease. IC / TLC ratio < 25% predicts a higher mortality in chronic obstructive pulmonary disease (COPD).(9)

The reference values for the static pulmonary volumes show remarkable differences between different authors.(10) These differences may be due to several factors, such as selection of individuals, methodological and technical differences, inclusion of different ethnic groups and types of equation used to calculate the expected values. In sample selection, ideally more than 100 adults of each gender for each ethnic group with a similar frequency distribution in the various age ranges should be included.(10)

Many studies about reference values are old, with small samples included.(11) In Brazil, reference values for pulmonary volumes were derived by Neder et al.(12) in 1999 in 50 men and 50 women of different races and are used in some centers.(12) In Brazil, the Crapo equation is also used as a reference for pulmonary volumes, but its adequacy to our population has never been tested.(12,13)

The aim of the present study was to determine reference values for pulmonary volumes in a white Brazilian multicenter sample and compare the results obtained by the Neder and Crapo equations.

**METHODS**

The data were obtained in seven Brazilian cities by plethysmographs of the same brand (SensorMedics, Yorba Linda, California) between 2015 and 2017 (Brazil Diagnostic Center; São Paulo; AMO Clinic, Salvador; Madre Teresa Hospital, Belo Horizonte; Matos Clinic, Criciúma; and others). The individuals were selected by verbal invitation, and were more commonly companions or family members of patients or staffs of the study institutions. The volunteers who accepted and agreed to participate in the study initially responded to a questionnaire translated from the American Thoracic Society / Division of Lung Diseases, validated in in Brazil and, when the inclusion criteria were completed, signed a written informed consent form.(14,15)

The project was approved by the Ethics and Research Committee of the Madre Teresa Hospital / Belo Horizonte, Minas Gerais, number 1617108. The project has not been submitted for approval in all centers; however, the complete documentation of all the centers involved was added to the project approved.

The inclusion criteria in the study were:

- Age over 20 years in females and 25 years in males;(16)
- Body Mass Index (BMI) between 18 and 30 kg / m²;
- Absence of significant respiratory symptoms, current or previous respiratory diseases, cardiac diseases, previous thoracic surgery and relevant occupational exposure;(15)
- Not had smoked for a lifetime. Women, whom cooked in wood stoves, as well as those exposed to cigarette smoke in the bedroom, were excluded;
- Color self-declared white as confirmed by the individual and by observers.

The exams were performed by technicians or medical certificates in pulmonary function by Brazilian Thoracic Society.

The spirometry tests followed the norms suggested by the Brazilian Thoracic Society and the ATS / ERS guidelines.(1,17) The volumes were measured by SensorMedics body plethysmographs with variable pressure, equipped by a pneumotachograph, according to the standards proposed by the American Thoracic Society and European Respiratory Society.(18) The volume signal was calibrated by a 3.0 L syringe connected to the pneumotachograph, according to the manufacturer’s recommendations, daily before of the workday start. The mouth pressure transducer and pressures and flows in the plethysmograph were calibrated daily. The functional parameters were expressed as BTPS.(17)

Procedures were conducted in the sitting position while subjects were using a nasal clamp. After detailed instructions regarding the test, the plethysmograph door was closed and the time to temperature equilibrium expected. The patient was then instructed to place the mouthpiece and breathe quietly until a plateau at the endo-expiratory level was reached out. When the breathing was at the Functional Residual Capacity (FRC) level, the shutter was closed and the patient instructed to pant softly, at a frequency between 0.5 and 1.0 Hz. The pressure-flow plots were recorded for airway resistance calculation (not included in the present study). The pressure-volume charts for determination of FRC were obtained by closing shutter at the end of a normal expiration. After opening the obturator, ERV and inspiratory vital capacity were determined. The RV was obtained by subtraction of the FRC and ERV, and the TLC was computed as the sum of the RV and VC. The inspiratory capacity was calculated by TLC-FRC. From these data, the RV / TLC ratio (%) was calculated. The system registers four loops by each maneuver, and at least three maneuvers were performed on all tested, therefore, with 12 loops. When the acceptance criteria were not met, more loops were
The comparisons between the values observed for the TLC and those predicted by the Crapo and Neder equations are shown in Table 4 and Figure 1. The values predicted by Neder were higher than those found in the present study. For males, the average difference was 0.48 L and for females, 0.24 L (p < 0.001 for both).

The average differences between the values predicted by Crapo and those found in the present study for TLC were small and not significant: in males, -0.09 (p=0.12) and for females, -0.02 L (p=0.60).

**RESULTS**

A total of 244 individuals (122 of each gender) were included in the study. The individuals were tested, in descending order, in São Paulo (62%), Salvador (13%), Criciúma (10%), Belo Horizonte (7%) and other places (8%).

The distribution for anthropometric data is shown in Table 1. Age in males varied from 25-88 years and from 21 to 92 years in females. The median stature in males was 173 cm (156-189 cm) and 160 cm (140-174 cm) in females.

The median values and the dispersion for the main functional data, expressed by quartiles 1 and 3, are shown in Table 2.

The Table 3 presents the final model estimates.

**DISCUSSION**

The present study derived by plethysmography new predicted values for pulmonary volumes in adults subjects who never smoked, of white race, in Brazil.

The measurement of TLC is essential for the diagnosis of restrictive lung disease. The VC may be reduced in both, restrictive and obstructive lung disease, in the latter due to increased residual volume. The elevated TLC indicates, in general, loss of lung elastic recoil, as occurs in emphysema and in some cases of asthma. Besides that, the measurement of lung volumes is essential for the interpretation of other functional parameters, such as airway resistance, which ranges inversely with the pulmonary volume.

Factors that determine normal lung size include stature, age, gender, body mass, altitude, ethnic group, and physical activity pattern. The maximum inspiratory level (TLC) is influenced by the strength developed by the inspiratory muscles, lung elastic recoil, and the elastic properties of the thorax and adjacent structures. Great swimmers, divers and rowers may have increased TLC by increased muscle strength.

The expected values for TLC are considered independent of age because the reduction in pulmonary elastic recoil is compensated by the combined effects of loss of muscle strength and increase in the rib cage stiffness with advancing age. This overlooks the fact that body fat, which on average increases with age, can reduce pulmonary volume. In the present study, only the stature influenced TLC in men; in women, the effect of age was significant, but with opposite effects, as observed by others. Women have a greater tendency to gain weight with age and men tend to lose more lung elastic recoil. In some studies, age influenced TLC in men and women, in others, only in women.

The gas volume at the end of full expiration reflects a balance between the strength of the accessory expiratory muscles, the inherent compressibility of the rib cage, and the closure of the airways. In adults, the RV limiting factor becomes the decreased elastic recoil; this leads to narrowing and eventual closure of the airways. With advancing age, the pulmonary elastic retraction decreases. As a result, both, RV and RV / TLC ratio increase with age. In addition to the loss of elastic recoil, the accumulation of fat and the decrease in the strength of the respiratory muscles lead to the reduction of VC, which is therefore multifactorial.
The fat is an important component of Body Mass Index (BMI), but this index also includes Fat Free Mass (FFM), of which the largest component is muscle. In the present study, IC correlated directly with weight, which can be explained by the correlation of muscle mass with weight, and FRC and ERV correlated negatively with weight, probably due to the effect of deposition of higher central fat, even with the inclusion in the study of individuals with BMI in the normal range. Half of the women and 65% of the men in the present study had BMI values above 25, indicating overweight.

The derived values in the present study were compared to the values suggested by Neder and Crapo. The selection method was not described. The pulmonary volumes may be higher in inhabitants born at sites with more than 1800 m high, presumably due to increased pulmonary growth due to hypoxemia. Therefore, this factor should not have influenced the values observed in the present study and that of Crapo et al. Only two male individuals were over 85 years of age. The technique used was the single breath by helium dilution, used to measure CO diffusion, which may underestimate TLC. The equations were derived by linear regression. The derived values in the present study were compared to the values suggested by Neder and Crapo. The selection method was not described. The pulmonary volumes may be higher in inhabitants born at sites with more than 1800 m high, presumably due to increased pulmonary growth due to hypoxemia. Therefore, this factor should not have influenced the values observed in the present study and that of Crapo et al. Only two male individuals were over 85 years of age. The technique used was the single breath by helium dilution, used to measure CO diffusion, which may underestimate TLC. The equations were derived by linear regression. The derived values in the present study were compared to the values suggested by Neder and Crapo. The selection method was not described. The pulmonary volumes may be higher in inhabitants born at sites with more than 1800 m high, presumably due to increased pulmonary growth due to hypoxemia. Therefore, this factor should not have influenced the values observed in the present study and that of Crapo et al. Only two male individuals were over 85 years of age. The technique used was the single breath by helium dilution, used to measure CO diffusion, which may underestimate TLC. The equations were derived by linear regression. The derived values in the present study were compared to the values suggested by Neder and Crapo. The selection method was not described. The pulmonary volumes may be higher in inhabitants born at sites with more than 1800 m high, presumably due to increased pulmonary growth due to hypoxemia. Therefore, this factor should not have influenced the values observed in the present study and that of Crapo et al. Only two male individuals were over 85 years of age. The technique used was the single breath by helium dilution, used to measure CO diffusion, which may underestimate TLC. The equations were derived by linear regression. The derived values in the present study were compared to the values suggested by Neder and Crapo. The selection method was not described. The pulmonary volumes may be higher in inhabitants born at sites with more than 1800 m high, presumably due to increased pulmonary growth due to hypoxemia. Therefore, this factor should not have influenced the values observed in the present study and that of Crapo et al. Only two male individuals were over 85 years of age. The technique used was the single breath by helium dilution, used to measure CO diffusion, which may underestimate TLC. The equations were derived by linear regression. The derived values in the present study were compared to the values suggested by Neder and Crapo. The selection method was not described. The pulmonary volumes may be higher in inhabitants born at sites with more than 1800 m high, presumably due to increased pulmonary growth due to hypoxemia. Therefore, this factor should not have influenced the values observed in the present study and that of Crapo et al. Only two male individuals were over 85 years of age. The technique used was the single breath by helium dilution, used to measure CO diffusion, which may underestimate TLC. The equations were derived by linear regression. The derived values in the present study were compared to the values suggested by Neder and Crapo. The selection method was not described. The pulmonary volumes may be higher in inhabitants born at sites with more than 1800 m high, presumably due to increased pulmonary growth due to hypoxemia. Therefore, this factor should not have influenced the values observed in the present study and that of Crapo et al. Only two male individuals were over 85 years of age. The technique used was the single breath by helium dilution, used to measure CO diffusion, which may underestimate TLC. The equations were derived by linear regression.
would be calculated by adding or subtracting 1.08 L from those expected limits for females and 1.61 L for males. However, common pulmonary diseases have a tendency to increase or decrease TLC data, and the calculation of limits by the 5th and 95th percentiles is accepted. By calculating the 5% limits for TLC in males by the Crapo equations (expected-1.30), the lower limit would be 80% of the mean value compared to 84% of the median expected by the current equation. In females, these values would be 82% for the Crapo equation and 86% for the current equation. Therefore, in the present study, the lower limits are closer to the expected value, increasing the sensitivity for the detection of restrictive disorder.

Neder et al. derived reference values in 50 individuals of each gender, aged 20-80 years, randomly selected among employees of a large hospital in São Paulo. The racial profile was variable, with inclusion of 34 non-white individuals. Race has a significant effect on lung volumes. Obese people were not excluded.

| Variable | Women | Men |
|----------|-------|-----|
| TLC      |       |     |
| P5°      | -4.8007 + 0.0559 x stature | -10.7100 + 0.0946 x stature |
| P50°     | -4.3419 + 0.065 x age² -0.0007 x age + 0.0483 x stature | -6.1250 + 0.0742 x stature |
| P95°     | -6.435 + 0.0755 x stature | -10.4536 + 0.0097 x age + 0.1020 x stature |
| VC       |       |     |
| P5°      | 22.9599 -0.0002 x age² -0.2864 x Stature + 0.001 x Stature² | -5.2936 -0.0158 x Age + 0.0580 x Stature |
| P50°     | -1.9753 -0.0001 x Age² + 0.0353 x Stature | -4.8522 -0.0216 x Age + 0.0615 x Stature |
| P95°     | -4.7539 + 0.0391 x Age -0.0005 x Age² + 0.0511 x Stature | -6.5653 -0.0117 x Age + 0.0729 x Stature |
| IC       |       |     |
| P5°      | -3.1738 + 0.0313 x Stature | -3.6500 + 0.0350 x Stature |
| P50°     | -0.8509 -0.0001 x Age² + 0.0151 x Stature + 0.0162 x Weight | 2.0383 -0.0124 x Age + 0.0239 x Weight |
| P95°     | -41.8650 + 0.0320 x Age -0.0004 x Age² + 0.5434 x Stature -0.0017 x Stature² | 3.7778 + 0.0287 x Stature + 0.0361 x Weight |
| FRC      |       |     |
| P5°      | -36.7215 + 0.0567 x Age -0.0004 x Age² + 0.4603 x Stature -0.0014 x Stature² | -3.5400 + 0.0500 x Stature -0.0325 x Weight |
| P50°     | -5.1544 + 0.0115 x Age + 0.0548 x Stature -0.0264 x Weight | -5.0085 + 0.0617 x Stature -0.0292 x Weight |
| P95°     | -8.2273 + 0.0123 x Age + 0.0729 x Stature -0.0137 x Weight | -4.2155 + 0.0171 x Age + 0.0444 x Stature |
| ERV      |       |     |
| P5°      | -3.0705 + 0.0214 x Stature | 0.9174 -0.0742 x Age + 0.0006 x Age² + 0.0001 x Stature² |
| P50°     | -2.332 + 0.033 x Age -0.0004 x Age² + 0.0208 x Stature -0.0123 x Weight | -5.2651 -0.0078 x Age + 0.052 x Stature -0.0257 x Weight |
| P95°     | -2.7024 + 0.0373 x Age -0.0004 x Age² + 0.0298 x Stature -0.0212 x Weight | 2.2800 |
| RV       |       |     |
| P5°      | -56.8440 + 0.0205 x Age + 0.7111 x Stature -0.0022 x Stature² | 0.9767 + 0.0001 x Age² |
| P50°     | -3.0184 + 0.0002 x Age² + 0.0257 x Stature | 0.4146 + 0.0153 x Age + 0.00003 x Stature² |
| P95°     | -5.8251 + 0.0499 x Age -0.0003 x Age² + 0.0448 x Stature -0.0139 x Weight | 2.2615 + 0.0002 x Age² |
| RV/TLC%  |       |     |
| P5°      | 10.3085 + 0.0041 x Age² | 856.3949 + 0.0027 x Age² -0.6007 x Stature + 0.0278 x Stature² -0.1902 x Weight |
| P50°     | 23.9599 + 0.0033 x Age² | 14.700 + 0.3000 x Age |
| P95°     | 27.0370 + 0.3148 x Age | 1.021.9540 -0.6122 x Age + 0.0086 x Age² -11.1571 x Stature + 0.0318 x Stature² |

TLC = Total Lung Capacity; P5° = 5th percentile; P50° = 50th percentile; P95° = 95th percentile; IC = Inspiratory Capacity; FRC = Functional Residual Capacity; ERV = Expiratory Reserve Volume; RV = Residual Volume; RV/TLC % = Residual Volume / Total Lung Capacity ratio (%).
The method used to determine FRC was the N2 washout by multiple breaths. The tests were performed in a Medical Graphics system, which provides greater results compared to other large systems, which may explain the high values found. The physical activity pattern and the body composition were determined and influenced the pulmonary volumes in the univariate analysis, but not in the multivariate analysis. The values were derived by linear equations. As shown in Table 4 and Figure 1, the values of Neder et al. significantly overestimate the values for TLC and VC, when compared to the present study.

Quantile regressions were used in the present study, as in other studies on reference values for pulmonary function. In the classical linear method, by the determination of the least squares line, the dispersion of y values around the regression line (residuals) is considered to have a normal distribution, and the same error occurs for different values of x. However, the covariates may affect the distribution of residuals.
in several ways. One advantage of using the quantile regression to estimate the median instead of the usual least squares regression to estimate the average is that the result of quantile regression is more stable in response to outliers.\(^{(19,34)}\)

The comparison between the current equation and that of Crapo et al.\(^{(14)}\) and Neder et al.\(^{(12)}\) should take into account that different regression models were used, but the differences cannot be explained by the statistical model. Additional data that should be considered are the type of equipment and the methods used, besides that, the selection criteria and the sample size. A careful revaluation of acceptance criteria of maneuver was applied in the present study by review of all cases.

The present study has limitations. The most obvious is the uncertain extrapolation of data to black race, which is important in Brazil. The participants’ level of physical activity was not assessed. In this study, volunteers were invited. For the derivation of reference values for pulmonary function, only non-smokers with no symptoms or cardiorespiratory diseases should be included. For this, a validated respiratory epidemiological questionnaire should be applied. Fulfilled these conditions, the use of volunteers to establish reference values is valid.\(^{(10,14)}\) A methodology very similar to the present study was applied in several centers in Canada, in volunteers, to obtain reference values for pulmonary function, including measurement of pulmonary volumes.\(^{(35)}\)

In summary, the present study derived new reference values for pulmonary function by plethysmography in white individuals in Brazil. The values differ from those expected by Neder and are close to those derived by Crapo.

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