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ORIGINAL ARTICLE

Lung volumes and airway resistance in patients with a possible restrictive pattern on spirometry

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Study carried out in the pulmonary function laboratories of Centro Diagnóstico Brasil and the Hospital do Servidor Público Estadual de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: Many patients with proportional reductions in FVC and FEV_1 on spirometry show no reduction in TLC. The aim of this study was to evaluate the role that measuring lung volumes and airway resistance plays in the correct classification of patients with a possible restrictive pattern on spirometry. **Methods:** This was a prospective study involving adults with reduced FVC and FEV_1, as well as an FEV_1/FV(C) ratio within the predicted range. Restrictive lung disease (RLD) was characterized by TLC below the 5th percentile, as determined by plethysmography.

Obstructive lung disease (OLD) was characterized by high specific airway resistance, significant changes in post-bronchodilator FEV_1, or an $FEF_{25-75\%}$ < 50% of predicted, together with a high RV/TLC ratio. Nonspecific lung disease (NLD) was characterized by TLC within the predicted range and no obstruction. Combined lung disease (CLD) was characterized by reduced TLC and findings indicative of airflow obstruction. Clinical diagnoses were based on clinical suspicion, a respiratory questionnaire, and the review of tests of interest. **Results:** We included 300 patients in the study, of whom 108 (36%) were diagnosed with RLD. In addition, 120 (40%) and 72 (24%) were diagnosed with OLD/CLD and NLD, respectively. Among the latter, 24 (33%) were clinically diagnosed with OLD. In this sample, 151 patients (50.3%) were obese, and obesity was associated with all patterns of lung disease. **Conclusions:** Measuring lung volumes and airway resistance is often necessary in order to provide an appropriate characterization of the pattern of lung disease in patients presenting with a spirometry pattern suggestive of restriction. Airflow obstruction is common in such cases.

Keywords: Spirometry; Airway resistance; Lung volume measurements.

INTRODUCTION

The American Thoracic Society (ATS)/European Respiratory Society (ERS) task force proposed definitions for the various patterns of lung disease.(1) Restrictive lung disease (RLD) was defined as a reduction in TLC below the 5th percentile of the predicted value and a normal FEV_1/VC ratio. Obstructive lung disease (OLD) was defined as an FEV_1/VC ratio below the 5th percentile of the predicted value. Mixed or combined lung disease (CLD) was characterized by FEV_1/VC and TLC below the 5th percentile of the predicted values.

A combination of reduced VC and preserved FEV_1/(F)VC is used in order to infer the presence of RLD; however, in approximately 40% of such cases, TLC is not reduced.(2,3) According to the ATS/ERS task force, OLD is characterized by a combination of reduced (F)VC, FEV_1/(F)VC above the lower limit of normal, and TLC within the predicted range.(1) This functional abnormality was later designated nonspecific lung disease (NLD).(4) In a sample of 100 patients presenting with reduced (F)VC, FEV_1/(F)VC above the lower limit of normal, and TLC within the predicted range, 68 had evidence of airway disease, whereas the remaining 32 had signs of restriction.(4)

The proportional reduction in FVC and FEV_1 in patients with OLD can be explained by airway closure with air trapping.(5) Obesity reduces (F)VC more than it does FEV_1(6) and can therefore result in a preserved FEV_1/(F)VC ratio in the presence of OLD. As occurs with diseases affecting respiratory mechanics or respiratory muscle strength, obesity can, in and of itself, result in NLD.(4) Although COPD and asthma account for most OLDs, a wide range of other diseases, including bronchiolar diseases and some interstitial lung diseases, are associated with airflow obstruction and can result in proportional reductions in FVC and FEV_1.(7) In addition, smoking (either current or past) is associated with various lung diseases and can contribute to an obstructive component.

Spirometry is considered the method of choice for detecting airflow limitation caused by OLD. However, airflow limitation is multifactorial. One such factor is high airway resistance (Raw).(8) In many patients with spirometry results suggestive of RLD, Raw measurements can reveal airflow obstruction. It is commonly believed that Raw is a parameter that is not sufficiently sensitive in cases of peripheral airway disease; however, a classic study showed a close correlation between airway conductance

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(Gaw) and bronchiolar diameter.[9] It is possible that Gaw alone is abnormal in patients with bronchiolitis.[10] In 2012, reference values for specific Raw were derived from a large sample of healthy adults.[11]

The objective of the present study was to evaluate the role that measuring lung volumes and Raw plays in the final functional classification of patients with spirometry results suggestive of RLD.

METHODS

Data collection was performed in the pulmonary function laboratories of *Centro Diagnóstico Brasil* (n = 217) and the São Paulo Hospital for State Civil Servants (n = 83) in the period between December of 2011 and December of 2013. Pulmonologists certified in pulmonary function testing by the Brazilian Thoracic Association (BTA) and the lead author of the present study prospectively selected all spirometry results suggestive of RLD. Clinical diagnosis was established by the pulmonologist requesting the test, by administering a standardized respiratory questionnaire adapted from a previously published questionnaire (Appendix 1: http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=46)[12] and by reviewing ancillary test results or analyzing the results of additional tests, including chest X-rays, chest CT scans, and echocardiograms, requested on the basis of clinical suspicion. All pulmonary function tests were performed in accordance with the BTA guidelines.[13] All patients gave written informed consent.

Inclusion criteria

The inclusion criteria were as follows: 1) being an adult whose age and height were within the reference range[14]; 2) having FVC below the lower limit of normal, i.e., below the 5th percentile of the reference population[14]; 3) having FEV_1/FVC and FEV_1/VC equal to or above the lower limit of normal, i.e., above the 5th percentile of the reference population[14]; 4) having a definitive clinical diagnosis (for asthma, physician-diagnosed asthma and a patient report of two or more episodes of wheezing, which were alleviated by bronchodilator use; for COPD, physician-diagnosed COPD, chronic cough/dyspnea—a Medical Research Council scale score ≥ 2—and past or current smoking; patients diagnosed with obesity were in most cases referred for preoperative evaluation for bariatric surgery, including those with a complaint of dyspnea without meeting criteria for diseases such as asthma); and 5) having performed pulmonary function tests in accordance with the BTA/ATS/ERS acceptability and reproducibility criteria.[13,15-17]

Patients whose tests were not in accordance with the aforementioned criteria were excluded, as were those without a definitive diagnosis by the end of the analysis period.

All pulmonary function tests were performed with a Sensor Medics 6200 Bodybox system and a Collins system (Ferraris Respiratory, Louisville, CO, USA). Lung volumes were determined by whole-body plethysmography. For lung volumes, the predicted values were those proposed by Crapo et al.[18] Reduced TLC was characterized by values below the 5th percentile. RV and the RV/TLC ratio were considered high when they were above the 95th percentile of the reference values.[18] Spirometry was repeated after administration of a bronchodilator (400 µg of albuterol aerosol). A significant bronchodilator response was characterized by $FEV_1 \geq 0.20$ L and 7% of predicted, in accordance with Soares et al.[19]

Raw was measured by mean linear intercept values, as recommended by Matthys et al., after analysis of at least five pressure-flow loops.[20] Only satisfactory, reproducible loops were accepted. The predicted values used for calculation were those proposed by Piatti et al.[11] Values above 8.0 cmH_2O/s in females and 8.6 cmH_2O/s in males were considered high (mean ± 1.64 SD).

Satisfactory single-breath DLCO measurements were obtained in 260 patients. The reference values were based on those proposed by Miller et al.[21]

After data collection, the patterns of lung disease were divided into four groups:

RLD—characterized by TLC below the lower limit of normal and no obstruction[1]

OLD—characterized by one or more of the following: high specific Raw corrected for lung volume (Raw × Lv); a significant change in FEV_1 after bronchodilator administration ($\Delta FEV_1 > 0.20$ L and 7% of predicted); and $FEF_{25-75\%} < 50\%$ of predicted with a high RV/TLC ratio (see the Results section)

CLD—characterized by reduced TLC and findings indicative of airflow obstruction, including high Raw × Lv; $FEF_{25-75\%} < 50\%$ with a high RV/TLC ratio; and a significant bronchodilator response

NLD—characterized by TLC within the predicted range and no functional findings indicative of obstruction

All values were expressed as mean ± standard deviation. The groups were compared by means of the Student's t-test and ANOVA (for continuous independent variables), and the chi-square test (for nominal variables). Correlations between Raw × Lv and functional parameters were determined by Spearman's test. The distribution of Raw × Lv was lognormal, and Raw × Lv values were transformed for comparison. ROC curve analysis was used in order to correlate functional parameters and the RV/TLC ratio with specific Raw. Statistical analysis was performed with the IBM SPSS Statistics software package, version 20 (IBM Corp., Armonk, NY, USA). The level of significance was set at $\alpha = 0.05$.

RESULTS

A total of 300 patients were included in the present study. Table 1 shows the general characteristics of the 300 patients included in the study, and Table 2 shows pulmonary function test results expressed as mean ± SD.

Clinical diagnoses were divided into four groups: obstructive diseases, interstitial diseases, obesity, and other diseases (Figure 1).

Of the 300 patients included in the present study, 151 (50.3%) were obese, but only 52 (17.3%) had a final diagnosis of obesity without other conditions. In addition, 172 (57.3%) had TLC below the lower limit of normal (RLD), and 128 (42.7%) had TLC within the predicted range (n = 127) or high TLC (n = 1).

RV and the RV/TLC ratio were above the upper limit of normal in 46 (15.3%) and 126 (42.0%), respectively. High Raw × Lv was observed in 97 patients (32.3%). Raw × Lv (and Gaw/Lv) correlated more strongly with $FEF_{25-75\%}$ (r_s = 0.55) than with FEV_1/FVC (r_s = 0.50) or percent predicted FEV_1 (r_s = 0.27; $p < 0.01$ for all). Raw × Lv also correlated significantly with the RV/TLC ratio (r_s = 0.46; $p < 0.001$). ROC curve analysis showed that the area under the ROC curve was higher for $FEF_{25-75\%}$ than for FEV_1/FVC or percent predicted FEV_1 (i.e., 0.75; $p < 0.001$) for differentiating between patients with and without high Raw × Lv. An $FEF_{25-75\%}$ of less than 50% had a sensitivity of 40% and a specificity of 89% for detecting high specific Raw. With regard to lung volume measurements, the RV/TLC ratio had the highest area under the curve for characterizing airflow obstruction (0.75; $p < 0.01$). Given that a high RV/TLC ratio and $FEF_{25-75\%}$ < 50% can each be found in patients with RLD or NLD, they were combined in order to characterize airflow obstruction. A combination of high RV/TLC and $FEF_{25-75\%}$ < 50% was found in 46 patients. In 14 of those, the aforementioned parameters constituted the only evidence of obstruction.

Table 1. General characteristics of patients with spirometry results suggestive of restrictive lung disease (n = 300).[a]

General characteristics	Results
Age, years	56.2 ± 14.4
Males/females, n/n	117/183
Nonsmokers/smokers/ former smokers, n/n/n	187/34/79
Body mass index, (kg/m^2)	31.0 ± 7.9

[a]Values expressed as mean ± SD, except where otherwise indicated.

Table 2. Functional characteristics of patients with spirometry results suggestive of restrictive lung disease (N = 300).[a]

Functional characteristics	Results
VC%	66.2 ± 11.0
FVC%	65.0 ± 10.6
FEV_1%	64.5 ± 10.8
FEV_1/FVC	0.81 ± 0.06
$FEF_{25-75\%}$	74.6 ± 28.8
RV%	99.5 ± 32.0
RV/TLC	0.44 ± 0.10
TLC%	78.6 ± 14.2
Raw× Lv	8.44 (4.17-9.09)

Raw × Lv: specific airway resistance corrected for lung volume. [a]Values expressed as mean ± SD or median (interquartile range).

A significant bronchodilator response was observed in 23 patients (7.7%). The most common clinical diagnoses in those patients were obstructive diseases (n = 12) and obesity (n = 5). Of the 14 patients diagnosed with congestive heart failure (CHF), only 1 (7.0%) had a significant bronchodilator response.

On the basis of one or more of the aforementioned criteria, 120 patients (40.0%) had airflow obstruction. Of the 120 patients with OLD, 64 (53.3%) had TLC below the lower limit of normal and were therefore considered to have CLD. Of the 128 patients with TLC within the predicted range, 72 (56.2%) had no airflow obstruction and were therefore classified as having NLD.

All patterns of lung disease found in the present study and the respective clinical diagnoses are shown in Figure 2. In the four groups of lung diseases there were patients diagnosed with obesity and patients diagnosed with other diseases. Four of the patients who were diagnosed with asthma had RLD, and 17 of the patients in the CLD group had a diagnosis of OLD, asthma being the most common obstructive disease (n = 10).

Of the 72 patients who were diagnosed with NLD, 24 (33.3%) had a clinical diagnosis of obstructive disease: asthma, in 11; COPD, in 8; bronchiectasis, in 3; and bronchiolitis, in 3. Therefore, of the 300 patients included in the present study, 144 (i.e., the aforementioned 24 plus the 120 who were diagnosed with OLD or CLD, accounting for 48.0% of the sample) had obstructive disease.

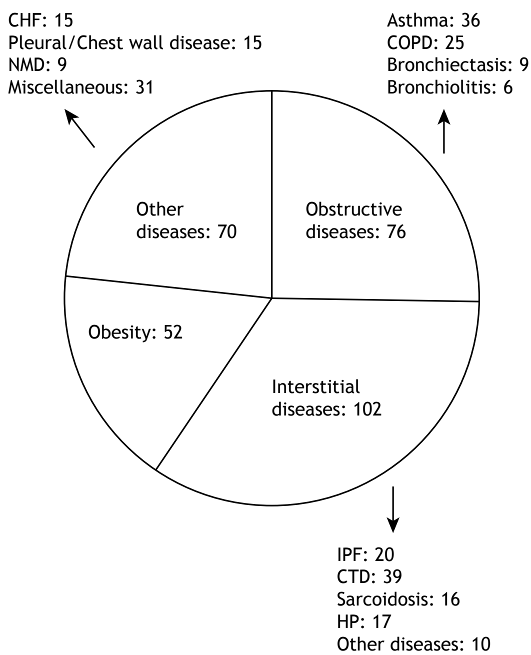

Figure 1. Clinical diagnoses in patients with spirometry results suggestive of restrictive lung disease (N = 300). CHF: congestive heart failure; NMD: neuromuscular disease; IPF: idiopathic pulmonary fibrosis; CTD: connective tissue disease; and HP: hypersensitivity pneumonia.

Several variables, including age, gender, and functional results, were compared among the four major clinical diagnostic groups (Table 3). The patients with a final diagnosis of obesity were younger and had a body mass index above 35 kg/m^2 (79%); therefore, most were referred for preoperative evaluation for bariatric surgery. Expiratory reserve volume (ERV) was lowest in the group of patients who were diagnosed with obesity, who, in comparison with the group of patients diagnosed with interstitial diseases, had higher percent predicted VC, FVC, RV, and TLC; more preserved DLCO; and similar Raw × Lv.

DISCUSSION

The present study confirms the findings of previous studies[2-4] showing that spirometric findings of reduced FVC and FEV_1 associated with a preserved FEV_1/FVC ratio are of limited value in establishing a functional diagnosis. In addition, the study shows that lung volume and Raw measurements provide a more consistent functional characterization.

It is widely recognized that adequate expiratory effort and time are required in order to characterize reduced FVC on spirometry. Incomplete exhalation often results in a restrictive pattern on spirometry. In the present study, all tests were carefully performed and reviewed.

The ATS/ERS task force defined RLD as a reduction in TLC below the 5th percentile of the predicted value and a normal FEV_1/FVC ratio.[1] The reference values for TLC are therefore of great importance. In the present study, we used the values proposed by Crapo et al.[18] Although one study derived reference values for lung volumes in a sample of healthy adults in Brazil,[22] the number of individuals included in that study was small. We cannot exclude the possibility that patients with obstructive diseases that were classified as having RLD or CLD in the present study would have been better classified had there been a more suitable equation for calculating predicted lung volumes. However, cases of asthma with true restriction (reduced TLC) not associated with obesity have been described in the literature, including those with changes in lung function.[23] Such cases are sometimes encountered in clinical practice.

RLD can be due to interstitial diseases, such as pulmonary fibrosis; non-respiratory conditions that secondarily impede lung expansion, such as muscle weakness, pleural diseases, obesity, and kyphoscoliosis; and conditions that directly affect lung function, such as CHF. Several studies have found the prevalence of spirometry-defined RLD to be 7-14%.[24-26] The prevalence of RLD is higher in males, heavy smokers, elderly individuals, individuals with a lower level of education, individuals with diabetes, individuals with CHF, and individuals with a very low or very high body mass index. Heavy smokers commonly have smoking-related interstitial lung disease, which can result in RLD or CLD.[27]

The obesity epidemic does not spare developing countries. For several reasons, obesity introduces confounding factors in the interpretation of lung function. Obesity affects lung volume measurements and spirometric values, particularly by reducing ERV and, consequently, functional residual capacity.[28] In the present study, ERV was significantly lower in the group of patients diagnosed with obesity. Proportional reductions in FVC and FEV_1 resulting in a preserved or slightly increased FEV_1/FVC ratio have been reported in obese individuals. However, although statistically significant, reductions in FVC and FEV_1 are typically small, and FEV_1, FVC, and TLC usually remain within the range of predicted values.[6,28]

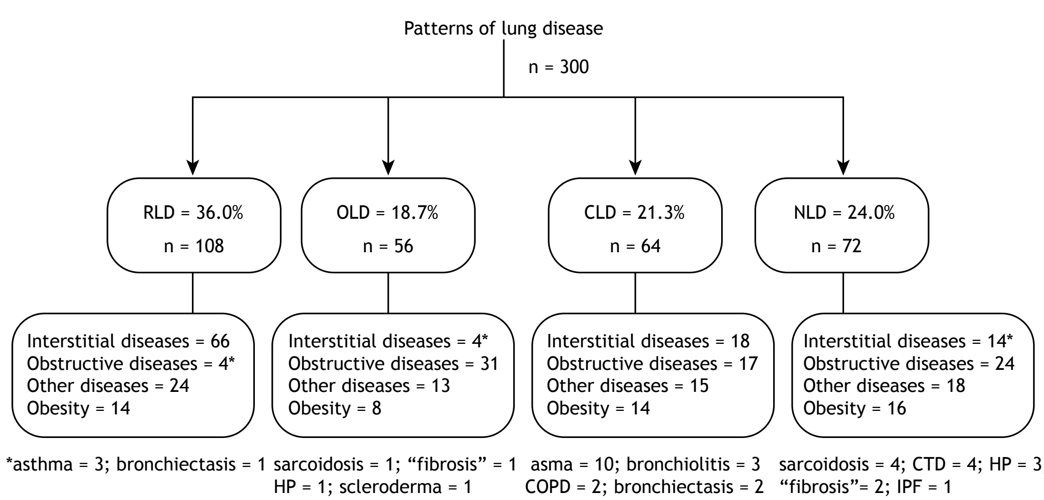

Figure 2. Functional diagnoses (based on lung volume and airway resistance measurements) and corresponding clinical diagnoses in 300 patients with spirometry results suggestive of restrictive lung disease. RLD: restrictive lung disease; OLD: obstructive lung disease; CLD: combined lung disease; NLD: nonspecific lung disease; HP: hypersensitivity pneumonia; CTD: connective tissue disease; and IPF: idiopathic pulmonary fibrosis.

In our study, obese individuals constituted half of the sample. Obesity was found in patients with RLD, OLD, CLD, and NLD. The interaction among obesity, lung function, asthma, and COPD has been the subject of several studies and excellent reviews.[6,29-31] Obesity is associated with an increased risk of asthma.[30,31] In obese individuals, dyspnea can be attributed to obesity itself or asthma, resulting in overdiagnosis and underdiagnosis.[32] Methacholine challenge testing is useful in such cases.[4]

Lung volume measurements can aid in differentiating between RLD and OLD in patients with spirometry results suggestive of restriction.[1] One study showed that the level of agreement between clinical diagnosis and diagnosis based on pulmonary function test results (including lung volume measurements) is low and therefore does not allow differentiation between RLD and OLD.[33]

In the present study, Raw measurements and the combination of $FEF_{25-75\%}$ and a high RV/TLC ratio allowed the diagnosis of airflow obstruction in several cases, the level of agreement between that diagnosis and clinical diagnosis being significant. Given that the total cross-sectional area of the airways decreases dramatically from the periphery to the central regions of the lung, Raw measurements are theoretically less sensitive to peripheral changes. However, measurements of specific Raw can be useful. One study showed that Gaw measurements were more sensitive than spirometry for detecting airflow obstruction in patients with bronchiolitis obliterans syndrome.[10]

In patients with COPD, in whom obstruction is peripheral and mostly mild, the FEV_1/FVC ratio is low and Raw or specific Gaw is within the predicted range; however, in the pulmonary function laboratory setting, the opposite has also been observed. A study conducted nearly 30 years ago showed that a combination of clinical and whole-body plethysmography data detected 18% of airflow obstruction cases.[34] In a classic study of 26 postmortem lungs from sudden death victims, a nearly perfect hyperbolic correlation was found between mean bronchiolar diameter and Raw (r = 0.89), whereas the correlation between mean segmental bronchial diameter and Raw was not significant.[9] In the present study, high Raw × Lv was significantly associated with reduced $FEF_{25-75\%}$ and increased RV/TLC, suggesting a correlation with peripheral airway obstruction. All patients had an FEV_1/FVC ratio within the predicted range.

As occurred with obesity, a final diagnosis of "other diseases" was made in patients with RLD, OLD, CLD, and NLD. Diseases included CHF, pleural disease, chest wall disease (particularly kyphoscoliosis), and neuromuscular disease. Of the 102 patients with interstitial lung disease, only 66 (65.0%) had RLD alone, as confirmed by TLC measurements. The remaining 36 had OLD alone (n = 4), CLD (n = 18), or NLD (n = 14). Combined pulmonary fibrosis and emphysema is a relatively common condition, given that both are smoking-related diseases.[35] In patients with connective tissue disease, bronchiolitis and emphysema associated with interstitial disease and muscle weakness can result in OLD and NLD, respectively.[36,37] In patients with hypersensitivity pneumonia or sarcoidosis, airway involvement is common and can result in OLD.[38,39]

In a study by Hyatt et al.,[4] 68% of the patients with NLD had a final diagnosis of OLD, which is in accordance with the ATS/ERS guidelines stating that proportional reductions in FVC and FEV_1 with TLC within the predicted range are indicative of OLD. However,

Table 3. Anthropometric and functional variables in patients with spirometry results suggestive of restrictive lung disease (N = 300), by clinical diagnosis.[a]

Variable	Clinical diagnosis				p
	Interstitial diseases (n = 102)	Obstructive diseases (n = 76)	Other diseases (n = 70)	Obesity (n = 52)	
Age, years	57.3 ± 12.9*	59.0 ± 15.7*	55.9 ± 14.4	50.2 ± 13.7	0.006
Female gender, %	70*	68*	49	50	0.007
BMI, kg/m²	28.3 ± 5.9*	29.8 ± 7.0*	28.6 ± 5.8*	41.3 ± 7.1	< 0.001
VC%	64.3 ± 10.9*	69.5 ± 8.6	62.4 ± 12.2*	70.3 ± 10.2	< 0.001
FVC%	63.0 ± 10.8*	67.8 ± 8.0	61.8 ± 11.9*	69.0 ± 9.3	< 0.001
FEV_1/FVC	0.83 ± 0.06	0.77 ± 0.06	0.80 ± 0.05	0.81 ± 0.04	< 0.001
FRC%	70.8 ± 19.1	96.6 ± 23.6*	85.2 ± 18.6	77.0 ± 17.7	< 0.001
ERV%	65.0 ± 36.3*	59.7 ± 41.4*	53.4 ± 27.3*	33.9 ± 18.1	< 0.001
RV%	77.3 ± 23.8*	118.6 ± 29.6	105.7 ± 29.7	99.5 ± 32.0	< 0.001
RV/TLC	0.40 ± 0.09	0.49 ± 0.09*	0.46 ± 0.10*	0.41 ± 0.10	< 0.001
TLC%	70.2 ± 12.9*	88.6 ± 12.8*	77.4 ± 13.0	82.2 ± 10.2	< 0.001
DLCO, %[b]	53.3 ± 16.8*	79.3 ± 19.8	59.1 ± 19.4*	82.9 ± 17.7	< 0.001
Raw × Lv, lognormal	1.42 ± 0.43	2.41 ± 0.43*	2.39 ± 0.70*	1.60 ± 0.37	< 0.001

FRC: functional residual capacity; ERV: expiratory reserve volume; and Raw × Lv: specific airway resistance corrected for lung volume. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]n = 260. *p < 0.05; obesity vs. the remaining groups. Tukey's test.

many of the patients with airway disease had a reduced FEV_1/slow VC ratio. In the present study, such cases were excluded, and, as a result, only one third of all NLD patients were clinically diagnosed with OLD.

Our sample selection strategy limits generalizability of results. Because of the large number of patients routinely treated at the study facilities, selected patients were not consecutive. It is possible that there was discrepancy between functional and clinical diagnoses, given that not all tests for other causes of RLD were performed. However, we believe that the objective of the present study was achieved.

In conclusion, lung volume and Raw measurements are often necessary in order to provide an appropriate characterization of the pattern of lung disease in patients with spirometry results suggestive of restriction. Diseases accompanied by airflow obstruction can result in a restrictive pattern on spirometry.

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