Original Article

Association of airway resistance measured by body plethysmography with clinical outcomes in COPD

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ABSTRACT

Background: The assessment of airway resistance (Raw) in chronic obstructive pulmonary disease (COPD) has been shown to be relevant for better understanding the symptoms and early diagnosis of the disease. Numerous studies have investigated the relationship between clinical outcomes and parameters of airway resistance obtained through impulse oscillometry in COPD. However, this relationship with airway resistance obtained by whole-body plethysmography remains unknown. **Objectives:** To investigate the association between specific airway resistance (sRaw, by whole body plethysmography) and clinical outcomes of lung function, functional and maximum exercise capacity, health status and dyspnea in individuals with COPD. **Methods:** Assessments included lung function (spirometry and whole body plethysmography), functional and maximum exercise capacity (6-minute walking test and cardiopulmonary exercise test, respectively); health status (COPD Assessment Test) and limitation by dyspnea in daily life (Medical Research Council scale). **Results:** Seventy-three individuals with moderate to very severe stable COPD were included. sRaw correlated moderately with spirometric variables such as FEV1%predicted ($r=-0.66$) and RV/TLC ratio ($r=0.53$) ($P<0.0001$, for both). However, there was no clinically relevant correlation with any other outcome. **Conclusions:** In subjects with stable COPD, sRaw assessed by body plethysmography correlates moderately with spirometric outcomes which are also indicative of obstructive disorder and air trapping, but does not correlate meaningfully with other clinical outcomes.

Keywords: Airway Resistance; Plethysmography, Whole Body; Chronic Obstructive Pulmonary Disease; Respiratory Function Tests.

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Conflict of Interest
The authors declare that they have no conflict of interest.

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a systemic lung condition characterized by progressive airflow limitation and systemic features such as muscle dysfunction and impaired functionality [1]. Since it is a heterogeneous disease with multifactorial limitations and symptoms, the literature has quested for assessments that help clarifying its multidimensionality [2,3].

Spirometry is a widely used method to detect chronic airflow limitation in COPD; however, it does not provide information about the pathophysiology of the small airways in addition to being a forced maneuver, which can cause small airways closure during the test, affecting its representability [1,4,5]. Assessment of airway resistance (Raw) provides additional information about airway dysfunction. Among the available techniques to assess Raw are impulse oscillometry (IOS) and whole body plethysmography [6]. IOS evaluates Raw through sound waves at different frequencies applied to the airways. Body plethysmography, on the other hand, has been considered the gold standard for assessing Raw, and evaluates the resistance based on changes in volume and pressure. Considering that Raw varies with lung volume, it is necessary to correct the volume in which it is measured. Hence, the resistance evaluated is called specific (i.e., sRaw) [7].

Several studies showed weak to moderate association of airway resistance parameters obtained by IOS with early diagnosis of COPD, small airway dysfunction and clinical outcomes of the disease [8-10]. However, this relationship is still unknown regarding airway resistance obtained by body plethysmography. We hypothesize that sRaw assessed by body plethysmography is at least moderately associated with clinical outcomes, as found in IOS, allowing sRaw to contribute to the understanding of multidimensional COPD phenotypes. Therefore, the aim of this study was to verify the association of sRaw assessed by body plethysmography with variables of lung function, functional and maximum exercise capacity, health status and limitation by dyspnea in COPD.

METHODS

Study design and sample

This was a cross-sectional analysis using baseline-only retrospective data from a convenience sample recruited between February/2016 and February/2020 for inclusion in a high-intensity exercise training program at the outpatient clinics of Respiratory Therapy and Pulmonology of the State University of Londrina, Brazil. Inclusion criteria for the training program were the diagnosis of COPD according to GOLD criteria [1]; clinical stability in the last 3 months; and absence of any severe/unstable cardiovascular disease and musculoskeletal impairment that could potentially hinder the assessments and training. For this specific cross-sectional analysis, individuals with complete data regarding assessment of airway resistance were included, and individuals with sRaw z-score above or below 3 standard deviations were excluded. The study was approved by the institution's Research Ethics Committee (1.730.247) and all participants signed an informed consent form.

Assessments

Lung function

Complete lung function was assessed using a plethysmograph (Vmax®Carefusion, Germany), according to the American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines [5]. Reference values specific to the Brazilian population were used, and post-bronchodilator values were employed for the analyses[11].

All pulmonary function tests were performed with the individuals seated while wearing a nose clip and instructed to keep their lips tightly sealed to prevent leaks. Participants kept their feet supported, hands resting on their laps, and maintained an upright posture without compensations during the maneuvers. For all tests, individuals received detailed instructions with practical demonstration and standardized verbal encouragement.

Specific airway resistance (sRaw)

sRaw was obtained by the same methodology described above. The plethysmograph consists of a hermetically sealed chamber resembling a glass-walled telephone box in shape and volume (about 600-1000 liters). The sRaw upper limits described by Piatti et al. [12] were adopted as recommended by Pereira et al. [7] (8.6 cmH2O/L/s/L for men and 8.0 cmH2O/L/s/L for women).

Exercise capacity

A cardiopulmonary exercise test (CPET) performed on a lower limb cycle ergometer was used to assess maximum exercise capacity, according to international recommendations [13]. Functional exercise capacity was assessed by the 6-minute walk test (6MWT), according to international recommendations [14] and reference values for Brazilians [15].

Dyspnea and health status

The Medical Research Council (MRC) scale assessed limitation due to dyspnea in daily life [16]; higher values indicate worse limitation. The COPD Assessment Test (CAT) assessed heath status and consists of eight domains that valuate patient's symptoms, limitations in activities of daily living, confidence and sleep [17]; higher scores indicate worse clinical impact of the disease.

Statistical analysis

Normality in data distribution was verified by the Shapiro-Wilk test, and results were described accordingly as mean±SD or median [interquartile range]. Correlations between sRaw and other outcomes were studied using Spearman's coefficient, and Kruskal-Wallis test was used to compare sRaw in different disease severities classified according to GOLD. Statistical significance was set as $P<0.05$.

RESULTS

Initially 74 subjects were included and after z-score analysis, one was excluded. Therefore, 73 subjects were analyzed (67±7 years; moderate to very severe airflow obstruction; Table 1). All subjects had sRaw values above the upper limit [7,12].

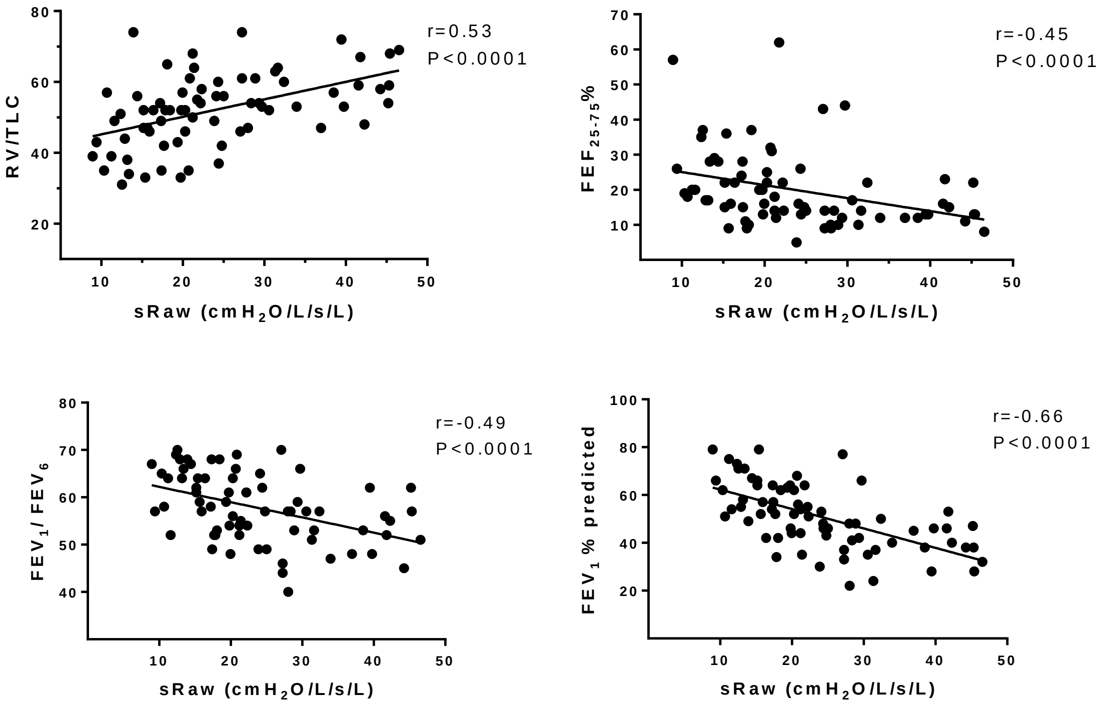
Table 1. Subject characteristics.

Variables	n=73
Male/female, n (%)	39 (53)/34 (47)
Age, y	67 ± 7
BMI, kg/m^2	28 ± 5
GOLD, n(%) II/III/IV	38(52%)/31(42%)/4(6%)
FEV_1, L	1.34 [1.00 – 1.90]
FEV_1, % predicted	51 ± 14
FVC, L	2.70 ± 0.77
FVC, % predicted	84 ± 19
VEF_1/CVF	50 ± 10
VEF_1/VEF_6	58 ± 7
$FEF_{25-75\%}$, L/s	0.41 [0.29 – 0.62]
$FEF_{25-75\%}$, % predicted	16 [13 – 24]
RV, L	3.28 [2.54 – 4.30]
RV, % predicted	155 [124 – 202]
TLC, L	7 ± 1.44
TLC, % predicted	120 [110 – 135]
RV/TLC	52 ± 10
sRaw, cmH_2O/L/s/L	21 [16 – 30]
6MWT, m	455 ± 78
Wmax CPET, W	43 ± 26
MRC, 1 to 5	3 [2 – 4]
CAT total, 0 to 40	16 [8 – 20]

Legend: BMI = Body mass index; GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV1 = Forced expiratory volume in the first second; FVC = Forced vital capacity; FEV6 = Forced expiratory volume in the sixth second; FEF25-75% = Mean forced expiratory flow between 25 and 75% of forced vital capacity; RV = Residual volume; TLC = Total lung capacity; sRaw = Specific airway resistance assessed by whole body plethysmography; 6MWT = Six-minute walk test; Wmax CPET = Maximum load achieved in the cardiopulmonary exercise test; MRC = Medical Research Council scale; CAT = COPD Assessment Test.

sRaw correlated moderately and positively with residual volume / total lung capacity ratio (RV/TLC) (r=0.53), and negatively with the mean expiratory flow between 25 and 75% of forced vital capacity ($FEF_{25-75\%}$), ratio between forced expiratory volume in the first and sixth second (FEV_1/FEV_6) and FEV_1%predicted (r=-0.45; r=-0.49 and r=-0.66, respectively) (Figure 1). No statistically significant or clinically meaningful correlations were found between sRaw and 6MWT, CPET, MRC and CAT (Table 2). Finally, individuals with GOLD III and IV had higher sRaw values compared to those with GOLD II ($P<0.003$ and $P<0.001$, respectively; Figure 2).

Figure 1. Correlations between sRaw and lung function variables



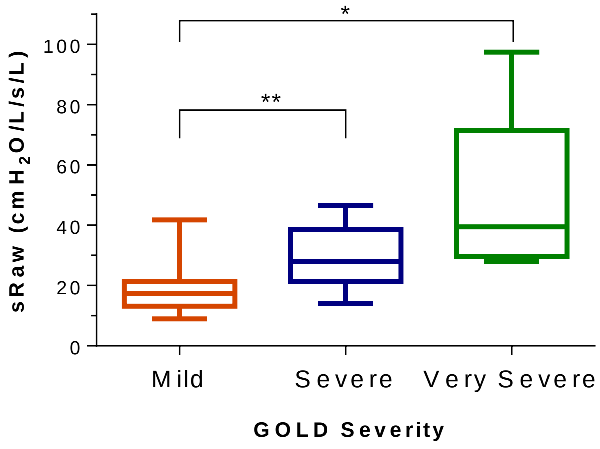
Legend: sRaw = Specific airway resistance assessed by whole body plethysmography; RV/TLC = ratio between residual volume and total lung capacity; FEF25-75% = forced expiratory flow between 25 and 75% of forced vital capacity; FEV1 / FEV6 = ratio between forced expiratory volume in the first and in the sixth second; FEV1 % predicted = forced expiratory volume in the first second in percentage of the predicted values.

Table 2. Correlation coefficients between sRaw and other outcomes

	r	*P*
FEV_1, % predicted	-0.66*	<0.0001
FEV_1/FEV_6	-0.49*	<0.0001
$FEF_{25-75\%}$, % predicted	-0.45*	<0.0001
RV/TLC	0.53*	<0.0001
6MWT, m	-0.13	0.313
Wmax CPET, W	-0.10	0.499
MRC	-0.01	0.933
CAT total	-0.09	0.492

Legend: sRaw = Specific airway resistance assessed by by whole body plethysmography; FEV1 = Forced expiratory volume in the first second; FEV6 = Forced expiratory volume in the sixth second; FEF25-75% = forced expiratory flow between 25 and 75% of forced vital capacity; RV/TLC = ratio between residual volume and total lung capacity; 6MWT = Six-minute walk test; Wmax CPET = Maximum load achieved in the cardiopulmonary exercise test; MRC = Medical Research Council scale; CAT = COPD Assessment Test.

Figure 2. Comparison of sRaw in different severities of COPD.



Legend: sRaw = Specific airway resistance; *P<0,001; **P<0,003.

DISCUSSION

Results of this study showed that there are moderate correlations between sRaw assessed by body plethysmography and lung function variables in individuals with moderate to very severe COPD, but no meaningful correlations with other clinical outcomes. The chronic inflammation and destruction of the airways developed in the course of the disease cause, among other consequences, a decrease in the caliber and number of efficient airways, resulting in increased Raw [1,3]. Even before FEV_1 declines, Raw can already be altered in mild COPD [4]. Subjects in this study presented at least moderate COPD, and therefore it is expected that they would have high sRaw [12].

FEV_1 is commonly used to identify airflow limitation, in addition to being an important marker in the disease progression [1]. In the present study, moderate correlation between sRaw and FEV_1 was found; similar results are also found with IOS. For example, Anderson et al. [8] showed moderate correlation between FEV_1 and variables that assess total airway resistance by IOS (R5: r=-0.42 and R5-R20: r=-0.49). In addition, the present study found moderate correlation between sRaw and FEF25-75%, which is one of the most used variables to assess small airway function due to its ease of being obtained by spirometry [18]. Changes in the small airways have a crucial importance in the pathophysiology of incipient COPD and sRaw is associated with these changes.

FVC is an essential element in the spirometry diagnosis of obstructive disease. However, the FVC maneuver requires a long expiration time and effort to reach the RV, somewhat limiting the use of the FVC in the elderly and individuals with obstructive diseases. Therefore, FEV_6 has been used as an alternative variable to FVC in the FEV_1/FVC ratio [5]. We found a moderate correlation between FEV_1/FEV_6 ratio and sRaw, which is in agreement with the literature in supporting the use of this ratio de identify obstructive disorder.

Progressive obstruction of the peripheral airways gradually causes air trapping that results in hyperinflation [1]. RV/TLC, as well as the ratio between inspiratory capacity (IC) and TLC (IC/TLC) are commonly used to identify static hyperinflation. Currently, RV/TLC has been shown to be more reliable and reproducible [19]. In the present study, there was correlation of greater magnitude between RV/TLC and sRaw (r=0.53) compared to that observed with R5-R20 evaluated by the IOS in the study by D'Ascanio et al.[20](r=0.3).

Hyperinflation reduces IC, so that this mechanism is responsible for the dynamic hyperinflation during exercise, resulting in exertional dyspnea and exercise limitation [1]. Although hyperinflation is closely related to dyspnea and sRaw correlated with air trapping and hyperinflation indices in the present study, there was no clinically relevant correlation between sRaw and dyspnea assessed by the MRC scale. Mahut et al. [21] found a weak correlation (r=0.24) between MRC scale (2 [1-3] points) and sRaw (23 ± 12cmH2O/L/s/L) assessed by body plethysmography. Their sample was composed by 108 individuals with COPD distributed among GOLD I (13%), GOLD II (44%), GOLD III (36%) and GOLD IV (7%). We hypothesize that the lack of relevant correlation between these variables in the present study may be due to the fact that our sample comprises a smaller proportion of individuals GOLD I and IV. Similarly, Anderson et al. [8] also did not find clinically relevant correlation between MRC scale and resistance assessed by IOS.

Yamamoto et al. [22] found only weak association between IOS resistance variables and 6MWT in COPD. The present study also did not show relevant correlations of sRaw not only with exercise capacity but also with health status. This may be due to the relatively preserved exercise capacity of our sample, although an actual absence of these associations is also possible.

Although the present study did not find statistically significant correlations with all the clinical and functional outcomes evaluated, it draws attention to the topic, encouraging researchers to perform more robust future studies. Examples include comparative studies between the two methods of Raw assessment and prospective cohort studies evaluating Raw using whole-body plethysmography for screening and early diagnosis of COPD. Additionally, whole-body plethysmography is more commonly used in clinical settings, and this study may be useful in highlighting the importance of the parameters obtained, which are often overlooked due to the lack of studies demonstrating their relevance, unlike what is observed with impulse oscillometry. Therefore, even without reflecting other clinical outcomes of COPD, sRaw assessed by body plethysmography is useful since it reflects important lung function outcomes, in addition to proving information that goes beyond sRaw (i.e., detailed assessment of lung volumes and capacities) and is more commonly found in clinical settings than IOS.

Study limitations

As limitations of the study, this was a convenience sample of patients, and an *a priori* sample size calculation was not performed. Furthermore, the sample did not comprise individuals with mild obstruction and only a few individuals with very severe disease, which at this moment limits the generalization of the findings. However, the sample represents a population typically recruited for pulmonary rehabilitation programs. Furthermore, this was a cross-sectional analysis, so causality cannot be inferred. Finally, due to the COVID-19 lockdown (2020/21) in Brazil, data collection was not feasible, making it necessary to use retrospectively collected data for this study.

CONCLUSIONS

In conclusion, in individuals with moderate to very severe and stable COPD, sRaw assessed by body plethysmography moderately correlates only with spirometric outcomes also indicative of air trapping and obstruction, but not with other clinical outcomes such as exercise capacity and dyspnea.

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