

Respiratory Oscillometry in Chronic Obstructive Pulmonary Disease: Association with Functional Capacity as Evaluated by Adl Glittre Test and Hand Grip Strength Test

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Purpose: Respiratory oscillometry has emerged as a powerful method for detecting respiratory abnormalities in COPD. However, this method has not been widely introduced into clinical practice. This limitation arises, at least in part, because the clinical meaning of the oscillometric parameters is not clear. In this paper, we evaluated the association of oscillometry with functional capacity and its ability to predict abnormal functional capacity in COPD.

Patients and Methods: This cross-sectional study investigated a control group formed by 30 healthy subjects and 30 outpatients with COPD. The subjects were classified by the Glittre-ADL test and handgrip strength according to the functional capacity.

Results: This study has shown initially that subjects with abnormal functional capacity had a higher value for resistance ($p < 0.05$), reactance area (A_x , $p < 0.01$), impedance modulus (Z_4 , $p < 0.05$), and reduced dynamic compliance (C_{dyn} , $p < 0.05$) when compared with subjects with normal functional capacity. This resulted in significant and consistent correlations among resistive oscillometric parameters ($R = -0.43$), C_{dyn} ($R = -0.40$), A_x ($R = 0.42$), and Z_4 ($R = 0.41$) with exercise performance. Additionally, the effects of exercise limitation in COPD were adequately predicted, as evaluated by the area under the curve (AUC) obtained by receiver operating characteristic analysis. The best parameters for this task were R_4-R_{20} ($AUC = 0.779$) and A_x ($AUC = 0.752$).

Conclusion: Respiratory oscillometry provides information related to functional capacity in COPD. This method is also able to predict low exercise tolerance in these patients. These findings elucidate the physiological and clinical meaning of the oscillometric parameters, improving the interpretation of these parameters in COPD patients.

Keywords: chronic obstructive pulmonary disease, COPD physiopathology, forced oscillation technique, respiratory impedance, Glittre-ADL test, handgrip strength, exercise limitation

Introduction

Chronic obstructive pulmonary disease (COPD) accounts for 6% of deaths worldwide, with more than 90% occurring in low- to middle-income countries.¹ This disease is usually caused by exposure to noxious particles or gases, resulting in persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities.² At present, spirometry is considered the gold standard in assessing airflow limitation in COPD. However, spirometry requires high cooperation on the volunteers and great effort in executing the expiratory maneuver. This may result in variation in the quality of the test results since this procedure can temporarily cause several changes in the bronchomotor tone, leading to underdiagnosis.³⁻⁵ It was previously reported that only 30% of patients could perform maneuvers that meet all the quality standards defined by ERS/ATS, and the proportion is even lower in the elderly.^{6,7}

The forced oscillation technique, also known as respiratory oscillometry, is a non-invasive approach to investigate mechanical properties of the respiratory system by assessing airway impedance (pressure/flow signal). The method is based on applying low amplitude oscillatory pressures into the airway entrance during spontaneous ventilation.⁸ Another significant advantage is that oscillometry can provide detailed information on the respiratory system's mechanical characteristics that are complementary to that provided by spirometry. Due to these characteristics, oscillometry has emerged as a powerful method to extract clinically relevant information and provide insight into the mechanisms responsible for smoking-induced respiratory diseases. Since this method was introduced in the mid-1950s,⁹ it has been applied in COPD by many investigators.¹⁰ Areas of application included the diagnosis of precocious respiratory abnormalities in smokers and early-stage COPD,^{11–14} the categorization of airway obstruction level,¹⁵ and the evaluation of bronchodilator response.¹⁶ This method has been continuously improving in the last decades and has reached a high level of sophistication, currently representing the state-of-the-art in assessing lung function.¹⁷

Despite several attractive characteristics of oscillometry, this method has not been widely introduced into clinical practice.¹⁷ This limitation arises, at least in part, because the physiological or clinical meaning of the derived parameters is not clear. The functional abnormalities associated with COPD cause dyspnea on exertion, reduced exercise capacity, and poor quality of life.¹⁸

The ADL – Glittre test is an effective, easy-to-apply, valid, and reliable test for assessing functional capacity in COPD¹⁹ and interstitial lung disease.²⁰ It can be considered more descriptive than the 6-minute walk test (6MWT) to assess functional capacity, as it involves, in addition to walking, activities such as sitting and getting up from a chair, going up and down steps, and arm movements with weight support, tasks considered difficult for these patients.²¹ This method is sensitive and specific to distinguish COPD patients with abnormal and normal functional capacity.²²

The loss of muscle strength is directly linked to physical performance, mobility, and functionality in patients with COPD. The handgrip test proved to be valid in assessing the strength and is considered cheap, simple, easy and can be performed with a portable measurement tool.^{23–25} Therefore, the ADL – Glittre and the handgrip test have the potential to elucidate the physiological and clinical meaning of oscillometric parameters.

Some recent reports investigate the association of oscillometric indices with the change in 6MWT during and after pulmonary rehabilitation²⁶ and the exercise tolerance in COPD.^{27,28} However, the relationships between oscillatory parameters and ADL – Glittre and the handgrip test were not evaluated, and the association of oscillometry and functional capacity is not fully understood.

Based on the abovementioned considerations, the objectives of the present study were (1) to investigate the association between oscillometric parameters and changes in ADL – Glittre and the handgrip test; (2) to evaluate the accuracy of oscillometry as a predictor of abnormal functional capacity in COPD.

Materials and Methods

Study Design

All analyses were conducted on the same examination day in this cross-sectional study. The subjects assessed symptoms, measurement of oscillometry, respiratory pressures, spirometry, handgrip test, and ADL–Glittre in that order. The research ethics board of the State University of Rio de Janeiro approved this research (protocol 2927/2011), and post-informed consent was obtained before inclusion in the study. The study was conducted following the principles of the Declaration of Helsinki.

Subjects

We studied subjects diagnosed according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria,² and over 40 years old. They have no history of respiratory infections in the last thirty days at the time of exams and no history of cardiovascular or orthopedic diseases. Before the exams were performed, all patients took their usual medication, except for bronchodilators (BD), to avoid interference in the assessment, as established by the American Thoracic Society/European Respiratory Society (ATS/ERS).²⁹

Healthy subjects were evaluated as a control group. They were clinically stable and with spirometric and oscillometric exams compatible with normality.^{30,31} They were also over 40 years old, non-smokers, with no history of respiratory infections in the last thirty days at the time of the exams, no cardiovascular, pulmonary, or orthopedic diseases.

The study involved a group of COPD patients with 30 subjects and a control group formed of 30 subjects. These numbers were based on similar previous works in the literature.^{26,32}

Spirometry

Spirometry analysis was conducted following the standard protocols of the American Thoracic Society/European Respiratory Society.^{29,33} The analyzed parameters were the forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), the FEV1/FVC ratio, and the forced expiratory flow (FEF) between 25% and 75% of the FVC (FEF/FVC) ratio. These parameters were expressed as absolute values and as a percentage of the predicted values (% of predicted), and the reference values were obtained from the equations of Pereira et al.³¹ Forced expiratory maneuvers were repeated until three sequential measurements were obtained. The studied indexes were obtained using the best curve, which was selected based on the higher values of FEV1 plus FVC. Lung function data were collected at post-bronchodilator test.²

The software automatically detected non-acceptable maneuvers according to ATS criteria, providing quality control of the spirometric exams.

Oscillometry

These measurements were performed using a previously described instrument³⁴ according to standard recommendations.⁸ Briefly, a pseudorandom sinusoidal signal with 2 cmH₂O peak-to-peak of amplitude, containing all harmonic of 2 Hz between 4 and 32 Hz, was applied by a loudspeaker. The pressure input (P) was measured with a Honeywell 176 PC pressure transducer (Microswitch, Boston, MA, USA), and the airway flows (V') with a screen pneumotachograph coupled to a similar transducer. The signals were digitized at a rate of 1024 Hz by a personal computer, and a fast Fourier transform (*F*) was computed using blocks of 4096 points with 50% overlap to evaluate respiratory impedance [$Z_{rs} = (F(P)/F(V'))$]. Three acceptable tests of 16s were performed, and the result adopted was the mean score. To exclude outlying values, the coefficient of variation of respiratory resistance at the lowest oscillation frequency (4 Hz) for the three measurements was $\leq 10\%$. The test was considered acceptable if the volunteers presented stable tidal volumes and rates and were free of pauses. Common artifacts such as swallows, coughs, and leaks were identified by evaluating flow and pressure signals, and the acquisition was repeated until three stable and without artifacts were obtained. Only exams with coherence function ≥ 0.9 in the whole frequency range studied were accepted to reduce the influence of spontaneous breathing.

The interpretation of the oscillometric results was performed according to recent international standards.⁸ We evaluated the resistance at 4 and 20 Hz (R4 and R20, respectively), related to the airway and tissue Newtonian resistance and the delayed airway resistance resulting from the gas redistribution. The difference between R4 and R20 (R4-R20) was evaluated as an indicator of the frequency dependence of the respiratory resistance. This parameter is related to respiratory system non-homogeneities.

Reactive properties were analyzed using the respiratory system dynamic compliance (C_{dyn}), resonance frequency (fr), the area under the reactance curve (A_x), and the impedance module. C_{dyn} is related to the total compliance of the respiratory system. The reactance at 4 Hz was used to calculate C_{dyn} ($C_{dyn} = 1/2\pi fX_4$). The frequency at which respiratory reactance becomes zero is known as the resonance frequency, which reflects the homogeneity of the respiratory system. A_x was analyzed using the area composed of the lowest frequency (4Hz), the associated reactance (X₄), and the fr. The respiratory system's total mechanical load was studied by analyzing the 4 Hz impedance module (Z₄), which integrates resistive and elastic respiratory load.²²

ADL - Glittre

The test started with the subjects seated on a chair.¹⁹ At a starting signal, they stood up and then walked 5 m, crossed over an interposed 2-step staircase, and walked another 5 m up to a 2-shelf fixture, which was adjusted individually to the

shoulder and waist height of each subject. Three bags weighing 1 kg each positioned on the top shelf had to be moved one by one to the bottom shelf, down to the floor, back to the bottom shelf, and finally to the top shelf again. The subjects then walked back to the initial chair where they had started, crossed over the 2-step stairs, sat down, and immediately started the next lap by rising again. Each step of the stair was 17 cm high and 27 cm deep. The subjects were asked to complete five laps as quickly as possible, and the primary outcome of the test is time to perform its five laps. They were allowed to rest if necessary but were told to resume activity as soon as possible. The chronometer was not stopped, and the subjects carried a backpack containing 2.5 kg (women) or 5.0 kg (men). Results in COPD patients were compared with reference values.³⁵

Handgrip Test

This analysis was performed using absolute and relative handgrip strength (HGS) measurements.³⁶ The handgrip test was performed using a handheld hydraulic dynamometer (Saehan, SH 5001). Participants were instructed to sit with their elbows flexed at a 90° angle, using the dynamometer in their hands in a neutral position. They were asked to squeeze the dynamometer with the maximal force for up to 3 s. They were allowed at least 60s of rest between measurements. Three attempts were made with each hand, and the highest value was used for analysis. These measurements were compared with a reference population.³⁷

Statistical Analysis

Data were initially tested for normality using the Shapiro–Wilk test (OriginLab Origin® 8.0, Microcal Software, Inc. Ostend, Belgium), and when the sample showed a normal (parametric) distribution behavior, the Two-Sample *t*-Test was used to analyze the groups. On the other hand, when the distribution presented a non-normal (non-parametric) characteristic, the Mann–Whitney test analyzed the groups.

Correlation analyses were performed using Pearson correlations for normally distributed data and Spearman correlations when the data were not normally distributed (GraphPad Prism 5.03, GraphPad Software, La Jolla, CA, USA). Those associations were classified as suggested by Dawson and Trapp.³⁸ The $p < 0.05$ was used to consider the statistically significant differences.

The accuracy of oscillometry as a predictor of exercise tolerance in COPD was evaluated using receiver operator characteristic (ROC) analysis. These evaluations were performed for the two studied exercise tolerance outcomes. The cut-off value used for the Glittre-ADL test was 210 s, which previous studies showed as sensitive and specific to distinguish COPD patients with an abnormal and normal functional capacity.²² In the handgrip analysis, we considered cut-off values of <30 kgf for men and <20 kgf for women (dominant hand) to identify dynapenia in COPD patients.^{39,40} We identified optimal prediction cut points as those yielding the best compromise between sensitivity and specificity. The area under the curve (AUC) was calculated to estimate the predictive capability of the poor functional performance and muscle function. In this analysis, AUCs >0.70 were considered adequate for predictive use,⁴¹ while values >0.90 were considered in the high predictive accuracy range.⁴² To complement ROC analysis, multivariate logistic regression (MLR) was used to determine the best oscillometric parameter to predict abnormal functional capacity in COPD.

Results

As shown in Table 1, we enrolled a group of 60 participants (30 controls and 30 patients). The airflow limitation severity was classified as mild in 4 patients, moderate in 16, severe in 7, and very severe in 3 patients. Spirometric parameters were significantly reduced in individuals with COPD. There was an increase in age and pack-years in the COPD group. Table 1 also shows biometric and spirometric characteristics in groups taking the Glittre-ADL test and Handgrip strength as reference. There was no change in height, body mass, and body mass index (BMI) in these groups.

Oscillometric Parameters Classified According to the Exercise Performance Tests

Taking the AVD-Glittre test as reference (Table 1), Figure 1 shows that the individuals with abnormal results presented significant changes ($p < 0.01$) in all parameters.

Table 1 Subject Demographics and Spirometric Characteristics Were Reported as Mean $\pm$ Standard Deviation Considering the Basic Group of Controls and COPD Volunteers, and Groups Taking the Glittre-ADL Test and Handgrip Strength as Reference. The Percentages of COPD Patients Presenting Abnormal Values According to Glittre-ADL Test and Handgrip Test Were 53.3% and 13.3%, Respectively

	Basic Groups			Glittre-ADL Test			Handgrip		
	Control (n = 30)	COPD (n = 30)	p	Normal (n = 32)	Abnormal (n = 28)	p	Normal (n = 52)	Abnormal (n = 8)	p
Age (years)	49.9 $\pm$ 15.5	64.4 $\pm$ 6.9	***	50.9 $\pm$ 15.5	64.3 $\pm$ 7.1	***	56.2 $\pm$ 14.5	63.6 $\pm$ 7.3	ns
Height (cm)	166.1 $\pm$ 8.5	161.6 $\pm$ 11.4	ns	166.3 $\pm$ 8.6	161.1 $\pm$ 11.3	ns	164.8 $\pm$ 10.4	157.9 $\pm$ 6.1	ns
Weight (kg)	69.4 $\pm$ 11.3	66.9 $\pm$ 21.1	ns	68.9 $\pm$ 11.3	67.3 $\pm$ 21.7	ns	69.6 $\pm$ 17.3	58.9 $\pm$ 8.5	ns
BMI (kg/m ²)	25.0 $\pm$ 2.5	25.3 $\pm$ 6.0	ns	24.8 $\pm$ 2.5	25.6 $\pm$ 6.1	ns	25.4 $\pm$ 4.7	23.7 $\pm$ 3.6	ns
Gender (male/female)	12/18	13/17	-	11/19	12/16	-	23/29	2/6	-
Pack-years	0	67.1 $\pm$ 43.4	-	2.5 $\pm$ 10.2	68.9 $\pm$ 44.2	***	25.2 $\pm$ 38.1	87.7 $\pm$ 54.6	***
FVC (L)	3.8 $\pm$ 1.1	2.7 $\pm$ 1.0	***	3.8 $\pm$ 1.1	2.7 $\pm$ 1.0	***	3.4 $\pm$ 1.2	2.5 $\pm$ 0.7	ns
FVC (%)	100.7 $\pm$ 15.2	79.9 $\pm$ 18.1	***	99.9 $\pm$ 15.2	79.3 $\pm$ 18.4	***	91.6 $\pm$ 19.9	81.8 $\pm$ 16.4	ns
FEV ₁ (L)	3.2 $\pm$ 0.8	1.6 $\pm$ 0.8	***	3.1 $\pm$ 0.9	1.6 $\pm$ 0.8	***	2.5 $\pm$ 1.1	1.5 $\pm$ 0.5	*
FEV ₁ (%)	103.0 $\pm$ 16.1	59.0 $\pm$ 19.5	***	101.3 $\pm$ 17.2	57.9 $\pm$ 19.6	***	84.3 $\pm$ 28.4	59.7 $\pm$ 18.1	*
FEV ₁ /FVC (%)	86.6 $\pm$ 7.6	57.4 $\pm$ 10.6	***	85.4 $\pm$ 8.9	56.8 $\pm$ 10.7	***	74.3 $\pm$ 17.2	56.9 $\pm$ 9.3	**
FEF ₂₅₋₇₅ (L)	3.7 $\pm$ 1.3	0.8 $\pm$ 0.5	***	3.6 $\pm$ 1.4	0.7 $\pm$ 0.5	***	2.5 $\pm$ 1.8	0.7 $\pm$ 0.3	**
FEF ₂₅₋₇₅ (%)	117.3 $\pm$ 33.8	30.5 $\pm$ 15.9	***	113.1 $\pm$ 36.8	29.2 $\pm$ 15.5	***	80.9 $\pm$ 51.1	28.7 $\pm$ 14.8	**
FEF ₂₅₋₇₅ /FVC (%)	102.9 $\pm$ 27.8	37.1 $\pm$ 14.9	***	99.9 $\pm$ 29.3	35.8 $\pm$ 14.5	***	75.5 $\pm$ 39.7	34.1 $\pm$ 14.5	**

Notes: *p < 0.05; **p < 0.01; ***p < 0.0001.

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV₁/FVC, Tiffeneau index; FEF₂₅₋₇₅, forced expiratory flow between 25% e 75%; n, number of evaluated patients; ns, not significant; (%), percentile of the predicted values; ns, not significant.

When the Handgrip test is used as a reference (Table 1), it observed increases in R4 and R4-R20 (Figure 2). Considering the reactive parameters, reduced Cdyn and increased values of fr, Ax, and Z4 were observed.

ADL – Glittre and Handgrip Strength Test

Table 2 depicts the results of the AVD-Glittre and Handgrip in the whole group of patients with COPD. There was a significant increase in performed time in the COPD group compared to predicted values (p < 0.0001). In similar comparisons, significant reductions were observed considering the handgrip strength (p < 0.01).

Correlation Analysis

These evaluations were performed considering the group of COPD patients. As can be seen in Table 3, one resistive (R4) and three reactive (Cdyn, Ax, Z4) parameters presented significant (p < 0.05) direct associations with the ADL-Glittre test.

Significant direct correlations (p < 0.045) were also observed between resistive (R4) and reactive (fr and Z4) oscillometric parameters with the handgrip strength test in the dominant hand (Table 3). Considering the non-dominant hand, significant direct correlations (p < 0.045) were observed between R4, Cdyn, fr, Ax, and Z4.

Oscillometry as a Predictor of Exercise Tolerance in COPD

Of the 60 obtained values, 32 had a Glittre-ADL test >210 s, in which thirty test times were estimated in the control group, and 2 were normal values measured in the COPD group. The 28 (46.7%) remaining values were obtained in COPD patients with a Glittre-ADL test <210 s. Table 4 depicts the accuracy, sensitivity, specificity, and cut-off point for the oscillometric parameters in predicting abnormal functional capacity in COPD, as evaluated by the Glittre-ADL test. Healthy subjects and COPD patients were used in this analysis. R4-R20, fr, and Ax achieved high prediction accuracy (AUC >0.90) among the studied parameters. Figure 3A shows the ROC curves of the two more accurate parameters obtained using the Glittre-ADL test as a reference. In this case, MLR showed that R4-R20 was the best oscillometric parameter to predict abnormal function capacity (p = 0.0004).

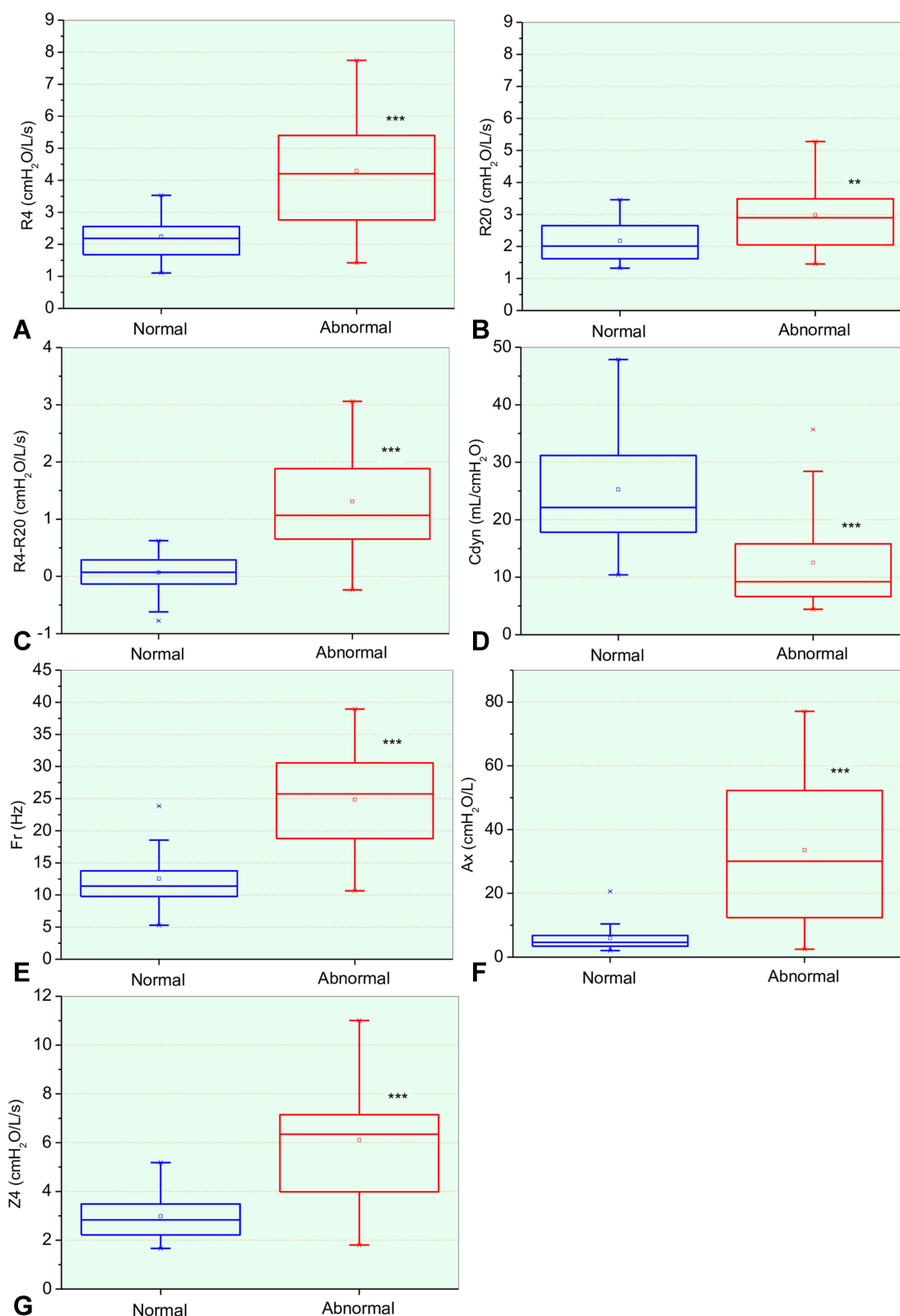


Figure 1 Oscillometric parameters in patients classified according to the ADL – Glittre test. R4, resistance at 4Hz (A); R20, resistance at 20Hz (B); difference between R4 and R20 (C); Cdyn, dynamic complacency (D); fr, resonance frequency (E); Ax, area under the reactance curve (F); Z4, respiratory impedance module (G); n, number of patients evaluated; ns, not significant; * p < 0.05; ** p < 0.01; *** p < 0.0001.

Abbreviations: R4, resistance at 4Hz; R20, resistance at 20Hz; R4-R20, frequency dependence of resistance; Cdyn, dynamic complacency; fr, resonance frequency; Ax, area under the reactance curve; Z4, respiratory impedance module.

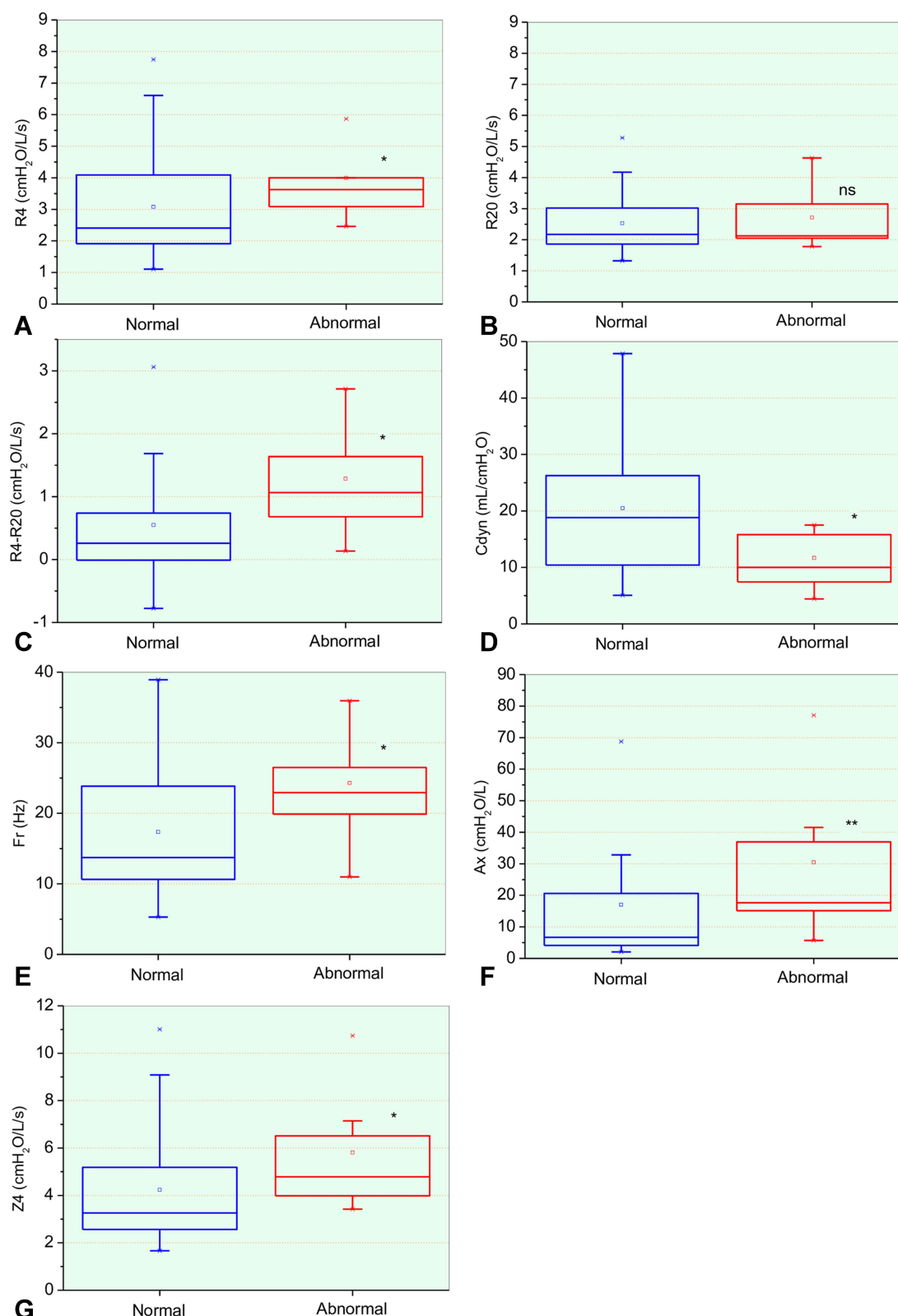


Figure 2 Oscillometric parameters classified in patients according to the Handgrip analysis. R4, resistance at 4Hz (A); R20, resistance at 20Hz (B); difference between R4 and R20 (C); Cdyn, dynamic complacency (D); fr, resonance frequency (E); Ax, area under the reactance curve (F); Z4, respiratory impedance module (G); n, number of patients evaluated; ns, not significant; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.0001$.

Abbreviations: R4, resistance at 4Hz; R20, resistance at 20Hz; R4-R20, frequency dependence of resistance; Cdyn, dynamic complacency; fr, resonance frequency; Ax, area under the reactance curve; Z4, respiratory impedance module; ns, not significant.

Table 2 Predicted and Measured Values in Patients with COPD for Total Glittre-ADL Test Time and Handgrip Analysis

	Predicted	Measured	p
ADL-Glittre test			
Test time (s)	182.7 ± 8.8	299.4 ± 59.2	**
Handgrip			
Dominant hand (kg)	31.9 ± 9.7	27.9 ± 9.1	*
Non-dominant hand (kg)	30.2 ± 8.6	26.7 ± 8.4	*

Notes: *p < 0.01; **p < 0.0001.

Table 3 Correlation Analysis in Patients with COPD Describing the Association of Oscillometric Parameters with Total Glittre-ADL Test Time and Handgrip Analysis

		R4	R4-R20	R20	Cdyn	Fr	Ax	Z4
ADL-Glittre test								
Test time (s)	r	0.365	0.304	0.311	-0.404	0.312	0.415	0.407
	p	0.047	0.103	0.094	0.025	0.094	0.022	0.026
Handgrip								
Dominant hand	r	-0.413	-0.231	-0.447	0.313	-0.379	-0.343	-0.368
	p	0.023	0.219	0.013	0.092	0.039	0.063	0.045
Non-dominant hand	r	-0.427	-0.256	-0.448	0.369	-0.416	-0.399	-0.395
	p	0.019	0.173	0.013	0.045	0.022	0.029	0.031

Note: Significant p-values (<0.05) are described in bold.

Abbreviations: R4, resistance at 4Hz; R20 resistance at 20 Hz; R4-R20, frequency dependence of the resistance; Cdyn, dynamic compliance; fr resonance frequency; Ax, area under the reactance curve; Z4, impedance module in 4Hz.

Table 4 Accuracy of Oscillometry in Predicting Abnormal Functional Capacity in COPD Based on Glittre-ADL Test

	AUC	95% CI	Se (%)	Sp (%)	Cut-Off
R4	0.859	0.745–0.936	71.43	93.75	3.278
R4-R20	0.906	0.803–0.966	82.14	96.87	0.546
R20	0.733	0.603–0.839	67.86	71.87	2.360
Cdyn	0.867	0.755–0.941	75.00	87.50	15.805
fr	0.903	0.799–0.964	85.71	84.37	15.113
Ax	0.904	0.800–0.965	78.57	93.75	15.143
Z4	0.874	0.763–0.946	82.14	84.37	3.766

Note: The two highest values of AUC are shown in bold.

Abbreviations: R4, resistance at 4Hz; R20 resistance at 20 Hz; R4-R20, frequency dependence of the resistance; Cdyn, dynamic compliance; fr resonance frequency; Ax, area under the reactance curve; Z4, impedance module in 4Hz; AUC, Area under the receiver operator characteristic curve; CI, 95% confidence interval; Se, sensitivity; Sp, specificity.

Considering the Handgrip analysis as a reference for abnormal functional capacity, of the 60 obtained values, 52 were in the normal range. Thirty were estimated in the control group, and 22 were normal values measured in the COPD group. The 8 (13.3%) abnormal values were obtained in COPD patients. The accuracies and cut-off points for the studied parameters in predicting abnormal functional capacity in COPD, as evaluated by the handgrip analysis, are presented in Table 5. All studied parameters provided an adequate predictive accuracy (AUC >0.70), except for R20. R4-R20 achieved the highest accuracy (AUC = 0.779), as shown in Figure 3B, which presents the ROC curves of the two more accurate parameters obtained using the handgrip analysis as a reference. The MLR revealed that R4-R20 was the most predictive parameter in detecting abnormal function capacity (p = 0.0443).

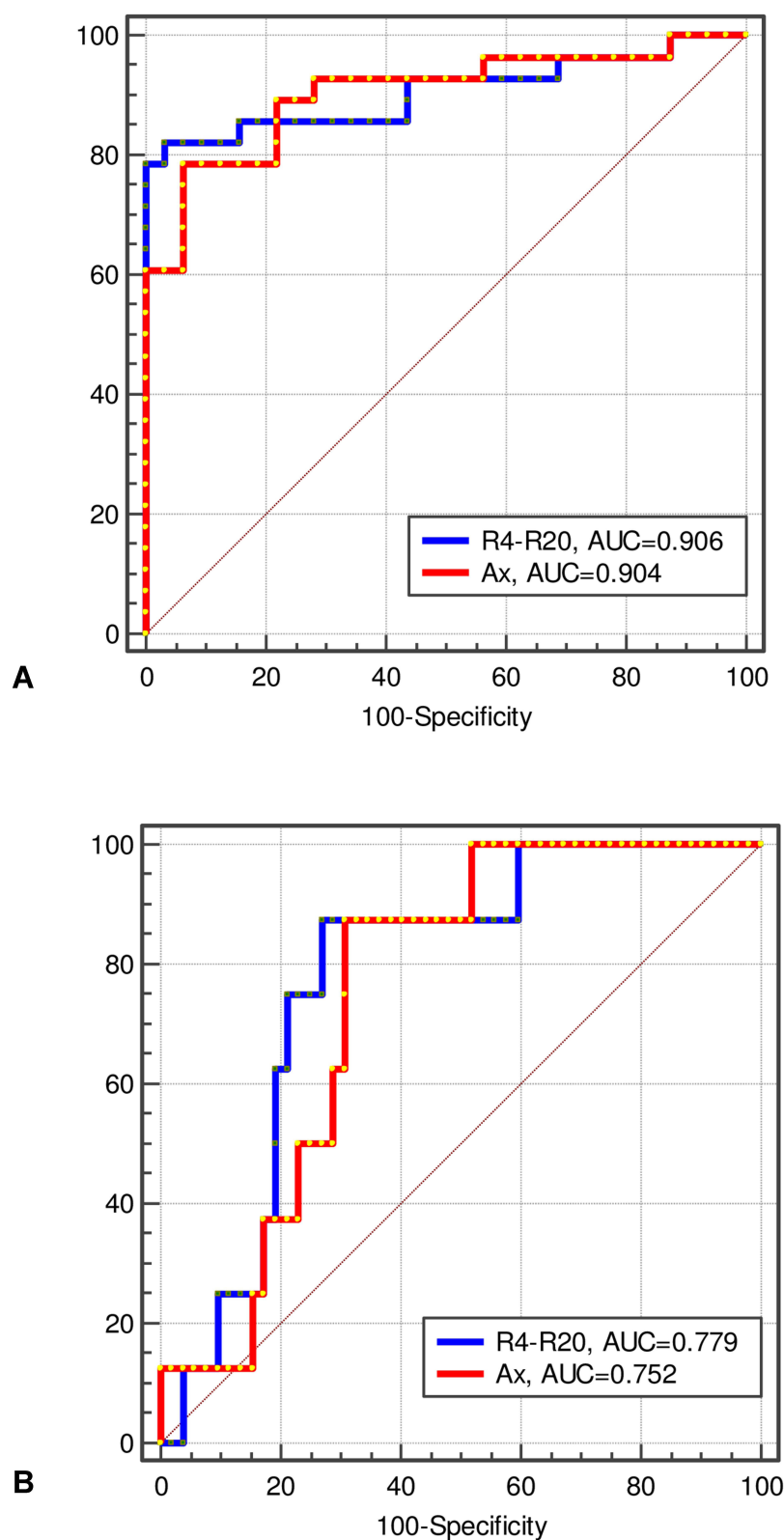


Figure 3 Analysis of receiver operator characteristic (ROC) for the two best parameters observed in predicting exercise tolerance in COPD. Results for the analysis are based on the ADL – Glittre test (**A**) and Handgrip analysis (**B**).

Abbreviations: AUC, the area under the ROC curve; R4-R20, resistance at 4Hz minus at 20Hz; Ax, area under the reactance curve.

Table 5 Accuracy of Oscillometry in Predicting Abnormal Functional Capacity in COPD Based on Handgrip Evaluations

	AUC	95% CI	Se (%)	Sp (%)	Cut-off
R4	0.724	0.593–0.831	87.50	61.54	2.806
R4-R20	0.779	0.653–0.876	87.50	73.08	0.652
R20	0.594	0.405–0.783	50.00	53.85	2.361
Cdyn	0.743	0.614–0.847	100.00	57.69	17.516
fr	0.726	0.595–0.833	87.50	67.31	18.779
Ax	0.752	0.624–0.855	87.50	69.23	16.904
Z4	0.745	0.616–0.849	100.00	51.92	3.275

Note: The two highest values of AUC are shown in bold.

Abbreviations: R4, resistance at 4Hz; R20 resistance at 20 Hz; R4-R20, frequency dependence of the resistance; Cdyn, dynamic compliance; fr resonance frequency; Ax, area under the reactance curve; Z4, impedance module in 4Hz; AUC, Area under the receiver operator characteristic curve; CI, 95% confidence interval; Se, sensibility; Sp, specificity.

Discussion

This study investigated the physiological and clinical meaning of the oscillometric parameters. It was evaluated whether oscillometry is correlated and would predict the poor exercise tolerance measured by the Glittre-ADL test and handgrip strength in 30 patients with COPD and 30 controls. It was revealed a clear association between oscillometry and functional capacity. The ROC curve analysis demonstrated that R4-R20 and Ax accurately predicted poor Glittre-ADL test and handgrip strength. These results provide clear evidence that oscillatory indices are related to physical performance and helpful in predicting poor exercise tolerance in COPD.

A functional limitation is a common and important finding in patients with COPD,² which is directly related to increased mortality,⁴³ a higher frequency of exacerbations and hospitalizations,⁴⁴ and a reduction in quality of life.²¹ The decrease in exercise capacity in individuals with COPD (Table 2) may be explained by ventilatory limitation, abnormalities in gas exchanges, and cardiovascular dysfunction.

Figure 1 shows how the drop in physical performance detected by the Glittre-ADL test impacts the respiratory mechanics evaluated by oscillometry. It is generally agreed that abnormal changes affecting primarily the lungs will also have significant systemic effects. Figure 1 supports this hypothesis and adds new information, revealing increased resistance values (R4, R20) in patients with Glittre-ADL test >210 s. The observed increases in ventilation heterogeneity (R4-R20, fr), respiratory work (Z4), elastic properties (Ax), and reduced compliance (Cdyn) were also in line with the changes typically observed in patients with COPD and exercise limitations. These changes reflect the worsening of airway obstruction, increased secretion, and changes in the pulmonary parenchyma in these patients.²

Considering the Handgrip as a reference method for detecting functional abnormalities, Figure 2 shows that the changes observed in oscillometric parameters were similar to those observed using the Glittre-ADL test as a reference. Interestingly, changes observed in oscillometry using Glittre-ADL test and Handgrip analysis are in close agreement with that previously observed using the 6MWD as a reference.²⁷

In agreement with the involved physiology,² Table 3 shows reasonable and significant direct associations between Glittre-ADL test time, Handgrip analysis, and parameters related to airway obstruction (R4), elastic properties (Ax), and respiratory work (Z4). The inverse association observed with Cdyn and Glittre-ADL test time and the direct correlation observed with Handgrip analysis are also consistent with these principles. The systemic effects due to lung abnormalities may also explain these relationships. The results presented in Table 3 are in close agreement with that obtained recently by Yamamoto et al²⁷ using the 6-minute walking distance (6MWD) as an index of exercise tolerance. Reasonable and significant associations were obtained among oscillometric parameters and 6MWD. The cited authors attributed the observed changes and associations to airflow limitation and dynamic hyperinflation as predominant factors defining exertional dyspnea and disease severity in COPD. These results also reflect Zeng et al,²⁸ who recently found correlations between resistive and reactive parameters with 6MWD in COPD. They are also in line with that obtained by Yamamoto et al.⁴⁵ The authors observed that oscillometric parameters correlated with exertional ventilatory parameters and reflected exercise tolerance in COPD subjects during cycle ergometer tests. Similar results were also observed in adults with sickle cell anemia, analyzing the correlations among 6MWD and oscillometric parameters.⁴⁶ The new information in Table 3 shows that these correlations extend to the ADL – Glittre test

and Handgrip analysis. The associations observed in Table 3 are also consistent with the weak to moderate correlations between respiratory mechanics evaluated by spirometric analysis and 6MWD^{47,48} and the ADL-Glittre test.¹⁹

Table 4 and Figure 3A show that R4-R20 achieved the highest accuracy among the oscillometric parameters in predicting exercise limitation, as evaluated by the ADL-Glittre test. MLR revealed that R4-R20 was the most predictive parameter in line with these findings. This high performance probably occurs because this parameter reflects ventilation heterogeneity, which results in abnormalities in gas exchanges. Other interesting findings were that *fr* and *AX* could also predict exercise limitation. It is also noteworthy that the three parameters mentioned achieved high accuracy in predicting exercise limitation (AUC >0.90).

As shown in Table 5 and Figure 3B, R4-R20 was the most accurate of the studied parameters in predicting abnormal functional capacity in COPD based on handgrip evaluations. MLR also described R4-R20 as the most predictive parameter. These findings are in close agreement with that obtained using ADL-Glittre test (Table 4), in which this parameter was also the most predictive. Another interesting finding was that *Ax* could also accurately predict using handgrip evaluations (Table 5) and the ADL-Glittre test (Table 4). A possible explanation for this might be that the changes in bronchial architecture resulting from COPD lead to an irregular ventilation distribution associated with imbalances in the pulmonary time constants.

There is currently a consensus in the literature on the need to develop new sensitive and non-invasive lung-function testing to allow early and accurate detection of pulmonary function decline.^{49–51} Respiratory oscillometry has been widely perceived as the state-of-the-art lung function analysis¹⁷ and one of the most promising emerging technologies in this area.^{52,53} However, although its advantages associated with a straightforward and detailed examination are particularly important, this method is not yet widely used. One of the main aspects limiting its wide routine application is that the obtained parameters are clinically challenging to interpret. In this practical context, the present study's findings could help improve clinical practice showing that the ventilatory changes evaluated by oscillometry may accurately anticipate the limitations during exercise in COPD. This ability is related to the causal relationships between adequate ventilation, oxygen availability, and physical performance.

A critical analysis of the potential limitations of the present study is necessary. First, it was a single-center study; hence, the results may not represent the entire patient population. One could argue that we only recruited 60 subjects and that the exact prediction accuracy remains unknown. Future studies should include a larger number of subjects. However, this preliminary analysis significantly contributes to an important debate in the literature concerning the clinical and physiological meaning of the oscillometric parameters and provides support for using these indexes in predicting the exercise performance in COPD.

One could argue that the study and reference populations are not well matched for age. However, the analyzed groups can be considered homogeneous because height is the determinant parameter in oscillometry, and this parameter is homogeneous among the studied groups.

One could also argue that we used estimated values of the AVD-Glittre test and Handgrip analysis in the control group. Although in practice, some value outside the normal range may arise in actual measurements, this is a rare event, so the use of normal values should not significantly influence the results. It is essential to consider also that the present study used worldwide-recognized cut-off values to distinguish normal and abnormal functional capacity parameters, which enhanced its generalizability.

Comparing oscillometric and standard spirometric measures to predict poor functional capacity would be very useful. This is an important issue to be addressed in future research.

The present study was intended to explore a possible connection between oscillometric parameters and functional performance and the accuracy of oscillometry as a predictor of abnormal functional capacity in COPD. The study was not designed to test the obtained cut-offs. It is a natural continuation of the present study and will be investigated in the following stages of this research.

Lastly, this study focused on whole-breath impedance measurements. Within-breath analysis was not evaluated. The development of similar analysis for within-breath impedance parameters is a clear direction for future research.

Conclusion

In conclusion, this study evaluated the association of oscillometry and functional capacity in COPD. It has been shown that the oscillometric parameters adequately described the presence of exercise limitation. This resulted in significant and consistent correlations among these parameters and indexes of functional capacity. The ROC analysis demonstrated that oscillometric parameters achieved adequate accuracy and that R4-R20 and Ax achieved high accuracy in predicting poor Glittre-ADL test and handgrip strength. These results support and add new information concerning Glittre-ADL and Handgrip analysis to previous findings using 6MWD. These results suggest that oscillometric parameters are associated with abnormal exercise performance in COPD, and may help predict poor functional performance in these patients.

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Disclosure

The authors report no conflicts of interest in this work.

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