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ORIGINAL RESEARCH

Oscillometry in Asthma: Respiratory Modeling and Analysis in Occupational and Work-Exacerbated Phenotypes

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Background: Asthma onset or worsening of the disease in adulthood may be associated with occupational asthma (OA) or work-exacerbated asthma (WEA). Oscillometry and respiratory modeling offer insight into the pathophysiology and contribute to the early diagnosis of respiratory abnormalities.

Purpose: This study aims to compare the changes due to OA and WEA and evaluate the diagnostic accuracy of this method.

Patients and Methods: Ninety-nine volunteers were evaluated: 33 in the control group, 33 in the OA group, and 33 in the WEA group. The area under the receiver operator characteristic curve (AUC) was used to describe diagnostic accuracy.

Results: Oscillometric analysis showed increased resistance at 4 hz (R4, $p<0.001$), 20 hz (R20, $p<0.05$), R4-R20 ($p<0.0001$), and respiratory work ($p<0.001$). Similar analysis showed reductions in dynamic compliance ($p<0.001$) and ventilation homogeneity, as evaluated by resonance frequency (Fr, $p<0.0001$) and reactance area ($p<0.0001$). Respiratory modeling showed increased peripheral resistance ($p<0.0001$), hysteresivity ($p<0.0001$), and damping ($p<0.0001$). No significant changes were observed comparing OA with WEA in any parameter. For OA, the diagnostic accuracy analyses showed Fr as the most accurate among oscillometric parameters (AUC=0.938), while the most accurate from respiratory modeling was hysteresivity (AUC=0.991). A similar analysis for WEA also showed that Fr was the most accurate among traditional parameters (AUC=0.972), and hysteresivity was the most accurate from modeling (AUC=0.987). The evaluation of differential diagnosis showed low accuracy.

Conclusion: Oscillometry and modeling have advanced our understanding of respiratory abnormalities in OA and WEA. Furthermore, our study presents evidence suggesting that these models could aid in the early diagnosis of these diseases. Respiratory oscillometry examinations necessitate only tidal breathing and are straightforward to conduct. Collectively, these practical considerations, coupled with the findings of our study, indicate that respiratory oscillometry in conjunction with respiratory modeling, may enhance lung function assessments in OA and WEA.

Keywords: occupational asthma, work-exacerbated asthma, pulmonary function, forced oscillations, respiratory modeling, fractional order modeling

Introduction

Asthma is defined by episodic and reversible airway constriction and inflammation in response to infection, environmental allergens, and irritants.[1] Adult-onset or worsening asthma may be work-related (WRA)[2] and is responsible for 5% to 10% of all cases of asthma in adults, preferably affecting young adults of working age.[3]

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WRA encompasses occupational asthma (OA) and work-exacerbated asthma (WEA).[2] OA is described as reversible airflow obstruction and/or bronchial hyperreactivity due to causes and conditions attributable to the work environment.[4] The diagnosis of OA is based on international consensus.[5] WEA is previously existing asthma, whether asymptomatic or not, that has worsened due to occupational exposure to chemical or physical agents.[6]

Spirometry establishes diagnosis and provides functional classification in asthma. However, the forced breathing maneuver requires cooperation and can alter bronchial tone.[7] Respiratory oscillometry is a non-invasive method that assesses the resistance and reactance of the respiratory system,[8] being performed under spontaneous ventilation.[9] The new information provided by this method contributes to a better understanding of pathophysiological abnormalities and allows the assessment of therapeutic response and optimization of treatment.[10]

The extended RIC (eRIC) model provides sensitive indicators of lung function and can differentiate between obstructed and non-obstructed airway conditions.[11] In these models, R is the analog of central airway resistance, Rp describes peripheral resistance, Rt reflects total resistance, and I and C are associated with lung inertia and compliance, respectively.[11–13] Recently, a fractional order model (FrOr) was proposed in combination with respiratory oscillometry,[14–16] allowing a more detailed description of the dynamic characteristics of the respiratory system. They are providing information on resistive properties, hysteresis, damping factor, and parenchymal elastance.[16]

Respiratory oscillometry has achieved high performance, representing the state of the art in terms of pulmonary function assessment.[17] Previous studies successfully evaluated the early diagnosis of respiratory changes in smokers,[18] in patients with sarcoidosis,[19] systemic sclerosis,[12] silicosis,[20] and work-related asthma.[21] However, oscillometry studies have not yet been conducted to investigate the differences between OA and WEA. Therefore, the objectives of the present work are 1) to analyze changes in respiratory mechanics in patients with OA and WEA; 2) compare changes due to OA and WEA through respiratory oscillometry, integer, and fractional order models, and 3) evaluate the diagnostic use of these methods.

Material and Methods

The pulmonary function test evaluations were carried out at the Biomedical Instrumentation Laboratory of the State University of Rio de Janeiro (LIB-UERJ) and approved by the Research Ethics Committee of the Pedro Ernesto University Hospital (HUPE). Before the test, all volunteers signed an informed consent form, and the principles of the Declaration of Helsinki were used to conduct the study.

Volunteers

The sample size calculation was initially performed using the MedCalc® 14.12.0 software (Medicalc Software, Mariakerke, Belgium) and based on a pilot study with fewer patients.[22] The assumed values of type I and type II errors were 10%. The minimum sample size obtained was 33 volunteers per group.

The control group was made up of healthy subjects, over 18 years old, with no history of previous lung disease, and with spirometric and respiratory oscillometry examinations compatible with normality. Volunteers with a history of occupational exposure were excluded, as it could introduce subclinical changes that could mask the abnormalities observed in patients with occupational asthma.

For the group with occupational asthma and asthma exacerbated at work, both sexes were included, over 18 years old, regardless of the treatment implemented, who had signed formal consent to the study, with or without a history of smoking. In all of the studied groups, exclusion criteria were previous lung disease and history of smoking or COVID-19. Before the exams, all patients were taking their usual medication. However, medications that could interfere with the assessment of the bronchodilator (BD) response were suspended, as established by the American Thoracic Society/European Respiratory Society (ATS/ERS).[23]

Spirometry

Spirometric analysis was performed by the standards of the Brazilian Society of Pneumology[24] and the American Thoracic Society/European Respiratory Society.[25] The parameters analyzed were forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC ratio, and forced expiratory flow (FEF_{25-75}) between 25 and

75% of the FVC ratio (FEF_{25-75}/FVC). Forced expiratory maneuvers were repeated until three sequential measurements were obtained. According to the American Thoracic Society (ATS) criteria, the software automatically detected unacceptable maneuvers, providing quality control of spirometric exams. The gradation of the severity of the obstruction is based on the FEV_1 values about those predicted: values ≤ 40%, severe obstruction; between 41 and 59%, moderate; and ≥ 60%, mild obstruction.[26]

Evaluation of Asthma Control

Asthma control was evaluated using the Asthma Control Test (ACT). Uncontrolled asthma was defined as an ACT score of less than 20, in accordance with the study conducted by Heijkenskjold-Rentzhog et al.[27]

Respiratory Oscillometry

Multifrequency respiratory oscillometry was performed. Pressure oscillations were applied in the frequency range of interest (4–32 hz) using an instrument developed in our laboratory and described previously[28] according to standard recommendations.[9] During the examination, the individual remained seated, using a nose clip, head in a neutral position, holding the cheeks and chin with both hands, minimizing the shunt effect of the upper airways, and breathing calmly through a mouthpiece. Three acceptable trials of sixteen seconds were carried out, obtaining the average result. Artifact-free exams with a coefficient of variation between measurements ≤ 10% were used. The oscillometric examination was performed before the spirometry test to avoid changes in the tone of the bronchial muscles due to the maximum effort performed in these maneuvers and their possible effects on oscillometric results.[7] Additionally, only examinations with a coherence function of 0.9[29,30] or greater across the entire frequency range were accepted, aiming to minimize the impact of spontaneous breathing.

Respiratory Impedance Models

The parameters of the studied models were estimated using the ModeLIB program, developed at LIB/UERJ using the LABVIEW™ 2018 environment (National Instruments, Austin, TX). Model parameters were estimated using the Levenberg-Marquardt algorithm to determine the nonlinear model coefficients that best represent the input data set in the sense of least squares.

Equation 1 Figure 1 shows the two-compartment (central and peripheral) integer-order model (eRIC) used to analyze respiratory impedance.[17] Resistance (R), inductance (I), and capacitance (C) are analogs of respiratory resistance, inertance, and compliance. Rp represents the peripheral resistance.

The fractional order model is described in Equation 2,3 and 4 and Figure 2. It includes frequency-dependent inertia (FrL), which considers the ability of fractional terms to approximate resistive properties ($0 \leq \alpha \leq 1$) and a tissue-related component described as a constant phase impedance in the form of fractional compliance (FrC) associated with a fractional impedance coefficient ($0 \leq \beta \leq 1$).

$$ZFrOr(j\omega) = FrL(j\omega)^{\alpha} + \frac{1}{FrC(jw)^{\beta}} \quad (1)$$

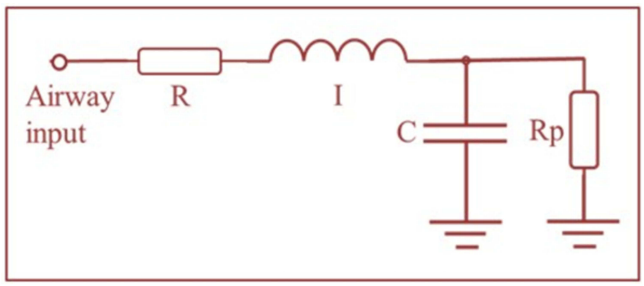

Figure 1 Two-compartment integer-order model used to analyze respiratory impedance.
Abbreviations: The resistance (R), inductance (I), and capacitance (C) are the analogs of respiratory resistance, inertance, and compliance, respectively. Rp represents the peripheral resistance.

Figure 2 Two-compartment fractional-order model evaluated in this study.
Abbreviations: Fractional inertance (FrL); fractional compliance (FrC) and ATM, atmospheric pressure.

These results were interpreted physiologically using the damping factor (G), elastance (H), and the hysteresis coefficient (η). The damping factor is associated with the dissipation of energy in the respiratory system, while H reflects the potential storage of elastic energy (elastance). Hysteresivity describes the heterogeneity of pulmonary ventilation.[16]

$$G = \frac{1}{C} cos\left(\frac{\pi}{2}\beta\right) \tag{2}$$

$$H = \frac{1}{C} sin\left(\frac{\pi}{2}\beta\right) \tag{3}$$

$$\eta = \frac{G}{H} \tag{4}$$

Statistical Analysis

Statistical analyses were performed using the OriginLab Origin® 8.0 program (USA). Initially, the distribution characteristics of the samples were evaluated using the Shapiro–Wilk normality test. Comparisons were performed using the control group, and asthmatics before BD as the baseline. When the sample presented a normal (parametric) distribution behavior, the independent *t*-test was used for analysis between the groups. On the other hand, when the distribution presented a non-normal (non-parametric) characteristic, the Mann–Whitney test was used. The dependent *t*-test was used when the sample presented a normal distribution (parametric) to compare pre-BD and post-BD conditions. When the distribution presented a non-normal characteristic (non-parametric), the Wilcoxon test was used.

To evaluate the diagnostic potential of the studied parameters, sensitivity and specificity assessment was applied through the ROC (Receiver Operating Curve) analysis using the MedCalc® program (Medicalc Software, Mariakerke, Belgium). The generated graphs describe the probability of the occurrence of true negatives (specificity), as a function of the probability of the occurrence of false positives (1-specificity) for various cutoff points. Test performance was described by the area under the ROC curve (AUC), and classified according to Greiner et al:[31]

a) AUC = 0.5 is considered uninformative;
b) 0.5 < AUC ≤ 0.7 indicates low diagnostic accuracy;
c) 0.7 < AUC ≤ 0.9 indicates moderate diagnostic accuracy;
d) 0.9 < AUC < 1 indicates high diagnostic accuracy;

According to previous studies, to consider adequate diagnostic performance, the AUC value was > 080.[32]

Results

Initially, 270 individuals were approached to participate in the study. Of these, 85 declined to participate, 68 missed the examination day and did not reschedule, and 17 were unable to undergo one or more of the proposed tests. Ninety-nine volunteers met all the inclusion criteria.

Table 1 Biometric and Spirometric Parameters of the Studied Groups

	Control (n=33)	OA (n=33)	WEA (n=33)
Age (years)	51.3 ± 12.5	61.1 ± 15.2*	54.5 ± 14.2
Weight (kg)	71.2 ± 10.9	75.8 ± 16.6	75.1 ± 16.4
Height (cm)	164.7 ± 7.3	162.1 ± 7.9	160.2 ± 7.5*
BMI (kg/m^2)	26.0 ± 4.0	28.2 ± 6.5	28.8 ± 6.4
Obese n (%)	4 (12.1)	12 (36.3)	13 (39.4)
Smokers	–	4	3
Pack-years	–	0.9 ± 4.3	1.0 ± 4.1
Gender (F/M)	16 / 17	22 / 11	27 / 6
FVC (L)	3.6 ± 0.8	2.8 ± 0.9*	2.7 ± 0.9*
FVC (%)	94.9 ± 14.8	80.6 ± 17.4*	82.4 ± 19.4*
FEV_1 (L)	2.9 ± 0.7	2.0 ± 0.9 *	1.9 ± 0.7 *
FEV_1 (%)	92.9 ± 14.6	72.1 ± 23.3*	73.8 ± 22.3*
FEV_1/FVC (%)	79.9 ± 6.5	74.7 ± 14.2*	75.2 ± 11.1*
FEF_{25-75} (L)	2.9 ± 1.1	2.1 ± 2.3*	1.6 ± 1.1*
FEF_{25-75}/FVC (L)	3.1 ± 1.1	1.9 ± 1.3*	1.9 ± 1.2*

Notes: Only significant difference ($p<0.05$) were described; *$p < 0.05$ compared with control. No significant differences were observed comparing the OA and WEA.
Abbreviations: BMI, Body Mass Index; FEV_1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; FEF_{25-75}, Mean forced expiratory flow; n, number of patients evaluated; OA, Occupational Asthma; WEA, work-related asthma. N = number of volunteers.

The anthropometric and spirometric characteristics of the studied groups are described in Table 1. There was a significant difference between the analyzed and the control groups regarding age and height parameters. Although an increased number of obese volunteers was observed in asthmatic patients, this introduced only small and not significant differences in weight and BMI. Four patients were smokers in the OA group, while 3 were smokers in the WEA group. Smoking history was similar between these groups.

Spirometric parameters showed reduced mean values in the presence of the disease, with a significant difference in all parameters. The OA group included 15 (45.5%) patients normal to the spirometric exam, 5 (15.1%) with mild airway obstruction, 9 (27.3%) with moderate, 3 (9.1%) severe, and one patient (3.0%) was not able to perform a technically acceptable exam. In the WEA group, one patient presented mixed disorder (3.0%). One patient showed unspecific disorder (3.0%), 11 were normal to the spirometric exam (33.3%), 13 showed mild obstructions (39.4%), while 4 were moderate (12.1%) and one was severe (3.0%). Two patients were not able to perform acceptable exams.

The asthma control test revealed that 23 (69.7%) of the OA patients presented uncontrolled asthma, while 21 (63.7%) of the WEA had uncontrolled asthma (ACT < 20).

Resistance in 4Hz increased in the groups, OA pre-BD and WEA post-BD (Figure 3A $p<0.001$), WEA pre-BD ($p<0.0001$). Bronchodilator use introduced a decrease in OA ($p<0.001$) and WEA ($p<0.01$). In the pre and post-BD comparisons, we observed no significant changes.

Resistance at 20Hz, presented in Figure 3B, showed an increase ($p<0.05$) in OA pre-BD and WEA pre-BD when compared with the control group. There was a decrease after the use of the bronchodilator in OA ($p<0.0001$) and WEA ($p<0.001$). There were no significant changes in the OA and WEA groups post-BD compared to the control group (p=ns).

The resistance difference between 4Hz and 20Hz (Figure 3C) showed a significant increase in OA pre-BD, WEA pre-BD, and WEA post-BD ($p<0.0001$), OA post-BD ($p<0.01$) when compared with the control group. There was no significant reduction after the use of the bronchodilator in both groups. There were no significant changes in the comparison of OA with WEA in any parameter in Figure 3.

The comparative analysis concerning Fr (Figure 4A) showed significant increases in all studied groups when compared with the control group ($p<0.0001$). There were significant differences in the OA ($p<0.01$) and WEA ($p<0.0001$) groups after the use of bronchodilators. No changes were observed comparing the asthmatic groups.

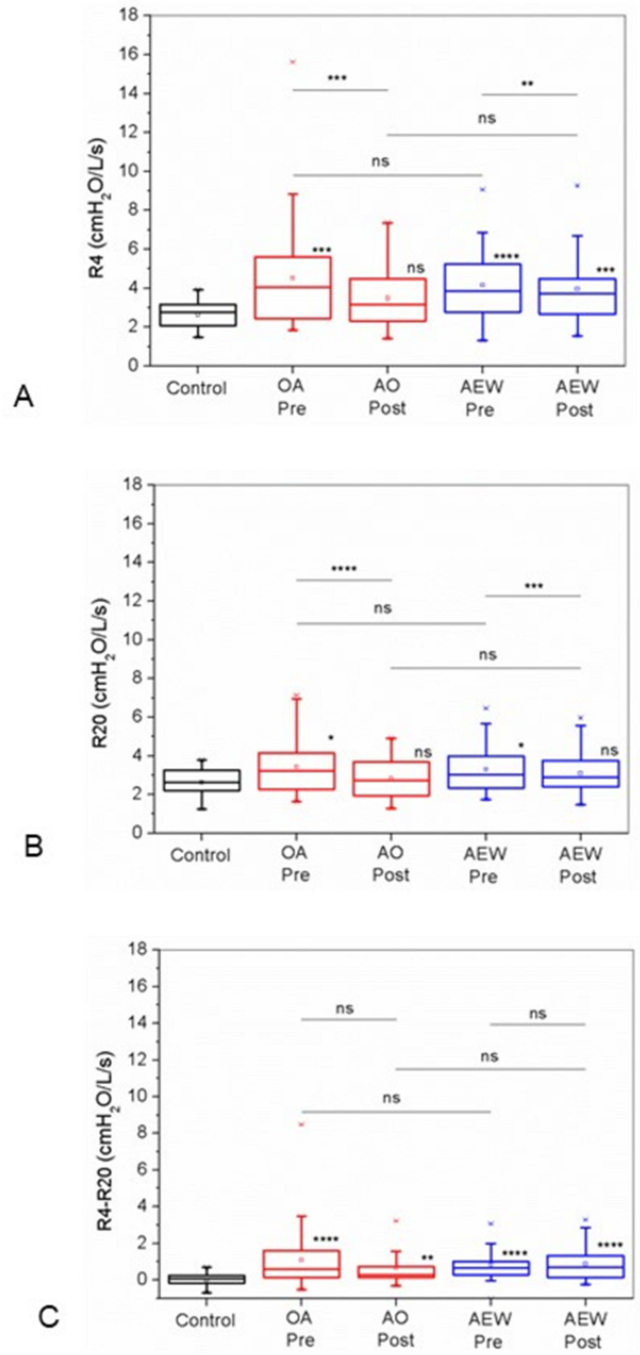

Figure 3 Comparative analysis of traditional FOT resistive parameters obtained from the control group, occupational asthma group (OA), and work-exacerbated asthma group (WEA).
Notes: **p<0.01; ***p<0.001; ****p<0.0001; p=ns, not significant.
Abbreviations: Resistance at 4 Hertz (R4; figure **A**), Resistance at 20 Hertz (R20, figure **B**), and Difference in resistance at 4 Hertz and 20 Hertz (R4-R20, figure **C**).

Dynamic compliance parameter (Figure 4B) showed a significant decrease in comparison with the control group in the OA pre-BD group (p<0.001), WEA pre-BD (p<0.001) and WEA post-BD (p<0.01). Regarding the response to bronchodilator use, there was a significant increase in the OA and WEA groups (p<0.05). The comparisons among the asthmatic groups showed no significant changes.

Reactance area (Figure 4C) increased in all groups when compared with the control group (p<0.0001). There were significant differences in the OA and WEA groups (p<0.01) after the use of bronchodilators. The comparative analysis among the asthmatic groups showed no significant changes.

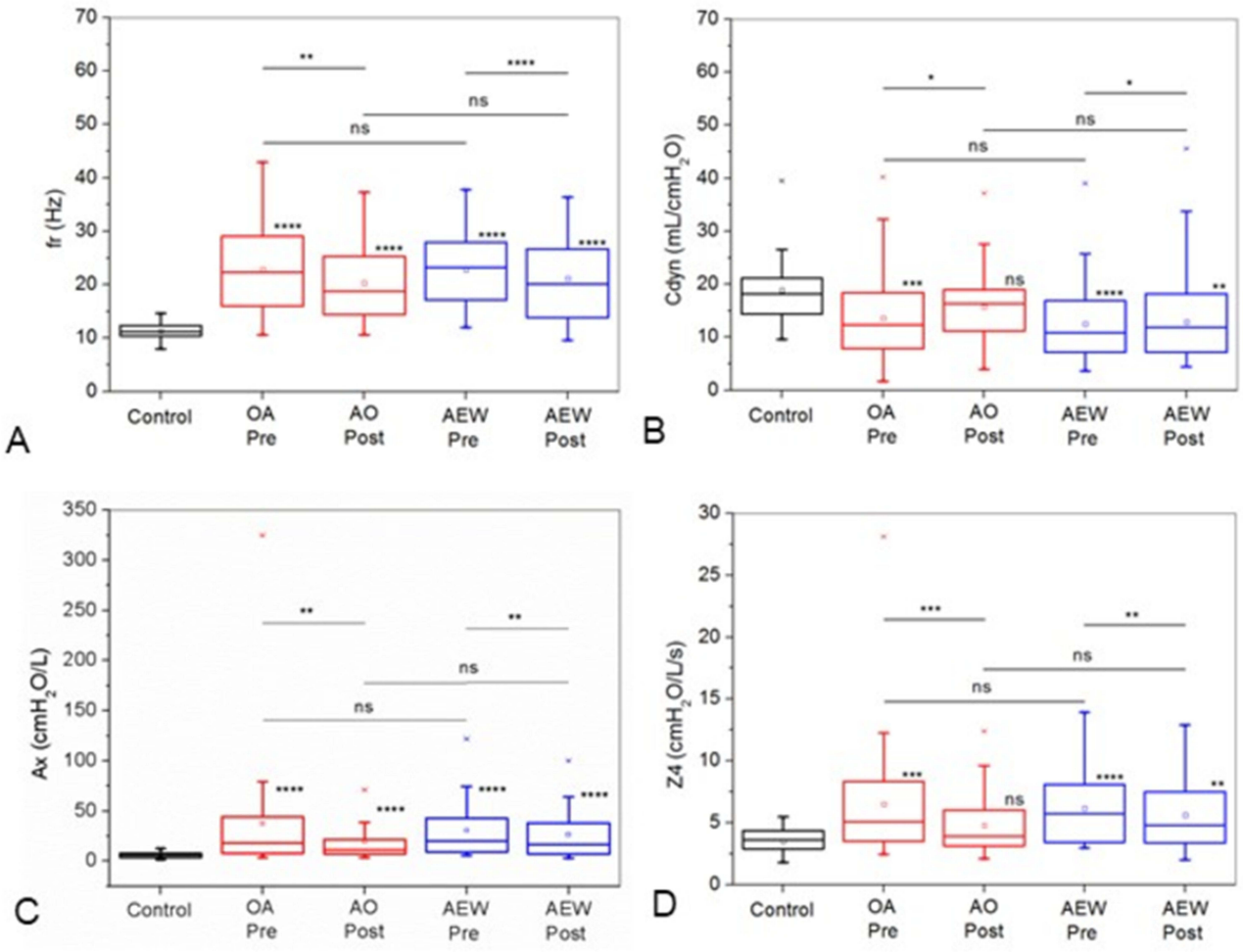

Figure 4 Comparative analysis of traditional FOT reactive parameters obtained from the control group, occupational asthma group (OA), and work-exacerbated asthma group (WEA).
Notes: *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; p=ns, not significant.
Abbreviations: Resonance frequency (fr; figure **A**), Dynamic compliance (Cdyn; figure **B**), area under the negative part of the reactance curve (Ax, figure **C**) and Impedance in 4 Hertz (Z4, figure **D**).

Regarding the impedance at 4 Hertz (Z4, Figure 4D), we observed significant increases when compared with controls in the OA pre-BD (p<0.001), WEA pre-BD (p<0.0001), and WEA post-BD (p<0.01) groups. There was also a significant decrease after the use of bronchodilators in both groups, OA (p<0.001) and WEA (p<0.01). The comparisons between the OA and WEA groups were insignificant in any of the parameters in Figure 4.

The changes observed from the eRIC model are described in Figure 5. Figure 5A shows that only R in the pre-BD WEA group increased significantly (p<0.05) in comparison with the control group. Regarding the use of bronchodilators, a significant decrease in OA (p<0.001) and WEA (p<0.01) was observed. Furthermore, there were no changes in the comparison between the OA and WEA groups.

Peripheral resistance (Figure 5B) significantly increased in all groups analyzed (p<0.0001) when compared to the control group. The bronchodilator use introduced significant changes only for the OA group (p<0.05). We observed no changes comparing the OA and WEA groups before and after using bronchodilators.

Total resistance (Figure 5C) increased in pre-BD OA and pre-BD WEA (p<0.0001), post-BD OA (p<0.01) and post-BD WEA BD (p<0.001). The bronchodilator use resulted in reduced values of Rt in the OA (p<0.001) and WEA (p<0.05) groups. There were no changes comparing the OA and WEA groups before and after use of bronchodilators.

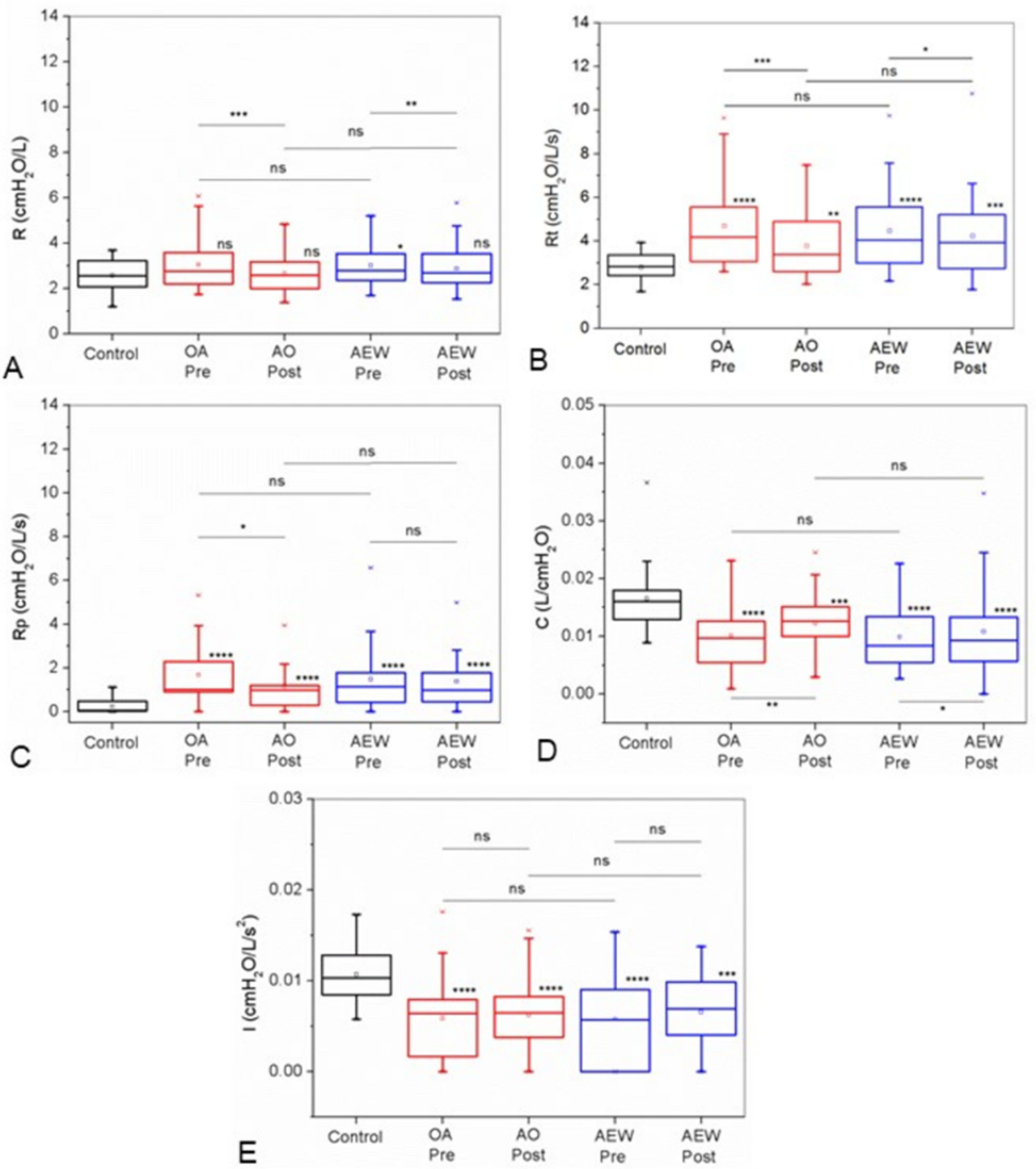

Figure 5 Comparative analysis using the eRIC model of the control group, occupational asthma group (OA) and asthma exacerbated at work group (WEA).
Notes: *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; p=ns, not significant.
Abbreviations: Central resistance (ReRIC, figure **A**), Total resistance (RteRIC, figure **B**), Peripheral resistance (RpeRIC, figure **C**), Dynamic Compliance (CeRIC, figure **D**), and Inertance (IeRIC, figure **E**).

Considering the respiratory compliance (Figure 5D), which reflects the lung compliance, there was a significant decrease in all groups OA pre-BD, WEA pre-BD, and WEA post-BD (p<0.0001), OA post-BD (p<0.001) when compared to controls. Bronchodilator use increased C values in both the OA (p<0.01) and WEA (p<0.05) groups. Similar to resistive parameters, no changes were observed when comparing the OA and WEA groups before and after using bronchodilators.

Respiratory inertance (Figure 5E) showed significant changes in all groups ($p< 0.0001$) when compared with the control group. Regarding the response to bronchodilator use, both groups showed no significant changes. The comparisons made between the OA and WEA groups were not significant.

The changes observed from the FrOr model are described in Figure 6. The damping factor (Figure 6A) increased significantly in all groups of patients when compared to the control group. The bronchodilator use resulted in smaller values of G in the WEA group ($p<0.05$). No changes were observed comparing the OA and WEA groups before and after bronchodilator use.

We can observe a significant decrease of H (Figure 6B) in all groups when compared with the control group. A significant reduction ($p<0.05$) in H due to the use of bronchodilators was observed in OA and WEA groups. The comparisons made between the OA and WEA groups were not significant.

Hysteresivity increased significantly in all groups (Figure 6B; $p<0.0001$) compared to the control group. Bronchodilator use introduced reduced values of η in both the OA ($p<0.05$) and WEA ($p<0.01$) groups. The comparisons made between the OA and WEA groups were not significant.

Table 2 shows the AUC values and the associated confidence interval obtained in the diagnostic of OA using traditional parameters, eRIC and FrOr models, while Table 3 shows a similar analysis for WEA.

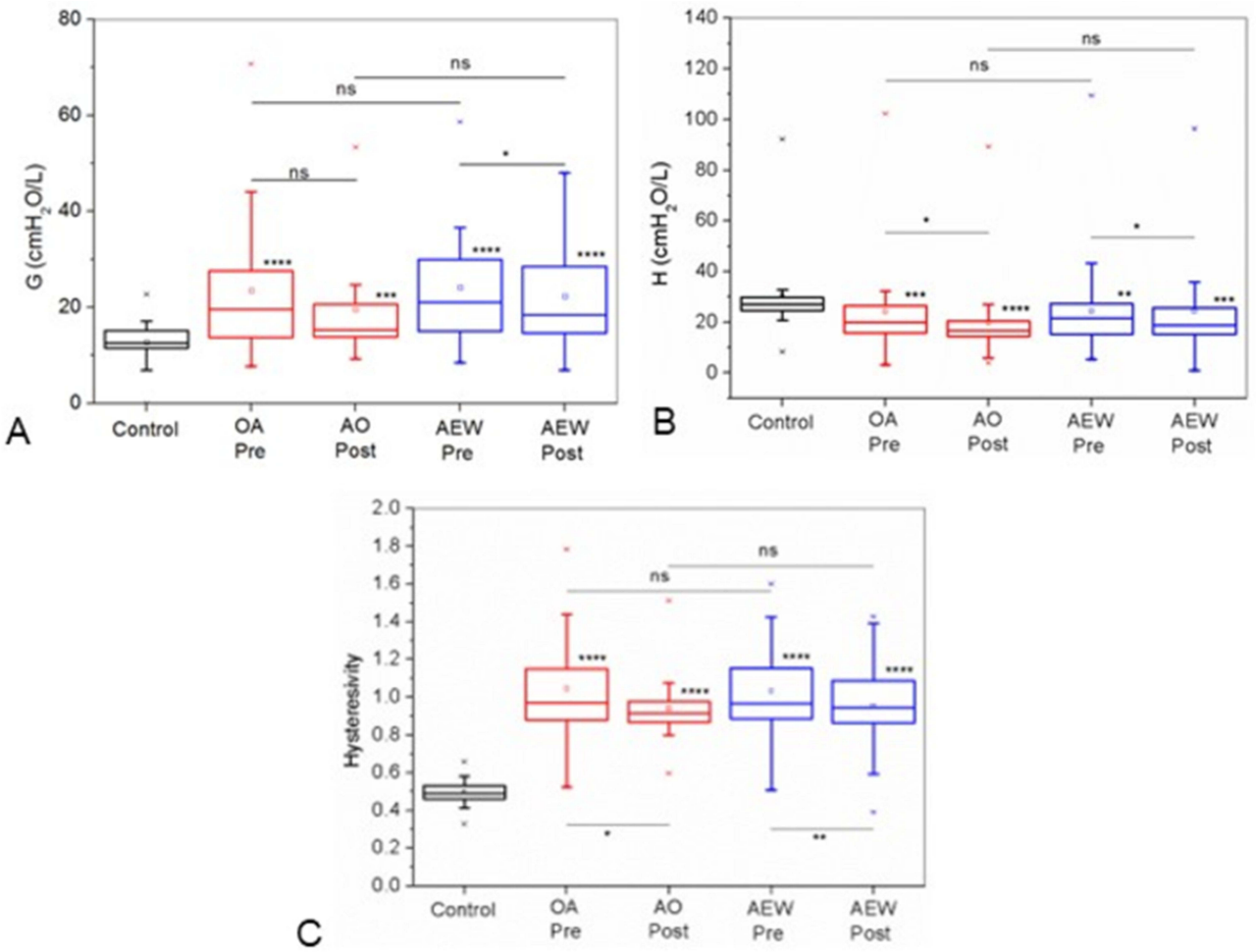

Figure 6 Comparative analysis using the FrOr model, Behavior of the parameters of the fractional order model of the control group, occupational asthma group (OA), and work-exacerbated asthma group (WEA). Damping factor (**G**, figure **A**), Elastance (H, figure **B**), Hysteresivity (figure **C**).
Notes: *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; p=ns, not significant.

Table 2 Area Under the ROC Curve (AUC) and 95% Confidence Interval (CI) Describing the Diagnostic Accuracy of the Studied Parameters in Occupational Asthma. Adequate Values of AUC (>0.80), and Values Describing High Accuracy (>0.90) are Described in Bold

	AUC	95% CI	Se (%)	Sp (%)	Cut-off
Traditional					
R4 ($cmH_2O/L/s$)	0.774	0.655–0.868	63.64	96.97	>3.7088
R20 ($cmH_2O/L/s$)	0.647	0.520–0.761	30.30	100.00	>3.7826
R4-R20 ($cmH_2O/L/s$)	**0.801**	0.684–0.889	69.70	84.85	>0.3014
Fr (Hz)	**0.938**	0.851–0.983	84.85	100.00	>14.6712
Cdyn (mL/cmH_2O)	0.738	0.615–0.839	57.58	87.88	≤12.671
Ax (cmH_2O/L)	**0.860**	0.752–0.933	72.73	81.82	>8.2107
Z4 ($cmH_2O/L/s$)	0.779	0.660–0.872	57.58	96.97	>4.8113
eRIC model					
R ($cmH_2O/L/s$)	0.601	0.473–0.720	57.58	54.55	>3.5245
Rp ($cmH_2O/L/s$)	**0.912**	0.816–0.968	81.82	96.97	>0.8122
Rt ($cmH_2O/L/s$)	**0.835**	0.723–0.915	63.64	96.97	>3.7088
C (mL/cmH_2O)	**0.817**	0.703–0.902	69.70	90.91	≤0.012
I ($cmH_2O/L/s^2$)	**0.815**	0.700–0.900	75.76	81.82	≤0.0079
FrOr model					
G (cmH_2O/L)	0.780	0.661–0.872	63.64	93.94	>17.0905
H (cmH_2O/L)	0.764	0.643–0.860	69.70	93.94	≤22.5253
η	**0.991**	0.929–1.000	96.97	100.00	>0.6583

Abbreviations: AUC, area under the curve; R4, Resistance at 4 Hertz; R20, Resistance at 20 Hertz; R4-R20, Difference in resistance at 4 Hertz and 20 Hertz; fr, Resonance frequency; Cdyn, Dynamic compliance; Ax, area under the negative part of the reactance curve; Z4, Impedance in 4 Hertz; R, Central resistance; Rp, Peripheral resistance; Rt, Total resistance; C, Dynamic Compliance; I, Inertance; G, Damping factor; H, Elastance; η, Hysteresivity; CI, confidence interval; If, sensitivity; Sp, specificity.

Table 3 Area Under the ROC Curve (AUC) and 95% Confidence Interval (CI) Describing the Diagnostic Accuracy of the Studied Parameters in Work-Exacerbated Asthma. Adequate Values of AUC (>0.80), and Values Describing High Accuracy (>0.90) are Described in Bold

	AUC	95% CI	Se (%)	Sp (%)	Cut-off
Traditional					
R4 ($cmH_2O/L/s$)	0.770	0.650–0.865	54.55	93.94	>3.5951
R20 ($cmH_2O/L/s$)	0.649	0.522–0.763	30.30	100.00	>3.7826
R4-R20 ($cmH_2O/L/s$)	**0.842**	0.731–0.920	75.76	81.82	>0.2868
Fr (Hz)	**0.972**	0.898–0.997	93.94	87.88	>12.7526

(*Continued*)

Table 3 (Continued).

	AUC	95% CI	Se (%)	Sp (%)	Cut-off
Cdyn (mL/cmH_2O)	0.785	0.667–0.877	60.61	96.97	≤11.4406
Ax (cmH_2O/L)	**0.899**	0.800–0.960	69.70	96.97	>10.1076
Z4 (cmH_2O/L/s)	0.798	0.681–0.887	57.58	96.97	>4.8113
eRIC model					
R (cmH_2O/L/s)	0.608	0.480–0.726	27.27	96.97	>3.5245
Rp (cmH_2O/L/s)	**0.814**	0.699–0.899	72.73	90.91	>0.5632
Rt (cmH_2O/L/s)	0.792	0.675–0.883	57.58	96.97	>3.6895
C (mL/cmH_2O)	**0.827**	0.714–0.909	66.67	93.94	≤0.0111
I (cmH_2O/L/s^2)	**0.804**	0.688–0.892	57.58	96.97	≤0.0067
FrOr model					
G (cmH_2O/L)	0.798	0.681–0.887	63.64	93.94	>17.0905
H (cmH_2O/L)	0.728	0.605–0.830	57.58	93.94	≤22.1889
η	**0.987**	0.922–1.000	96.97	100.00	>0.6583

Abbreviations: AUC, area under the curve; R4, Resistance at 4 Hertz; R20, Resistance at 20 Hertz; R4-R20, Difference in resistance at 4 Hertz and 20 Hertz; fr, Resonance frequency; Cdyn, Dynamic compliance; Ax, area under the negative part of the reactance curve; Z4, Impedance in 4 Hertz; R, Central resistance; Rp, Peripheral resistance; Rt, Total resistance; C, Dynamic Compliance; I, Inertance; G, Damping factor; H, Elastance; η, Hysteresivity; CI, confidence interval; If, sensitivity; Sp, specificity.

Table 4 Area Under the ROC Curve (AUC) and 95% Confidence Interval (CI) Describing the Diagnostic Accuracy of the Studied Parameters

	AUC	95% CI	Se (%)	Sp (%)	Cut-off
ΔRp (cmH_2O/L/s)	0.601	0.473–0.720	84.85	45.45	>-0.6311
ΔG (cmH_2O/L)	0.530	0.403–0.654	81.82	36.36	>-4.7989

Abbreviations: AUC, area under the curve; ΔRp, variation in peripheral resistance; ΔG, damping factor variation, CI, confidence interval; If, sensitivity; Sp, specificity.

Table 4 describes the results of the diagnostic accuracy assessment considering the variation in Rp (ΔRp) and G (ΔG) due to bronchodilator use. These evaluations were conducted using the two most discriminative parameters according to the comparative analysis in Figures 3 and 4.

Discussion

To our knowledge, this study represents the first attempt to evaluate OA and WEA utilizing oscillometry and respiratory modeling techniques. Three key findings were obtained: (1) These methods provided a comprehensive understanding of OA and WEA pathophysiology, allowing physiological insight into the initial effects of these diseases on lung mechanics; (2) Traditional oscillometric parameters and the eRIC model effectively identified early abnormal changes; (3) FrOr modeling improved the diagnostic process, enabling the early detection of these changes with a high degree of accuracy.

In a previous study, Ribeiro et al showed that height was the best predictor of respiratory impedance parameters,[33] with shorter individuals tending to have higher resistance values. This way, the small but significant difference in high observed comparing the WEA and control groups (Table 1) must be considered in the interpretation of the resistive results.

There was an increased number of obese volunteers in the asthmatic groups, although no significant difference was observed in the body mass index (Table 1). Chan and Lipworth[34] showed that obesity and morbid obesity in asthmatic patients were associated with a worse resistance heterogeneity, as compared with patients presenting normal weight. Thus, although the differences in body mass index observed in Table 1 are small, they should be taken into account when interpreting the results regarding heterogeneity.

As expected, the asthmatic groups showed reduced values in all spirometric parameters. These results are consistent with previous studies in work-related asthma, in which several patients have normal spirometry when evaluated on an outpatient basis.[35] These findings are especially true when they are away from work activities or without contact with the asthma-exacerbating agent. Smoking history was small and similar between OA and WEA groups.

The resistive changes observed in traditional respiratory oscillometry parameters are described in Figure 3. The structural remodeling process present in asthma is a product of bronchial hyperresponsiveness and airway obstruction caused by chronic inflammation with a high potential for deterioration of lung function. These results are consistent with a recent work showing that resistance evaluated by oscillometry is closely related to airway remodeling, as shown indirectly using HRCT bronchial wall thickening.[36] The presence of mucus hypersecretion can lead to a decrease in airway caliber and consequent increase in resistance.[36] The literature shows that changes in the mechanical properties of the respiratory system are more evident at low frequencies.[37] The increase observed in R4 can be explained either by bronchoconstriction, edema, or secretion that reduces the airway diameter, causing increased resistance.[38,39] In WEA, airway obstruction and possible irreversible structural changes, such as airway remodeling, for example, caused by chronic inflammation, can lead to deterioration of lung function and increased resistance.[24,40]

Resistance at 20 hz (Figure 3B) is usually associated with obstructive changes, being consistent with the interpretation that changes in these resistive parameters are related to the caliber of the airways, the greater the resistance, the lower the expiratory flow and the lower the exhaled volume, leading to common obstructive disorders in these individuals.[24] In our study, an increase in resistance was observed in the OA and WEA groups compared to the control group. In previous studies, changes in mean resistance described a decrease in airway caliber due to narrowed mucosa.[41] This situation may explain the increase in the values of this parameter in our study.

The pathophysiology of asthma starts in the peripheral airways, which may explain the increased values of R4-R20 observed in Figure 3C. The heterogeneity of the ventilation due to the presence of bronchospasms and edema increases airway resistance and reduces air conductance.[27] This condition may be associated with the presence of an inflammatory process with reduced bronchial lumen, either due to the presence of bronchospasm or secretion.[42] Inflammation, which may be caused by contraction of airway smooth muscle, edema, and fluid accumulation in the airways, may result in loss of elastic support of the lung parenchyma, contributing to local changes in elasticity. This change, in turn, can cause an imbalance in the time constants of the respiratory system and contribute to increased ventilation heterogeneity.[42]

The obtained values of R4-R20 may be considered low compared with studies using impulse oscillometry.[34] The present study was conducted using a forced oscillation (FOT) instrument, and there are differences between impulse oscillometry systems (IOS) and the traditional FOT system.[43] IOS measurements tend to show increased values of resistance, which may explain these low values.

There were an increased number of obese volunteers in the asthmatic groups, although no significant difference was observed in weight and the body mass index (Table 1). Chan and Lipworth[34] showed that obesity and morbid obesity in asthmatic patients were associated with a worse resistance heterogeneity, as compared with patients presenting normal weight. Thus, although the differences in body mass index observed in Table 1 are small, they should be taken into account when interpreting the cited results.

The bronchodilator uses reduced R4 and R20 values (Figure 3). This finding can be explained by the relaxation of the smooth muscles, introducing increased airway radius and reducing resistance. Even so, resistance in the OA and WEA

groups remained higher than in the control group, even after the use of the bronchodilator. It is probably associated with the effect of the inflammatory component of the disease.[10]

The oscillometric reactive parameters are described in Figure 4. Regarding the resonance frequency (fr, Figure 4A), high results were found in the OA and WEA groups compared to the CG. It reflects ventilation inhomogeneity in the airways that reduces dynamic compliance and tissue changes associated with remodeling. The higher the value of this parameter, the greater the individual's level of pulmonary obstruction or restriction, as well as tissue changes associated with remodeling, and the lower the homogeneity of the system.[44] Studies with interstitial lung diseases,[45] COPD,[8] and asthma[10,46] have also described more negative reactance values. These studies associated their findings with decreased homogeneity of the respiratory system. This study is in agreement with the results obtained by Kim et al,[47] Also in line with the present results, Cauberghs and Woestijne found fr helpful in discriminating between healthy individuals and obstructive patients.[30]

Dynamic compliance (Figure 4B) includes the elastic effects of all components involved in ventilation, such as lungs, rib cage, abdominal compartment, and upper airways.[11,48] Decreased values in OA pre-BD, WEA pre-BD, and WEA post-BD can be explained by the intermittent and reversible bronchial narrowing caused by contraction of the bronchial smooth muscle, by mucosal edema, remodeling, and hypersecretion of the mucosa. These changes in the lung tissue and chest wall increase the resistance and modify the distensibility of the airways. Furthermore, bronchospasm, common in work-related asthma, affects conductance, increasing resistance and interfering with the elastic recoil of the lung.[49,50] The observed changes are also in line with the structural changes related to bronchial remodeling, including collagen deposition in the airway basement membrane due to chronic inflammation, which is associated with decreased airway wall compliance in individuals with asthma.

The presence of OA and WEA resulted in increased Ax values (Figure 4C). These findings are related to changes in the respiratory system's elastic properties. They also reflect an increase in the degree of obstruction of the more peripheral airways and consequent reductions in dynamic compliance.[11]

Z4 reflects the total work necessary to promote air circulation in the respiratory system, including resistive and elastic elements. The present study showed higher values for OA pre-BD, WEA pre-BD, and WEA post-BD. This finding is consistent with the increased resistance (Figure 3A) and reduced compliance (Figure 4B) described previously and can be explained by the same physiological fundamentals.[10,51] The observed increase in Z4 is in close agreement with the usual complaints of these patients concerning ventilation difficulties.

Bronchodilator medication introduced significantly higher values of Cdyn in AO and AEW (Figure 4B). It is known that the contraction of the smooth muscles of the bronchi works as a factor in stiffening them.[10] According to other authors,[51] bronchodilator medication works by improving the compliance of the airway wall by relaxing the smooth muscles of the bronchi, resulting in better gas distribution, increasing expiratory flows, and optimizing lung compliance. This fact could explain the improvement in Cdyn after the use of salbutamol.[10] These changes, considered in conjunction with the associated reductions in resistance due to smooth muscle relaxation, may explain the decrease in Fr (Figure 4A) and Ax (Figure 4C), as well as the decrease in respiratory work (Figure 4D).

Analyzing the eRIC model provides complementary information on the resistance of the respiratory system in the presence of occupational and work-exacerbated asthma. More central resistance (Figure 5A) only showed changes in the WEA pre-BD group compared to the control group. The change that occurred only in this group can be explained by the fact that this parameter represents the resistance of the central airways, and asthma initially affects the peripheral airways. This resistive parameter is related to the increase in secretion and changes in the lung parenchyma compatible with the pathology in which, due to inflammation, there is the presence of secretion, with a consequent increase in the resistance of the central airways.[52]

Rp (Figure 5B) increased in both groups compared to the CG. This fact is compatible with this disease's pathophysiology, where changes in the peripheral airways resulting from frequent bronchoconstrictor reactions are notable Considering that the disease begins in the peripheral airways, we can speculate that the changes found in Rp may reflect changes in this section of the bronchial tree.[21]

Regarding the Rt parameter (Figure 5C), which corresponds to the amount of obstruction throughout the respiratory system, the sum of the R and Rp factors, the changes found were pathophysiologically compatible. This finding reflects

the fact that there is an increase in total resistance resulting from the inhomogeneity of the respiratory system in asthma.[30,50]

Lung compliance obtained from the eRIC model (Figure 3D) showed a significant decrease in all groups compared to the control group. It reflects the pathophysiology of asthma, which includes intermittent and reversible bronchial narrowing caused by contraction of bronchial smooth muscle, mucosal edema, and mucosal hypersecretion.[53] Furthermore, changes in bronchial architecture and walls also reduce compliance.[10]

Similarly, in Figure 5E, dynamic inertance showed a significant reduction. This phenomenon can be elucidated through consideration of the recently introduced concept of dynamic inertance.[54] Respiratory inertance primarily describes the mass of gas displaced during spontaneous ventilation. In individuals without respiratory disease, inertance reflects the inertial characteristics of the entire respiratory system. However, as the disease advances, airway obstruction intensifies, particularly affecting the small airways. Consequently, the oscillometric pressure signal is unable to penetrate beyond the choke point where obstruction arises, leading oscillometric measurements to exclusively capture the mechanical properties of airways proximal to these choke points. Consequently, there is a reduction in the apparent mass of the gas probed by the oscillometric signal, resulting in a reduction in the measured inertance.[55] Based on this premise, it is plausible to infer that airway obstruction may engender an apparent inertance, akin to the process observed in apparent compliance.[56] In this context, the observed reduction in inertance (Figure 5E) can be explained by the decrease in lung volumes and the increase in lower airway obstruction observed in patients with OA and WEA (Table 1).

Figure 3 also shows that the OA group's bronchodilator use reduced R and Rp. Total resistance had a significant decrease after the use of salbutamol. As a result of the asthma pathology characterized by chronic inflammation, which induces airway obstruction through constriction of bronchial smooth muscles, resistance escalates. The administration of bronchodilators prompts relaxation of the airway wall muscles, thereby enhancing gas distribution and reducing airway resistance.[21] Respiratory compliance showed a significant increase after BD, which may be explained by the reduction in peripheral resistance. This reduction increases the number of alveolar units probed by the oscillometric pressure signal, increasing dynamic compliance.

The improved ability of FrOr models to capture the characteristics of respiratory mechanics makes them a promising tool for evaluating pathological changes. In this work, the fractional order model is used in Figure 4. The increased damping factor values (Figure 4A) in the diseased groups compared to the CG are consistent with previous experimental findings in patients with asthma.[16] The damping factor is a measure of energy dissipation in respiratory tissues.[14] Therefore, the results found can be explained, at least in part, by the increase in parenchymal distortion that occurs in conjunction with irreversible airway remodeling, with more significant deformity, greater force to be exerted for ventilation, and greater energy dissipation.[57] These results may also be related to the proportional increase in airflow heterogeneity throughout the lung due to changes in peripheral compliance and airway resistance.[16,38,57]

The significant reduction in elastance (Figure 4B) compared to the control group can be explained by the increase in parenchymal deformity.[16,55] Ionescu et al showed reduced elastance values in patients with severe COPD, which may be associated with decreased lung parenchymal elastance.[15] Finally, hysteresivity (Figure 4C) characterizes the heterogeneity of lung tissue and is proportional to the area of hysteresis in the pressure-volume curve.[58] It is associated with the work involved in ventilation. The increase found in our study agrees with previous studies[16,17] and may reflect increased heterogeneity and structural changes in the lungs. These findings are in close agreement with the pathophysiology of asthma, which includes bronchial narrowing, associated with a significant increase in resistance, mainly peripheral, and an increase in respiratory work.[10,51]

Regarding the bronchodilator use, there was a significant decrease in all parameters presented in Figure 4, except in the OA group in G. We did not observe any significant difference in any model parameter in the comparative analysis between the OA and the WEA groups. In the present study, 20 (60.6%) individuals in the OA and 24 (72.7%) individuals in the WEA are classified as having normal to mild airway obstruction.[24] It is possible to infer that increased changes are found in groups with higher degrees of the disease, as seen in previous studies,[10,16,18] and that these changes in more advanced stages of asthma may be more evident. Because this sample consists of most individuals in the early stages of the disease, it can be speculated that these changes are insufficient to introduce significant changes due to bronchodilator use in OA and WEA groups.

Respiratory oscillometry demonstrates many practical advantages as a screening tool for asthma in occupational settings. The characteristics of non-invasiveness and the demand for minimal cooperation from the patient make it well-suited for screening in occupational settings where individuals may have varying levels of respiratory function or may be hesitant to undergo more invasive tests. This characteristic reduces barriers to participation and facilitates widespread screening efforts. Another significant advantage is that oscillometry tests are typically quick to perform, taking only a few minutes to assess lung function. It is advantageous in occupational settings where time is often limited, allowing for efficient screening of large numbers of individuals without disrupting workflow or productivity. Therefore, there is ongoing debate in the literature regarding the efficacy of oscillometry as a diagnostic tool for asthma in occupational settings.[59,60] The diagnostic accuracy of the studied parameters in OA was evaluated to contribute in this regard (Table 2), showing adequate values for R4-R20 and Ax, as well as high accuracy considering Fr. At this point, it is essential to emphasize that most studied OA patients either exhibit normal spirometric results (45.5%) or present mild obstruction (15.1%). Therefore, this finding agrees with the hypothesis that the lung periphery is the initial site of changes in OA. Also in agreement with this hypothesis, Rp showed the best performance among the eRIC parameters, and η presented the best performance in the FrOr model, achieving high accuracy.

Receiver-operator analysis in WEA resulted in very similar results (Table 3); adequate accuracy was obtained for R4-R20 and Ax, while Fr showed high accuracy. C presented the best performance among the eRIC parameters, achieving adequate accuracy. In agreement with the results obtained in OA (Table 2), η was the most accurate parameter in the FrOr model, achieving high diagnostic accuracy. These results agree with the hypothesis that lung periphery is the initial site of changes in WEA. Similar to patients with OA, most studied WEA patients exhibit normal spirometric results (33.3%) or mild obstruction (39.4%).

The AUC values obtained in the present study for traditional parameters were similar to those obtained in previous studies in nonspecific asthma,[30] smokers and mild COPD,[61] and sarcoidosis.[19] The attainment of higher accuracy values through the FrOr model is consistent with previous studies in mild COPD.[13,61] Two factors can explain the improvement obtained from this model. First, in the control group, this outcome demonstrates the model's capability to depict the positive frequency-dependence of resistance observed experimentally in certain healthy subjects. Secondly, in patients, this phenomenon may be attributed to the FrOr models' capacity to accommodate fractional values of 20 dB/dec instead of integer-order models, which are confined to integer multiples of 20 dB/dec.

As management differs in the case of WEA and OA,[62] the differential diagnosis of these phenotypes is essential to guarantee adequate treatment of the disease and prevention of its adverse effects. To contribute to this direction, we analyzed the ability of the studied parameters to differentiate these groups. Figures 1 to 4 showed no significant differences between the OA and WEA groups. However, bronchodilator use introduced different responses in the cited groups. Thus, we investigated the ability of the change in Rp and G to discriminate between OA and WEA. The results obtained were of low accuracy (Table 4) and were unsuitable for differentiating between WEA and OA.

A growing body of evidence suggests that oscillometry may play a crucial role in diagnosing and managing asthma.[27,63] Because oscillometry is performed during tidal volume breathing and requires minimal cooperation, it appears highly suitable for patients, particularly in work-related environments, who encounter challenges performing traditional lung function tests. This method has a longstanding history of contributions to respiratory diseases,[64] and evidence suggests that it enables a sensitive[65] and detailed[61,64] analysis of respiratory mechanics, which could serve as a valuable complement to conventional methods. However, further studies involving larger patient cohorts are necessary to confirm these findings in asthma, including disease phenotyping and asthma related to environmental and occupational exposures.[64]

Recognizing and sharing this research's limitations may help push research forward and contextualize the findings. The present study examined a relatively small sample size. Further investigations involving a larger number of subjects are warranted.

The subjects were drawn from a Brazilian population at a single practice site, which may restrict the generalizability of the study's findings. Hence, multicenter studies are essential in the future to enhance the applicability and generalizability of these findings.

Studies using oscillometry ratios in asthma have recently garnered interest.[66] This method may help further clarify the lung function assessments in OA and WEA, and we believe these analyses deserve further studies.

The study focused on whole-breath impedance measurements and did not assess within-breath analysis.[67,68] Exploring similar analyses centered on within-breath impedance parameters is recommended in future investigations. This direction holds promise for further research.

This paper evaluated predominantly patients with OA and WEA, which were normal to spirometry, and patients with mild obstruction. A comprehensive evaluation of respiratory abnormalities in groups with moderate, severe, and very severe obstruction could further deepen our understanding of the potential of respiratory oscillometry in the context of these diseases.

One could argue that oscillometry and respiratory modeling were not able to differentiate OA and WEA (Table 4). Previous studies from our group have shown that the use of artificial intelligence methods can enhance the use of oscillometry in the diagnosis of respiratory abnormalities in cystic fibrosis,[69] the detection of airway obstruction in asthma,[70] and the differential diagnosis of asthma and restrictive respiratory diseases.[71] Utilizing these methods may improve the differential diagnosis of OA and WEA, and we plan to do these analyses in the next steps of this research.

Conclusion

This study supports oscillometry associated with respiratory modeling as an adequate method to describe the pathophysiology of OA and WEA. These analyses provide physiological insight into the initial effects of these diseases on lung mechanics.

Although it was impossible to make a differential diagnosis between OA and WEA, our results underscore the value of oscillometric parameters and eRIC modeling in adequately identifying these abnormalities. Of particular significance, the utilization of FrOr modeling substantially enhanced the diagnostic process, enabling the early detection of these changes with a high degree of accuracy.

Our findings emphasize the importance of incorporating oscillometry into standard respiratory assessments of OA and WEA, especially in patients with preserved spirometry.

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Disclosure

The authors report no conflicts of interest in this work.

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