

Forced oscillation, integer and fractional-order modeling in asthma

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ABSTRACT

The purpose of this study was to evaluate the use of fractional-order (FrOr) modeling in asthma. To this end, three FrOr models were compared with traditional parameters and an integer-order model (InOr). We investigated which model would best fit the data, the correlation with traditional lung function tests and the contribution to the diagnostic of airway obstruction. The data consisted of forced oscillation (FO) measurements obtained from healthy ($n=22$) and asthmatic volunteers with mild ($n=22$), moderate ($n=19$) and severe ($n=19$) obstructions. The first part of this study showed that a FrOr was the model that best fit the data (relative distance: FrOr = 4.3 ± 2.4 ; InOr = $5.1 \pm 2.6\%$). The correlation analysis resulted in reasonable ($R=0.36$) to very good ($R=0.77$) associations between FrOr parameters and spirometry. The closest associations were observed between parameters related to peripheral airway obstruction, showing a clear relationship between the FrOr models and lung mechanics. Receiver–operator analysis showed that FrOr parameters presented a high potential to contribute to the detection of the mild obstruction in a clinical setting. The accuracy [area under the Receiver Operating Characteristic curve (AUC)] observed in these parameters (AUC = 0.954) was higher than that observed in traditional FO parameters (AUC = 0.732) and that obtained from the InOr model (AUC = 0.861). Patients with moderate and severe obstruction were identified with high accuracy (AUC = 0.972 and 0.977, respectively). In conclusion, the results obtained are in close agreement with asthma pathology, and provide evidence that FO measurement associated with FrOr models is a non-invasive, simple and radiation-free method for the detection of biomechanical abnormalities in asthma.

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1. Introduction

Asthma is a global health problem affecting 1–18% of the population in different countries. Given the increasing prevalence of this disease [1], it is necessary to focus on the investigation

and routine evaluation of pulmonary function. The respiratory effects of asthma are usually evaluated with spirometry and body plethysmography. These tests, however, require a high degree of collaboration and maximal effort on the part of the subject. In addition, forced inspiratory and expiratory

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maneuvers may change the bronchial tone and modify the airway patency, rendering the indices obtained hardly physiologic.

The Forced Oscillation Technique (FOT) allows for the assessment of airway mechanics, examining subjects of any age with minimal cooperation and without any invasiveness [2]. It consists of applying small sinusoidal pressure variations (P) to stimulate the respiratory system at frequencies higher than that of normal breathing and measuring the flow response (V). This method is currently the state-of-the-art for the assessment of lung function [3], allowing for the measurement of respiratory system impedance ($Z_{rs}=P/V$). Recent studies used this technique in the diagnostic of airway obstruction in adult asthmatics [4–8]. This method may help to simplify the routine evaluation of asthmatic patients [5] and the understanding of the pathophysiology of asthma [9].

FOT yields frequency-dependent curves of respiratory impedance that may be visually analyzed to recognize changes in shape and magnitude of the curves and distinguish healthy respiratory function from its diseased state. In addition, simple parameters, such as R_{rs} and X_{rs} data measured at a given frequency, may be obtained. To complement this basic analysis, inverse modeling is employed as an alternative approach to obtain detailed mechanical information about the respiratory system [3,10,11]. In these models, electrical components analogous to mechanical resistance, compliance, and inertance inherent in the respiratory system are used [12,13], allowing us to gain additional insight into the anatomical or pathophysiological changes that occur in respiratory diseases. In addition to being useful in furthering our understanding of respiratory biomechanical function, these model parameters could improve the detection, diagnosis, and treatment of different respiratory diseases.

Fractional-order (FrOr) modeling is increasingly used in biological systems [14–16]. The tools of fractional calculus support mathematical models that in many cases describe more accurately the dynamic response of living systems. In fact, many traditional areas of physical science and engineering (e.g., electromagnetics, electrochemistry, viscoelasticity, transport phenomena) currently have advocates of the fractional approach [15]. Of particular interest in respiratory physiology is the ability of fractional calculus to effectively describe (qualitatively and quantitatively) fractional power laws, hysteresis, and system memory. In this context, there is agreement in the literature that FrOr models have the potential to improve pulmonary clinical science and practice [3,10,11]. They would help us obtain new insight into the lung periphery mechanism of the disease and could be used to help classify patients. These models were previously used in asthmatic adults [17], in a mouse model of asthma [18], and with induced bronchoconstriction in humans [19]. Recently, new FrOr models were introduced [10,20–23] and have been found to be especially useful for the analysis of patients with COPD [20,21] and children with asthma [22] and cystic fibrosis [23]. Although promising, FrOr models are far from mature in clinical practice due to their difficult interpretation and high number of parameters to be related to lung pathology [20]. Recently, Ionescu et al. [21] emphasized that studies in groups of patients with various degrees of airway obstruction

and lung abnormalities may also offer interesting information on the sensitivity of the fractional-order parameters and its possible use in a classification strategy.

The changes associated with asthma pathophysiology include inflammatory and structural changes in the small airways and in lung parenchyma [24]. Thus, FrOr models may provide a significant contribution to the particular case of asthma. However, to the best of our knowledge, these new FrOr models have never been used in the evaluation of groups of adult asthmatics with different degrees of airway obstruction and lung abnormalities.

In the present study, our first objective was to investigate whether the new FrOr model parameters are sensitive to asthma pathophysiology, and if so, which model would best fit the data. Another objective was to evaluate the correlations between the model parameters and lung function tests, contributing to elucidate an important debate in the literature concerning the relationship of these parameters and lung pathology. We also evaluated the contribution of these models in the diagnostic of airway obstruction in asthma.

2. Methods

2.1. Study population and pulmonary function

Sixty asthmatic patients were evaluated and classified into four categories based on their degree of airway obstruction [25], including those with mild ($n=22$), moderate ($n=19$) and severe ($n=19$) airflow obstruction. The exclusion criteria for patients in this study included a history of tobacco use, evidence of current airway infection, acute exacerbation, or any cardiorespiratory disease other than asthma.

The control group was composed of 22 healthy subjects with no history of pulmonary or cardiac disease or tobacco use. The study conformed to the principles outlined in the Declaration of Helsinki and have been approved by the Medical Research Ethics Committee of the State University of Rio de Janeiro. The baseline data, including age, height and weight, were obtained from each subject at the time of the procedures. Informed consent was obtained from all volunteers before inclusion in the study.

Using a closed circuit spirometer (Vitrace VT-139; Promédico, Rio de Janeiro, Brazil), the following measurements were obtained for all subjects while they were in a sitting position: forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), forced expiratory flow (FEF) between 25% and 75% of the FVC, the FEF/FVC ratio and the FEV_1/FVC ratio.

2.2. Respiratory impedance measurements

The respiratory system impedance was measured between 4 and 32 Hz with 2-Hz increments using a pseudorandom noise forced oscillation system that was built in our laboratory and described previously [26,27]. Briefly, pressure oscillations, which were produced by a loudspeaker coupled to the respiratory system by means of a mouthpiece, were applied with amplitude of approximately 2 cmH₂O. The resulting flow (V') and pressure (P) signals were measured near the mouth by means of a screen pneumotachograph (PT-36 Jaeger-Tonnie)

and a pressure transducer (Honeywell 176PC), respectively. The respiratory system impedance ($Z_{rs}(f)$) was estimated from the Fourier analysis of these signals, as described by Eq. (1):

$$Z_{rs}(f) = \frac{\overline{G_{PV}}}{\overline{G_{VV}}} \quad (1)$$

where $\overline{G_{PV}}$ and $\overline{G_{VV}}$ are the mean cross spectrum between pressure and flow and mean autospectrum of flow, respectively. Three FOT exams were performed; each exam lasted approximately 16 s, and the exams were separated by 1-min intervals. The common mode rejection ratio of the airflow measurement system (65.2 dB) was adequate for these studies [28]. These measurements were taken at the mouth, with the individual seated and breathing spontaneously, using a nasal clip, and holding his or her cheeks and mouth floor with the hands to avoid the shunt effect of the upper airways. To express the amount of noise on the pressure and flow signal, a coherence function was calculated at each investigated frequency. Only exams with a coherence function between 0.9 and 1.0 were retained [26,29]. The final result of the tests was estimated by calculating the average of three satisfactory exams.

2.3. Identification methods

The first FrOr model proposed for evaluation in this paper includes a Newtonian resistance R , a frequency-dependent inertance L , and a tissue part described as a constant-phase impedance [10,21]:

$$Z_{FrOr1}(j\omega) = R + L(j\omega) + \frac{1}{C(j\omega)^\beta} \quad (2)$$

where $0 \leq \beta \leq 1$, and C is the compliance. This approximation, however, will not be able to characterize the frequency-dependence of the resistance observed experimentally in some healthy subjects, asthmatic subjects, etc. [20,30]. Thus, a better model would include a real part that is dependent on frequency, and it was suggested [10,20,21] to identify the model parameters using:

$$Z_{FrOr2}(j\omega) = R + L(j\omega)^\alpha + \frac{1}{C(j\omega)^\beta} \quad (3)$$

with $0 \leq \alpha \leq 1$. Because the real part of the impedance in Eq. (3) depends on frequency in both inertance and compliance terms, it allows both to increase or decrease with increasing frequency. The last model investigated in this study (FrOr3) takes into account the ability of the fractional-order terms to approximate the resistive properties. This results in a simplification of the FrOr2 model to

$$Z_{FrOr3}(j\omega) = L(j\omega)^\alpha + \frac{1}{C(j\omega)^\beta} \quad (4)$$

Theoretically, the effects of R are indirectly captured in the values of the FrOr terms and coefficients [31], which may result that the R term in FrOr2 will not give significant values.

Hysteresivity is a concept that addresses the heterogeneity of the lung, with greater η often associated with more

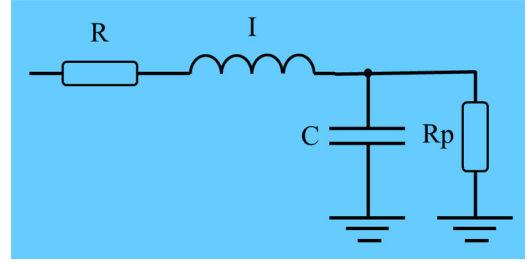


Fig. 1 – Electrical representation of a two-compartment model used to analyze respiratory impedance. Resistance, inductance and capacitance are the analogs of mechanical resistance, inertance and compliance, respectively. R is analogous to central airway resistance and R_p describes peripheral resistance, I is associated with lung inertance and C with alveolar compliance. This analysis also evaluated the total resistance ($R_t = R + R_p$), which included the effects of central and peripheral airways.

heterogeneity [10]. The damping (G), elastance (H) and the hysteresivity coefficient (η) are described by:

$$G = \frac{1}{C} \cos\left(\frac{\pi}{2}\beta\right) \quad (5)$$

$$H = \frac{1}{C} \sin\left(\frac{\pi}{2}\beta\right) \quad (6)$$

$$\eta = \frac{G}{H} \quad (7)$$

To allow a comparison with more traditional models, we also investigated the use of an integer order model. To this end, we used the extended RIC (eRIC) model (Fig. 1), where R describes the central airway resistance and R_p the peripheral resistance, while I is associated with the lung inertance obtained by this model and C with alveolar compliance. The interested reader may find the equations for the eRIC complex impedance in [13].

This model is proposed as an improvement to the basic RIC model [3], where the added peripheral resistance R_p allows for the frequency dependence observed in typical real impedance data. This is beyond the RIC model's capability, and its physiological justification is the increase in the resistance of the respiratory system's small airways.

Model parameters were estimated using the Levenberg–Marquardt algorithm to determine the set of coefficients of the nonlinear model that best represents the input data set in the least squares sense. Along with the corresponding model estimates, this analysis also provides the evaluation of the root mean square error value in the real (MSE_r) and imaginary (MSE_i) parts of the impedance, as well as the total error value (MSE_t), an overall measure of “goodness of fit” for the model. This parameter is defined herein as the square root of the sum of the real and imaginary impedance estimation errors. We also measured the mean relative distance (R_d) from the model and measured resistance and reactance values [32,33].

Table 1 – Biometric and spirometric characteristics of control individuals and patients with asthma.

	Control group (n = 22)	Mild (n = 22)	Moderate (n = 19)	Severe (n = 19)	ANOVA p
Age (years)	47.1 ± 12.1	40.0 ± 18.6	50.2 ± 15.7	52.0 ± 18.5	ns
Body mass (kg)	63.7 ± 10.6	68.6 ± 12.1	70.8 ± 10.2	64.9 ± 13.6	ns
Height (cm)	160.9 ± 8.24	164.6 ± 12.2	158.7 ± 10.2	158.8 ± 9.94	ns
Gender (M/F)	6/16	10/12	5/14	10/9	–
FEV ₁ (L)	2.82 ± 0.82	2.83 ± 0.94	1.60 ± 0.62***	0.96 ± 0.40***	0.0001
FEV ₁ (%)	100.9 ± 17.2	87.7 ± 13.8	59.6 ± 6.58***	36.2 ± 7.83***	0.0001
FVC (L)	3.38 ± 1.05	3.86 ± 1.13	2.81 ± 1.03	2.07 ± 0.80**	0.0001
FVC (%)	100.7 ± 19.2	100.8 ± 12.6	87.0 ± 13.5*	65.3 ± 15.9**	0.0001
FEV ₁ /FVC	87.9 ± 9.07	72.6 ± 5.36***	57.5 ± 8.51***	47.0 ± 8.17***	0.0001
FEF _{25–75%} (L)	3.17 ± 1.00	2.11 ± 1.03**	0.77 ± 0.38***	0.35 ± 0.17***	0.0001
FEF _{25–75%} (%)	104.1 ± 20.6	57.6 ± 17.1***	25.7 ± 6.27***	12.0 ± 4.11***	0.0001
FEF/FVC	95.0 ± 24.2	52.5 ± 13.7***	28.0 ± 10.1***	17.5 ± 6.25***	0.0001

ns, non-significance.

* $p < 0.05$ related to control group.** $p < 0.001$.*** $p < 0.0001$.

2.4. Traditional FOT parameters

Classical FOT parameters were also evaluated to allow direct comparisons with previous studies. A linear regression analysis of the resistance values in the frequency range between 4 and 16 Hz was used to determine the slope of the resistive component of the impedance (S). S reflects both spatial and temporal ventilatory non-homogeneity [27,28]. The mean resistance value in this frequency range was also analyzed. This parameter is related to the airway caliber [34]. The respiratory resistance at 4 Hz (R_4) was also analyzed. The reactance between 4 and 32 Hz was used to measure the resonant frequency (f_r), and the respiratory system mean reactance (X_m). f_r is defined as the lowest frequency at which the reactance crossed 0 from negative to positive. f_r reflects the airway heterogeneity changes and elastic changes. X_m is usually related to respiratory system non-homogeneity [35]. The absolute value of the respiratory impedance was evaluated at 4 Hz (Z_4). This parameter is associated with the work performed by the respiratory muscles to overcome resistive and elastic loads, promoting the movement of air in the respiratory system [34,36].

2.5. Statistical analysis

Statistical analysis was performed using STATISTICA 5.0 (StatSoft, Inc., Tulsa, OK, USA) and Microcal Origin version 6.0 (Microcal Software, Inc. Ostend, Belgium). Initially, a Shapiro–Wilk W test was used to analyze whether the data were normally distributed. Then, Student's t test was used to analyze normally distributed data, and a Mann–Whitney U test and a Wilcoxon Matched Pairs Test were used when the data were not normally distributed. The results with p values < 0.05 were considered statistically significant.

Based on this analysis, the five FrOr parameters that presented the more significant differences considering controls and asthma in mild patients were further investigated in terms of their clinical use to detect respiratory alterations in asthmatic patients. To allow a comparison with the other methods used in this study, we also included the evaluation of the best traditional and eRIC parameters. This was

performed by means of receiver operating characteristic (ROC) analyses, which were conducted using MedCalc 12 using the methodology of DeLong et al. [37]. The discriminating criterion used in the studied groups was based on spirometric evaluations of airway obstruction, which were performed according to the recommendations of the American Thoracic Society/European Respiratory Society [38]. The optimal cut-off point was chosen to balance the highest values of sensitivity and specificity. These analyses were performed by comparing each of the three studied asthmatic groups with normal subjects. ROC curves with AUCs ≥ 0.80 were considered adequate for diagnostic use [39], while AUCs between 0.90 and 1.00 were considered indicative of a high diagnostic accuracy [39,40]. For minimizing the statistical problem of finite patients in our study, leave-one-out cross-validation (LOOCV) was employed. It is the most accurate way to estimate the performance of method when the training data is small. These analyses were performed according to [41] using a custom-written program developed in LabVIEW 8.2 (National Instruments, Austin, TX) environment.

To measure the overall agreement between the variables related to FrOr modeling and spirometric indexes of central and peripheral obstruction, we calculated Pearson's correlation coefficient for the whole group of studied volunteers when data are normally distributed and Spearman's rank sum correlation for skewed data. The correlations between 0 and 0.25 (or 0 and -0.25) were considered small or non-existent, between 0.25 and 0.50 (or -0.25 to -0.50) were considered reasonable, between 0.50 and 0.75 (or -0.50 to -0.75) were considered moderate to good, and greater than 0.75 (or -0.75) were considered very good to excellent [42].

3. Results

3.1. Study population and pulmonary function

There were no significant differences in weight, height or age among the studied groups (Table 1). In general, the spirometric parameters were highest in normal subjects and decreased significantly in the asthmatic groups ($p < 0.0001$).

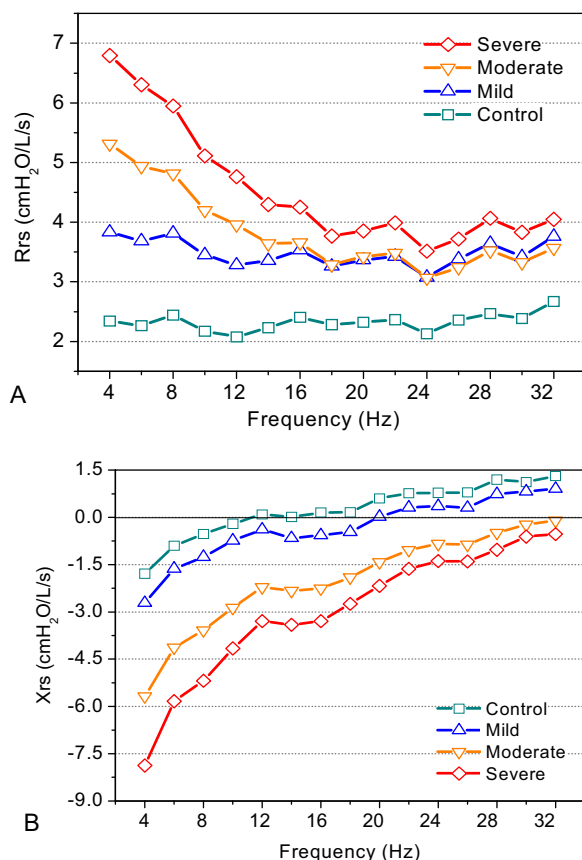


Fig. 2 – Mean respiratory resistance (A) and reactance (B) curves as a function of frequency of the control group and patients with asthma.

3.2. Forced oscillation curves and parameters

Fig. 2 shows the mean curves of Rrs and Xrs as functions of the frequency in normal and asthmatic subjects.

Associated classical FOT parameters are described in Table 2. All FOT parameters changed significantly with airway obstruction ($p < 0.0001$). Similar significant changes were also observed in all parameters obtained with the eRIC model ($p < 0.0001$, Table 2). Detailed graphical descriptions of the results obtained for the FOT parameters and with the eRIC model are provided in the online supplement (Figs. S1 and S2).

3.3. Fractional-order models

Considering the FrOr1 model, R was found to increase slightly, but significantly, with airway obstruction ($p < 0.013$; Fig. 3A). However, changes in the inertance were not observed (Fig. 3B). The increase in airway obstruction caused a significant decrease in C ($p < 0.0003$, Fig. 3C) and β ($p < 0.0001$, Fig. 3D) and increase in G and η ($p < 0.0001$; Fig. 3E and G, respectively). A significant increase was also observed in H ($p < 0.02$, Fig. 3F).

The analysis of the parameters obtained from the FrOr2 model revealed non-significant changes in R (Fig. 4A). The increase in airway obstruction in asthma caused a significant increase in G, H, and η ($p < 0.0001$, Fig. 4F–H, respectively) and a significant decrease in L, α , C, and β ($p < 0.0001$, Fig. 4B–E, respectively).

Examining the parameters obtained from the FrOr3 model (Fig. 5), significant increases in L, G and η ($p < 0.0001$, Fig. 5A, E and G, respectively) were observed. It was also observed a significant increase in H ($p < 0.02$; Fig. 5F). Changes in α were not significant (Fig. 5B). C and β presented a significant decrease with airway obstruction ($p < 0.0003$; Fig. 5C and D, respectively).

Table 3 shows the error values in the real and imaginary parts of the impedance, as well as the mean relative distances for the studied models. The interested reader may find a detailed graphical description of how well the studied models fits the data for the different frequencies in the online supplement (Fig. S3).

Table 2 – Parameters obtained from traditional FOT analysis and using the eRIC model in the studied groups. The right column shows the comparisons of the four groups (ANOVA).

	Control (n = 22)	Mild (n = 22)	Moderate (n = 19)	Severe (n = 19)	ANOVA p
<i>Traditional</i>					
R4 (cmH ₂ O/L/s)	2.3 ± 0.7	3.8 ± 1.5****	5.3 ± 2.6****	6.8 ± 2.3****	<0.00001
Rm (cmH ₂ O/L/s)	2.3 ± 0.7	3.6 ± 1.2**	4.5 ± 1.8**	5.3 ± 1.5****	<0.00001
S (cmH ₂ O/L/s ²)	−4.4 ± 20.4	−37.3 ± 59.2	−161.2 ± 150.7**	−227.7 ± 127.8****	<0.00001
Xm (cmH ₂ O/L/s)	0.2 ± 0.4	−0.3 ± 0.7*	−2.0 ± 2.1****	−3.0 ± 1.7****	<0.00001
Fr (Hz)	12.9 ± 3.0	16.6 ± 5.8*	30.1 ± 7.9****	34.7 ± 5.6****	<0.00001
Z4 (cmH ₂ O/L/s)	3.0 ± 0.9	4.7 ± 1.9*	8.1 ± 5.0**	10.5 ± 4.4****	<0.00001
<i>eRIC model</i>					
R (cmH ₂ O/L/s)	2.2 ± 0.8	3.2 ± 1.1**	3.1 ± 0.9*	3.6 ± 0.7****	<0.0001
Rp (cmH ₂ O/L/s)	0.3 ± 0.3	0.9 ± 1.1	3.6 ± 2.3****	4.6 ± 2.1****	<0.00001
Rt (cmH ₂ O/L/s)	2.6 ± 0.7	4.2 ± 1.4****	6.7 ± 3.0****	8.2 ± 2.6****	<0.00001
I (cmH ₂ O/L/s ²)	0.008 ± 0.005	0.006 ± 0.003	0.002 ± 0.003****	0.001 ± 0.002****	<0.00001
C (ml/cmH ₂ O)	0.021 ± 0.009	0.014 ± 0.007*	0.010 ± 0.011**	0.005 ± 0.003****	<0.00001

ns, non-significance.

* $p < 0.05$ related to control group.

** $p < 0.001$.

*** $p < 0.0001$.

**** $p < 0.00001$.

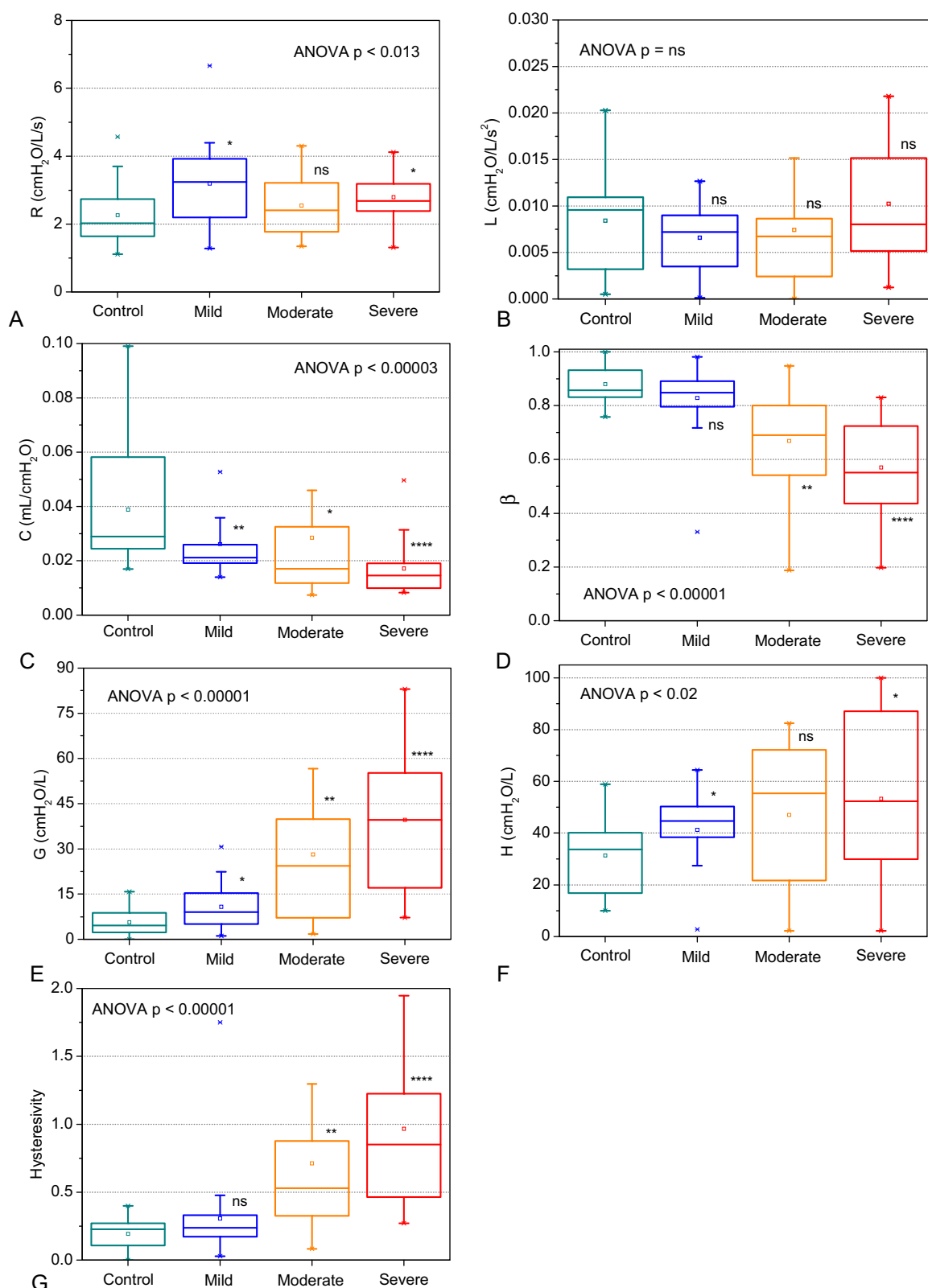


Fig. 3 – Comparative analysis of the parameters obtained from the fractional-order model number 1 in groups of adults with asthma and control: Resistance (R; A), inertance (L; B), compliance (C; C), beta coefficient (β ; D), damping (G; E), elastance (H; F), and hysteresivity (G). The top and the bottom of the box plot represent the 25th- to 75th-percentile values, while the circle represents the mean value, and the bar across the box represents the 50th-percentile value. The whiskers outside the box represent the 10th- to 90th-percentile values.

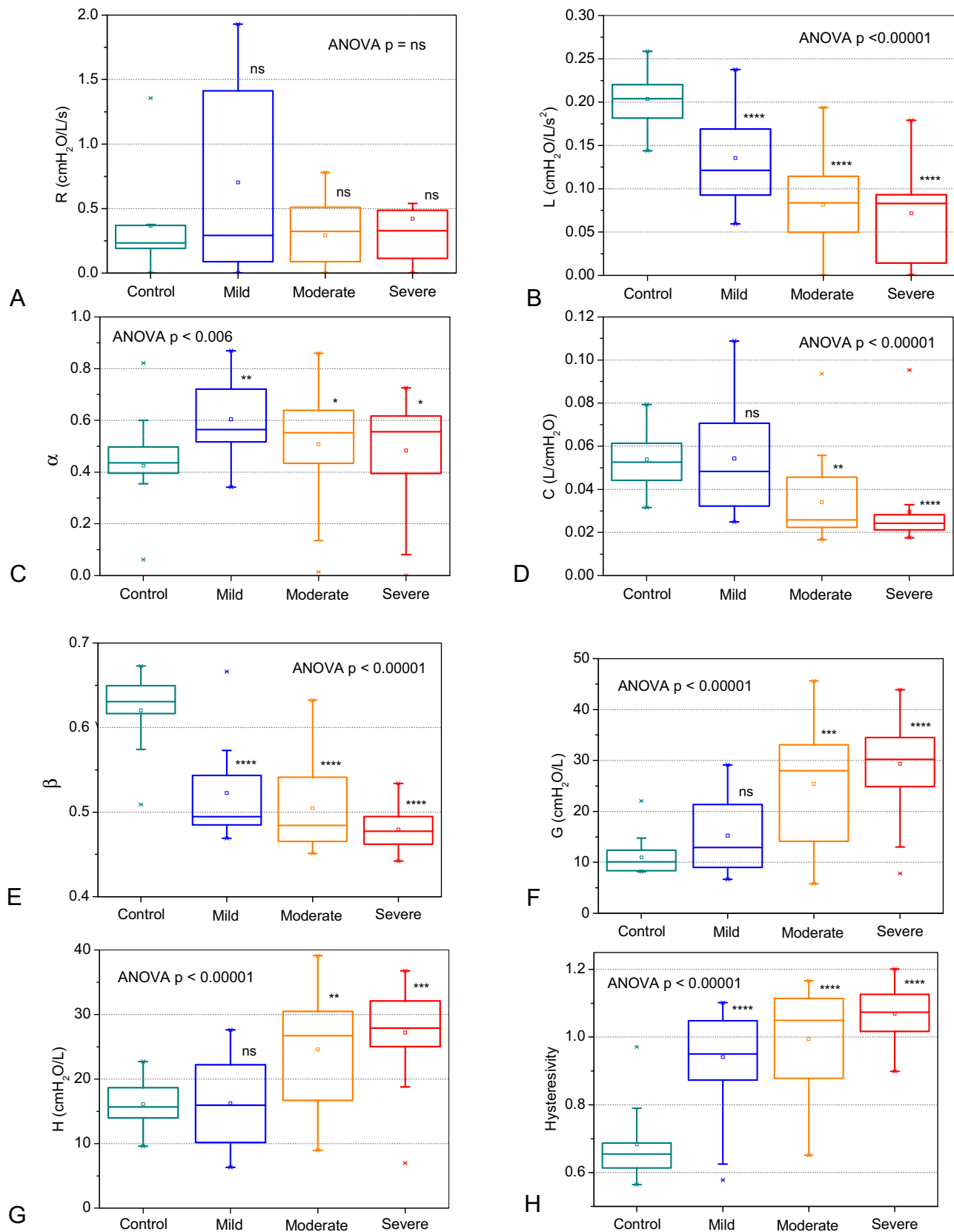


Fig. 4 – Comparative analysis of the parameters obtained from the fractional-order model number 2 in groups of adults with asthma and control: Resistance (R; A), inertance (L; B), α coefficient (α ; C), compliance (C; D), β coefficient (β ; E), damping (G; F), elastance (H; G), and hysteresivity (H).

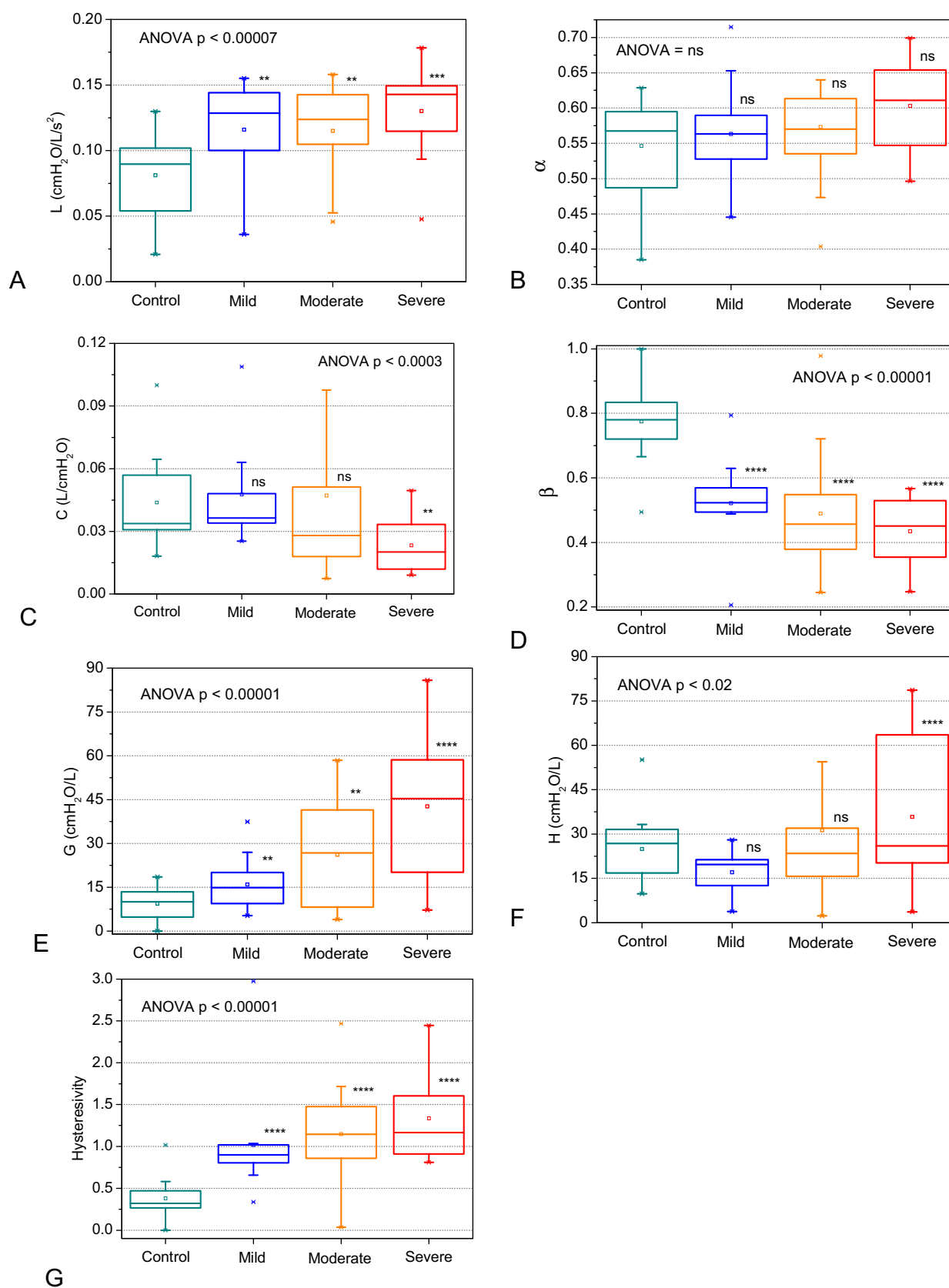


Fig. 5 – Comparative analysis of the parameters obtained from the fractional-order model number 3 in groups of adults with asthma and control: Inertance (L; A), alpha coefficient (α ; B), compliance (C; C), beta coefficient (β ; D), damping (G; E), elastance (H; F) and hysteresivity (G).

Table 3 – Mean square errors (MSE) and relative distances (Rd) in the integer and fractional-order models studied in control individuals and patients with asthma.

	eRIC	FrOr1	FrOr2	FrOr3
<i>Control</i>				
MSEr (cmH ₂ O/L/s)	0.079 ± 0.079	0.074 ± 0.079	0.041 ± 0.052*	0.064 ± 0.095
MSEx (cmH ₂ O/L/s)	0.033 ± 0.025	0.032 ± 0.026	0.032 ± 0.023*	0.032 ± 0.023
MSEt (cmH ₂ O/L/s)	0.088 ± 0.081	0.083 ± 0.081	0.054 ± 0.054*	0.077 ± 0.093
Rd (%)	5.078 ± 2.636	4.806 ± 2.205	4.303 ± 2.418*	4.950 ± 2.777
<i>Mild</i>				
MSEr (cmH ₂ O/L/s)	0.087 ± 0.062	0.089 ± 0.091	0.055 ± 0.045*	0.059 ± 0.044
MSEx (cmH ₂ O/L/s)	0.080 ± 0.092	0.070 ± 0.068*	0.072 ± 0.077	0.072 ± 0.077
MSEt (cmH ₂ O/L/s)	0.132 ± 0.093	0.124 ± 0.101	0.095 ± 0.084*	0.096 ± 0.085
Rd (%)	3.375 ± 2.107	3.204 ± 1.885	2.794 ± 1.756*	2.809 ± 1.725
<i>Moderate</i>				
MSEr (cmH ₂ O/L/s)	0.191 ± 0.312	0.127 ± 0.156	0.117 ± 0.138	0.105 ± 0.133*
MSEx (cmH ₂ O/L/s)	0.587 ± 1.243	0.092 ± 0.083	0.084 ± 0.073*	0.084 ± 0.073
MSEt (cmH ₂ O/L/s)	0.712 ± 1.228	0.168 ± 0.168	0.151 ± 0.149	0.140 ± 0.147*
Rd (%)	3.481 ± 2.178	2.577 ± 1.799	2.534 ± 1.936*	2.549 ± 1.963
<i>Severe</i>				
MSEr (cmH ₂ O/L/s)	0.127 ± 0.106	0.126 ± 0.094	0.116 ± 0.088*	0.117 ± 0.084
MSEx (cmH ₂ O/L/s)	0.566 ± 0.537	0.096 ± 0.059	0.090 ± 0.047*	0.090 ± 0.047
MSEt (cmH ₂ O/L/s)	0.608 ± 0.515	0.165 ± 0.099	0.152 ± 0.091*	0.152 ± 0.089
Rd (%)	2.712 ± 1.505	1.803 ± 0.939	1.763 ± 0.931*	1.772 ± 0.917

* The smallest errors are identified in bold and with *.

The FrOr2 model showed the smallest MSE among the evaluated models in the controls and severe patients. In asthmatics with mild and moderate obstruction, this model showed MSEs that were the smallest or near the smallest. The Rd decreased with airway obstruction in all models. The FrOr2 model showed the smallest value of Rd in all of the studied conditions. The interested reader may find a detailed graphical description of Rd in the online supplement (Fig. S4).

The correlations between the studied FrOr models and spirometric parameters are presented in Tables 4–6. R and L in the FrOr1 model were not correlated with spirometry (Table 4). However, all of the remaining parameters (C, β , G, H, η) presented significant correlations with the spirometric parameters. The highest associations presented by β and η were with FEV₁ (L), while the highest associations presented by C, G and H were with FEF_{25–75%} (L) and FEF_{25–75%} (%). Considering the FrOr2 model (Table 5), R and α were the only parameters that did not correlate with spirometry. C and H presented more association with FEV₁ (L) and FEF_{25–75%} (L), while the strongest association of L, β , G, and η were with FEV₁/FVC, FEF_{25–75%} (%) and FEF/FVC. Similar to the FrOr2 model, the correlation analysis in the FrOr3 model (Table 6) resulted in a stronger association of C and H with FEV₁ (L) and FEF_{25–75%} (L), while the strongest association of L, β , G and η and ε were with FEF_{25–75%} (%) and FEF/FVC.

Among all the studied FrOr parameters, the five parameters that presented the best performance ($p < 0.00001$) in discriminating mild obstruction in Figs. 3–5 were L, β and η in the FrOr2 model and β and η in the FrOr3 model. ROC analyses showed that all of these five parameters presented adequate diagnostic performance (Table 7; AUC ≥ 0.80). A detailed description of the ROC curves for detecting mild asthma using the most accurate parameters for the different studied models is described in the online supplement (Fig. S5).

Beta and η in the FrOr3 model were the most adequate parameters to correctly identify the mild obstruction, presenting AUCs = 0.954, with a sensitivity of 90.9% and a specificity of 95.5%. R4 was the best traditional parameter (AUC = 0.732), while Rt was the more discriminative parameter (AUC = 0.861) in the eRIC model. All of the studied parameters showed increasing AUC values in groups with moderate and severe obstruction.

4. Discussion

Previous work has compared groups of controls and patients with COPD [20,21] and children with asthma [22] and cystic fibrosis [23], observing clear modifications in FrOr parameters. This raises the question: are the FrOr parameters able to detect the changes in respiratory mechanics associated with airways obstruction in adult asthmatics? In this study, we have demonstrated for the first time that these parameters change proportionally to airway obstruction in these patients. Moderate to very good associations were observed between FrOr analysis and spirometry. It was also shown that, among the three studied FrOr models, FrOr2 was the model that best fit the data. Interestingly, an ROC analysis showed that FrOr parameters presented a great potential to contribute to the detection of the early airway obstruction in a clinical setting. The accuracy observed in these parameters was higher than that observed in traditional FOT and that obtained from the eRIC model. Such findings may help clinicians improve diagnosis methods and track treatments.

In line with previous studies in COPD [21], we observed that the FrOr2 model identified lower values for the resistance (Fig. 4A) when compared to the FrOr1 model (Fig. 3A), within each subject group. This happens because the real part is well characterized by the real parts of inertance and compliance

Table 4 – Correlation analysis between the parameters from the FrOr1 model and spirometry.

	FEV ₁ (L)	FEV ₁ (%)	FVC (L)	FVC (%)	FEV ₁ /FVC	FEF _{25–75%} (L)	FEF _{25–75%} (%)	FEF/FVC
R	ns	ns	ns	ns	ns	ns	ns	ns
L	ns	ns	ns	ns	ns	ns	ns	ns
C	0.46 ^{****}	0.48 ^{****}	0.34 ^{**}	0.33 ^{**}	0.50 ^{****}	0.53^{****}	0.53^{****}	0.51^{****}
β	0.71^{****}	0.66 ^{****}	0.59 ^{****}	0.48 ^{****}	0.64 ^{****}	0.69 ^{****}	0.67 ^{****}	0.63 ^{****}
G	–0.67 ^{****}	–0.66 ^{****}	–0.51 ^{****}	–0.46 ^{****}	–0.65 ^{****}	–0.71^{****}	–0.70^{****}	–0.67 ^{****}
H	–0.35 ^{**}	–0.37 ^{***}	–0.27 [*]	–0.24 [*]	–0.34 ^{***}	–0.43^{****}	–0.43^{****}	–0.41 ^{****}
η	–0.71^{****}	–0.66 ^{****}	–0.58	–0.48 ^{****}	–0.64 ^{****}	–0.69 ^{****}	–0.67	–0.63 ^{****}

ns, non-significant.
The highest correlations are identified in bold.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
**** $p < 0.0001$.

Table 5 – Correlation analysis between the parameters obtained from FrOr2 model and spirometry.

	FEV ₁ (L)	FEV ₁ (%)	FVC (L)	FVC (%)	FEV ₁ /FVC	FEF _{25–75%} (L)	FEF _{25–75%} (%)	FEF/FVC
R	ns	ns	ns	ns	ns	ns	ns	ns
L	0.67 ^{**}	0.71 ^{**}	0.46 ^{**}	0.40 [*]	0.77^{**}	0.75^{**}	0.76^{**}	0.76^{**}
α	ns	ns	ns	ns	ns	ns	ns	ns
C	0.62 ^{**}	0.58 ^{**}	0.48 ^{**}	0.37 [*]	0.60 ^{**}	0.63^{**}	0.60 ^{**}	0.57 ^{**}
β	0.60 ^{**}	0.65 ^{**}	0.39 [*]	0.36 [*]	0.72^{**}	0.70 ^{**}	0.72^{**}	0.72^{**}
G	–0.65 ^{**}	–0.62 ^{**}	–0.49 ^{**}	–0.38 [*]	–0.64 ^{**}	–0.68^{**}	–0.66 ^{**}	–0.64 ^{**}
H	–0.60^{**}	–0.56 ^{**}	–0.47 ^{**}	–0.37 [*]	–0.55 ^{**}	–0.59^{**}	–0.57 ^{**}	–0.54 ^{**}
η	–0.60 ^{**}	–0.65 ^{**}	–0.39 [*]	–0.36 [*]	–0.72^{**}	–0.70 ^{**}	–0.72^{**}	–0.72^{**}

ns, non-significant.
The highest correlations are identified in bold.
* $p < 0.001$.
** $p < 0.0001$.

fractional-order terms [21]. In agreement with this hypothesis, R obtained with the models FrOr1 (Table 4) and FrOr2 (Table 5) did not show associations with spirometry.

Increased values in L were obtained with FrOr2 (Fig. 4B) in comparison with the FrOr1 model (Fig. 3B). This may be explained as compensation for the lower resistance values observed in the FrOr2 model. This compensation is clearly described in Table 5, in which the increased obstruction is accompanied by an increase in L. A clear reduction in L with the obstruction was observed with the FrOr2 model, while similar analyses in the FrOr1 model showed no changes.

These results are consistent with the study developed by Ionescu et al. [21], in which patients with COPD were compared with a control group. The reduction in L is also in line with that observed in the eRIC model (Table 2) and previous studies in cystic fibrosis [43] and obstructive lung disease [13,44–46]. This change may be interpreted using the concepts of choke points [47] and apparent compliance [48]. Under normal conditions, inertance reflects the inertial properties of the entire respiratory system. However, when an obstruction is present, the oscillatory signal cannot pass through these choke points to reach the alveoli, which prevent the FOT from

Table 6 – Correlation analysis between parameters from the FrOr3 model and spirometry.

	FEV ₁ (L)	FEV ₁ (%)	FVC (L)	FVC (%)	FEV ₁ /FVC	FEF _{25–75%} (L)	FEF _{25–75%} (%)	FEF/FVC
L	–0.25 [*]	–0.37 ^{***}	ns	ns	–0.41 ^{****}	–0.38 ^{***}	–0.44^{****}	–0.43 ^{****}
α	ns	–0.29[*]	ns	–0.23 [*]	–0.22 [*]	ns	–0.26 [*]	–0.24 [*]
C	0.48^{****}	0.48^{****}	0.38 ^{***}	0.35 ^{**}	0.46 ^{****}	0.49^{****}	0.48^{****}	0.46 ^{****}
β	0.50 ^{****}	0.57 ^{****}	0.30 ^{**}	0.31 ^{**}	0.63 ^{****}	0.61 ^{****}	0.64 ^{****}	0.64^{****}
G	–0.57 ^{****}	–0.61 ^{****}	–0.39 ^{***}	–0.39 ^{***}	–0.62 ^{****}	–0.54 ^{****}	–0.66^{****}	–0.63^{****}
H	–0.29^{**}	–0.24 [*]	–0.28 ^{**}	–0.25 [*]	ns	–0.24 [*]	–0.22 [*]	ns
η	–0.50 ^{****}	–0.57 ^{****}	–0.30 ^{**}	–0.31 ^{**}	–0.63 ^{****}	–0.61 ^{****}	–0.64^{****}	–0.64^{****}

ns, non-significant.
The highest correlations are identified in bold.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
**** $p < 0.0001$.

Table 7 – Analysis of the clinical potential of the more discriminative parameters in the detection of the respiratory alterations in asthmatic patients. Values of area under the curve (AUC), sensitivity (Se), specificity (Sp) for the optimal cut-off points obtained using receiver operating characteristic (ROC) curves and leave-one-out cross-validation (LOOCV).

	AUC			Se (%)			Sp (%)			Cut-off		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
ROC												
L (FrOr2)	0.895	0.976	0.990	79.1	90.7	94.7	86.4	95.5	85.2	0.177	0.145	0.137
β (FrOr2)	0.897	0.940	0.995	81.8	94.7	91.1	95.5	86.4	95.5	0.549	0.573	0.534
η (FrOr2)	0.897	0.940	0.995	81.8	94.7	100	95.5	86.4	95.5	0.853	0.709	0.853
β (FrOr3)	0.946	0.940	0.986	92.3	89.5	100	95.5	95.5	95.5	0.629	0.618	0.567
η (FrOr3)	0.946	0.926	0.986	95.5	88.0	89.5	95.5	95.5	95.5	0.580	0.580	0.580
R4	0.835	0.864	0.983	77.3	78.9	100	86.4	81.8	90.9	2.960	3.061	3.061
Rt	0.903	0.935	0.998	90.9	94.7	100	86.4	86.4	95.5	2.976	2.976	3.968
LOOCV												
L (FrOr2)	0.859	0.972	0.974	86.4	89.5	89.5	86.4	95.5	100	0.177	0.144	0.136
β (FrOr2)	0.921	0.880	0.977	77.3	89.5	94.7	86.4	86.4	95.5	0.551	0.573	0.533
η (FrOr2)	0.921	0.880	0.977	81.8	94.7	100	86.4	81.8	86.4	0.847	0.789	0.853
β (FrOr3)	0.954	0.922	0.977	90.9	84.2	94.7	95.5	95.5	95.5	0.628	0.616	0.566
η (FrOr3)	0.954	0.922	0.977	95.5	89.5	100	90.9	90.9	90.9	0.579	0.578	0.577
R4	0.732	0.767	0.952	77.3	73.7	100	81.8	86.4	86.4	2.960	3.130	3.060
Rt	0.861	0.882	0.998	90.9	94.7	100	77.3	81.8	90.9	2.960	2.970	3.970

The highest AUC values are identified in bold.

being able to probe the lung beyond the choke point where obstruction occurs. In this manner, FOT measurements reflect the mechanical properties of airways proximal to the choke points. This results in a reduction of the apparent mass of the gas accelerated by the FOT signal, and consequently a reduction in the pressure required for gas acceleration and in the measured inertance. This hypothesis is supported by the very good direct correlation observed between L and spirometric indexes of peripheral obstruction (Table 5). Thus, we may speculate that the airway obstruction may result in an apparent inertance, similar to the process observed in the apparent compliance. In contrast with the FrOr1 and FrOr2 models, FrOr3 presented increasing values of L in asthmatics (Fig. 5A). This is in agreement with the interpretation that resistive properties are captured, at least in part in this model, by the real part of the inertance fractional-order term [21]. In this model, L was significantly correlated with spirometric indexes of airway obstruction (Table 6), which provides additional support to this hypothesis.

In Fig. 4C, we can observe that the α values obtained in the control groups using the FrOr2 model is coherent with that presented in the study of Ionescu et al. [20]. The increased values of α in severe patients are also consistent with previous experimental findings of the cited study. It is important to note that L presents an inversely proportional relationship with α (Eqs. (3) and (4)). This indicates that the results observed for L and α may be attributed to the fact that the real part of the impedance in asthma (Fig. 2A) does not increase with frequency. Therefore, it does not depend on the inertance term. In line with this proposition, we found that α did not change in the FrOr3 model (Fig. 5B). A further support is provided by the correlation analysis, in which we did not observe association (Table 5) or only weak associations (Table 6) between α and spirometric parameters describing the obstruction level.

The mean values of C and β obtained in normal subjects in all of the studied FrOr models (Figs. 3C, D, 4D, E, 5C and D) are similar to those recently observed by other researchers

[10,21]. The increasing obstruction was accompanied by a corresponding reduction of C and β . This is clearly described by the direct correlations observed between these parameters and the spirometric indexes (Tables 4–6). The reduction in C is consistent with that presented using the eRIC model (Table 2, Fig. S2E) and previous results [5], reflecting the progressive functional consequences of airway inflammation and remodeling, as well as the reduction in the dynamic compliance of the chest wall/abdomen compartment and thoracic gas compression.

Reductions in C and its corresponding fractional-order parameter β significantly increased in the damping and elastance in all FrOr model studied (Figs. 3E, F, 4F, G, 5E and G). These results are in close agreement with the typical asthma pathology [1,24] and may reflect the closing of lung units [49], a decrease in the volume of air contained in the peripheral airways, and an increase in parallel airway heterogeneity [50]. G is a measure of energy dissipation in the respiratory tissues [10]. Therefore, we can suppose that the increase in G observed in Figs. 3E, 4F and 5E may be explained, at least in part, by the increase in parenchymal distortion that occurs when the airways constrict, as well as a proportional increase in air-flow heterogeneity throughout the lung [50]. In line with these interpretations, the correlation analysis showed inverse moderate to good associations between G and spirometric indexes, mainly those related to peripheral obstruction (Tables 4–6).

The increased values of H could be associated with an increase in intrinsic tissue stiffness, which could result from the distortion of the parenchyma produced as the airways narrow [51], as well as airway remodeling [9,24]. The correlation analysis provides support to this interpretation, showing inverse relationships between H and the spirometric indexes of peripheral and central obstruction (Tables 4–6).

The heterogeneity of the lung tissue is characterized by the hysteresivity [10]. This parameter is proportional to the area in the hysteresis of the pressure–volume loop [52], associated with work of breathing [20]. The observed values of

hysteresivity in normal subjects (Figs. 3G, 4H, and 5G) were coherent with the typical values described in previous works [3,11]. The increase in the hysteresivity observed in the three studied models are also in line with the cited authors [3,11], and may reflect increased heterogeneities and structural changes in the lungs. These findings are in close agreement with the pathophysiology of asthma [9], which includes significant increases in respiratory work [1].

Table 3 and Fig. S4 show that the FrOr2 model presented the smallest errors in the control group. This result is coherent with that presented in recent studies [10,21] and reflects the ability of this model to characterize the positive frequency-dependence of the resistance observed experimentally in some healthy subjects. In contrast with the FrOr2 model, the eRIC and the FrOr1 model does not allow for positive change in resistance with oscillation frequency. Although FrOr3 model also allowed fitting a positive frequency-dependent resistance, the observed error was higher than that obtained in the FrOr2 model. This could possibly be seen due to the presence of R , which may further fine-tune the resistance data.

Considering the errors in the asthmatic patients, the eRIC model has the poorest performance in terms of MSE_t and R_d in all of the studied groups. The underlying reason is that the model can only capture a decrease in the real part values of the impedance with frequency, whereas some patients may present an increase [10]. The FrOr2 model presented the smallest MSE_t in two of the three classes of patients studied (mild and severe obstruction). From the point of view of the reported R_d , this model presented the best performance for all studied groups (Fig. S4). The highest errors were with the eRIC model. This indicates that the FrOr2 model is the structure with the smallest errors in the parametric estimations between the studied models. This finding may also be explained by the ability of the FrOr models to adjust to fractional values of 20 dB/dec, in contrast with integer-order models, which are limited to integer multiples of 20 dB/dec.

There is a general agreement in the literature that it is necessary to develop new accurate and noninvasive methods of lung function analysis [53–55]. In an effort to contribute in this direction, the present study investigated the clinical use of the new studied parameters.

It was shown that L , β and η are very promising parameters to non-invasively evaluate the modifications due to asthma (Table 7). In the studied sample, β and η in the FrOr3 model were the most adequate parameters to correctly identify initial changes (LOOCV, AUCs=0.954), showing a high accuracy ($AUC \geq 0.90$) [37,38]. The diagnostic accuracy of these parameters was higher than that observed for the best traditional FOT parameter (R_4 ; $AUC=0.732$) and that exhibited by the more discriminative parameter in the eRIC model (R_t ; $AUC=0.861$), which also obtained an adequate diagnostic accuracy. This suggests that these FrOr parameters, as well as R_t , may be useful as a screening tool in the management of asthma.

As expected, increasing AUC values were observed in groups with moderate and severe obstruction. The more accurate parameter to detect patients with moderate obstruction was L , obtained from the FrOr2 model (Table 7; $AUC=0.972$). A high diagnostic accuracy was observed in all of the studied methods in the identification of severe obstruction, and the highest accuracy was obtained by R_t ($AUC=0.998$).

Comparing with previous studies using FOT to identify asthmatic patients, we observe that the accuracy using FrOr models (Table 7) was higher than that obtained previously using traditional FOT parameters [5] and in patients with suspected occupational asthma [8]. The observed accuracy was also higher than that obtained using the fluctuation analysis of the respiratory impedance waveform to identify asthma [7] and in the distinction between asthma and COPD [4]. These results are in line with previous studies in which the use of fractional-order dynamics provided a significant improvement in cancer detection [56].

Although the FrOr parameters are intuitively related to the pathophysiology of respiratory diseases, the relationship between these parameters and structural changes is not clear [21]. Recurrent fractal geometry may lead to the appearance of fractional-order terms, with the intrinsic property of phase constancy [10]. Previous work has shown that the bronchial tree is a complex fractal structure [57,58]. It is significant to note that the self-similarity is closely related to the healthy lung, whereas a diseased lung contains considerable inhomogeneities and thus asymmetry. Recent studies from our group using single frequency respiratory impedance measurements provided evidence that the increase in airway obstruction in asthma resulted in a reduction of the respiratory system complexity [7]. Boser et al. [59] observed a loss of complexity in silicone rubber casts of the lungs of patients with fatal or nonfatal asthma. A typical fatal asthma cast showed a loss of complexity associated with architectural remodeling throughout its length; many segments showed marked tapering, irregular constrictions, longitudinal ridges, and surface protrusions. Truncation of airways due to mucous plugs was also a common feature [59]. Therefore, we can hypothesize that the changes in the FrOr parameters observed in Figs. 3–5 may be explained, at least in part, by the progressive reduction in the spatial complexity of the airway tree of the studied patients. If this hypothesis is confirmed, the use of FrOr models to characterize respiratory diseases may complement the information obtained by traditional methods, potentially providing new information that can increase our understanding of these diseases.

Spirometric and plethysmographic measurements require good co-operation and are effort-dependent. These measurements can lead to temporary alterations in bronchomotor tone due to the deep inspiration required, which can have implications for respiratory mechanics. In contrast, FOT is easy to perform, and no respiratory maneuvers are needed. These practical considerations, together with the results of the present study, indicate that FOT measurements associated with FrOr modeling may be added to other conventional exams to help the clinical evaluations of patients with asthma that are not able to adequately perform the more traditional pulmonary function measurements.

Finally, we must consider some potential shortcomings of our study. First, the present report is a cross-sectional study in which the volunteers were recruited at one center, which might hinder the generalizability of the results. A second limitation arises from the fact that, during the exams, part of the oscillatory flow is shunted by the impedance of the compliant cheeks and pharynx, which are placed in parallel with the respiratory system. The resulting effect is to reduce

the impedance measured in comparison to its actual value [2]. This effect is minimal at low frequencies and becomes increasingly important as the oscillation frequency rises. The changes observed in Fig. 2A may be, at least partially, explained by this effect. In this study, this effect was minimized by asking the patients to firmly support their cheeks and mouth floors. Another limitation in our study is that there is not a consensus in the literature concerning the interpretation of FOT data. Previous studies used other FOT parameters that were not included in present study, which could be potentially useful in the identification of airway obstruction in asthma. These parameters include the resistance and reactance measured in specific frequencies and that obtained by other respiratory models [3,11,10]. The contribution of these parameters should be addressed in future research.

In this study, the adequacy of the models was evaluated using the root mean square errors and the mean relative distance from the model and measured resistance and reactance values. Further validation of the models to the data may be performed using various dedicated tools (e.g. Akaike Information, Bayesian Information, Akaike's Final Prediction Error criterions) [60]. These analyses could provide a more detailed examination of the models adequacy and should therefore be addressed in future studies.

It was previously noted that one needs to be careful when using η for diagnostic purposes because there are situations in which an increase in η can be produced by phenomena other than heterogeneity. Nevertheless, when the onset of heterogeneities is expected, an increase in η can serve as a useful indicator for their presence [11]. Non-uniform distribution of inspired gas within the lung is present in patients with even mild asthma [61]. In addition, the closest associations between η and spirometric parameters were observed with parameters related with peripheral airways obstruction and heterogeneity (Tables S2 and S3), providing evidence that η reflects these alterations. Thus, this limitation is probably not a relevant problem in the present study.

The interrupter technique (IT) may also be used to measure respiratory impedance with minimal patient co-operation [62–64]. The use of fractional-order models in the interpretation of the exams based on IT could contribute with new potentially useful information and therefore deserve further studies.

5. Conclusions

The present study provided evidence that FrOr parameters are sensitive to the different mechanical properties expected in healthy subjects and patients with asthma. A correlation analysis revealed a clear association of these parameters with spirometric measurements. Among the three studied FrOr models, the FrOr2 model best fit the data, presenting an error smaller than that presented by the integer-order eRIC model. Furthermore, a preliminary ROC analysis indicated that FrOr parameters were more accurate than traditional FOT parameters and those obtained by eRIC modeling, being able to adequately detect mild alterations. FOT associated with fractional-order models is a non-invasive, simple and radiation-free method for the detection of biomechanical

abnormalities. Thus, this method has a promising application as a complementary pulmonary function test in adult asthmatic patients.

Future Plans

Integrating the results of this work with other research under development in our lab, future plans include the following: initially to contribute to the diagnosis of abnormalities in cystic fibrosis [43] and develop automatic classifiers to simplify the clinical use of FrOr models in patients with asthma [65]. Long-term plans include integrating automatic classifiers algorithms, FOT, FrOr modeling and telemedicine instrumentation services to improve the home monitoring of patients with asthma [66].

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.cmpb.2016.02.010>.

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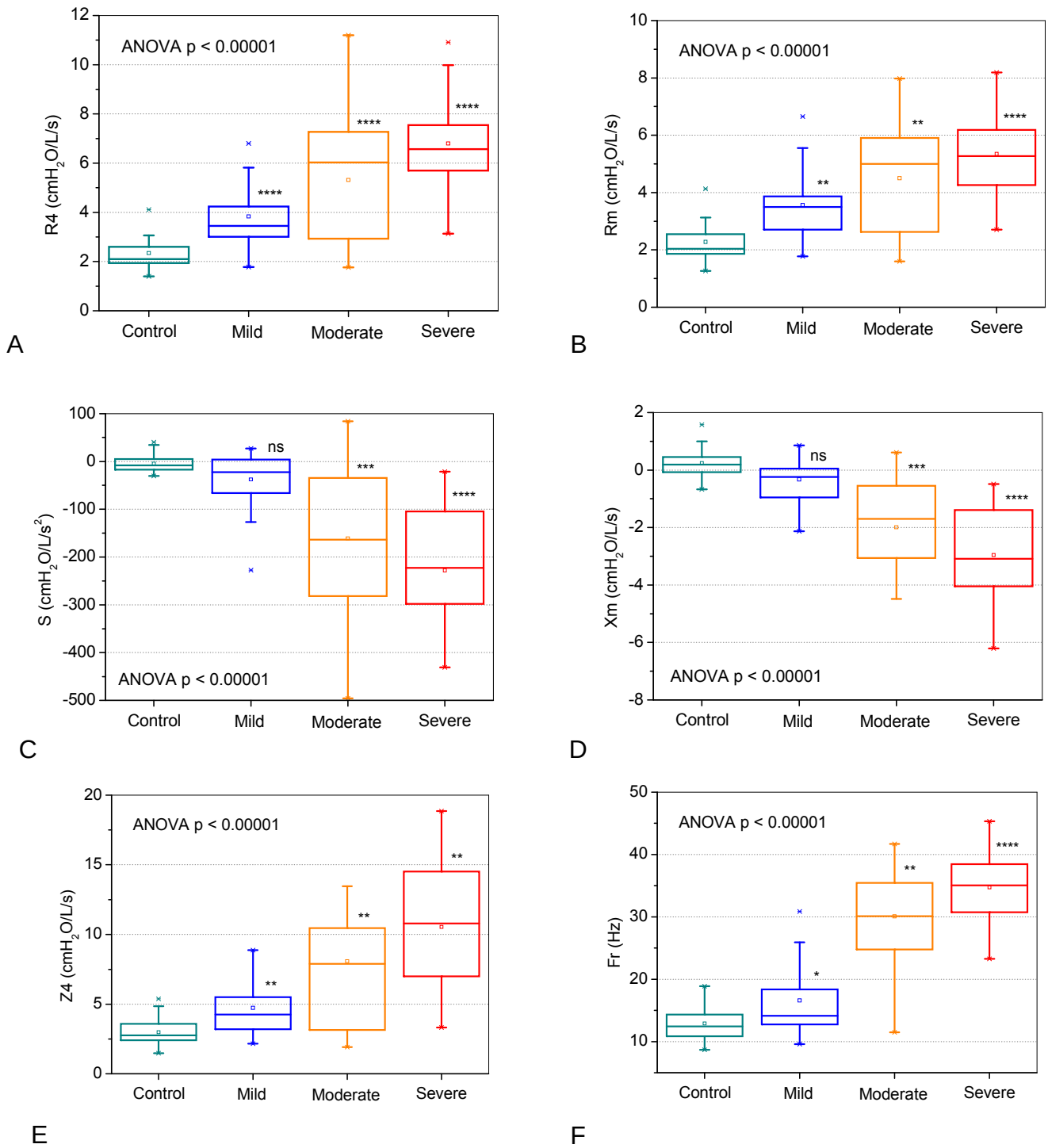


Fig. S1. Comparative analysis of the traditional parameters obtained in groups of adults with asthma and control: Resistance in 4 Hz ($R4$; Figure A), mean resistance (Rm ; Figure B), slopes of the resistance values (S ; Figure C), mean reactance (Xm ; Figure D), impedance modulus in 4 Hz ($Z4$; Figure E) and resonance frequency (Fr ; Figure F). The top and the bottom of the box plot represent the 25th- to 75th-percentile values, while the circle represents the mean value, and the bar across the box represents the 50th-percentile value. The whiskers outside the box represent the 10th-to90th-percentile values.

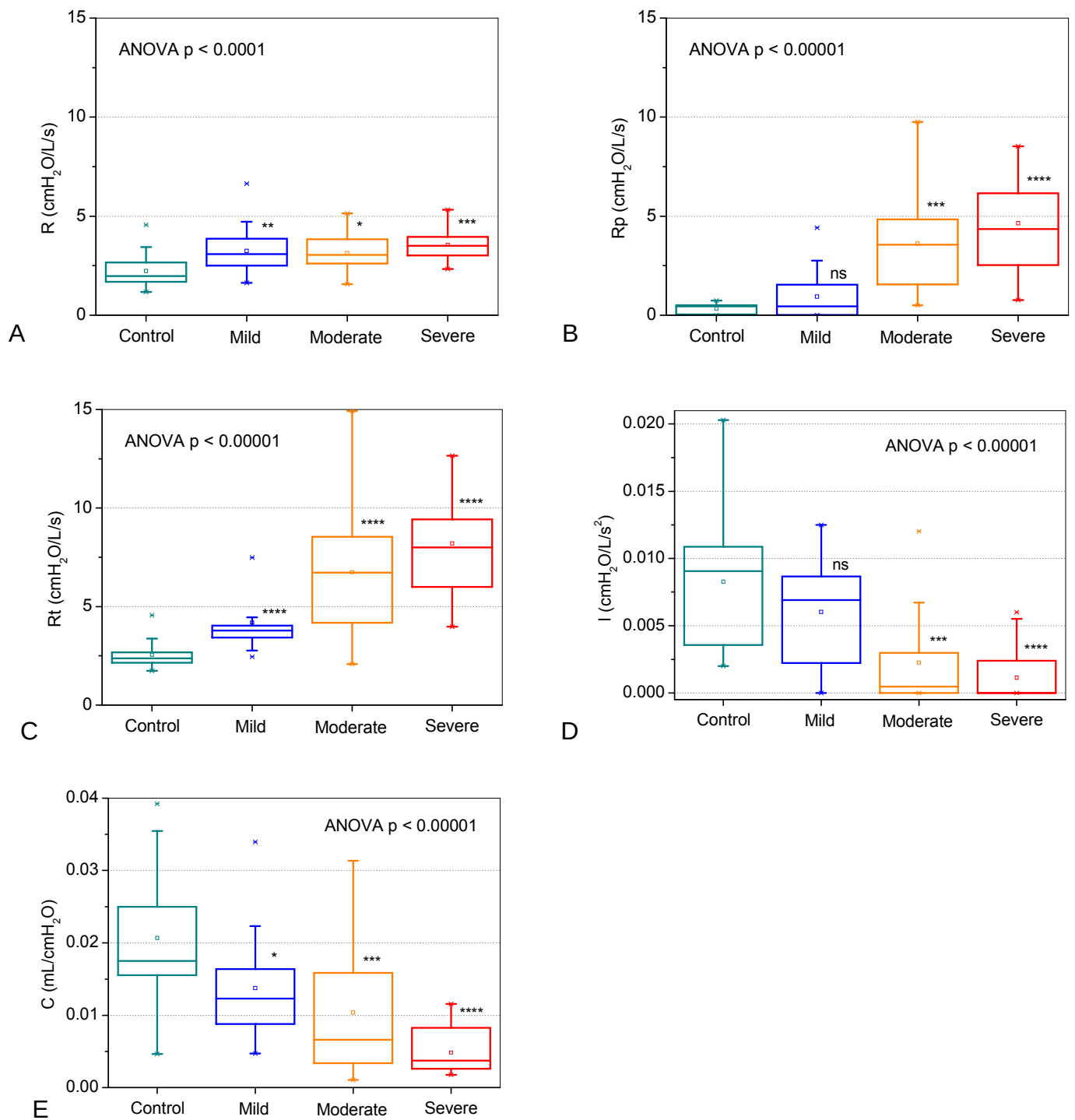
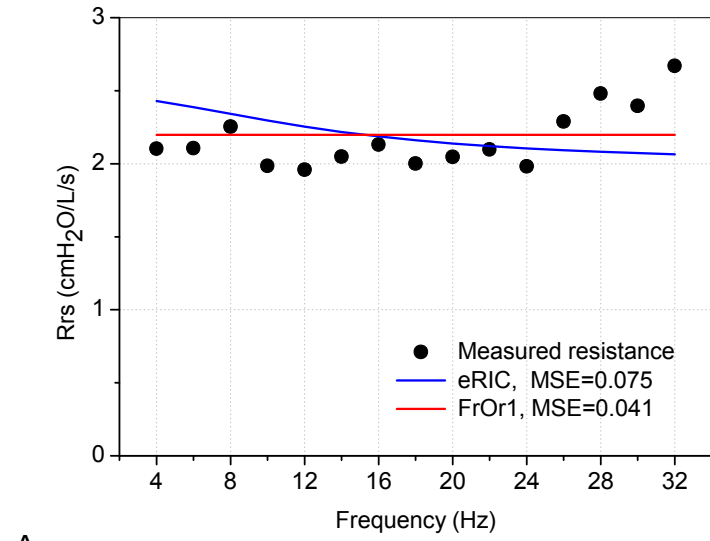
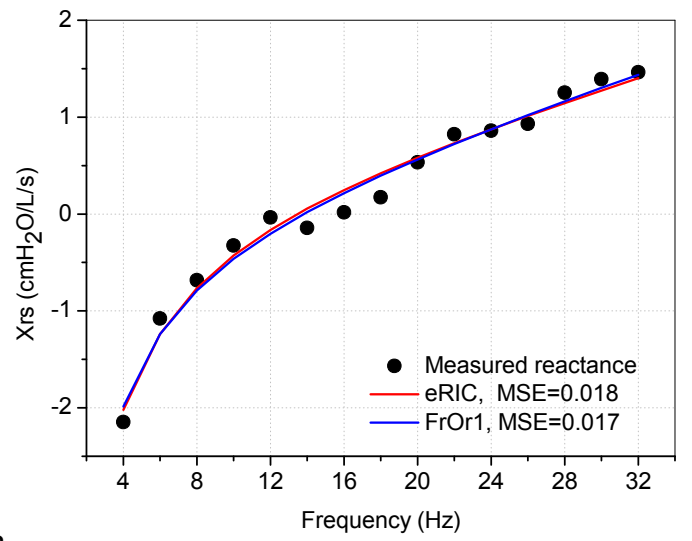


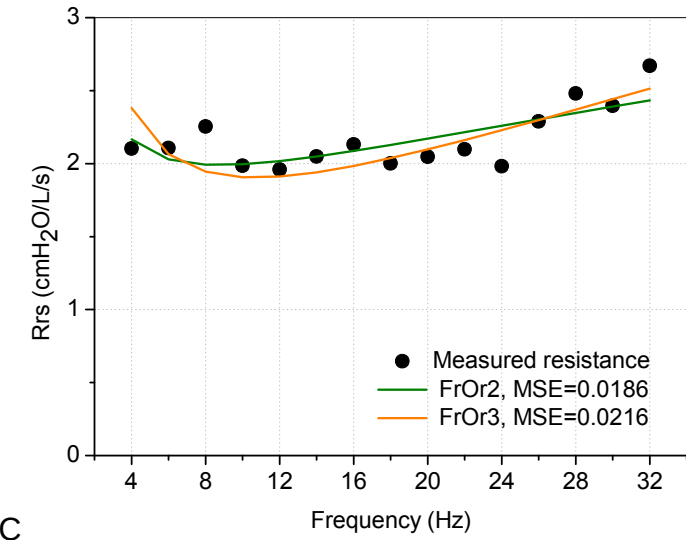
Fig. S2. Influence of asthma in adult patients on parameter values estimated from the model described in Figure 1: central airway resistance (R ; Figure A), peripheral resistance (R_p ; Figure B), total resistance (R_t ; Figure C), lung inertance (I ; Figure D) and alveolar compliance (C ; Figure E). The top and the bottom of the box plot represent the 25th- to 75th-percentile values, while the circle represents the mean value, and the bar across the box represents the 50th-percentile value. The whiskers outside the box represent the 10th-to 90th-percentile values.



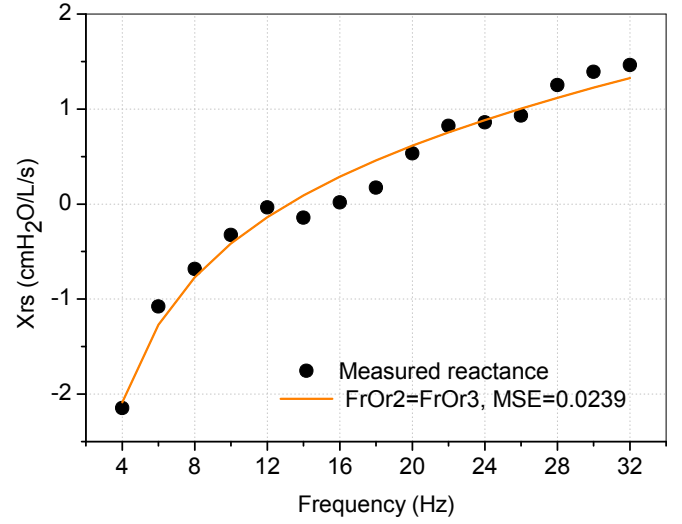
A



B



C



D

Fig. S3. Example of how well the studied models fits the data for the different frequencies. Measured values and associated fittings and Mean Square Errors for the eRIC and FrOr1 models in resistance (A) and reactance (B). Similar examples for resistance (C) and reactance (D) are also presented for the FrOr2 and FrOr3 models.

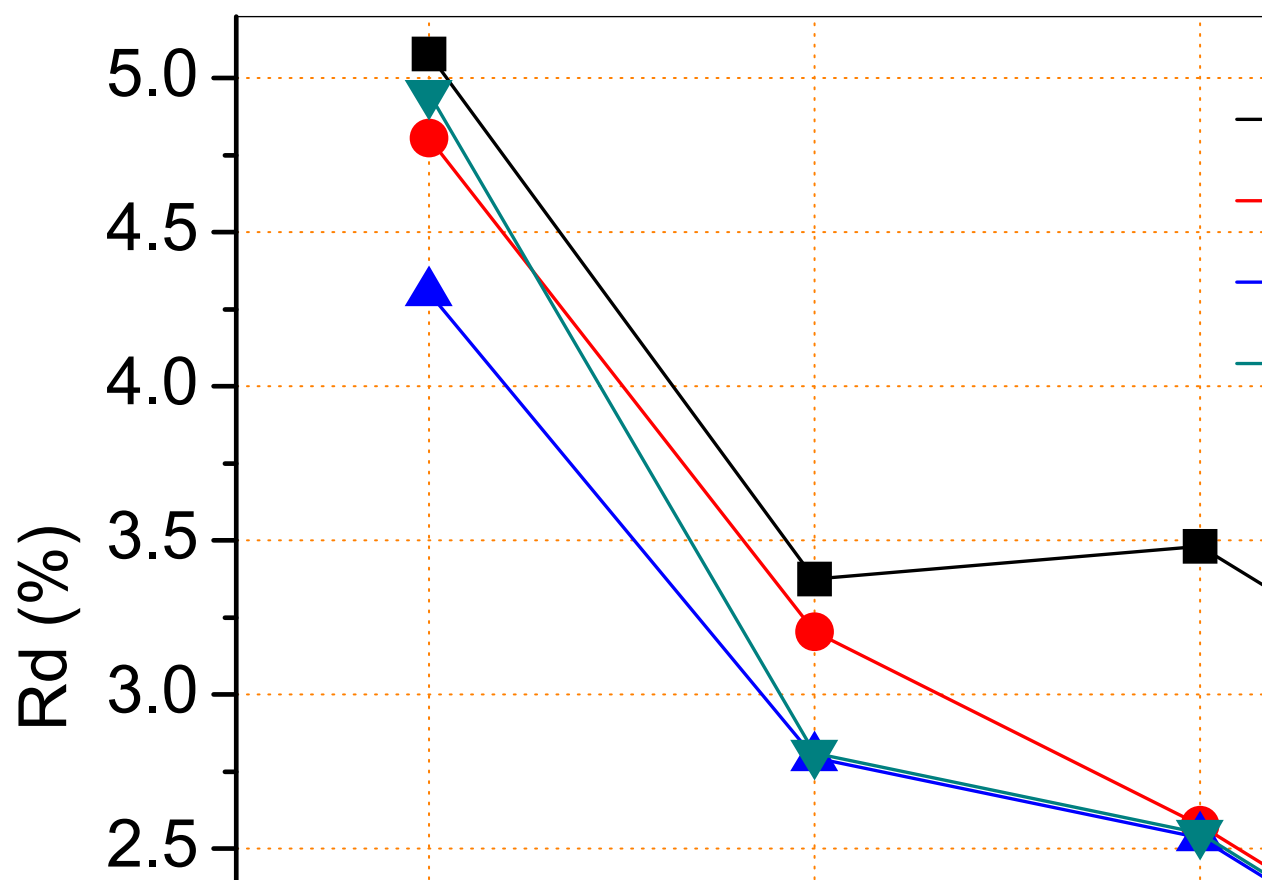
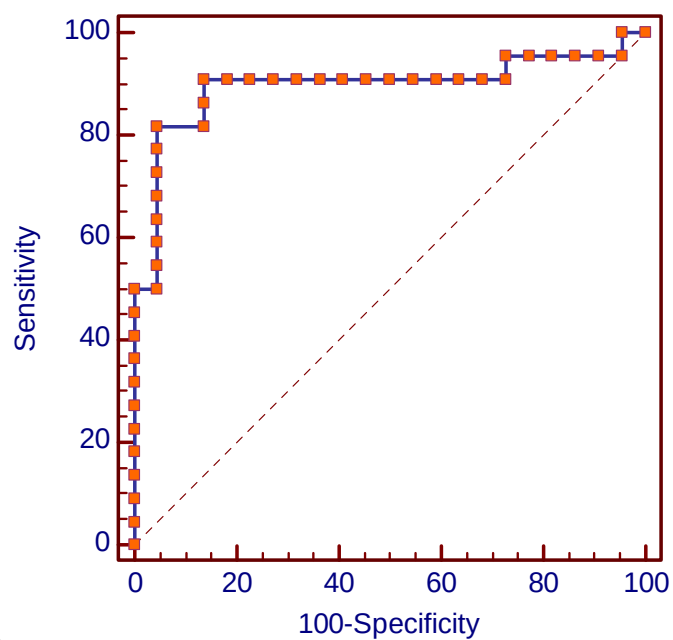
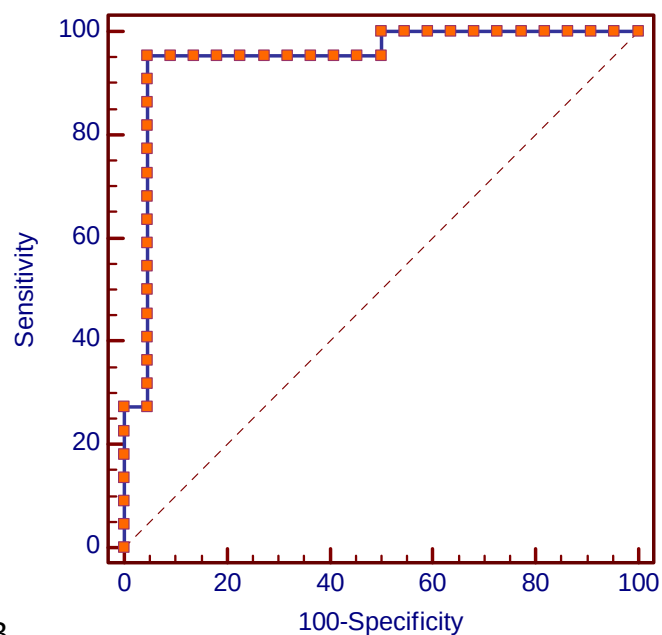


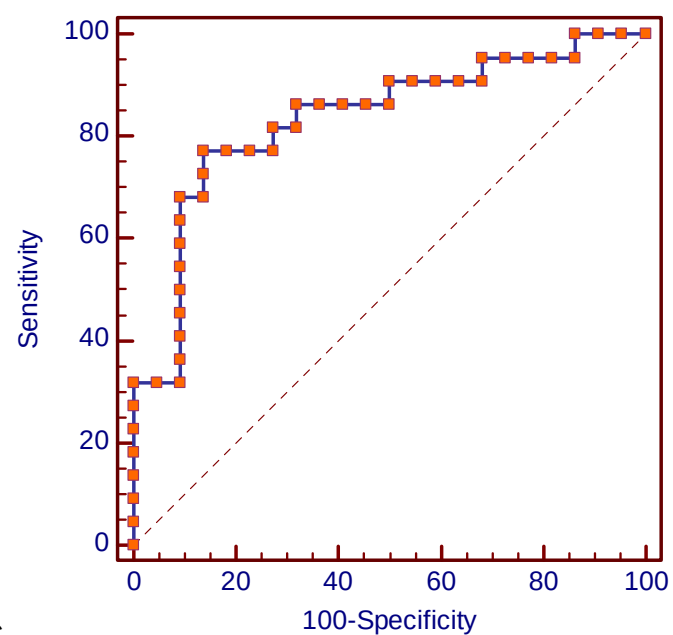
Fig. S4. Mean relative distance from the studied models and measured resistance and reactance values.



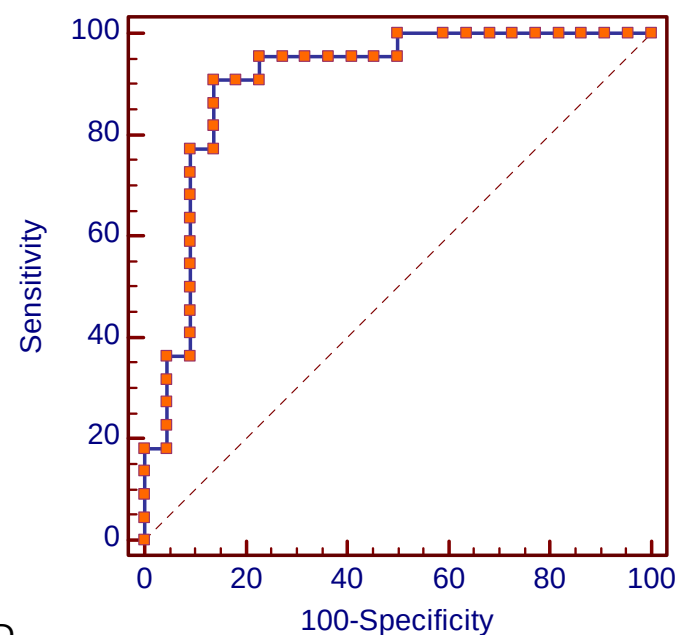
A



B



C



D

Fig. S5. Receiver Operating Characteristic curves for detecting mild asthma using the most accurate parameters for the different models. Fractional-order model 2 (β , AUC=0.897, Graph A), Fractional-order model 3 (β , AUC=0.946, Graph B), traditional FOT parameter (R4, AUC=0.835, Graph C), and extended RIC model (Rt, AUC=0.903, Graph D).