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Respiratory Impedance and Response to Salbutamol in Healthy Individuals and Patients with COPD

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Key Words
Bronchodilator response · Airway obstruction · COPD · Forced oscillation technique · Salbutamol

Abstract
Background: Recent studies suggested that the bronchodilator response depends on airway obstruction. The forced oscillation technique (FOT) may help improve our understanding of the changes in respiratory mechanics that occur after the application of a bronchodilator. ***Objectives:*** We aimed to (1) assess the response to salbutamol and to compare the impedance changes in healthy individuals and COPD patients, (2) investigate the effects of airway obstruction on this response and (3) evaluate the utility of the FOT as a complementary measurement to assess the response to the bronchodilator. ***Methods:*** Twenty-five healthy individuals and 82 patients with COPD were assessed with the FOT followed by spirometry before and after the use of salbutamol. ***Results:*** The changes exhibited by the COPD subgroups were greater than in the healthy individuals ($p < 0.05$). Increased obstruction resulted in decreased reductions in mean resistance and increased improvements in mean reactance ($p < 0.001$). In addition, the bronchodilation reduced the ventilation heterogeneity and the impedance modulus in all COPD stages ($p < 0.05$). The correlation coefficients for the spirometric and FOT changes were low (0.21–0.38). ***Conclusions:*** In the initial phases of COPD (stage I), the effects of bronchodilation are greater than in healthy volunteers. The bronchodilator use improved the oscillatory mechanics in all of the studied groups of COPD patients. These improvements are reduced in more advanced phases of airway obstruction (II, III and IV). The FOT provides information that complements the data supplied by spirometry, contributing to an improvement in the evaluation of the bronchodilator response in COPD.

Introduction

Previous studies suggested that the bronchodilator response in COPD depends on airway obstruction [1, 2]. This difference may arise from changes in lung volume that occur secondary to the pathophysiological alterations associated with the progression of the disease [3, 4]. Little is known about the effect of airway obstruction on the bronchodilator response.

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The forced oscillation technique (FOT) [5, 6] is a complementary method that measures the total resistance (Rrs) and reactance (Xrs) of the respiratory system. It is able to provide a detailed analysis of respiratory mechanics, supplying new information on airway obstruction, respiratory compliance and ventilation homogeneity. This method may thus contribute to increasing our understanding of the effect of airway obstruction on the bronchodilator response in COPD. However, to our knowledge, there are no studies in the literature exclusively dedicated to this analysis.

In this context, the aim of our study was to investigate the effect of airway obstruction on the bronchodilator response, analyzing the changes of respiratory impedance to salbutamol in healthy individuals and COPD patients.

Methods

Participants and Ethical Approval

Between November 2010 and November 2012, the study assessed individuals of 40–80 years of age of both genders who were assisted at the Newton Bethlem Polyclinics of the Rio de Janeiro City Council. The sample included 25 healthy individuals without history of smoking and 82 patients with stable COPD [7] who were classified as having a mild (I), moderate (II), severe (III) or very severe (IV) obstruction. The eligibility criteria for COPD included a history of smoking of >10 packs of cigarettes per year, an FEV_1/FVC ratio of <0.7, no respiratory infections in the previous 3 weeks and an absence of other respiratory diseases or extrathoracic comorbidities including cardiovascular disease, malignant disease and chest deformities. All patients were stable at study entry. Before the study, all patients were taking their usual medication as recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [7], but medication that could interfere with the assessment of the BD response was suspended [as established by the American Thoracic Society/European Respiratory Society (ATS/ERS)] [8].

The research protocol was approved by the Ethics Committee of the State University of Rio de Janeiro and registered at ClinicalTrials.gov [ClinicalTrials.gov; Identifier: NCT01521572]. All the participants signed an informed consent form.

Study Design

The patients were subjected first to the FOT and then to spirometry to avoid bronchomotor tone alterations and the effect of the forced expiratory maneuver on the airways. Next, a short-acting β_2-agonist was administered to assess the bronchodilator response.

Spirometry

The flow-volume curves were obtained by means of a bellows spirometer (Vitatrace VT 130 SL model; Pro Médico Ind Ltd., Rio de Janeiro, Brazil) to assess FEV_1 and FVC expressed in liters and as a percentage of the predicted values. These exams were performed according to the ATS/ERS guidelines for spirometry [8]. To make sure that the increase in FVC in COPD patients was not associated with a longer expiratory time, we only considered patients in which the expiratory time after bronchodilation did not exceed 10% of that before bronchodilation [9].

Bronchodilator Action

Bronchodilation was induced by inhalation of 400 μg of salbutamol spray in four 100-μg puffs using a spacer with a mouthpiece. After a gentle and incomplete expiration, each dose of salbutamol was inhaled in one breath to total lung capacity. The breath was then held for 5–10 s before the subject exhaled [8]. The doses were delivered at 1-min intervals. The FOT and spirometry readings were repeated 15 min after the administration of the bronchodilator. The ATS/ERS criteria [10] were used to define a positive bronchodilator response.

Forced Oscillation

The respiratory impedance was measured using a multifrequency impedance analyzer described previously in detail [11]. The measurements were obtained using the ERS Taskforce recommendations [5]. This FOT analysis is performed by superposing sinusoidal pressure signals at frequencies that are whole multiples of 2 Hz within the 4–32 Hz range on the individual's spontaneous breathing. Measuring the pressure applied and the resulting flow allows the estimation of the respiratory impedance by subjecting the signals to a Fourier analysis. Three consecutive assays were performed (each for 16 s) and their average was considered as the final result. A minimal coherence function of 0.9 was considered adequate. Any time that the coherence computed for any of the frequencies was smaller than this threshold, the maneuver was considered not valid, and the examination was repeated. The individuals were examined seated with their heads in a neutral position and they wore a nasal clip during the tests. The volunteers were asked to breathe calmly and to hold their cheeks with their hands to minimize the shunt effect [5, 11].

Analysis

The resistance data were subjected to linear regression over a frequency range of 4–16 Hz [12, 13]. The intercept resistance (R0) was obtained from this analysis. This parameter estimates how the cited properties work at low frequencies, and is usually used as an indicator of airway obstruction. The mean resistance (Rm) is mainly associated with the caliber of the central airways and it was also calculated at the abovementioned frequency range. The slope of the resistive component of respiratory impedance (S), which indicates the homogeneity of the respiratory system, was also obtained from this analysis. S reflects the frequency-dependent alteration in the distribution of gas flow within the system, i.e. both spatial and temporal inhomogeneity.

The imaginary component of the respiratory impedance was characterized by the mean reactance (Xm), a parameter related to the nonhomogeneity of the respiratory system [14]. This parameter was calculated over a frequency range of 4–32 Hz. The dynamic compliance of the respiratory system (Crs,dyn) was estimated using the reactance of the respiratory system at 4 Hz (Xrs4) [$Crs,dyn = -1/(2\pi f\, Xrs4)$]. This same frequency was used to assess the absolute value of the respiratory impedance (Z4Hz). This variable represents the total mechanical load of the respiratory system and is associated with respiratory work. In this study, Z4Hz mainly describes the effect resulting from the total resistance and compliance of the respiratory system [15].

Statistical Methods

The statistical analysis was performed using Microcal Origin 8.0 software. The results are presented as the mean ± standard deviation. The impact of the β_2-agonist on pulmonary mechanics was

Table 1. Anthropometric and smoking characteristics of the group of healthy individuals and the patient subgroups classified according to COPD severity[a]

GOLD	Control (n = 25)	I (n = 22)	II (n = 24)	III (n = 21)	IV (n = 15)	ANOVA
Sex, male/female	10/15	15/7	18/6	18/3	6/9	–
Age, years	65.9 (10.3)	62.9 (10.8)	67.7 (11.4)	65.5 (7.7)	66.4 (9.6)	n.s.
Height, cm	162.0 (9.7)	161.0 (7.2)	162.5 (8.1)	166.7 (9.8)	163.2 (7.8)	n.s.
Weight, kg	63.6 (12.3)	58.1 (8.0)	60.7 (13.0)	59.6 (13.0)	62.5 (12.4)	n.s.
BMI, kg/m^2	24.1 (3.2)	22.5 (3.4)	23.0 (4.6)	21.3 (3.7)	23.4 (3.8)	n.s.
Current/former smoker	–	7/15	8/16	11/10	4/10[b]	–

Data are presented as mean (SD) unless otherwise indicated. n.s. = Not significant.
[a] Defined according to the 2010 GOLD classification stages I (mild), II (moderate), III (severe) and IV (very severe).
[b] One of these patients never smoked.

assessed as the difference of the after-before use of bronchodilator values (Δ) and the percentage variation [(Δ%) = 100 × (postbronchodilator – prebronchodilator)/prebronchodilator]. The percentage variations were derived from the average values of the sample. The paired Student t test was used when the data exhibited a normal distribution and a nonparametric test (Wilcoxon) was used when the distribution was not normal. A one-way ANOVA was used to compare the percentage of variation among the subgroups of individuals with COPD when the data exhibited a normal distribution, and a nonparametric test (Kruskal-Wallis) was used when the distribution was not normal. The Tukey test was used for the between-group analysis when the data exhibited a normal distribution; otherwise, a nonparametric Mann-Whitney test was used. The Spearman correlation was used to investigate the correlation between the salbutamol-induced changes in the FOT and spirometry measurements. $p < 0.05$ was considered statistically significant.

Results

Study Population

The anthropometric characteristics of the subjects are described in table 1. The proportion of women was higher in the control group. Although some small differences in age, body mass, height and body mass index were found between the groups, these were not significant ($p > 0.05$).

Spirometry

Table 2 describes the results of the spirometric parameters recorded before and after bronchodilator use. As expected, these values gradually decreased with the progression of COPD both before and after the use of the medication (ANOVA, $p < 0.0001$).

The healthy individuals exhibited nonsignificant changes after using the bronchodilator. The bronchodilator significantly decreased airway obstruction in all stages of COPD. Using the ATS criteria, GOLD I patients did not have evidence of reversibility by either FEV_1 or FVC. For GOLD II patients, there was reversibility by FEV_1 but not FVC. For GOLD III and IV patients, there was evidence of reversibility for FVC but not for FEV_1.

Forced Oscillation Technique

Figure 1a–d shows the resistance curves as a function of the frequency of the control group and the patients with COPD before and after the use of salbutamol. The average Rrs values for the COPD subgroups increased with airway obstruction. The Rrs values decreased over the entire frequency range after the administration of the bronchodilator. Such events were more pronounced at the 4–16 Hz range.

Figure 1e–h depicts the reactance curves as a function of the frequency of all of the investigated groups. A comparison of the COPD groups showed that the Xrs values became increasingly negative as the severity of the disease increased. In these patients, the short-acting β_2-agonist influenced the average Xrs values over the entire frequency range. The changes induced by the bronchodilator became more pronounced with increasing disease severity.

Figure 2a depicts the changes in R0 as a function of the COPD severity. The changes following bronchodilation were significant in the control and COPD groups ($p < 0.05$). On average, the COPD patients exhibited greater reductions in R0 percentage values. However, statistical analysis showed that the reduction in R0 in the patients was only greater than the reduction in the control group in patient group I ($p < 0.02$). The increase in airway obstruction significantly reduced the percentage of the reductions in R0 (ANOVA, $p = 0.0001$).

Table 2. FEV_1 and FVC at baseline, after salbutamol and the resulting change

GOLD	Control	I	II	III	IV	ANOVA all	ANOVA only COPD
Flow							
FEV_1 before BD, l	2.71 (0.9)	2.14 (0.4)*	1.41 (0.3)	1.07 (0.2)	0.58 (0.1)	<0.0001	<0.0001
FEV_1 after BD, l	2.74 (0.9)	2.24 (0.5)	1.62 (0.4)	1.18 (0.2)	0.67 (0.2)	<0.0001	<0.0001
ΔFEV_1, l	0.03 (0.1)n.s.	0.10 (0.3)*	0.21 (0.2)†	0.11 (0.1)†	0.08 (0.1)†	<0.0001	<0.0001
ΔFEV_1, %	1.06 (2.9)	5.47 (15.6)	15.87 (14.9)	11.63 (11.7)	14.56 (14.3)	<0.0001	<0.0001
FEV_1 before BD, %p	106.6 (21.5)	84.6 (10.3)	58.3 (12.2)	38.5 (7.87)	24.5 (4.83)	<0.0001	<0.0001
FEV_1 after BD, %p	107.5 (20.4)	89.3 (10.7)	66.3 (10.1)	42.4 (6.15)	28.0 (6.92)	<0.0001	<0.0001
FEV_1, Δ%p	0.9 (3.45)n.s.	4.7 (10.2)*	8.0 (6.33)†	3.9 (4.18)‡	3.5 (4.12)‡	<0.0001	<0.0001
Volume							
FVC before BD, l	3.27 (1.1)	3. 41 (0.6)	2.75 (0.6)	2.66 (0.6)	1.67 (0.4)	<0.0001	<0.0001
FVC after BD, l	3.24 (1.1)	3.36 (0.7)	3.02 (0.6)	3.04 (0.7)	1.93 (0.6)	<0.0001	<0.0001
ΔFVC, l	–0.03 (0.1)n.s.	–0.05 (0.3)n.s.	0.26 (0.3)†	0.38 (0.3)†	0.26 (0.2)†	<0.0001	<0.0001
ΔFVC, %	–1.17 (4.7)	–1.47 (8.6)	10.46 (11.6)	14.73 (13.3)	15.27 (12.9)	<0.0001	<0.0001
FVC before BD, %p	104.5 (20.6)	107.5 (11.1)	90.0 (14.8)	77.2 (14.2)	57.2 (10.6)	<0.0001	<0.0001
FVC after BD, %p	103.1 (21.8)	106.5 (12.3)	98.6 (15.1)	87.8 (15.5)	63.6 (13.8)	<0.0001	<0.0001
FVC, Δ%p	–1.4 (4.2)n.s.	–0.95 (6.60)n.s.	8.65 (9.50)‡	10.7 (9.36)†	6.42 (9.82)*	<0.0001	<0.0001
FEV_1/FVC before BD	81.8 (6.60)	62.9 (5.89)	52.1 (10.7)	40.1 (8.80)	35.7 (6.24)	<0.0001	<0.0001
FEV_1/FVC after BD	83.8 (6.43)	66.74 (4.54)	54.4 (10.3)	39.1 (8.23)	35.8 (8.33)	<0.0001	<0.0001
ΔFEV_1/FVC	2.03 (3.12)n.s.	3.79 (5.23)‡	2.29 (4.32)*	–1.01 (2.85)n.s.	0.09 (4.18)n.s.	<0.0001	<0.0001

Data are presented as mean (SD). The far right column is the comparisons including only groups of patients with COPD. BD = Bronchodilator; n.s. = not significant; Δ = absolute change (post-BD – pre-BD); Δ% = percentage change (post-BD – pre-BD/pre-BD)·100; %p = percent predicted; Δ%p = %p post-BD – %p pre-BD.

* $p < 0.05$, ‡ $p < 0.006$, † $p < 0.0001$ (baseline comparisons).

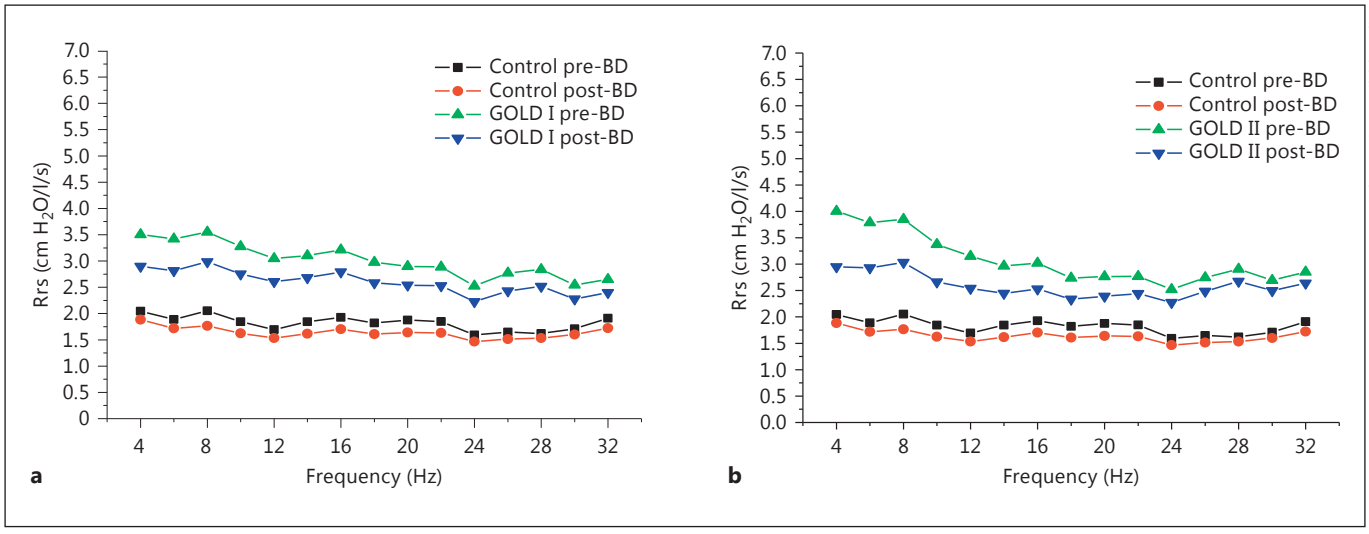
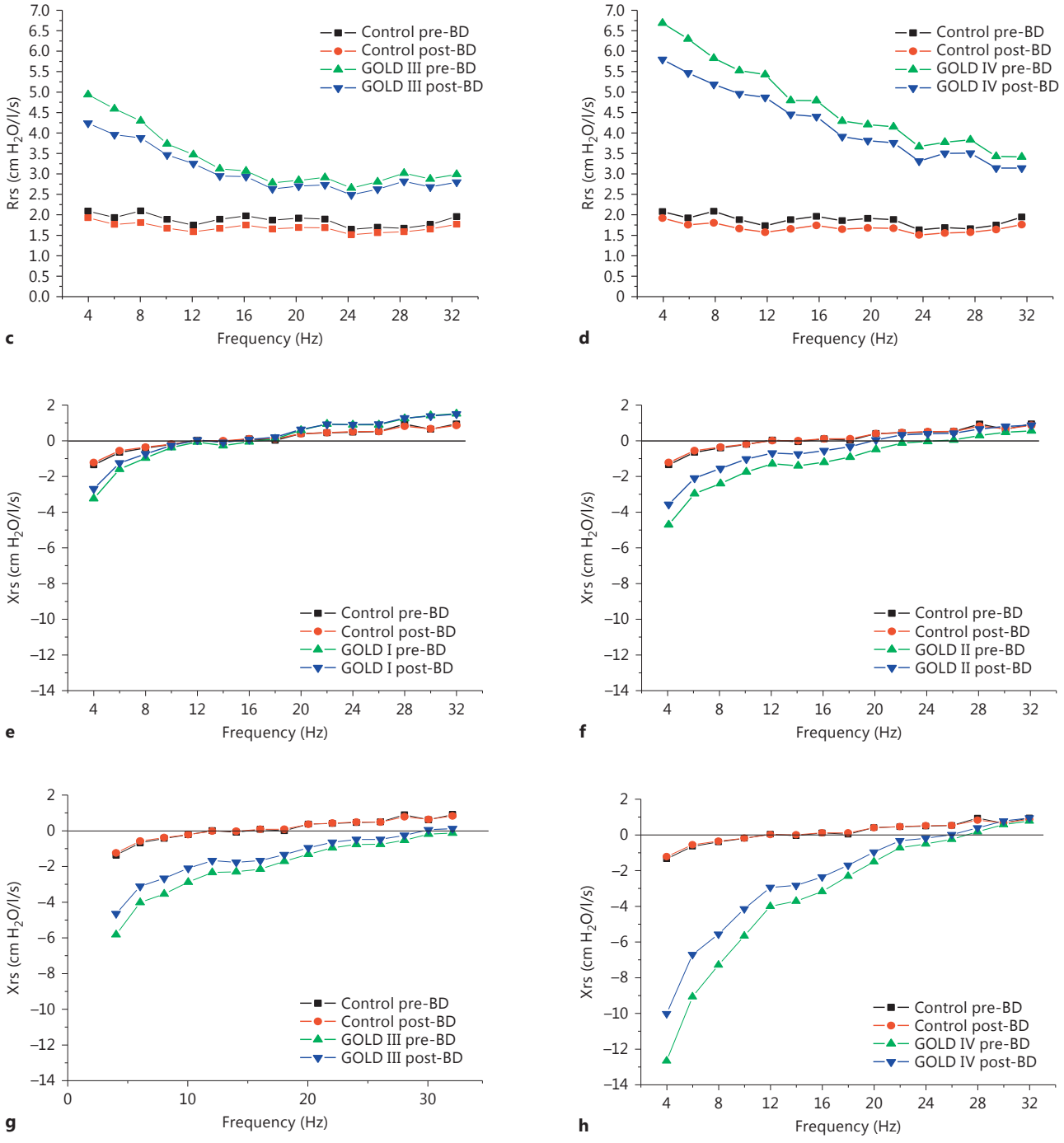
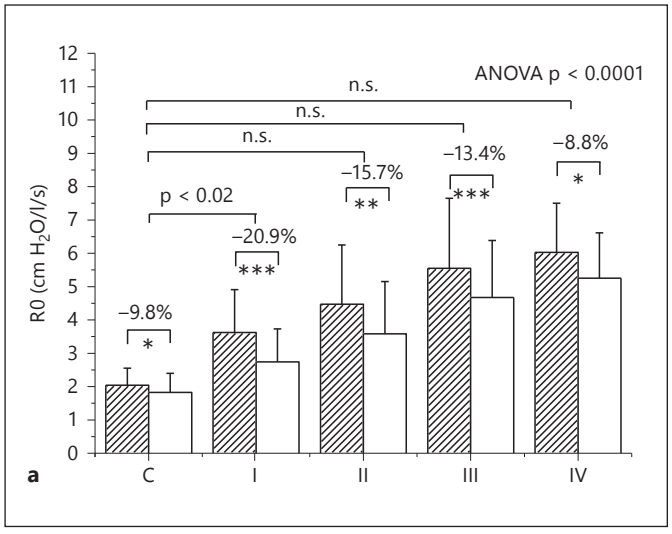


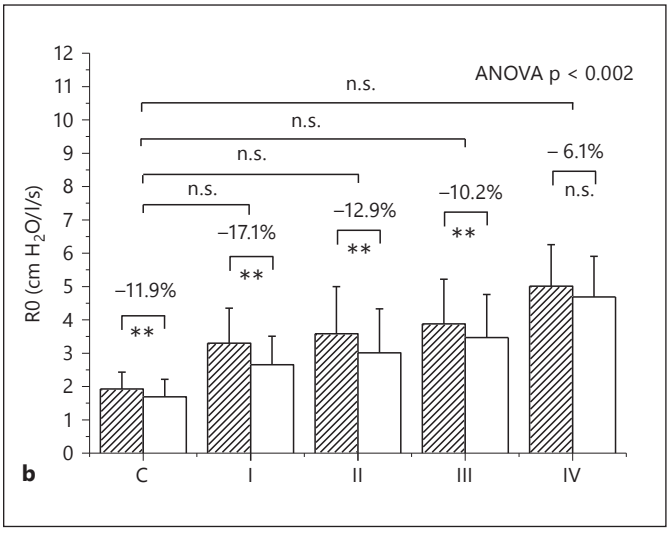
Fig. 1. Respiratory resistance (**a–d**) and reactance (**e–h**) as a function of frequency before and after bronchodilator application (BD) in the control group and the COPD subgroups according to the degree of airway obstruction.

(*For figure 1c–h see next page.*)


Color version available online
Rrs (cm H2O/l/s)
Frequency (Hz)
Control pre-BD
Control post-BD
GOLD III pre-BD
GOLD III post-BD
c
Control pre-BD
Control post-BD
GOLD IV pre-BD
GOLD IV post-BD
d
Xrs (cm H2O/l/s)
Frequency (Hz)
Control pre-BD
Control post-BD
GOLD I pre-BD
GOLD I post-BD
e
Control pre-BD
Control post-BD
GOLD II pre-BD
GOLD II post-BD
f
Control pre-BD
Control post-BD
GOLD III pre-BD
GOLD III post-BD
g
Control pre-BD
Control post-BD
GOLD IV pre-BD
GOLD IV post-BD
h

1





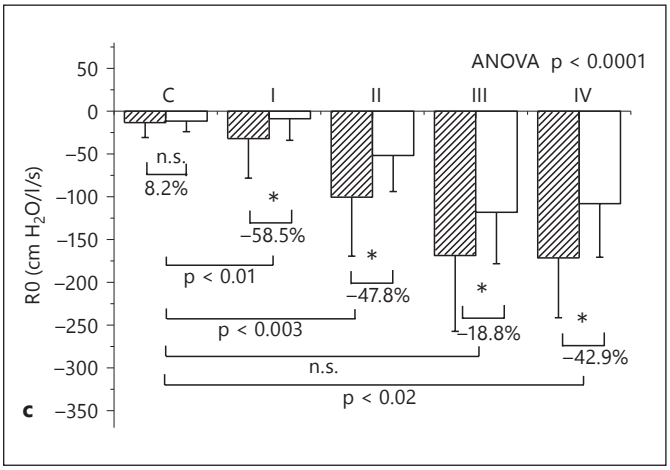
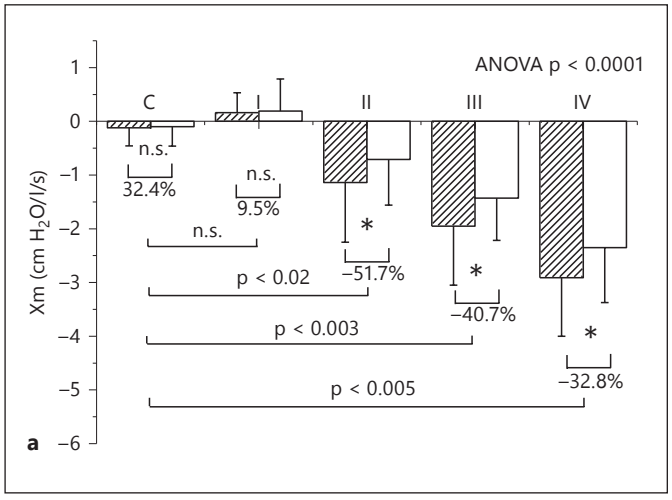


Fig. 2. Total respiratory resistance (**a**), mean resistance (**b**) and slope of the resistance values (**c**) before (dense column) and after (white column) salbutamol administration in the control group (C) and in the COPD subgroups. % = Average value of percentage change in each studied subgroup. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.0001$ show significant differences. n.s. = Not significant.



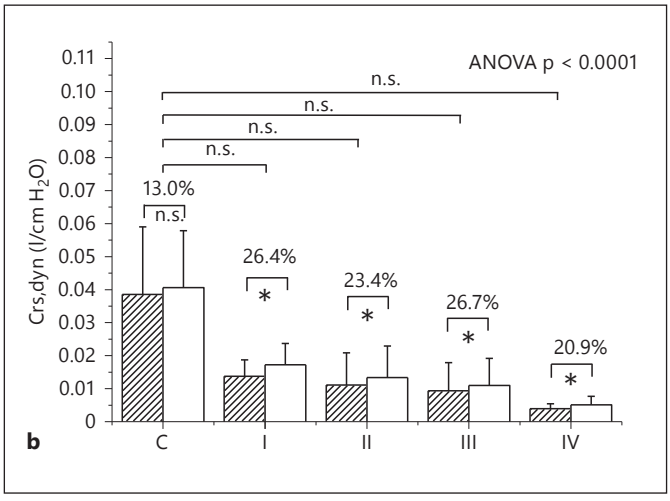


Fig. 3. Mean respiratory reactance (**a**) and dynamic compliance (**b**) before (dense column) and after (white column) salbutamol administration in the control group (C) and in the COPD subgroups. % = Average value of percentage change in each studied subgroup. * $p < 0.05$ show significant differences. n.s. = Not significant.

Table 3. Absolutes value of the difference in resistive and reactive parameters

	Control	I	II	III	IV	ANOVA only COPD, p	ANOVA all, p	Adjacent groups
ΔR0 (cm H_2O/l/s)	–0.21 (0.4)	–0.89 (0.9)	–0.89 (1.7)	–0.87 (1.1)	–0.77 (1.4)	<0.0001	<0.0001	C-I, II, III, IV
ΔRm (cm H_2O/l/s)	–0.23 (0.3)	–0.65 (0.8)	–0.57 (1.0)	–0.41 (0.5)	–0.33 (0.6)	<0.001	<0.0001	C-I, II, III, IV
ΔS (cm H_2O/l/s^2)	1.76 (16.1)	25.22 (40.9)	48.87 (54.5)	50.31 (67.2)	63.38 (64.5)	<0.0001	<0.0001	C-I, II, III, IV
ΔXm (cm H_2O/l/s)	0.02 (0.1)	0.03 (0.5)	0.44 (0.7)	0.52 (0.7)	0.56 (0.8)	<0.0001	<0.0001	C, I-II, III, IV
ΔCrs,dyn (ml/cm H_2O)	2.1 (15.3)	3.3 (4.3)	1.5 (3.8)	1.4 (2.4)	0.7 (0.8)	<0.0001	<0.0001	C, I, II, III, IV
ΔZ4Hz (cm H_2O/l/s)	–0.22 (0.3)	–0.99 (1.3)	–1.25 (1.7)	–1.38 (1.6)	–1.95 (2.3)	<0.0001	<0.0001	C-I, II, III, IV

Data are presented as mean (SD). Δ = absolute change (postbronchodilator – prebronchodilator). $p < 0.05$ is significant. The far right column is the comparison between adjacent groups: a dash indicates a significant difference.

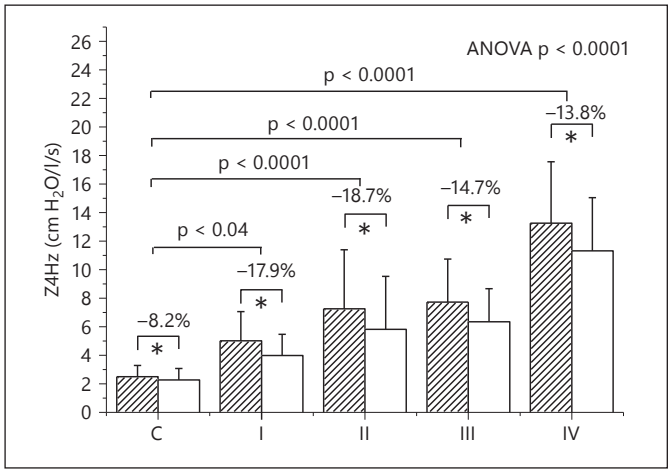


Fig. 4. Respiratory impedance modulus in 4 Hz (Z4Hz) before (dense column) and after (white column) salbutamol administration in the control group (C) and in the COPD subgroups. % = Average value of percentage change in each studied subgroup. * $p < 0.005$, significant difference.

Salbutamol administration significantly reduced Rm in all groups (fig. 2b; $p < 0.05$), with the exception of patients with very severe obstruction (group IV). The changes in the percentage values were not significantly different between the patients and the controls. The percentage variation in Rm decreased significantly as the respiratory obstruction increased (ANOVA, $p < 0.002$).

While the control group did not exhibit significant changes in S, all the COPD groups exhibited a significant reduction (fig. 2c; $p < 0.05$). The percentage reduction in S was, on average, larger in the patients with COPD. Groups I, II and IV exhibited statistically ($p < 0.02$) greater changes than the control group.

Following bronchodilation, Xm became less negative in all groups ($p < 0.05$) except for the control group (fig. 3a). On average, the percentage changes were greater in the patients; these changes were significantly different from the control group in groups II, III and IV. The percentage variation in Xm decreased significantly (ANOVA, $p < 0.0001$) with the progression of airway obstruction in COPD patients.

Figure 3b shows that the changes in Crs,dyn in the control group were not significant. Conversely, Crs,dyn increased significantly in the individuals with COPD at all levels of bronchial obstruction ($p < 0.01$). The percentage changes did not differ between the COPD groups and the control group, and such changes decreased with the airway obstruction (ANOVA, $p = 0.0001$).

Figure 4 shows a significant reduction in Z4Hz in the control group after bronchodilation ($p < 0.005$). This effect was also significant in the patients ($p < 0.005$). The reduction in Z4Hz was greater in the patients in all stages of COPD than in the control group ($p < 0.04$). The percentage variation in this parameter was reduced by the severity of bronchial obstruction (ANOVA, $p = 0.0001$).

Table 3 shows the absolute values for the differences in the measurements taken before and after salbutamol administration in the healthy individuals and the COPD patients. In general, the changes were greater in the patients than in the healthy subjects in R0, Rm, S, Xm, and Z4Hz. The change in the absolute value of Crs,dyn was greater in controls than in groups II, III and IV. The magnitude of the changes in these parameters due to bronchodilation was influenced by the severity of the disease. The changes in R0, Rm and Crs,dyn decreased whereas the changes in S, Xm and Z4Hz increased with airway obstruction ($p < 0.0001$).

Correlations between Changes due to Bronchodilator Use in Forced Oscillation and Spirometric Parameters

These correlations were mainly not significant, and the statistically significant ones were weak. The changes in R0 and Rm did not correlate with spirometric parameters. Conversely, ΔS exhibited a weak, albeit significant, inverse correlation with ΔFVC ($r = -0.24$; $p = 0.02$), ΔFEV_1 % ($r = -0.28$; $p = 0.003$) and $\Delta FEV_1/FVC$ % ($r = -0.31$; $p = 0.002$). ΔXm was associated with ΔFEV_1 ($r = 0.23$; $p = 0.02$) and ΔFVC ($r = 0.38$; $p = 0.0001$), while ΔCrs,dyn was correlated with ΔFVC % ($r = 0.21$; $p = 0.03$). ΔZ4Hz was associated with ΔFVC ($r = -0.27$; $p = 0.01$).

Discussion

In healthy individuals, the bronchodilator response was associated with slight changes in the respiratory impedance. In the initial phases of COPD (stage I), the bronchodilation effects in the respiratory impedance were greater than in the healthy volunteers. These effects are related mainly to an increase in central airway bronchodilation, and improvements in ventilation homogeneity and total mechanical load. The bronchodilator use improved the respiratory impedance in all of the COPD patients; these improvements were reduced in the more advanced phases of airway obstruction (II, III and IV).

The individuals with stage I COPD did not exhibit a significant change after the use of the bronchodilator (table 2). In contrast, those with more advanced obstructions (stages II–IV; table 2) exhibited statistically significant bronchodilator responses. These results are in agreement with Schermer et al. [1], who suggest that the response measured as FVC is greater at the most severe stages of disease; the results in table 2 are also in agreement with this. According to O'Donnell [16], the airway becomes even narrower and is associated with remodeling, the loss of elastic recoil and airway collapse during the more advanced stages of COPD (stages II–IV). These changes promote air trapping. This description is coherent with the FVC reduction described in table 2.

Resistance and Reactance Curves before and after Bronchodilation

Figure 1a shows that after the administration of the bronchodilator, Rrs exhibited a proportional reduction of between 4 and 32 Hz in the control group, confirming previous results [17]. This reduction may be associated with the reduction in peripheral airway resistance caused by smooth muscle relaxation.

The changes became more pronounced as airway obstruction increased in the COPD patients (fig. 1a–d), consistent with structural alterations observed in this disease [18]. After the use of the short-acting β_2-agonist, Rrs decreased in all of the COPD patient subgroups. A reduction in the negative dependence of the Rrs curve with frequency was also evident. Previous studies investigating adults with asthma and COPD have reported similar results [19–21].

After the use of the bronchodilator in the control group (fig. 1e), Xrs exhibited small changes at the investigated frequency range, confirming previous findings [17]. In agreement with a study by Dellacá et al. [21], the reactance values decreased following bronchodilator use in the COPD patients; the reduction of Xrs was proportional to the increase in bronchial obstruction (fig. 1e–h). Such changes occur mainly at the lower frequencies.

It was demonstrated that COPD progression is related to distal airway impairment due to luminal obstruction and wall thickening in its early stages [22]. These changes would result in more pronounced changes in resistance than in reactance (fig. 1a vs. fig. 1e). Loss of elastic recoil due to the disruptions of alveolar attaches is supposed to occur afterwards [22]. These changes are clearly illustrated by the increases in reactance (fig. 1f–h) and indicate that the FOT may contribute to better monitoring of the progression of COPD.

Resistive Properties of the Respiratory System

In agreement with previous studies [23–26], we found a slight reduction in the total respiratory resistance of healthy individuals following the use of salbutamol (fig. 1, 2a, b). Salbutamol did not have a significant impact on the homogeneity of their respiratory system (fig. 2c). This result might be explained by the fact that the respiratory system of healthy individuals is considered to be a homogeneous system.

The percentage reductions in R0 (fig. 2a) agree with the studies performed by Lorino et al. [27] and Zerah et al. [20] that examined moderately ill patients and those with severe obstructions, respectively. Table 3 shows that the variation in R0 tends to decrease as obstruction increases. The observed decrease may be probably explained by the increasing effects of remodeling in respiratory resistance along with COPD stage.

Figure 2b shows that Rm decreased in almost all of the investigated groups, and that the reduction in Rm variation

that occurs as airway obstruction increases. Such a reduction was also observed for the average Rm values described in table 3. According to Jeffery [28], airway remodeling occurs at the more advanced stages of COPD. This finding could explain the reduced central airway bronchodilation (measured by Rm) observed in the advanced stages.

Our results for severe COPD (fig. 2c; table 3) agree with the findings by Zerah et al. [20]. The decrease in S might reflect an improvement in ventilation homogeneity [20] that could explain the improvement of dyspnea in COPD patients after bronchodilator use. It is worth emphasizing that the percentage variation in S decreased as airway obstruction decreased (fig. 2c), indicating a lesser effect in patients at the more severe stages.

Reactive Properties of the Respiratory System

Houghton et al. [24, 25] and Singh et al. [26] did not find significant changes in reactance at 5 Hz following the use of short- and long-acting bronchodilators in healthy individuals. These results agree with our findings (fig. 3a; table 3) and indicate that the reactive properties of the respiratory system of healthy individuals do not change following bronchodilation.

The abnormalities in Xm decreased following the use of bronchodilators (fig. 3a; table 3). These findings agree with previous results [19, 29] and reflect an improvement in pulmonary ventilation. According to Wouters et al. [29], the inhalation of 400 μg of salbutamol increases the absolute value of reactance variation at all frequencies. In agreement with our results, Van Noord et al. [19] found more pronounced absolute and percentage variation at low frequencies. Studies by Dellacá et al. [30–32] indicate that changes in Xrs5Hz may reflect the number and distribution of choke points along the bronchial tree. Based on this concept, we hypothesize that the bronchodilator reduced the number of choke points and consequently reduced the airflow limitations in our patients [33].

The increase in Crs,dyn (fig. 3b) may be explained by the fact that bronchodilators improve the compliance of the airway walls and relax the bronchial smooth muscle [34]. The percentage (fig. 3b) and the absolute value (table 3) of the Crs,dyn variation were reduced with the severity of COPD. Changes in compliance mainly reflect events occurring in the peripheral airways. Therefore, increased compliance most likely reflects an improvement in lung expansion that is associated with the dilation of the peripheral airways.

Impedance Modulus

The total mechanical load, described by Z4Hz, may be related to the increase in respiratory work, fatigue and shortness of breath typical in COPD patients [15, 35, 36]. The control group exhibited little variation (fig. 4); this was most likely associated with a physiological response involving the airway epithelium, nerves, mediators and bronchial smooth muscle [6, 10, 37]. The greater (fig. 4) and increasing (table 3) reductions exhibited in COPD patients may be explained by the increased bronchial reactivity that occurs at the more severe stages of the disease; this is usually attributed to an excessive reduction in airway caliber that amplifies the effect of the bronchodilator on the expiratory flow. Changes in the radial traction favoring airway narrowing may be found at any stage of severity because these changes are associated with the COPD phenotype [22, 38]. Our data (fig. 1–4; table 3) lend further support to the hypothesis that COPD is not a fully irreversible disease, recently suggested in 2 large clinical trials [39, 40].

Impulse oscillometry (IOS) is a relatively new method that is able to measure respiratory impedance. This differs from the classic FOT with regard to excitation, data processing and the parameters used to interpret the raw data [41, 42]. It has been used to evaluate the response to bronchodilators in asthma. Park et al. [43] suggested that IOS may complement the estimation of obstruction and bronchodilation in asthmatic adults, and that its discriminative power for airway obstruction and sensitivities for bronchodilation are comparable to FEV_1. Nair et al. [44] compared spirometry and IOS in the ongoing bronchodilator response, showing that R5Hz and FEV_1 correlate in patients with asthma and healthy subjects. Short et al. [45] observed that IOS has a more sensitive response outcome than spirometry with respect to bronchoconstriction to oral propranolol and bronchodilation after salbutamol in patients with mild to moderate asthma.

Correlation of the Bronchodilator Response with Volume and Impedance

These results are in agreement with what has been described previously in chronic bronchitis [46] and asthma [44], suggesting that the FOT assessment supplies information that is different from the information obtained on spirometry. ΔXm and ΔFVC exhibited the strongest correlation, indicating that ΔXm is related to the reduction of hyperinflation.

Limitations of the Study

The presence of a shunt can induce changes in respiratory impedance that may mask physiological and pathophysiological information [5, 6]. To minimize these errors, the participants were asked to hold their cheeks firmly with their hands during the tests. Another source of error is the noise signal associated with spontaneous ventilation. We reduced this by adopting a minimal coherence function of 0.9, which ensures an error of <5%.

The impact of the bronchodilator on the reduction of ventilation heterogeneity and its relationship with dyspnea, exercise capacity and hyperinflation at the different stages of COPD can also influence the bronchodilator response, but we did not address these issues.

Study guidelines [7, 47] and clinical trials [48, 49] do not insist on the determination of the predominant COPD phenotype in individual patients. However, we believe that studies focusing on groups of COPD patients with clearly characterized pulmonary emphysema or chronic bronchitis could contribute to a more detailed examination of the effects of salbutamol and should therefore be addressed in future research.

The weak correlations between changes in the FOT and spirometric parameters indicate that the FOT may provide new information concerning bronchodilator response. The use of clinical criteria as a gold standard may contribute to indicate the added value of the FOT over conventional spirometry. This hypothesis warrants further study.

Conclusion

We showed that the bronchodilator response in healthy individuals is associated with slight changes in the resistive and reactive properties of the respiratory system. Our study provides evidences that the increase in airway obstruction due to COPD introduces significant changes in the bronchodilator response. In general, the bronchodilation effects in the initial phases of COPD (i.e. stage I) were greater than in healthy volunteers. These effects were related mainly to an increase in central airway bronchodilation and improvements in ventilation homogeneity and total mechanical load. These improvements were reduced in the more advanced phases of airway obstruction (II, III and IV). In spite of this decrease, the bronchodilator use improved the respiratory mechanics in all the COPD patient subgroups. These results provide a physiological base for the assessment of bronchodilator therapy, particularly for patients in the first stages of COPD.

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References

1 Schermer T, Heijdra Y, Zadel S, van den Bemt L, Boonman-de Winter L, Dekhuijzen R, Smeele I: Flow and volume responses after routine salbutamol reversibility testing in mild to very severe COPD. Respir Med 2007; 101:1355–1362.
2 Terzano C, Petroianni A, Ricci A, Allegra L: Combination therapy in COPD: Different response of COPD stages and predictivity of functional parameters. Eur Rev Med Pharmacol Sci 2005;9:209–215.
3 Walker PP, Calverley PM: The volumetric response to bronchodilators in stable chronic obstructive pulmonary disease. COPD 2008; 5:147–152.
4 Russi EW, Karrer W, Brutsche M, Eich C, Fitting JW, Frey M, Geiser T, Kuhn M, Nicod L, Quadri F, Rochat T, Steurer-Stey C, Stolz D: Diagnosis and management of chronic obstructive pulmonary disease: the Swiss guidelines. Official guidelines of the Swiss Respiratory Society. Respiration 2013;85: 160–174.
5 Oostveen E, MacLeod D, Lorino H, Farre R, Hantos Z, Desager K, Marchal F; ERS Task Force on Respiratory Impedance Measurements: The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J 2003;22:1026–1041.
6 Kaczka DW, Dellaca RL: Oscillation mechanics of the respiratory system: applications to lung disease. Crit Rev Biomed Eng 2011;39: 337–359.
7 GOLD: Global Initiative for Chronic Obstructive Lung Disease – Update (2013). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO, 2013. http://www.goldcopd.com.
8 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET: Standardisation of spirometry. Eur Respir J 2005;26: 319–338.
9 Girard WM, Light RW: Should the FVC be considered in evaluating response to bronchodilator? Chest 1983;84:87–89.
10 Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J: Interpretative strategies for lung function tests. Eur Respir J 2005;26:948–968.
11 de Melo PL, Werneck MM, Giannella-Neto A: New impedance spectrometer for scientific and clinical studies of the respiratory system. Rev Sci Instr 2000;71:2867–2872.
12 Di Mango AM, Lopes AJ, Jansen JM, Melo PL: Changes in respiratory mechanics with increasing degrees of airway obstruction in COPD: detection by forced oscillation technique. Respir Med 2006;100:399–410.

13 Cavalcanti JV, Lopes AJ, Jansen JM, Melo PL: Detection of changes in respiratory mechanics due to increasing degrees of airway obstruction in asthma by the forced oscillation technique. Respir Med 2006;100:2207–2219.
14 Ying Y, Peslin R, Duvivier C, Gallina C, Felicio da Silva J: Respiratory input and transfer mechanical impedances in patients with chronic obstructive pulmonary disease. Eur Respir J 1990;3:1186–1192.
15 Miranda IA, Dias Faria AC, Lopes AJ, Jansen JM, Lopes de Melo P: On the respiratory mechanics measured by forced oscillation technique in patients with systemic sclerosis. PloS One 2013;8:e61657.
16 O'Donnell DE: Dynamic lung hyperinflation and its clinical implication in COPD. Rev Mal Respir 2008;25:1305–1318.
17 Oostveen E, Boda K, van der Grinten CP, James AL, Young S, Nieland H, Hantos Z: Respiratory impedance in healthy subjects: baseline values and bronchodilator response. Eur Respir J 2013;42:1513–1523.
18 Baraldo S, Turato G, Saetta M: Pathophysiology of the small airways in chronic obstructive pulmonary disease. Respiration 2012;84:89–97.
19 Van Noord JA, Smeets J, Clement J, Van de Woestijne KP, Demedts M: Assessment of reversibility of airflow obstruction. Am J Respir Crit Care Med 1994;150:551–554.
20 Zerah F, Lorino AM, Lorino H, Harf A, Macquin-Mavier I: Forced oscillation technique versus spirometry to assess bronchodilatation in patients with asthma and COPD. Chest 1995;108:41–47.
21 Dellacá RL, Pompilio PP, Walker PP, Duffy N, Pedotti A, Calverley PM: Effect of bronchodilation on expiratory flow limitation and resting lung mechanics in COPD. Eur Respir J 2009;33:1329–1337.
22 McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, Wright AC, Gefter WB, Litzky L, Coxson HO, Pare PD, Sin DD, Pierce RA, Woods JC, McWilliams AM, Mayo JR, Lam SC, Cooper JD, Hogg JC: Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med 2011;365:1567–1575.
23 Manco JC, Hyatt RE, Rodarte JR: Respiratory impedance in normal humans: Effects of bronchodilatation and bronchoconstriction. Mayo Clin Proc 1987;62:487–497.
24 Houghton CM, Woodcock AA, Singh D: A comparison of lung function methods for assessing dose-response effects of salbutamol. Br J Clin Pharmacol 2004;58:134–141.
25 Houghton CM, Woodcock AA, Singh D: A comparison of plethysmography, spirometry and oscillometry for assessing the pulmonary effects of inhaled ipratropium bromide in healthy subjects and patients with asthma. Br J Clin Pharmacol 2005;59:152–159.
26 Singh D, Tal-Singer R, Faiferman I, Lasenby S, Henderson A, Wessels D, Goosen A, Dallow N, Vessey R, Goldman M: Plethysmography and impulse oscillometry assessment of tiotropium and ipratropium bromide; a randomized, double-blind, placebo-controlled, cross-over study in healthy subjects. Br J Clin Pharmacol 2006;61:398–404.
27 Lorino AM, Zerah F, Mariette C, Harf A, Lorino H: Respiratory resistive impedance in obstructive patients: linear regression analysis vs. viscoelastic modelling. Eur Respir J 1997;10:150–155.
28 Jeffery PK: Remodeling in asthma and chronic obstructive lung disease. Am J Respir Crit Care Med 2001;164:S28–S38.
29 Wouters EF, Verschoof AC, Polko AH, Visser BF: Impedance measurements of the respiratory system before and after salbutamol in COPD patients. Respir Med 1989;83:309–313.
30 Dellacá RL, Santus P, Aliverti A, Stevenson N, Centanni S, Macklem PT, Pedotti A, Calverley PM: Detection of expiratory flow limitation in COPD using the forced oscillation technique. Eur Respir J 2004;23:232–240.
31 Dellacá RL, Rotger M, Aliverti A, Navajas D, Pedotti A, Farre R: Noninvasive detection of expiratory flow limitation in COPD patients during nasal CPAP. Eur Respir J 2006;27:983–991.
32 Dellacá RL, Duffy N, Pompilio PP, Aliverti A, Koulouris NG, Pedotti A, Calverley PM: Expiratory flow limitation detected by forced oscillation and negative expiratory pressure. Eur Respir J 2007;29:363–374.
33 Verbanck S: Physiological measurement of the small airways. Respiration 2012;84:177–188.
34 Delacourt C, Lorino H, Herve-Guillot M, Reinert P, Harf A, Housset B: Use of the forced oscillation technique to assess airway obstruction and reversibility in children. Am J Respir Crit Care Med 2000;161:730–736.
35 Faria AC, Lopes AJ, Jansen JM, Melo PL: Assessment of respiratory mechanics in patients with sarcoidosis using forced oscillation: correlations with spirometric and volumetric measurements and diagnostic accuracy. Respiration 2009;78:93–104.
36 Faria AC, Lopes AJ, Jansen JM, Melo PL: Evaluating the forced oscillation technique in the detection of early smoking-induced respiratory changes. Biomed Eng Online 2009;8:22.
37 Baldi S, Dellaca R, Govoni L, Torchio R, Aliverti A, Pompilio P, Corda L, Tantucci C, Gulotta C, Brusasco V, Pellegrino R: Airway distensibility and volume recruitment with lung inflation in COPD. J Appl Physiol 2010;109:1019–1026.
38 Friedlander AL, Lynch D, Dyar LA, Bowler RP: Phenotypes of chronic obstructive pulmonary disease. COPD 2007;4:355–384.
39 Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, Anderson J, Maden C; Trial of Inhaled Steroids and Long-Acting beta2 Agonists Study Group: Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003;361:449–456.
40 Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M; Investigators US: A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359:1543–1554.
41 MacLeod D, Birch M: Respiratory input impedance measurement: forced oscillation methods. Med Biol Eng Comput 2001;39:505–516.
42 Faria ACD, Dames da Silva KK, Costa GM, Lopes AJ, Melo PL: Forced oscillation technique in the detection of smoking-induced respiratory changes; in Hudak R, Penhaker M, Majernik J (eds): Biomedical Engineering – Technical Applications in Medicine, vol 1. Rijeka, InTech, 2012.
43 Park JW, Lee YW, Jung YH, Park SE, Hong CS: Impulse oscillometry for estimation of airway obstruction and bronchodilation in adults with mild obstructive asthma. Ann Allergy Asthma Immunol 2007;98:546–552.
44 Nair A, Ward J, Lipworth BJ: Comparison of bronchodilator response in patients with asthma and healthy subjects using spirometry and oscillometry. Ann allergy Asthma Immunol 2011;107:317–322.
45 Short PM, Williamson PA, Lipworth BJ: Sensitivity of impulse oscillometry and spirometry in beta-blocker induced bronchoconstriction and beta-agonist bronchodilatation in asthma. Ann Allergy Asthma Immunol 2012;109:412–415.
46 Wesseling GJ, Wouters EF: Analysis of respiratory impedance characteristics in chronic bronchitis. Respiration 1992;59:81–88.
47 National Collaborating Centre for Chronic Conditions: Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004;59(suppl 1):1–232.
48 Calverley PM, Burge PS, Spencer S, Anderson JA, Jones PW: Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax 2003;58:659–664.
49 Tashkin DP, Celli B, Decramer M, Liu D, Burkhart D, Cassino C, Kesten S: Bronchodilator responsiveness in patients with COPD. Eur Respir J 2008;31:742–750.