Changes in respiratory mechanics with increasing degrees of airway obstruction in COPD: Detection by forced oscillation technique

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Summary The Forced Oscillation Technique (FOT) is a method for non-invasively assessing respiratory mechanics during spontaneous breathing, demanding little cooperation. The aim of this study was to test the ability of FOT to describe the changes in respiratory mechanics in progressive COPD. The study was performed in a control group formed by 21 healthy subjects and 79 outpatients with COPD, which were classified by spirometry, according to the degree of airway obstruction, in mild, moderate and severe groups. Resistive impedance data were submitted to linear regression analysis over the 4–16 Hz frequency range, which yielded the total respiratory system resistance extrapolated at 0 Hz ($R_0$), the respiratory system conductance ($G_{rs}$), mean respiratory resistance ($R_m$), and the resistance/frequency slope ($S$). Reactance data were interpreted using the mean values ($X_m$) over the 4–32 Hz frequency range, the dynamic compliance ($C_{rs,dyn}$), the dynamic elastance ($E_{rs,dyn}$), and the resonant frequency ($f_r$) data.

Considering the control and mild groups, the increase of airway obstruction resulted in a significant increase of $R_0$ ($P<0.008$), $R_m$ ($P<0.001$), and a significant reduction in $G_{rs}$ ($P<0.002$). Reactive parameters, $C_{rs,dyn}$ and $E_{rs,dyn}$ also presented significant modifications. The subsequent increase (mild to moderate) showed a significant raise of $R_0$ ($P<0.007$), $S$ ($P<0.001$), and a reduction in $G_{rs}$ ($P<0.015$), while significant increases in $X_m$ ($P<0.001$), and $E_{rs,dyn}$ ($P<0.02$), and also a reduction in $C_{rs,dyn}$ ($P<0.02$) were also observed. In contrast to earlier stages, in the late stage of the...
airway obstruction increase (moderate to severe obstruction), resistive parameters did not present statistically significant modifications, while significant modifications were observed in $X_{rs}$ ($P < 0.02$), $C_{rs,\text{dyn}}$ ($P < 0.003$) and $E_{rs,\text{dyn}}$ ($P < 0.003$).

The results of this study demonstrated that the FOT is useful for detecting the respiratory mechanics modifications in COPD patients. The initial phases of airway obstruction in COPD can be described mainly by resistive parameters, while in more advanced phases, reactive parameters seem to be more useful. Since the FOT has the advantage of being a simple method, such a technique may give a significant clinical contribution, representing an alternative and/or complement to the evaluation of respiratory mechanics by means of forced expiration.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterized by a progressive airflow limitation, which is usually evaluated by spirometric tests. However, these tests require good subject cooperation and maximal effort. Accordingly, these tests may be unreliable and variable if sub-optimal manoeuvres are performed. Forced Oscillation Technique (FOT) is a method for non-invasively assessing respiratory resistance ($R_{rs}$) and reactance ($X_{rs}$) during spontaneous breathing, demanding little patient cooperation. These features make this technique suitable for routine evaluation of respiratory function in a variety of clinical applications. For pathophysiological research, another important advantage of FOT is that it provides a detailed characterization of the patient’s respiratory mechanics. FOT has been successfully applied to undertake difficult studies, including sleep disorders, nasal obstruction and the evaluation of pediatric subjects. Detailed analysis of the abnormal respiratory mechanics in asthma, COPD, chronic bronchitis, diffuse interstitial lung disease and emphysema were also obtained. However, to the best of our knowledge, there is no data in the literature concerning the use of FOT to verify the influence of the increase of the airflow limitation in the total respiratory resistance and reactance of COPD patients.

Objective

The aim of the present study was to evaluate the clinical potential of the FOT in the detection of the alterations in respiratory mechanics of COPD patients, analysing a large number of control and COPD subjects who exhibited various degrees of airway obstruction.

First, we analyzed the behaviour of respiratory resistance and reactance curves of a healthy control group, in comparison to COPD subjects with increasing degrees of airflow obstruction, as determined by the reduction in spirometric volumes and flows. Then, we investigated the influence of the increasing airflow obstruction in the FOT parameters associated with the resistive properties of the respiratory system. Finally, the abnormal effects due to the increase in airflow obstruction on the reactive parameters are presented and discussed.

Patients and methods

Subjects

This study involved 100 volunteers, including 21 never smoking controls with normal spirometric evaluations, and 79 patients with COPD from our out-patient clinic. COPD was clinically diagnosed on the basis of cough and sputum production for at least 3 months per year during 2 years or more, epidemiological and laboratorial data, and the presence of spirometric obstruction. In addition, all patients had irreversible obstructive airway disease (%12% improvement of FEV1 predicted baseline after β2-agonist inhalation). Exclusion criteria for this study were evidence of current airway infection, acute exacerbation or any cardio-respiratory disease other than COPD. All patients were in stable clinical condition. The control group was composed by healthy subjects who presented no history of pulmonary or cardiac disease, nor tobacco use. Baseline data, including age, height and weight were obtained from each subject at time of procedures. Informed consent was obtained before inclusion in the study. The ethics committee of the State University of Rio de Janeiro Hospital approved the study protocol.

Spirometry and classification of the degree of airway obstruction

Measurements for forced expiratory volume in the first second (FEV1), forced vital capacity (FVC),
FEV₁/FVC ratio and the forced expiratory flow (FEF) between 25% and 75% of FVC, and FVC (FEF/FVC) ratio, were obtained for all patients in a sitting position, using a closed circuit spirometer (Vitrace VT-139; Pro-médico, Rio de Janeiro, Brazil). These parameters were used to evaluate airflow obstruction, and were presented as raw data and percentile of the predicted values (% pred). Predicted values for spirometry were obtained from Knudson et al. and Pereira et al. To subdivide airway obstruction in COPD patients, they were classified as mild according to FEF/FVC (%), and moderate and severe according to FEV₁/FVC (%) values. The boundaries chosen to subdivide the patients are described in Table 1. Note that there are small reductions in the boundaries with increasing age.

Forced expiratory manoeuvres were repeated until three sequential measurements were obtained. The indexes studied were those obtained through the better curve, which was selected based on the higher values of FEV₁ plus CVF.

**Forced oscillation technique**

The instrument used for the evaluation of respiratory impedance ($Z_{rs}$) by FOT has been described in detail elsewhere. Briefly, a pseudorandom sinusoidal signal with 2 cm H₂O peak-to-peak of amplitude, containing all harmonics of 2 Hz between 4 and 32 Hz, was applied by a loudspeaker. Phases were chosen in order to minimize signal amplitude. The pressure input was measured with a Honeywell 176 PC pressure transducer (Microswitch, Boston, MA, USA), and the airway flows with a screen pneumothoracometer coupled to a similar transducer with a matched frequency response. The signals were digitized at a rate of 1024 Hz, for periods of 16 s, by a personal computer, and a fast Fourier transform was computed using blocks of 4096 points with 50% overlap. Three measurements were made and the final result of the test was calculated as the mean of these three measurements. To perform the FOT analysis the volunteer remained in a sitting position, keeping the head in a normal position and breathing at FRC through a mouthpiece. During the measurements, the subjects firmly supported his/her cheeks and mouth floor using both hands, while a noseclip was worn.

The data acquisition started 30 s after the beginning of the exam in order to allow the volunteer to be accommodated to the equipment. In the present study, a minimal coherence function of 0.9 was considered adequate. Anytime the coherence computed, (for any of the studied frequencies) was less than this threshold, the manoeuvre was not considered valid and the exam was repeated. Whenever correct manoeuvres could not be obtained according to these criteria, the patient was excluded from the study.

**Data processing, presentation and statistical analysis**

Analysis of a linear regression in the resistive component of the impedance in the frequency range between 4 and 16 Hz was used in order to achieve intercept resistance ($R_0$). This is related to total resistance of the respiratory system, and is usually used as an index of airway obstruction. The slope of the resistive component of the impedance ($S$), which is associated with respiratory system non-homogeneity and the mean resistance ($R_m$), commonly related to airways resistance, were also calculated for this frequency range. Respiratory system conductance ($G_{rs}$), was calculated as the reciprocal of intercept resistance ($G_{rs} = 1/R_0$).

The imaginary component of $Z_{rs}$ ($X_{rs}$) was used to evaluate the parameters related to accumulation of energy in the respiratory system. One of them is the mean reactance ($X_m$), usually related to respiratory system non-homogeneity, which was calculated based on the whole studied frequency range (4–32 Hz). Three other parameters, the dynamic compliance of the respiratory system ($C_{rs,dyn}$), the respiratory system dynamic elastance ($E_{rs,dyn}$) and the resonant frequency of the respiratory system ($f_r$), were also determined. $C_{rs,dyn}$, which includes the airways, lungs and chest wall, was estimated using the $X_{rs}$ at 4 Hz by the equation

**Table 1** Boundaries used to subdivide patients into mild, moderate and severe subgroups.

<table>
<thead>
<tr>
<th></th>
<th>36–45 years</th>
<th>46–55 years</th>
<th>≥56 years</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>FEF/FVC (%)</td>
<td>58</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>—</td>
<td>64</td>
<td>49</td>
</tr>
</tbody>
</table>
C_{rs, dyn} = -1/(2\pi f X_{rs})$, whilst $E_{rs, dyn}$ was calculated by the reciprocal of $C_{rs, dyn}$ ($E_{rs, dyn} = 1/C_{rs, dyn}$). Resonance frequency is the frequency in which $X_{rs}$ becomes zero, meaning that there is no phase difference between the signals for pressure and flow. Whenever $X_{rs}$ remained negative at frequencies higher than 32 Hz, the $f_r$ was achieved by extrapolation using a third-order polynomial.

The results are presented as mean ± sd, with a box plot graphical description. A commercial software package (STATISTICA for Windows, release 5.0) was used to compare alterations between groups. One-way ANOVA, further corrected by Bonferroni’s method, was used when the achieved frequencies higher than 32 Hz, the $f_r$ was achieved by extrapolation using a third-order polynomial. A non-parametric test (Kruskal-Wallis), associated with a Mann-Whitney $U$ test was applied when they did not. Results with $P<0.05$ were considered statistically significant.

### Results

The general characteristics of the studied subjects are given in Table 2. Although the mean age of the control group is slightly lower when compared to those of the other groups, these differences are not significant.

Volunteers in all four groups were also comparable considering weights and heights, showing no statistically significant differences. In general, the spirometric parameters were highest in normal subjects and lower in severe patients, with the mild and moderate subjects in between. Group B had absolute FEV$_1$ values similar to control group A because group A was composed by a higher number of women.

Mean $R_{rs}$ and $X_{rs}$ curves for the different conditions are shown in Fig. 1. Respiratory resistance curves in COPD were significantly different from the control curve. The increment in airway obstruction caused an increase of total resistance, mainly at the lower frequencies, not at the higher ones, and resulted in a frequency-dependent $R_{rs}$.

Mean $X_{rs}$ curves were also significantly changed with respect to the control group. The decrease of $X_{rs}$ was proportional to the grade of airway obstruction, being more marked at lower frequencies, which resulted in an increase of the resonant frequency.

Figure 2 depicts the alterations of the resistive properties with the advance of airway obstruction. In this study, all resistive parameters presented statistically significant modifications ($P<0.0001$). Mean values of $R_s$ and $R_m$ increased significantly when groups of normal and COPD patients with mild airway obstruction were compared. Although further increases of the cited resistances can be visually observed in the subsequent classes, the comparisons between adjacent groups were statistically significant comparing $R_s$ between mild and moderate groups only. A similar behaviour was observed in $G_{rs}$. On the other hand, $S$ presented a not statistically significant increase comparing the control and mild groups. The increase between mild and moderate groups was, otherwise, highly significant ($P<0.0002$) contrasting with that between moderate and severe, which was not significant.

Results related to reactive proprieties of the respiratory system are presented in Fig. 3. All parameters showed significant alterations among the studied groups ($P<0.006$). Considering the modifications between adjacent classes, significant modifications were almost always observed.

### Table 2 Characteristics of the investigated subjects.

<table>
<thead>
<tr>
<th></th>
<th>Group A control (n = 21)</th>
<th>Group B mild (n = 16)</th>
<th>Group C moderate (n = 23)</th>
<th>Group D severe (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.1 ± 11.9</td>
<td>64.0 ± 11.5</td>
<td>64.3 ± 9.2</td>
<td>64.5 ± 8.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.6 ± 12.1</td>
<td>70.5 ± 15.8</td>
<td>65.0 ± 15.0</td>
<td>63.3 ± 12.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.9 ± 7.3</td>
<td>164.5 ± 6.1</td>
<td>166.0 ± 7.4</td>
<td>164.6 ± 7.4</td>
</tr>
<tr>
<td>Men/women</td>
<td>6/15</td>
<td>14/2</td>
<td>18/5</td>
<td>32/8</td>
</tr>
<tr>
<td>FEV$_1$ (L)</td>
<td>2.4 ± 0.8</td>
<td>2.3 ± 0.9</td>
<td>1.5 ± 0.5</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td>FEV$_1$ (%pred)</td>
<td>97.9 ± 21.9</td>
<td>92.7 ± 20.3</td>
<td>58.7 ± 17.7</td>
<td>32.5 ± 12.4</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.9 ± 0.9</td>
<td>3.3 ± 0.9</td>
<td>2.7 ± 0.8</td>
<td>2.3 ± 0.8</td>
</tr>
<tr>
<td>FVC (%pred)</td>
<td>95.2 ± 22.1</td>
<td>105.9 ± 23.9</td>
<td>83.9 ± 21.6</td>
<td>72.4 ± 22.3</td>
</tr>
<tr>
<td>FEF/FVC (%)</td>
<td>92.0 ± 31.6</td>
<td>47.1 ± 9.2</td>
<td>22.6 ± 5.3</td>
<td>12.2 ± 3.3</td>
</tr>
<tr>
<td>FEV$_1$/FVC (%)</td>
<td>82.4 ± 6.6</td>
<td>70.5 ± 4.0</td>
<td>55.3 ± 4.5</td>
<td>36.0 ± 8.2</td>
</tr>
</tbody>
</table>

n: Number of subjects; Comparisons of the four groups/comparisons between adjacent groups: dashes indicate significant difference.
in $X_{rs}$, $C_{rs}$, dyn and $E_{rs,dyn}$. On the other hand, none of the comparisons carried out with $f_r$ presented significant modifications.

Discussion

Although many other works in literature use FOT to compare control and COPD patients groups, as far as we know, this is the first study comparing changes in FOT parameters in clearly defined groups of healthy individuals and COPD patients with increasing degrees of airway obstruction. It has been shown that, as airway obstruction increased, $R_{rs}$ increased and $X_{rs}$ became more negative. Interestingly, FOT resistive parameters presented important modifications in low airway obstruction conditions, while in more advanced phases reactive parameters were the most sensitive ones.

Total respiratory system resistance and reactance vs. frequency curves

In the control group (Fig. 1A), mean resistance values (2.4–1.9 cmH$_2$O/L/s) were similar to those reported in other studies.$^{29,31-34}$ Also in accordance with previous studies,$^{6,21,23}$ the values were maintained fairly constantly throughout the investigated frequency range, which is consistent with the behaviour of a homogeneous respiratory system usually found among healthy subjects. Higher resistance values were found among patients classified as mild when compared to those of the control group. Moreover, the values augmented as the degree of airway obstruction increased in the moderate group. In the severe group, however, resistance values did not present a further increase. Analysis of Fig. 1A also shows a sharp difference between the control group and COPD patients in the frequency range of 4–16 Hz. An increase in mean resistances among COPD patients has also been documented by Ying et al.$^{15}$ These authors had observed that higher resistance values were found at low-frequency ranges (4–16 Hz), becoming almost constant between 16 and 32 Hz. The results described in Fig. 1A are also in line with the study of Van Noord et al.$^{35}$ The increase in respiratory resistance with the increase of airway obstruction evaluated by spirometric exams was also observed by Kim et al.$^{36}$ studying asthmatic subjects with an impulse oscillation system. Ländser et al.$^{31}$ observed increased values of $R_{rs}$ between 4 and 24 Hz in heavy smokers. The results presented in Fig. 1A are also consistent with previous experimental findings of Clement et al.$^{30}$ studying the total impedance in subjects with respiratory complaints and patients suffering from moderate airways obstruction associated with COPD or asthma, and severe COPD. Accordingly, increased resistance values were obtained in moderate and severe patients. In the present study, mean resistive values in the moderate and severe groups are slightly higher than those described in the cited work. Resistance values between 16 and 32 Hz showed little difference among the COPD groups, but they were distinct from control. This can be associated with the upper airway shunt effect, which increases as $Z_{rs}$ and/or oscillation frequency rises.$^{4}$

Mean $X_{rs}$ curves in COPD patients (Fig. 1B) are in line with previous studies in COPD$^{31,32}$ and results obtained in the evaluation of patients with bronchial asthma with increasing degrees of airway obstruction.$^{36}$ The presence of more negative values of $X_{rs}$ with increasing airway obstruction was associated with the increase of respiratory system
non-homogeneity and to a fall in the dynamic compliance, which is related to lower frequencies. This is also consistent with the previously observed frequency-dependent decreasing of lung compliance in airflow obstruction. The reactance modifications in response to increased airflow obstruction also conforms with prior studies conducted in patients with asthma and COPD by Clement et al. An important finding of the present study is the clear separation between moderate and severe groups by the reactance mean values seen in Fig. 1B, in contrast to resistive mean curves described in Fig. 1A. This behaviour was also described by Clement et al. It may probably, at least partially, be explained by a smaller influence of the upper airway shunt on the reactance, compared with the respiratory resistance.

Resistive properties of the respiratory system

The resistive properties of the respiratory system described by FOT include airways, lung tissue and chest wall resistance. Intercept resistance values in healthy subjects (Fig. 2A) are similar to those found in previous studies. With the increase of airway obstruction, $R_0$ tends to increase, showing a progressive degree of respiratory obstruction. Janssens et al. studied elderly patients referred for pulmonary function testing, reporting mean $R_0$ results that were between our control and mild groups. Increased $R_0$ values in COPD patients were also obtained by Lorino et al. and Zerah et al. Brochardt et al. analyzed non-smokers, ex-smokers and smokers and observed an increase in $R_0$ that was within the range of the control and mild groups described in Fig. 2A. COPD begins in the peripheral small airways, where large increases in resistance do not significantly augment the total resistance, and so the spirometric results. However, with the progression of the airway obstruction, the pathophysiological abnormalities affect the wider airways. The increase in $R_0$ reflects the worsening of the airway obstruction in COPD, which further supports this interpretation as a deterioration of...
Changes in respiratory mechanics with increasing degrees of airway obstruction in COPD

the pathophysiological process. Significant differences were observed between the control, mild and moderate groups, while under more advanced airway obstruction conditions, between the moderate and severe classes, there was no significant difference. This suggests that $R_0$ values could be useful to detect the initial airway obstruction changes in COPD.

Our $R_m$ results (Fig. 2B) for the control group are similar to those obtained in healthy and asymptomatic subjects. This parameter is usually associated with the resistance of the central airways. In such a way, the obstruction of these airways could explain the increase in $R_m$ values. The results presented in Fig. 2(B) are consistent with those described by Janssens et al. who obtained increased $R_m$ values in the presence of OLD. Heavy smokers studied by Ländsér et al. had mean $R_m$ values between those of control and mild patients groups shown in Fig. 2B. Hayes et al. found no significant difference in $R_m$ comparing non-smokers and smokers. Results that are closer to those of the mild group of COPD patients shown in Fig. 2B were found by Pham et al., in an epidemiological study screening occupational respiratory diseases among miners. The difference between the control group and the COPD groups were highly significant; however, there were no significant differences among COPD groups. This behaviour is similar to that presented by $R_0$ and suggests that $R_m$ could be useful to detect early changes in COPD, but not adequate to qualify obstruction severity.

The $G_{rs}$ mean values obtained in the control group of the present study were similar to those reported by Navajas et al. (Fig. 2C). Theoretically, as the obstruction progresses, conductance tends to diminish, and the experimental confirmation of this behaviour is shown in Fig. 2C. Zerah et al. verified a reduction in $FEV_1$ equivalent to the reduction of $G_{rs}$, results that are in line with that describes in Fig. 2C. Similar to $R_0$ and $R_m$, $G_{rs}$ showed highly significant statistically differences among the control group and the COPD groups. A significant difference was also observed between mild and moderate groups, but not between

Figure 3 Box plot description of reactive parameters, $X_m$ (A), $C_{rs, dyn}$ (B), $E_{rs, dyn}$ (C) and $f_r$ (D) in control and COPD patients according to airway obstruction.
moderate and severe groups, which suggests that $G_n$ could also be useful to detect early changes in COPD.

Results associated to $S$ are described in Fig. 2(D). In contrast to the negative mean value observed in our control group, previous works reported $S$ values near zero$^{22,31}$ in healthy younger subjects. This discrepancy may be associated with the older age of our control group, and the consequent physiological increase of non-homogeneity.$^{43}$ In agreement with this hypothesis, negative $S$ values were also found by Carvalhães-Neto et al.$^{44}$ in healthy elderly subjects. Fig. 2(D) shows that the respiratory system of COPD patients became progressively less homogeneous with the increase in airway obstruction. This observation is in agreement with that of Zerah et al.$^{14}$ Conflicting results have been reported about $S$ in smokers. Significant differences were reported among non-smokers, ex-smokers and smokers by Brochardt et al.$^{24}$ while Lånsèr et al.$^{31}$ showed that, although there were greater negative $S$ values for heavy smokers than in non-smokers, the difference was small and non-significant. Accordingly, Hayes et al.$^{45}$ also found a non-significant difference when comparing non-smokers and smokers. In the present study, it was not statistically possible to separate mean $S$ values of the control group from those of our mild group. On the other hand, comparisons between the control group and the moderate and severe ones, presented significant differences, associated with the more pronounced mechanical modifications present in these groups. Significant differences between adjacent groups can be found only when the mild and the moderate groups were compared. As the upper airway walls, in particular the cheeks and mouth floor, are mechanically in parallel with the proper respiratory system, airway shunt increasingly introduces underestimation of respiratory resistances as airway obstruction rises. This effect is more pronounced in high frequencies.$^{27}$ This way, besides respiratory system non-homogeneity, airway wall shunt probably plays an important role in the $S$ results described in Figure 2D, mainly in conditions of high airway obstruction, contributing to the non-significant difference between the moderate and severe groups.

**Reactive properties of the respiratory system**

Mean reactance results are presented in Fig. 3(A). In the control group, $X_m$ values are similar to that obtained by Lånsèr et al.$^{31}$ and Rotger et al.$^{46}$ showing a lower negative $X_m$ mean value in relation to COPD patients. This result can be explained by the presence of a more homogeneous respiratory system and a higher dynamic compliance in healthy subjects. The significant tendency of modification in $X_m$ values, otherwise, reflects the reduction of the cited properties in the studied COPD patients. These results are consistent with those of Pasker et al.$^{34}$ which showed a progressive deterioration of $X_m$ with the severity of respiratory complaints. All comparisons between groups were statistically significant, except the one between the control and the mild groups. It suggests that $X_m$ could be useful to qualify airway obstruction severity, mainly in the more advanced stages of COPD.

Dynamic compliance $C_{rs, dyn}$ reflects the combined effect of pulmonary tissue and chest wall, as well as the distensibility of the airways.$^{5,47}$ For both the control and the obstructed groups, the $C_{rs, dyn}$ values shown (Fig. 3B) are in agreement to those found in other works.$^{32,45,46}$ However, the values shown for $C_{rs, dyn}$ are much lower than those obtained with other techniques. This can be explained, at least partially, by two factors: compliance is often measured in static conditions or during quiet breathing and, at these low frequencies, $C_{rs}$ express primarily the elastic properties of the tissue. On the other hand, at 4 Hz, the frequency at which we determine the $C_{rs, dyn}$, the respiratory system impedance reflects elastic and, at a minor extent, inertial properties. Moreover, in COPD patients, $C_{rs, dyn}$ is systematically lower than that in controls because of the frequency dependence of dynamic compliance met in these patients due to non-uniform ventilation.

The values of $C_{rs, dyn}$ diminished significantly with the increase of the airway obstruction. A highly significant decrease could already be noted comparing the control and the mild groups. Hayes et al.$^{45}$ found no differences comparing $C_{rs, dyn}$ in non-smokers and asymptomatic smokers with normal spirometry. However, in that work, the airway obstruction severity of the studied patients was smaller than that observed in the mild group of the present work. The comparisons of the mild and moderate and moderate and severe groups also showed significant statistical differences, evidencing a clear reduction of $C_{rs, dyn}$ with the severity of airway obstruction. According to Hyatt et al.$^{46}$ a reduction in $C_{rs, dyn}$ values can indicate a decrease of pulmonary compliance or an increase in the airway resistance. When this reduction is associated with aging, the phenomenon is due to the presence of non-uniform time constants caused by alterations in the peripheral airways.$^{41}$ Another explanation could be a deformation of the thoracic wall associated with lung hyperinflation, which
introduces an important restrictive factor in the interaction between the lung and thoracic wall. In this way, the reduction of $C_{rs, \text{ dyn}}$ in the studied COPD subjects can be associated with the progressive increase of peripheral airways resistance or to a reduction in the compliance of the respiratory system.

Dynamic elastance results are shown in Fig. 3C. A clear increase of this parameter can be observed with the increment of the obstruction. Similarly, Kaczka et al.\textsuperscript{49} observed increased values of total lung elastance, comparing groups of asthmatics with increasing obstruction evaluated by FEV\textsubscript{1}. The cited authors suggested that this probably reflects the degree of airway constriction in the lung periphery. Studying healthy, smokers and non-smokers Navajas et al.\textsuperscript{42} found $E_{rs, \text{ dyn}}$ values in the control group similar to those found in our study. More recently, the same group\textsuperscript{50} evaluated respiratory mechanics in control and COPD patients during non-invasive ventilation, and again their $E_{rs, \text{ dyn}}$ values in controls were similar to those in the present work. Moreover, the values in COPD patients come between those of our control and mild groups. $E_{rs, \text{ dyn}}$ behaviour in COPD patients can be associated with the presence of high pulmonary volumes (residual volume) where the elastic recoil increases until the distensibility limit is reached.\textsuperscript{51}

Additional factors, such as rib horizontality, enlarged intercostals spaces and the rectification of the diaphragm should also be considered. Considering the comparisons between groups, it is important to point out that there are always significant differences and the highly significant statistical difference observed between the moderate and severe groups, which suggests the usefulness of $E_{rs, \text{ dyn}}$ as an indirect index of airway obstruction severity.

Resonant frequency results are presented in Fig. 3(D). Mean results for the control group are higher than those found by other authors\textsuperscript{24,32,42,45,46,52} who analyzed younger control groups. Since $f_r$ physiologically increases with age\textsuperscript{31} and our control group was older than those of the cited studies, this result is not surprising. This evidence of a small inhomogeneous behaviour in our control group was in line with the $S$ results (Fig. 2D), in which $S$ was more negative in our control group than that reported in other works with younger controls. This way, it is likely that the age range of our control group was a factor that justified the similitude among the control, mild and moderate groups. Considering the results of mild, moderate and severe patients, however, an increase of $f_r$ with airway obstruction can be clearly observed. It is probably responsible by the statistical significance observed in the alterations of this parameter. All of the subjects in the control and mild groups presented $f_r$ within the 4–32 Hz range. As expected, $f_r$ out of this range is more frequent in more sick patients, with four and eight subjects out of this range in moderate and severe groups, respectively. Peslin et al.\textsuperscript{32} found $f_r$ values similar to those presented in Fig. 3D, also indicating the presence of increased values of $f_r$ in COPD patients. Similar results were also observed by Hayes et al.\textsuperscript{45} and Lorino et al.\textsuperscript{26} in subjects with respiratory obstruction.

**Increases in COPD airflow obstruction and FOT parameters**

Forced oscillation parameters do not show systematic changes to go in parallel with spirometry. Linear correlation coefficients between all spirometric and FOT parameters were evaluated and, similar to other studies,\textsuperscript{53,54} these coefficients were low, ranging between −0.61 and 0.62. It means that FOT and spirometry data are complementary, each one providing unique data. It confirms the FOT ability to provide additional information on the mechanical characteristics of the respiratory system. However, there is not a consensus in the literature concerning what are the better parameters to evaluate respiratory mechanics by FOT. Some authors use $R_0$ and $C_{rs, \text{ dyn}}$ while others use their reciprocals. An unusual feature of this work is the reporting of reciprocal measurements ($R_0/G_{rs}$, $C_{rs, \text{ dyn}}/E_{rs, \text{ dyn}}$). By using both, we aimed a comparison with a wide range of literature data, as well as among themselves, contributing to find which parameters provide a better description of the mechanical modifications due to COPD.

Comparing the behaviour of FEV\textsubscript{1} and FEV\textsubscript{1}(% pred) with $R_0$, $R_m$ and $G_0$ in the early changes (mild to control), it is interesting to note that even in the absence of significant modifications in FEV\textsubscript{1} and FEV\textsubscript{1}(% pred), one can observe significant alterations in the cited resistive FOT parameters. On the other hand, in comparisons among mild, moderate and severe groups, where FEV\textsubscript{1} and FEV\textsubscript{1}(% pred) presented significant reductions, resistive FOT parameters were not as selective as the spirometric parameters. This suggests that the cited resistive FOT parameters may be used as a complement to spirometry in order to help the detection of early changes (e.g. mild vs. control), and that they may be not helpful to qualify severity in COPD.
Similarly to resistive parameters, the early stage of COPD appear to be well identified by the reactive parameters $C_{rs, dyn}$ and $E_{rs,dyn}$. However, contrasting with the results obtained in resistive parameters for more advanced stages, the parameters related to reactance ($X_m$, $C_{rs, dyn}$ and $E_{rs,dyn}$) seem to be able to evaluate the increase of airway obstruction in COPD patients.

Limitations of this study

Since other influences beyond physiological and pathophysiological ones cause changes in respiratory impedance, the limitations of the FOT and its consequences must be addressed. An important source of measuring errors is the noise due to breathing, which introduces random and systematic errors around the 0.25–8 Hz range, limiting the reliability of the results in this range. This, indeed, was not a huge problem in the present study, since anytime a minimal coherence function of 0.9 could not be achieved in any point (from 4 to 32 Hz) the entire exam was discarded and a new one was carried out. This way, all of the analyzed data have, at least, this minimal coherence, which considering the number of data assembles, results in an error smaller than 5%.

Lung volume at which FOT measurements are done can alter resistance and compliance considerably. In order to minimize this problem, all the measurements were conducted during tidal breathing at FRC.

When comparing FOT parameters in healthy subjects and patients, care should always be taken with the effect of age, height and weight. It was observed that the main biometric parameter affecting these parameters is height, which decreases the $R_s$ values, while sex has no influence. In this study, to reduce the effect of biometric parameters, comparable volunteers were chosen in all four groups, showing no statistically significant differences.

The ability of a method to detect physiological modifications is dependent on its repeatability and variability. Previous studies suggest that $R_s$ measured by FOT is sufficiently repeatable for clinical applications. In adults, within-day variations introduced a coefficient of variation around 8.5% in FOT indices. On a day-to-day basis, the coefficient of variation for $R_s$ was 13.6% and 8.8% in normal subjects and COPD, respectively. For reactance, repeatability decreased to 14.6% in normals. These variations may have consequences for the FOT as a tool for detecting pathophysiological events, and it is important to have this error in mind during the interpretation of the results.

The compliance of floppy upper airways composes an impedance that is mechanically parallel to the respiratory system, which can introduce a significant error, making impedance measurements lower than the real ones. This error is more pronounced when the respiratory system has high impedance, and that is the case of highly obstructed patients. Clement et al. pointed out that the influence of the cheeks should be taken into account in the interpretation of the factors distinguishing healthy subjects from patients. In this study, this effect was minimized by asking the subject to firmly support his/her cheeks and the mouth floor.

Conclusions

Earlier studies have found that COPD introduces increases in respiratory resistance, and reductions in respiratory reactance. Our study supports and adds to these results by showing that these modifications are proportional to the intensity of airway obstruction. Our data demonstrated that the FOT is useful for detecting the respiratory mechanics modifications in COPD patients. The initial phases of airway obstruction in COPD are described mainly by the increase of respiratory system resistive parameters. In more advanced phases of airway obstruction, there is an important reduction of respiratory system dynamic compliance, which is consistent with the mixed pattern usually developed in the more advanced phases of COPD. Since FOT has the advantage of being a simple method, requiring only the passive cooperation of the subject, such a technique may give a significant clinical contribution, representing an alternative and/or complement to the evaluation of respiratory mechanics by means of forced expiration.

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