Impulse oscillometry system: association with pulmonary function in patients with COPD and healthy subjects

Sistema de oscilometria de impulso: associação com função pulmonar em indivíduos com DPOC e saudáveis

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Abstract

Background: Spirometry is the gold-standard diagnosis test for COPD. However, the impulse oscillometry system (IOS) has proven to be effective for early detection of COPD and little is known about the association between the two techniques in the presence or absence of pulmonary disease. **Objective:** To investigate the association between lung function and lung mechanics using the IOS in patients with COPD and healthy subjects. **Methodology:** Eighteen patients with COPD and 18 healthy individuals performed spirometry and the IOS. **Results:** FEV_1 and $FEF_{25-75\%}$ correlated with X5Hz (r=0.74; r=0.63), and with R5Hz-R20Hz (r=-0.67; r=-0.51), and FVC moderately correlated with most of the oscillometric parameters (R5Hz, Z5Hz, R5Hz – R20Hz, X5Hz and Fres) in the COPD group. **Conclusions:** Reactance is related to pulmonary airflow obstruction and peripheral resistance is associated with mean forced expiratory flow. Thus, IOS is a method that can complement spirometric findings in patients with COPD.

Key-words: Pulmonary Disease, Chronic Obstructive; Respiratory Function Tests; Spirometry; Respiratory Mechanics; Pulmonary Medicine.

Resumo

Introdução: A espirometria é o padrão ouro para diagnosticar a DPOC. Contudo, o sistema de oscilometria de impulso (IOS) tem se mostrado eficaz no diagnóstico precoce da doença e pouco se sabe sobre a associação entre as técnicas na presença e na ausência de doença. **Objetivo:** Investigar a associação entre função e mecânica pulmonar utilizando o IOS em indivíduos saudáveis e com DPOC. **Métodos:** Dezoito indivíduos com DPOC e 18 saudáveis realizaram espirometria e IOS. **Resultados:** O VEF_1 e $FEF_{25-75\%}$ correlacionaram com X5Hz (r=0,74, r=0,63) e com R5Hz-R20Hz (r=-0.67, r=-0,51); a CVF correlacionou moderadamente com a maioria das variáveis oscilométricas (R5Hz, Z5Hz, R5Hz–R20Hz, X5Hz e Fres) no grupo com DPOC. **Conclusões:** A reatância está relacionada com a obstrução ao fluxo aéreo pulmonar e a resistência periférica está associada com o fluxo expiratório forçado médio. Portanto, o IOS é um método que pode complementar os achados espirométricos em pacientes com DPOC.

Descritores: Doença Pulmonar Obstrutiva Crônica; Testes de Função Respiratória; Espirometria; Mecânica Respiratória; Pneumologia.

Artigos

Revisões de literatura

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease that causes airflow restriction that is often irreversible. This restriction is combined with an exaggerated inflammatory response by the lungs to particles or noxious gases.[1] Early diagnosis of COPD is vital to reduce the progression and severity of the disease.[1]

Currently, the gold-standard test for COPD diagnosis is spirometry,[1] however this maneuver depends on the patient's effort and often cannot be reproduced.[2, 3] Additionally, the technique does not allow a detailed assessment of lung function, making it difficult to detect COPD in its initial stages. Lung mechanics can be assessed by measuring airway resistance.[4] One of the viable methods for this assessment is the Impulse Oscillometry System (IOS), which has been shown in the literature to be effective in early detection of changes in airway resistance, because it tests specifics lung areas and is able to detect small changes in the peripheral areas of the lung.[4, 5]

IOS is a relatively new system that assesses lung mechanics from the peripheral to the central areas by using impulses that generate flow oscillations, which superimpose spontaneous breathing and determine the basic parameter as respiratory impedance (Z). Respiratory impedance is divided into resistance (R) and reactance (X), with low-frequency resistance representing total airway resistance (R5Hz), high-frequency representing central airway resistance (R20Hz), and the difference between them representing peripheral airway resistance (R5Hz – R20Hz).[6] This method requires minimal patient cooperation because it uses the patient's normal breathing pattern and only a few seconds are required to obtain the measurement.[7, 8]

By measuring resistance and reactance, IOS appears to have great potential for assessing obstruction in the more distal airways, a vital component in early COPD detection[4]. Crim et al. (2011),[2] showed small correlation between peripheral airway resistance and mean forced expiratory flow between 25-75% of forced vital capacity ($FEF_{25-75\%}$) in patients with COPD and healthy smokers subjects, without mentioning the association of other IOS variables and spirometry. Thus, IOS could complement spirometric findings because of its ability to detect changes in the small airways even in patients who do not fit the spirometric criteria for COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[1] Moreover, information regarding correlation between IOS and spirometry assessment in healthy non-smokers subjects remains unclear.

Once the IOS is a relatively new and promising to detect changes in the early stages of the diseases technique, it is necessary to investigate the relationship between all the parameters of both techniques in the presence or absence of lung disease. Therefore, the present study aims to investigate the association between lung function and lung mechanics in patients with COPD and compare COPD's lung mechanics with healthy individuals.

Material and methods

The present study is characterized as a cross-sectional observational study with quantitative approach. It was approved by the Human Research Ethics Committee of Universidade do Estado de Santa Catarina (protocol 223/2011).

Subjects

The study included 36 adults of both genders. The subjects with COPD were recruited from pulmonology outpatient services of public hospitals and private clinics. The healthy subjects were recruited from the community using a convenience sample. The COPD group included 18 subjects and the inclusion criteria for this group were: diagnosis of stage 2, 3, or 4 COPD;[1] smoking history ≥ 20 pack-years; clinical stability in the month prior to the protocol; age ≥ 40 years. The exclusion criteria were: inability to

perform any of the study's assessments; current smoking or having stopped smoking within the last six months; presence of associated diseases such as myocardiopathy, musculoskeletal disease, cancer, tuberculosis or asthma. The other 18 individuals were included in the healthy group (HG) according to the following criteria: no history of smoking and age ≥ 40 years. The exclusion criteria for this group were: forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) < 80% of predicted value, FEV_1/FVC ratio < 0.7, acute or chronic respiratory disorder, and inability to perform the study's assessments. The healthy subjects were paired with the COPD subjects according to gender, age, weight, and height. All of the subjects signed an informed consent form.

Data collection procedures

The first day of data collection included an anthropometric assessment and forced spirometry. The individuals who met the spirometric criteria returned on the second day for the IOS assessment.

Anthropometric Assessment

Weight and height were measured using a previously calibrated digital scale (Filizola - Brazil) and a stadiometer (Sanny - Brazil), respectively. The subjects were measured with bare feet, standing upright, and with their head in the neutral position. Patients were classified as low weight, normal, overweight and obese according to their BMI.[9]

Spirometry

For the forced spirometry, we followed the methods and criteria recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS).[10] FEV_1 and FVC were measured in liters and percentage of the predicted value (%pred), and mean forced expiratory flow between 25-75% of FVC ($FEF_{25-75\%}$) was also measured. We used the EasyOne spirometer (NDD Medical Technologies Inc. – Switzerland) with daily calibration check. The assessments were conducted before and 15 minutes after inhalation of 400µg of salbutamol. The subject was placed in the sitting position with feet on the ground, knees bent at a 90-degree angle, and nasal clip. The subject was then instructed to perform maximum inspiration followed by forced expiration. The reference values set by Pereira et al.[11] were used.

Impulse Oscillometry

Airway resistance was measured using an Impulse Oscillometry System (Jaeger-MasterScope IOS - Germany), with daily calibration check. The assessments were conducted before and 15 minutes after inhalation of 400µg of salbutamol. In the sitting position, with head slightly extended, nasal clip, and buccinator muscles held by the assessor, the subject was instructed to breathe calmly at tidal volume through a mouthpiece connected to the pneumotachometer for 30 seconds without talking or coughing. Measurements were only considered acceptable if the time segment chosen for analysis had the established duration. Total airway resistance (R5Hz), central airway resistance (R20Hz), the difference between them characterized as peripheral resistance (R5Hz-R20Hz), respiratory reactance (X5Hz), respiratory impedance (Z5Hz), and resonant frequency (Fres) were measured. Values post-bronchodilator were used.

Data treatment

The data were analyzed using SPSS version 20.0 (IBM - USA). The following variables were considered: gender, age, weight, height, BMI, FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$, Z5Hz, R5Hz, R20Hz, R5Hz-R20Hz, X5Hz, and Fres. Measures of dispersion such as arithmetic mean, standard deviation, and median were applied to all variables. Data normality was checked by Shapiro-Wilk test. The COPD group was compared to the

healthy group using the Student's independent t-test. The correlation between the spirometric variables and the impulse oscillometry variables of the overall sample were tested using the Spearman's test. In the COPD group, the correlation between the spirometric and oscillometry variables was tested with Pearson's test, with the exception of R20Hz in the COPD group, for which Spearman's test was used. In the healthy group, the Pearson's test was used for all variables. The significance level was set at 5% ($p < 0.05$).

Results

Thirty-six individuals took part in the present study. Eighteen were included in the COPD group (9 males). Regarding COPD stage, 6 subjects were GOLD 2, 4 were GOLD 4, and the remaining subjects were GOLD 3. According to the BMI, 3 subjects with COPD had low weight,

2 were normal, 7 were overweight, and 6 were obese. Eighteen subjects were included in the healthy group (9 males). According to the BMI, 2 subjects had normal weight, 9 were overweight, and 6 were obese. (Table 1).

In the COPD group, lower values were found ($p < 0.05$) for all spirometric variables (FEV_1/FVC; FEV_1; FVC; $FEF_{25-75\%}$) compared to the healthy group. Regarding the pulmonary mechanics assessment using IOS, we found higher values in the COPD group in all analyzed variables (Table 1), except for reactance, which was more negative in the COPD group.

Table 2 shows the correlations of the COPD group. In the healthy group, the only correlation found was between pulmonary reactance (X5Hz) and the spirometric variables FEV_1 and FVC (Table 3). The correlations between the spirometric variables FEV_1 and $FEF_{25-75\%}$ and between X5Hz and R5Hz-R20Hz in the COPD group are shown in Figure 1.

Table 1: Sample characterization (n=36)				
	Healthy (n=18)	COPD (n=18)	Mean difference (%)	p
Age	62 ± 5.6	61.9 ± 5.5		0.976
Weight (kg)	76.5 ± 14.9	73.6 ± 15.7		0.575
Height (m)	1.65 ± 0.1	1.63 ± 0.1		0.449
BMI (kg/m²)	27.9 ± 3.5	27.7 ± 5.1		0.889
Spirometry				
FEV_1/FVC	0.81 ± 0.04	0.46 ± 0.11	56.9 ± 12.2	<0.001
FEV_1 (L)	2.84 ± 0.75	1.21 ± 0.55	42.5 ± 16.7	<0.001
FEV1 (%pred)	96.9 ± 7.65	41.8 ± 15.9	42.9 ± 15.8	<0.001
FVC (L)	3.50 ± 0.89	2.55 ± 0.79	74.0 ± 21.1	0.002
FVC (%pred)	95.2 ± 5.56	70.9 ± 17.0	74.7 ± 18.7	<0.001
$FEF_{25-75\%}$ (L/s)	2.89 ± 1.01	0.45 ± 0.25	15.5 ± 7.00	<0.001
IOS				
Z5Hz (cmH$_2$O/L/s)	3.34 ± 0.89	5.97 ± 2.29	47.7 (36.2 – 66.0)*	<0.001
R5Hz(cmH$_2$O/L/s)	3.21 ± 0.19	5.97 ± 0.54	54.3 (40.8 – 72.0)*	<0.001
R20Hz (cmH$_2$O/L/s)	2.85 (2.3 – 3.3)*	3.46 (3.1 – 4.3)*	69.6 (55.7 – 102)*	0.004
R5Hz – R20Hz (cmH$_2$O/L/s)	0.50 ± 0.29	2.27 ± 1.36	54.6 ± 30.2	<0.001
X5Hz (cmH$_2$O/L/s)	-1.05 ± 0.38	-3.16 ± 1.55	38.7 (22.1 – 50.0)*	<0.001
Resonant Frequency (Hz)	13.1 ± 2.8	23.5 ± 7.7	63.5 ± 35.7	<0.001

BMI: body mass index; FEV_1: forced expiratory flow in one second in liters; FVC: forced vital capacity in liters; %pred: percentage of the predicted value; FEV_1/FVC = relationship between forced expiratory volume in one second and forced vital capacity in liters; $FEF_{25-75\%}$ (L/s) = forced expiratory flow between 25-75% of FVC; Z5Hz: respiratory impedance; R20Hz: central airway resistance; X5Hz: respiratory reactance; R5Hz – R20Hz; difference between R5Hz and R20Hz; Fres: resonant frequency; Mean difference (%): percentage difference between healthy and patients with COPD; * median (interquartile range 25th – 75th).

Table 2: Correlations between spirometry and IOS in the COPD group (n=18).

	FEV$_1$/FVC	FEV$_1$ (L)	FEV$_1$ (%pred)	FVC (L)	FVC (%pred)	FEF$_{25-75\%}$ (L/s)
Z5Hz (cmH$_2$O/L/s)	-0.32	-0.59*	-0.45	-0.60*	-0.34	-0.42
R5Hz (cmH$_2$O/L/s)	-0.23	-0.51*	-0.36	-0.56*	-0.27	-0.34
R20Hz (cmH$_2$O/L/s)	0.15	-0.20	0.02	-0.47	-0.04	-0.06
R5Hz–R20Hz (cmH$_2$O/L/s)	-0.45	-0.67*	-0.57*	-0.62*	-0.40	-0.51*
X5Hz (cmH$_2$O/L/s)	0.55*	0.74*	0.70*	0.65*	0.54*	0.63*
Resonant Frequency (Hz)	-0.43	-0.65*	-0.58*	-0.62*	-0.46	-0.47*

BMI: body mass index; FEV$_1$: forced expiratory flow in one second in liters; FVC: forced vital capacity in liters; %pred: percentage of the predicted value; FEV$_1$/FVC = relationship between forced expiratory volume in one second in liters and forced vital capacity in liters; FEF$_{25-75\%}$ (L/s) = forced expiratory flow between 25-75% of FVC; Z5Hz: respiratory impedance; R20Hz: central airway resistance; X5Hz: respiratory reactance; R5Hz – R20Hz; difference between R5Hz and R20Hz; Fres: resonant frequency; * p < 0.05.

Table 3: Correlations between spirometry, and IOS in the healthy group (n=18).

	FEV$_1$/FVC	FEV$_1$ (L)	FEV$_1$ (%pred)	FVC (L)	FVC (%pred)	FEF$_{25-75\%}$ (L/s)
Z5Hz (cmH$_2$O/L/s)	-0.16	-0.42	-0.40	-0.42	-0.28	-0.38
R5Hz (cmH$_2$O/L/s)	-0.23	-0.27	-0.31	-0.24	-0.12	-0.33
R20HZ (cmH$_2$O/L/s)	-0.30	-0.35	-0.37	-0.32	-0.11	-0.44
R5Hz–R20Hz (cmH$_2$O/L/s)	0.04	0.04	-0.05	0.02	-0.10	0.07
X5Hz (cmH$_2$O/L/s)	0.10	0.51*	0.46	0.53§	0.41	0.40
Resonant Frequency (Hz)	-0.13	0.09	-0.06	0.09	-0.70	0.06

BMI: body mass index; FEV$_1$: forced expiratory flow in one second in liters; FVC: forced vital capacity in liters; %pred: percentage of the predicted value; FEV$_1$/FVC = relationship between forced expiratory volume in one second in liters and forced vital capacity in liters; FEF$_{25-75\%}$ (L/s) = forced expiratory flow between 25-75% of FVC; Z5Hz: respiratory impedance; R20Hz: central airway resistance; X5Hz: respiratory reactance; R5Hz – R20Hz; difference between R5Hz and R20Hz; Fres: resonant frequency; * p = 0.03, §p = 0.02.

Discussion

The present study aimed to investigate the association between lung function and lung mechanics assessed by IOS in patients with COPD. Once this association was not known in healthy individuals, the study included this population.

The differences in lung function and mechanics between the COPD group and the healthy group were expected.[4, 12] However, little was known about the magnitude of these differences in the IOS variables or about their relationship with spirometric variables. The findings of this study show that individuals with COPD had pulmonary resistance approximately 54% higher and approximately 39% more negative reactance than healthy individuals (Table 1).

The Fres is related to the size of the airway, and is a graphic representation that enables the identification of obstructives disorders.[13] In the COPD group the value of Fres was higher, due to displacement of the graphics in the representative sense of obstruction.[13]

Respiratory reactance is a reactive component of respiratory impedance and consists of the measurement of dynamic complaisance and respiratory inertance. Changes in pulmonary reactance in respiratory diseases refer to respiratory complaisance, which in turn refers to the elastic properties of the lung, the upper and lower airways, and the thoracic and abdominal compartments.[14] Reactance is a negative measure, therefore more negative values indicate reduced complaisance, which occurs especially in
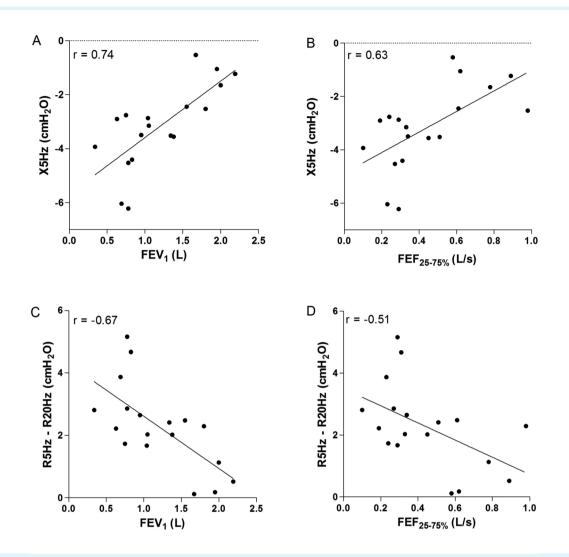
Figure 1: Correlations between spirometric and oscillometric variables in the COPD group
A) Correlation between respiratory reactance (X5Hz) and forced expiratory volume in one second (FEV_1) (r = 0.74; p < 0.001). B) Correation between X5Hz and forced expiratory flow between 25-75% of FVC ($FEF_{25-75\%}$) (r = 0.63; p = 0.006). C) Correlation between peripheral resistance (R5Hz-R20Hz) and FEV_1 (r = -0.67; p = 0.002). D) Correlation between R5Hz-R20Hz and $FEF_{25-75\%}$ (r = -0.51; p = 0.03).

peripheral airways. In individuals with COPD, the total complaisance of the respiratory system is reduced, probably due to airflow obstruction, although lung tissue complaisance is increased in patients with emphysema due to parenchymal destruction.[3, 14]

It has long been accepted that the early pathological change in COPD patients is respiratory bronchiolitis that begins in the small airways. These early changes in airflow can be detected with impulse oscillometry because X5Hz seems to be a sensitive variable for this. These findings further reinforce the potential utility of X5Hz as a physiologically relevant alternative measurement of pulmonary mechanics in COPD patients.[2, 3]

Theoretically, more peripheral lung changes are indicated by low frequencies, whereas more central lung changes are indicated by high frequencies.[14] Total airway resistance (R5Hz) and central airway resistance (R20Hz) are always greater than their peripheral resistance (R5Hz-R20Hz), and in patients with COPD peripheral resistance is also increased due to lung

parenchymal destruction.[1] Similarly, the present study found greater values for total resistance, central resistance, and peripheral resistance in the COPD group compared to the healthy group, with peripheral resistance being approximately four times greater in the COPD group.

Corroborating the literature, there was also correlation between peripheral resistance (R5Hz-R20Hz) and FEV_1 and $FEF_{25-75\%}$, spirometric variables that are known to be related to airflow obstruction. According to Williamson et al.,[15] the difference between total resistance and central resistance is a way to detect dysfunctions in the more peripheral areas of the lung, which may explain the association found since changes in $FEF_{25-75\%}$ also reflect dysfunction in the peripheral airways.[16] Anderson and Lipworth[8] found correlation coefficient (r) of -0.40 (p = 0,002) between the variables $FEF_{25-75\%}$ and R5Hz-R20Hz in patients with COPD. Crim et al.,[2] found similar correlation (r = -0.34; p < 0.001) in patients with COPD and r = -0.31 (p < 0.001) in smokers control. On the other hand, the present study has shown stronger correlation in the COPD group (r = -0.51; p = 0.03). However, no correlation was found in the control group, probably because of the absence of smoking history. Anderson and Lipworth[8] also found correlation between FEV_1 and R5Hz-R20Hz in patients with COPD (r = −0.50; p < 0.001), however, not so strong as the one found in the current study (r = 0.67; p = 0.002).

Although the correlation between pulmonary reactance (X5Hz) and FEV_1 found here has already been shown in the literature,[3, 8, 12, 17] the present study found stronger correlation (r = 0.74; p < 0.000) than the one found by Anderson and Lipworth[8] (r = 0.28; p < 0.05) and by Kanda et al.[12] (r = 0.43; p < 0.05). Kolsum et al.[3] showed that X5Hz was the only variable that correlated with the changes in FEV_1 after a year of follow-up. A pilot study conducted by Ohishi et al.[17] assessed X5Hz in eight fractions of the respiratory cycle time and found that, regardless of the respiratory phase, there was more negative reactance (X5Hz) in patients with COPD compared to healthy individuals, with even more

prominent negativity during the half of the expiratory cycle. These data confirm the relationship between pulmonary reactance and airflow obstruction.

As expected, the FVC also correlated significantly with most oscillometric parameters in the COPD group, particularly with R5Hz. This can be justified by the fact that FVC is related to the sum of the forces of pulmonary mechanics. However, this isolated spirometric variable is not representative of airflow obstruction or airway resistance. While in the COPD group important correlations were found between lung function and mechanics, the healthy group only showed correlation between X5Hz and FEV_1 and FVC. It is possible that the lack of changes in lung function and, perhaps in lung mechanics, is responsible for this result.

IOS allows the analysis of the distribution of airway obstruction, given that it provides values for total resistance, central resistance, and peripheral resistance. It can also provide early diagnosis of COPD, once airflow obstruction in this disease occurs in the more distal airways.[6, 18] One of the advantages of using IOS in clinical practice is that it is conducted during tidal volume, does not involve forced maneuvers, and requires only minimal understanding from the individual[3]. Because it is a new method, information is still scarce in the literature, especially regarding its applicability in adults. As far as we know, this is the first study to assess correlation between lung function and mechanics in healthy subjects.

Normal values for respiratory resistance and reactance using forced oscillation technique had been studied.[19-21] But, there are still only few studies on IOS related to reference values and only one equation has been proposed by Shiota et al.[22] for the Japanese population. This mathematical model was not applied to the data obtained here because it was developed for younger individuals with a different ethnic background. However, we included a group of healthy individuals paired by gender, age, weight, and height, whose data were compared

to those of the subjects with COPD. It was cared to exclude current and former smokers from the healthy group, once IOS is a sensitive method that can detect lung changes resulting from this habit, even in the absence of lung disease.[4] A statistical power of 80% was found for the main correlations in the COPD sample and of 95% for the comparisons between groups. Therefore, the sample size was sufficient to answer the study's main question.

Conclusions

In conclusion, the present study suggests that individuals with COPD have increased airway resistance and more negative reactance, which is associated with airflow obstruction. Peripheral resistance (R5Hz-R20Hz) is associated with mean forced expiratory flow and FEV_1 and can be an alternative method to detect obstruction in the more peripheral areas of the lung. Thus, IOS is a system that can complement spirometric findings in patients with COPD. Future studies involving larger sample and stratification by age and GOLD stages would be enriching for the better understanding of evaluation using IOS.

Acknowledgments

Conflicts of interest

The authors declare no conflicts of interest.

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Artigos

Revisões
de literatura

257