CLINICAL SCIENCE

Forced oscillation technique in the detection of smoking-induced respiratory alterations: diagnostic accuracy and comparison with spirometry

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INTRODUCTION: Detection of smoking effects is of utmost importance in the prevention of cigarette-induced chronic airway obstruction. The forced oscillation technique offers a simple and detailed approach to investigate the mechanical properties of the respiratory system. However, there have been no data concerning the use of the forced oscillation technique to evaluate respiratory mechanics in groups with different degrees of tobacco consumption.

OBJECTIVES: (1) to evaluate the ability of the forced oscillation technique to detect smoking-induced respiratory alterations, with special emphasis on early alterations; and (2) to compare the diagnostic accuracy of the forced oscillation technique and spirometric parameters.

METHODS: One hundred and seventy subjects were divided into five groups according to the number of pack–years smoked: four groups of smokers classified as <20, 20–39, 40–59, and >60 pack–years and a control group. The four groups of smokers were compared with the control group using receiver operating characteristic (ROC) curves.

RESULTS: The early adverse effects of smoking in the group with <20 pack–years were adequately detected by forced oscillation technique parameters. In this group, the comparisons of the ROC curves showed significantly better diagnostic accuracy ($p<0.01$) for forced oscillation technique parameters. On the other hand, in groups of 20–39, 40–59, and >60 pack–years, the diagnostic performance of the forced oscillation technique was similar to that observed with spirometry.

CONCLUSIONS: This study revealed that forced oscillation technique parameters were able to detect early smoking-induced respiratory involvement when pathologic changes are still potentially reversible. These findings support the use of the forced oscillation technique as a versatile clinical diagnostic tool in helping with chronic obstructive lung disease prevention, diagnosis, and treatment.

KEYWORDS: Tobacco consumption; Chronic obstructive pulmonary disease; Respiratory mechanics; Forced oscillation technique; Diagnosis.

INTRODUCTION

Recently, it was reported that the deterioration in pulmonary function associated with the development of chronic obstructive lung disease (COPD) is directly related to both the duration of the smoking habit and the number of pack–years consumed.[1,2] A better understanding of how the smoking habit influences the deterioration in respiratory mechanics would be useful in the precocious diagnosis of COPD, which is usually obtained only in the later stages when respiratory function is already impaired. Owing to the high prevalence of and medical costs associated with COPD, the precocious identification and treatment of these patients is important in order to avoid the severe and expensive stages of this disease.[3]

The alterations in respiratory mechanics due to smoking are usually evaluated using respiratory flows and volumes obtained by spirometry. However, the modifications in respiratory mechanics are not always detected by this test.[4] Moreover, some patients are not able to perform spirometry reliably, as it requires good subject cooperation and maximal effort.[5] The forced oscillation technique (FOT)

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offers a simple and detailed approach to investigate the mechanical properties of the respiratory system. This method characterizes the respiratory impedance and its two components, respiratory system resistance (Rrs) and reactance (Xrs). These parameters are usually measured at various frequencies by means of small pressure oscillations (about 2 cmH$_2$O) superimposed at the mouth during spontaneous breathing. The method is simple, requires only passive cooperation, and no forced expiratory maneuvers. Another important advantage, particularly in pathophysiological research, is that the FOT is able to provide information on the mechanical characteristics of the respiratory system that are complementary to spirometry.[6–8] The FOT was applied successfully by a number of investigators to obtain a detailed analysis of the respiratory mechanics in smokers compared with non-smokers,[4,9–11] as well as comparisons among non-smokers, former smokers, and smokers.[12] Recently, this technique has also been applied successfully in our laboratory in physiological studies of the aging process,[13] in the detection of early respiratory changes in smokers,[14] as well as in studies conducted in asthmatic[15] and sarcoidotic[16] patients.

Therefore, the FOT has great potential to increase our knowledge regarding the pathophysiology of smoking, as well as in helping in the clinical diagnosis of respiratory alterations in this disease. However, to the best of our knowledge, there are no available data using the FOT to investigate changes in respiratory impedance in groups with different degrees of tobacco consumption.

In this context, the purpose of this study was twofold: (1) to evaluate the ability of the FOT indices to detect smoking-induced respiratory alterations, with special emphasis on early alterations; and (2) to compare the diagnostic accuracy of FOT and spirometric parameters in groups with different numbers of pack–years.

First, we investigated the influence of the increasing pack–years on the FOT parameters. Then, the sensitivity and specificity of the FOT parameters in identifying respiratory alterations in groups with different numbers of pack–years were analyzed. Finally, the diagnostic accuracy of FOT parameters was compared with the figures obtained by spirometric volumes and flows.

METHODS

As it is impossible to answer the questions proposed in this study based on a follow-up of individual subjects, a cross-sectional study in comparable groups of healthy individuals and smoking patients with several degrees of tobacco consumption was performed, in a similar way to the work conducted by Verbanck et al.[17] Therefore, healthy control subjects with normal spirometry who had never smoked, as well as smoking subjects who were on no regular medications and had no allergic, respiratory, cardiovascular, gastrointestinal, renal, or neurological symptoms were recruited. All subjects had stable health for at least four consecutive weeks and had signed written informed consent. The institutional ethics committee approved the protocol. Baseline data, including age, height, and weight, were obtained from each subject at the time of the procedures. All smokers were current smokers and had been instructed to abstain from smoking for at least 2 h before the testing.

The amount of tobacco smoked and the duration of smoking were quantified using the number of pack–years,

which was calculated by multiplying the mean number of packs (20 cigarettes) consumed daily by the number of years that the subject had their smoking habit.[18] The smoking subjects were then stratified into subgroups of <20, 20–39, 40–59, and >60 pack–years.

Smokers were recruited from both university personnel who smoke and patients who visited the smoking cessation clinic. In addition, another 26 patients with documented COPD and a smoking history of >23.5 pack–years were recruited from the outpatient clinic. These patients were stable at the time of testing.

Total respiratory resistance and reactance were measured using a forced oscillation system as described previously.[19–21] These measurements were conducted in conformity with the recommendations issued by a task force from the European Respiratory Society.[8] Briefly, small-amplitude pressure variations from 4 to 32 Hz generated by a loudspeaker were applied at the mouth, using a mouthpiece. The pressure input was measured with a Honeywell 176 PC pressure transducer (Honeywell Microswitch, Boston, MA, USA) and airway flow with a screen pneumotachograph. The signals were digitized by a personal computer, and their fast Fourier transform (FFT) was computed using blocks of 4,096 points. Three measurements were made of 16 s each, and the result of the test was calculated as the mean of these measurements. To perform the FOT analysis, the volunteer remained in a sitting position, keeping the head in a normal position and breathing at functional residual capacity (FRC) through a mouthpiece. During the measurements, the subjects wore a nose clip and firmly supported their cheeks and submandibular tissue with their hands.[8,22,23]

The validity of the data was measured by computing the coherence function. Only values with a coherence function of 0.9 or more were considered adequate.[11,24,25] Any time the computed coherence was less than this threshold, the maneuver was not considered valid, and the examination was repeated. Whenever adequate coherence measurements could not be obtained according to these criteria, the patient was excluded from the study.[16,14,22,23]

Resistive impedance data were subjected to linear regression analysis over the frequency range of 4–16 Hz. The resistive impedance at 0 Hz (R0) was extrapolated from this analysis. This parameter is related to the total resistance of the respiratory system.[24] The mean resistance (Rm), commonly related to the airway caliber,[7] was also calculated for this frequency range. Increases in these flow resistive properties are associated with increased work of breathing. Additionally, the slope of the resistive component of the respiratory impedance (S), which is associated with respiratory system homogeneity,[12,26] was also obtained from this analysis. Negative values of this parameter reflect abnormal patterns of ventilation distribution, which are related to alterations in ventilation–perfusion relationships.

The mean reactance (Xm), a property usually related to respiratory system nonhomogeneity,[27] was calculated based on the entire studied frequency range (4–32 Hz). Respiratory mechanical properties were also characterized by the resonance frequency (fr), which is defined as the frequency at which the Xrs equals zero, and the respiratory system dynamic compliance (Crs,dyn). Dynamic compliance reflects the lungs and bronchial wall compliances, the compliance of the chest wall/abdomen compartment, and

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Table 1 - Biometric and spirometric parameters of the investigated subjects.

	Group A Control (n = 34)	Group B <20 (n = 34)	Group C 20-39 (n = 34)	Group D 40-59 (n = 34)	Group E >60 (n = 34)	
Age (years)	42.3 ± 15.3	33.3 ± 10.8	48.9 ± 7.4	55.4 ± 9.9	59.6 ± 9.6	0.0001/A-B-C-D,E
Weight (kg)	63.8 ± 11.6	68.9 ± 14.1	60.6 ± 11.3	65.0 ± 14.3	69.4 ± 17.3	ns/A,B,C,D,E
Height (cm)	164.5 ± 9.0	168.1 ± 7.5	161.4 ± 9.0	162.0 ± 8.9	165.3 ± 9.1	0.01/A,B-C,D,E
Male/female	15/19	16/18	10/24	12/22	18/16	-
Pack-years	-	7.3 ± 5.4	29.1 ± 5.6	47.6 ± 5.3	92.8 ± 35.7	-
FEV_1 (L)	3.4 ± 1.0	3.7 ± 0.8	2.7 ± 0.6	2.2 ± 0.7	1.8 ± 0.9	$p<0.00001$/ A,B-C,D,E
FEV_1 (%pred)	109.9 ± 17.7	106.1 ± 14.1	98.9 ± 17.3	85.0 ± 23.6	66.8 ± 28.8	$p<0.00001$/ A,B,C-D-E
FVC (L)	3.9 ± 1.0	4.3 ± 0.8	3.5 ± 0.7	3.1 ± 0.8	2.9 ± 0.8	$p<0.00001$/ A,B-C,D,E
FVC (%pred)	106.6 ± 17.2	105.6 ± 13.6	108.0 ± 15.9	97.7 ± 20.4	88.9 ± 20.5	$p<0.0001$/ A,B,C,D,E
FEF/FVC (%)	105.3 ± 26.0	94.5 ± 27.8	66.3 ± 22.7	52.5 ± 23.9	39.3 ± 28.9	$p<0.0001$/ A,B-C-D-E
FEV_1/FVC (%)	85.8 ± 4.4	85.2 ± 6.6	75.9 ± 7.7	70.6 ± 9.9	59.2 ± 17.7	$p<0.0001$/A,B-C-D-E

Values are presented as mean $\pm$ SD. n: number of subjects; The far right column is the comparisons of the five groups/comparisons between adjacent groups and dashes indicate a significant difference; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; FEF: forced expiratory flow; % pred: percentage of the predicted value.

thoracic gas compression. The time lag between spirometric and FOT measurements was always <15 min.

Using a closed circuit spirometer (Vitrace VT-139; Pro-médico, Rio de Janeiro, Brazil), measurements of forced vital capacity (FVC), forced expiratory volume for the first second (FEV_1), FEV_1/FVC, and the ratio of forced expiratory flow (FEF) between 25% and 75% of FVC to FVC (FEF/FVC) were obtained for subjects in a sitting position. These parameters were presented as raw data and percentiles of the predicted values (%). Predicted values for spirometry were obtained from Knudson et al.[28] and Pereira et al.[29] Forced expiratory maneuvers were repeated until three sequential measurements were obtained. The indices studied were those obtained through the better curve, which was selected based on the higher value of FEV_1 plus FVC. Quality control of spirometry is given by the American Thoracic Society (ATS) criteria, with the software allowing the detection of non-acceptable maneuvers.

The sample size for this study was calculated using the software MedCalc version 8.2 (Medicalc Software, Mariakerke, Belgium). It was based on an anticipated comparison of means obtained in preliminary studies and an assumption of type I and type II errors of 5%. The minimal sample size required was 32 subjects per group. In the present study, there were 34 volunteers in each group.

Initially, univariate and multiple regression analyses were adjusted for pack–years and age and then applied to identify the association of these variables with the FOT parameters. These analyses were performed using Stata 8.2 software. The volunteers were then stratified and, when the achieved data presented a statistically normal distribution, the data were reanalyzed using one-way analysis of variance (ANOVA), which was further corrected by the Tukey significant difference test. A nonparametric test (Kruskal–Wallis (KW)), associated with a Mann–Whitney U test, was applied when the data did not present in a normal distribution. These analyses were performed using Statistica 5.0 software. The results are presented as mean $\pm \parallel$ standard deviation. A p value of <0.05 was considered statistically significant.

The performance of the FOT indices in the detection of smoking-induced respiratory alterations in the several pack–years groups was evaluated by means of receiver operating characteristic (ROC) analysis.[30] These evaluations were constructed using MedCalc 8.2.

Comparisons of the AUC among parameters obtained from FOT and spirometry were conducted using MedCalc 8.2, according to the theory described by Metz.[31] The values of sensitivity, specificity, and area under the curve (AUC) for spirometry and FOT were obtained based on the optimal cut-off point, as determined from the ROC curve analysis.[30]

RESULTS

There were no significant differences in weight or height among the groups. However, there were significant differences in age among the groups. In general, the spirometric parameters were highest in normal subjects and decreased significantly as the pack–years increased ($p<0.0001$).

Univariate analyses (Table 2) show that all the FOT parameters presented highly significant correlations with pack–years ($p<0.001$). All the FOT parameters, except Crs,dyn, also correlated with age.

The multivariate analyses showed that the contribution of pack–years was highly significant for all the FOT parameters ($p<0.001$, Table 3). In contrast, the contribution of age was only significant for fr, Xm and Crs,dyn, whereas for R0, it was not significant, and S and Rm were near the limit of significance.

Table 2 - Univariate regressions for respiratory impedance variables based on pack-years and age.

	Variables	Coefficient	95% CI	r^2	p-value
Pack-years	R0	0.0241	0.0189-0.0292	0.3356	<0.001
	S	-0.905	-1.096- -0.714	0.3430	<0.001
	Rm	0.015	0.011-0.019	0.2254	<0.001
	fr	0.086	0.064-0.109	0.2558	<0.001
	Xm	-0.014	-0.017- -0.011	0.3632	<0.001
	Cdyn,rs	-0.00017	0.00022-0.00012	0.1940	<0.001
Age	R0	0.032	0.017-0.048	0.0902	<0.001
	S	-1.778	-2.326- -1.230	0.1961	<0.001
	Rm	0.015	0.002-0.027	0.0317	<0.001
	fr	0.225	0.167-0.284	0.2588	<0.001
	Xm	-0.029	-0.037- -0.021	0.2231	<0.001
	Cdyn,rs	-0.000035	0.00019-0.00012	0.0012	0.659

95% CI: 95% confidence intervals; r^2: variability of impedance variables explained by pack-years or age; R0: intercept resistance; S: resistance curve angular coefficient; Rm: mean resistance between 4-16H z; fr: resonant frequency; Xm: mean reactance between 4-32 Hz; Crs,dyn: dynamic compliance of the respiratory system. n = 170.

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Table 3 - Predictive equations for impedance variables derived from a multiple regression analysis

Variables	Coefficient	SE	95% CI	p-value	r^2
R0					0.3381
Pack-years	0.026	0.003	0.019-0.032	<0.001	
Age	-0.007	0.008	-0.023-0.010	0.434	
Constant	2.757	0.360	2.046-3.469	<0.001	
S					0.3580
Pack-years	-0.768	0.118	-1.002- -0.534	<0.001	
Age	-0.606	0.308	-1.213-0.002	0.051	
Constant	29.749	13.211	3.667-55.831	0.026	
Rm					0.2409
Pack-years	0.0179	0.003	0.013-0.023	<0.001	
Age	-0.0126	0.007	-0.026-0.001	0.066	
Constant	3.055	0.294	2.475-3.635	<0.001	
fr					0.3242
Pack-years	0.0539	0.013	0.027-0.080	<0.001	
Age	0.143	0.035	0.074-0.212	<0.001	
Constant	7.844	1.496	4.891-10.798	<0.001	
Xm					0.3846
Pack-years	-0.012	0.002	-0.015- -0.008	<0.001	
Age	-0.011	0.005	-0.020- -0.002	0.017	
Constant	0.826	0.199	0.433-1.219	<0.001	
Cdyn,rs					0.2710
Pack-years	-0.003	0.00003	-0.0003- -0.0002	<0.001	
Age	0.0003	0.0001	0.0002-0.0005	<0.001	
Constant	0.012	0.004	0.005-0.019	0.001	

95% CI: 95% confidence intervals; SE: standard error of the mean; r^2: variability of impedance varaibles explained by pack-years or age; R0: intercept resistance; S: resistance curve angular coefficient; Rm: mean resistance between 4-16H z; fr: resonant frequency; Xm: mean reactance between 4-32 Hz; Crs,dyn: dynamic compliance of the respiratory system. n = 170.

The amount of tobacco smoked significantly increased R0 (KW-ANOVA, $p<0.0001$), Rm (KW-ANOVA, $p<0.0001$), and S (KW-ANOVA, $p<0.0001$), as seen in Figure 1. Mean values of R0 and Rm increased significantly when groups of normal and smoking subjects of <20 pack–years were compared ($p<0.0001$ and $p<0.00001$ respectively). R0 and Rm were also increased with higher pack–years, which resulted in increasing statistical significance when compared with the control group. The comparisons between adjacent groups were statistically significant only for R0 when comparing the two highest pack–years groups. On the other hand, S was not statistically significant when comparing the control with the <20 or 20–39 pack–years groups, but was significantly increased in comparison with the two highest pack–years groups ($p<0.001$).

As the amount of tobacco smoked increased, Crs,dyn (KW-ANOVA, $p<0.0001$) and Xm (KW-ANOVA, $p<0.0001$) were significantly reduced, whereas fr (KW-ANOVA, $p<0.0001$) was increased (Figure 2). The differences comparing the control group with the <20 and 20–39 pack–years groups were not significant for fr and Xm (Figure 2A and B). In contrast, the same comparisons resulted in significant reductions in Crs,dyn (Figure 2C). Considering the comparisons between adjacent classes, significant modifications were observed between the two highest pack–years groups in all three of the reactive parameters studied.

Figure 3 presents the ROC curves for FOT and spirometric parameters in all the studied groups. The performance of the FOT and spirometric indices in the detection of smoking-induced respiratory alterations is described in Figure 4. Table 4 shows detailed values of area under the
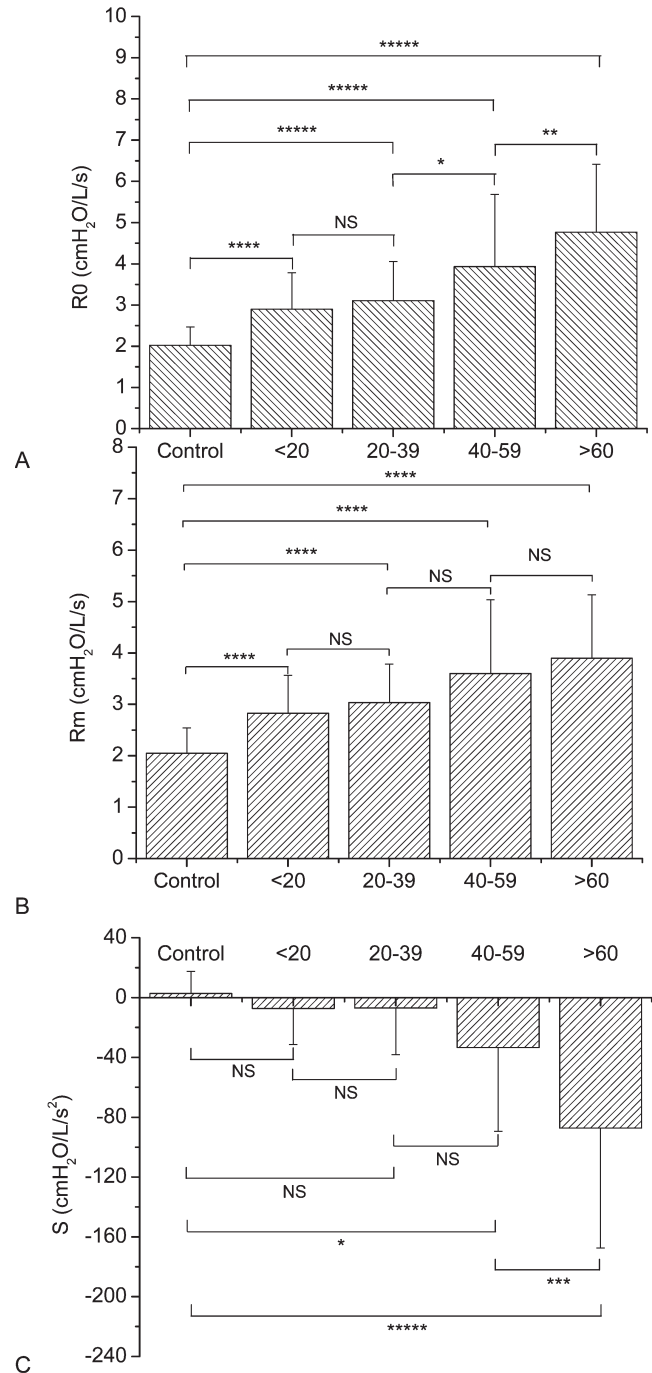

Figure 1 - Effect of the increase in pack-years on resistive parameters. (A) The total respiratory resistance (R0) increases. (B) The mean respiratory resistance (Rm) increases. (C) The slope of the resistive component (S) becomes more negative. P-values: * $p<0.03$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$, ***** $p<0.00001$.

ROC curve (AUC), sensitivity, and specificity for the optimal cut-off point for the FOT indices.

The results of the comparative analysis among the AUC of FOT and spirometric parameters are described in Figure 5. In general, R0 (Figure 5A), Rm (Figure 5C), and Crs,dyn (Figure 5E) presented significantly higher AUC in smoking subjects with <20 pack–years, and AUC similar to that
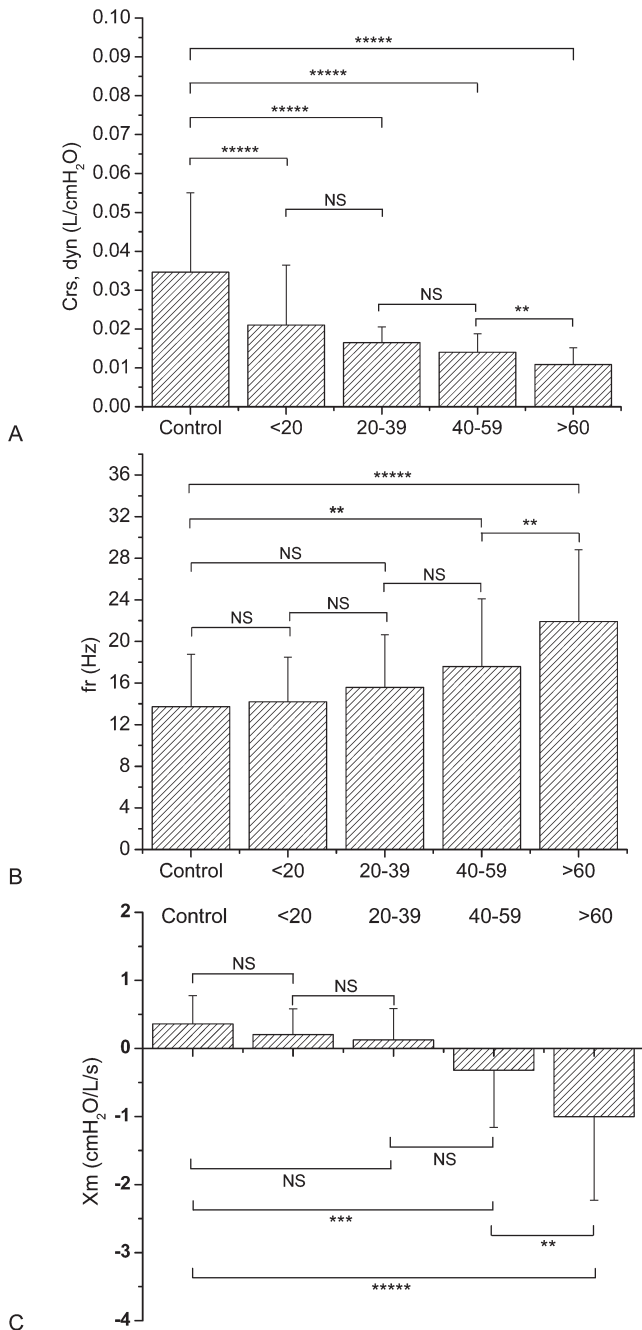
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Figure 2 - Effect of the increase in pack-years on reactive parameters. (A) The dynamic compliance (Crs,dyn) decreased. (B) The resonance frequency (fr) increased. (C) The mean reactance (Xm) values were more negative.

presented by spirometric parameters as the amount of tobacco smoked increased. Spirometric parameters presented significantly higher AUC than S (Figure 5B), fr (Figure 5D), and Xm (Figure 5F) considering groups of smoking subjects with 20–39 pack–years and 40–59 pack–years.

DISCUSSION

This study documented a significantly deleterious effect of smoking on the impedance of the respiratory system. Although many other published reports have used the FOT

to compare control groups with ex-smokers and/or smoking subjects, to the best of our knowledge, this study is the first study to investigate respiratory impedance in groups with different degrees of tobacco consumption. Earlier studies have found deleterious alterations in the respiratory impedance of smokers. The present study supports these results and also shows that these modifications are proportional to the number of pack–years the subjects smoked.

In agreement with earlier studies,[18,32] we found that the spirometric parameters decreased as the pack–years increased. Our groups, defined by pack–years, had significant differences in age (Table 1), which is expected because the increase in pack–years demands time for exposure.

In the present study, we found that univariate analysis (Table 2) showed a higher relationship between the FOT parameters and pack–years (mean $r^2 = 0.28$) than between the FOT parameters and age (mean $r^2 = 0.13$). In fact, age was not significantly related to the resistive FOT parameters (Table 3), whereas in the reactive parameters, the contributions of age were similar to pack–years in fr and Xm, and negligible in Csr,dyn. Comparing r^2 in univariate (Table 2) and multivariate analysis (Table 3), it is apparent that the introduction of age slightly increased this parameter.

The significant increase in R0 (Figure 1A, KW-ANOVA, $p<0.0001$) and the moderate ($r^2 = 0.34$), but significant ($p<0.001$), correlation with pack–years link high levels of tobacco consumption with respiratory obstruction. Smoking leads to a series of bronchial modifications that are consistent with these results, including edema, inflammation in the mucosa, and hypertrophy of the mucosal glands, resulting in hypersecretion of mucus. Hypertrophy of smooth muscle and fibrosis of the bronchial wall are two additional factors that can contribute to elevations in both airway and tissue resistances.[2] Increased R0 values for smoking subjects have been reported before.[4,10–12] The increase in R0 with pack–years can be explained given that modifications resulting from smoking begin in the small, peripheral airways, where large increases in resistance do not significantly increase total resistance. However, as the pack–years increase, the pathophysiological abnormalities start affecting the larger airways. Significant differences were observed comparing the control and the <20 and 20–39 pack–years groups. This suggests that R0 values could be useful in detecting initial airway obstructions that are associated with smoking.

Mean resistance (Rm) is associated with the caliber of the central airways.[7] Therefore, obstruction of these airways could explain the increases in Rm values (Figure 1B), which could be related to inflammatory alterations.[2] More specifically, Rm increased significantly with pack–years (KW-ANOVA, $p<0.0001$), showing a significant ($p<0.001$) relationship, which would explain 24% of the variance in this index. Hayes and colleagues[10] found no significant difference in Rm comparing non-smokers and smokers. In contrast, we found significant differences between the control group and the smoking groups, even with the fewest pack–years group (<20) (Figure 1B). This suggests that Rm could also be useful in detecting early changes from smoking.

Not all studies that have evaluated S values in smokers agree. Although Làndsér and colleagues[9] and Hayes and colleagues[10] reported a small, but not significant, difference comparing values of non-smokers with smokers, significant

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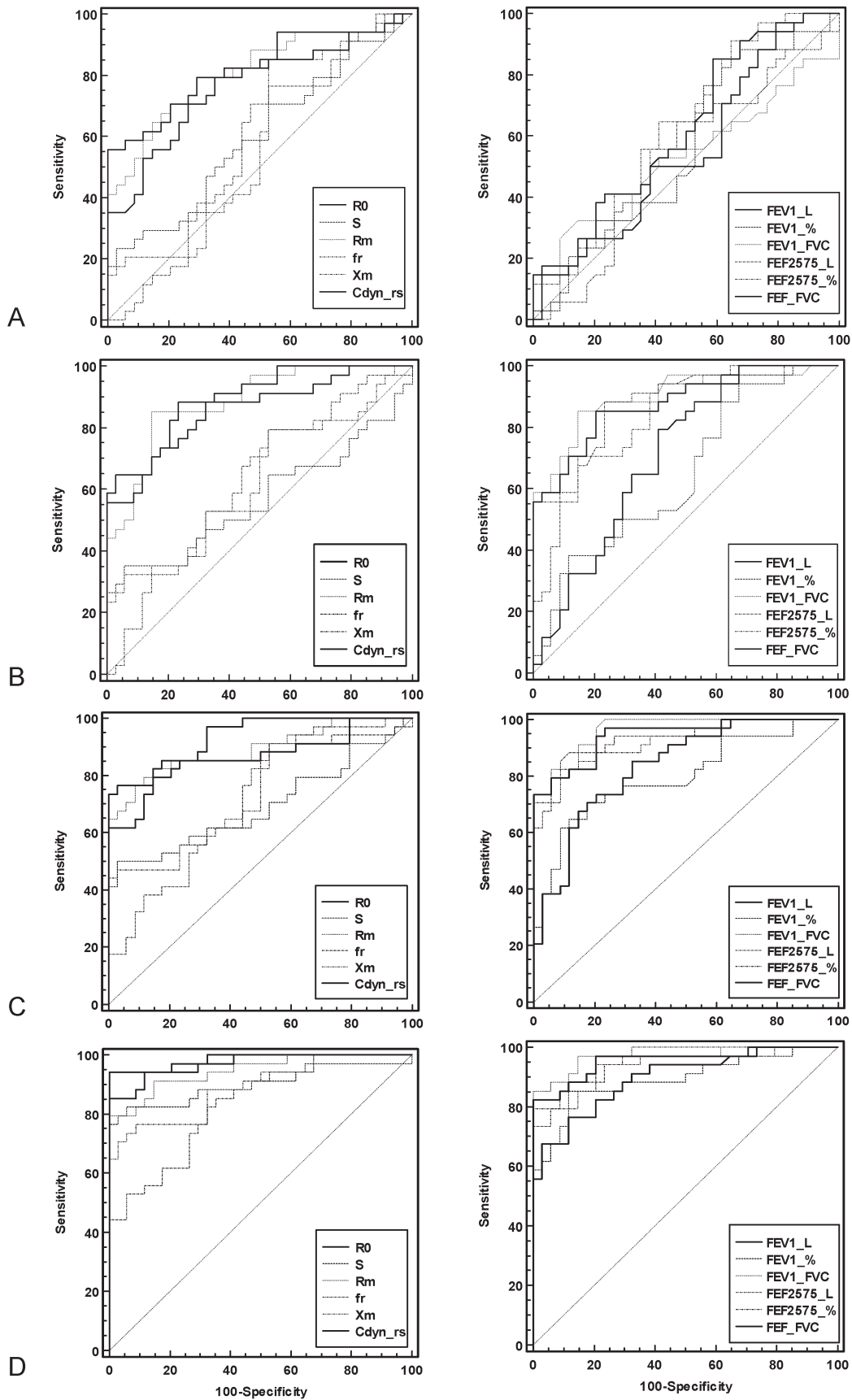**Figure 3** - Receiver operating characteristic (ROC) curves of FOT (left) and spirometric (right) parameters obtained considering the, < 20 pack-years (A), 20-39 pack-years (B), 40-59 pack-years (C), and > 60 pack-years (D) groups.

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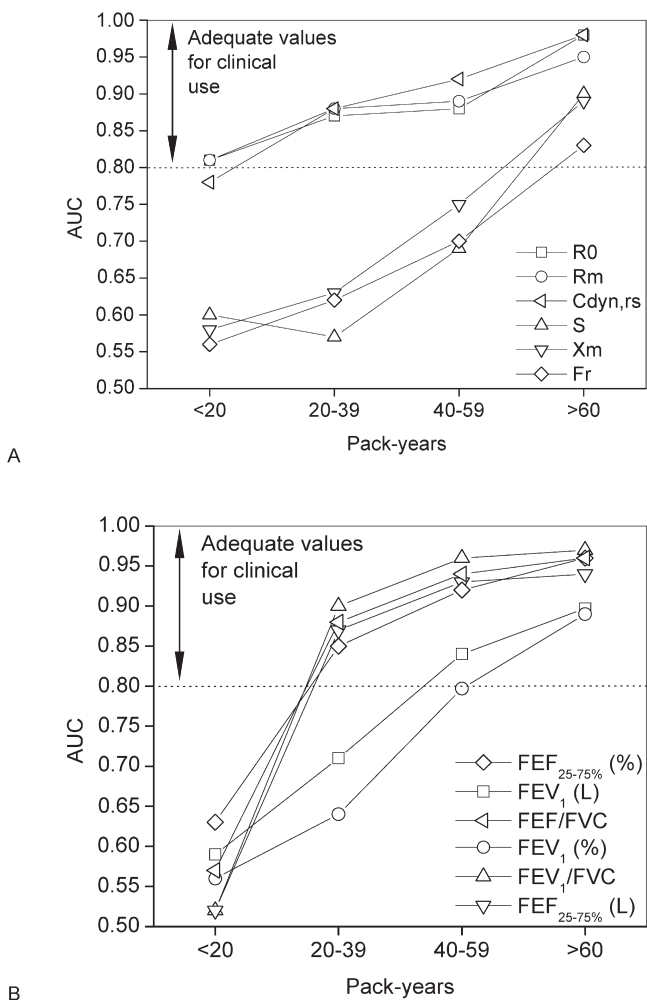Faria ACD et al.

Figure 4 - Area under the ROC curve (AUC) of FOT (A) and spirometric (B) parameters obtained in all of the studied groups.

differences were reported by Brochard and colleagues[11] in similar studies conducted among non-smokers, ex-smokers, and smokers. Figure 1C shows that the respiratory system of the smoking subjects became more inhomogeneous with increasing pack–years. The significant modification in S (KW-ANOVA, $p < 0.0001$) had moderate ($r^2 = 0.36$) and significant ($p < 0.0001$) correlation with pack–years, which links increased tobacco consumption with decreased respiratory system homogeneity. This can be explained by inflammatory alterations[2] and tissue modifications. It was not statistically possible to separate the mean S values of the control group from those of the <20 and 20–39 pack–years groups. On the other hand, comparisons between the control group and the 40–59 and >60 pack–years groups displayed significant differences ($p < 0.006$), often associated with the more pronounced mechanical modifications present in these groups. Significant differences between adjacent groups can be found when comparing the groups with higher tobacco consumption. The shunt impedance of the upper airway walls, which are mechanically in parallel with the respiratory system, introduces an error that is expected to be large in obstructed patients[33] and results in artifactual frequency dependence on the Rrs values. Therefore, besides respiratory system nonhomogeneity, the

upper airway wall shunt probably affects the results described in Figure 1C.

In the studied groups, increased pack–years of tobacco smoking were significantly associated with a decline in Crs,dyn (Figure 2A, KW-ANOVA, $p < 0.0001$; r = −0.37, $p < 0.0001$). Interestingly, a highly significant decrease could already be noted comparing the control and the <20 pack–years groups. In contrast to these results, Hayes and colleagues[10] found no differences when comparing the Crs,dyn in non-smokers and asymptotic smokers with normal spirometry. A reduction in Crs,dyn values reflects a change in pulmonary tissue, chest wall, modification of the distensibility of the airways,[7] and/or an increase in airway resistance.[34] Therefore, the reduction in the Crs,dyn value observed in the smokers could be associated with a progressive increase in peripheral airway resistance or a reduction in respiratory system compliance. There are always highly significant statistical differences in the comparisons between non-smoking and smoking groups, which suggests the usefulness of Crs,dyn as a sensitive index of smoking effects.

Increasing tobacco use in the studied groups was associated with an increase in fr (Figure 2B; KW-ANOVA, $p < 0.0001$; r = 0.50, $p < 0.0001$). The comparisons of fr values between control and smoking groups do not reveal a significant difference until comparison with the >60 pack–years of tobacco exposure group. This suggests that fr is not useful as an index for the initial effects of smoking.

The increase in pack–years in the different groups studied resulted in decreased Xm mean values (Figure 2C; KW-ANOVA, $p < 0.0001$). The significant inverse correlation between Xm and pack–years (r = −0.57, $p < 0.0001$) reflects the impact of smoking on the reduction in respiratory system homogeneity and dynamic compliance of the studied subjects. Comparing the control and smoking groups, statistically significant modifications were only observed between the control and the 40–59 pack–years group and between the control and the >60 pack–years group. Significant differences between adjacent groups could also be found when comparing the higher pack–years groups. These results suggest that Xm might be useful in detecting the respiratory effects of smoking, predominantly in the more advanced stages.

Another point for discussion concerns the characteristics of the subjects investigated in this study. It must be pointed out that the results presented here need to be interpreted with caution. As several of the subjects studied were recruited from the University Hospital smoking cessation and outpatient clinics, these results can probably be limited to describe this population. This is particularly true in groups with high pack–years. New studies are necessary to extrapolate these results to the general population.

Recently, the National Heart, Lung and Blood Institute recommended that research on new technologies to improve non-invasive tests of lung function in COPD should be a priority.[35] The FOT was suggested by Crapo et al.[5] as an attractive alternative for diagnosing obstruction in COPD, as it requires little patient effort and cooperation.

Cosio and colleagues[36] pointed out that the pathological changes induced by tobacco use were still potentially reversible up to 770 cigarettes/day × years smoked (38.5 pack–years). Our results comparing R0, Rm, and Crs,dyn in the group with <20 pack–years (mean = 7.3 ± 5.4 pack–years) and the group with 20–39 pack–years

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Table 4 - Values of area under the ROC curve (AUC), sensitivity and specificity for the optimal cut-off point for the FOT indices.

	AUC				Sensitivity (%)				Specificity (%)				Cut-off point			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
R0 (cmH$_2$O/L/s)	0.81	0.87	0.88	0.98	73.5	85.3	85.3	94.1	73.5	76.5	82.4	97.1	2.22	2.26	2.38	2.72
Rm (cmH$_2$O/L/s)	0.81	0.88	0.89	0.95	70.6	82.4	82.4	91.2	70.6	85.3	85.3	85.3	2.40	2.48	2.48	2.48
S (cmH$_2$O/L/s^2)	0.60	0.57	0.69	0.90	58.8	52.9	61.8	82.4	50.0	52.9	61.8	82.4	-0.66	-0.84	-3.77	-12.9
Xm (cmH$_2$O/L/s)	0.58	0.63	0.75	0.89	50.0	58.8	64.7	76.5	50.0	52.9	61.8	76.5	0.23	0.195	0.12	-0.06
Fr (Hz)	0.56	0.62	0.70	0.83	64.7	67.6	61.8	73.5	55.9	55.9	61.8	73.5	11.8	11.8	13.5	17.2
Crs,dyn (L/cmH$_2$O)	0.78	0.88	0.92	0.98	70.6	73.5	82.4	94.1	70.6	79.4	79.4	88.2	0.019	0.018	0.018	0.017

A: group < 20 pack-years; B: group 20-39 pack-years; C: group 40-59 pack-years; D: group > 60 pack-years.

(mean = 29.3 ± 5.6 pack–years) suggest that small abnormalities exist prior to 38.5 pack–years (Figures 1 and 2) and that FOT could be useful in detecting the effects of smoking, while they are still potentially reversible. In order to investigate this possibility, ROC curves were elaborated. According to the literature, ROC curves with AUCs between 0.50 and 0.70 indicate low diagnostic accuracy, AUCs between 0.70 and 0.90 indicate moderate accuracy, and AUCs between 0.90 and 1.00 indicate high accuracy.[30,37] An AUC >0.80 is usually considered adequate for clinical use.[30,37] Thus, S, Xm, and fr reached acceptable values for clinical use only in the group with the higher duration of the smoking habit (Figures 3 and 4, Table 4). In contrast, AUC values for R0, Rm, and Crs,dyn near to those considered for high accuracy measurements were obtained for the 20–39 pack–years group (Figures 3 and 4, Table 4). In this condition, Rm was the most adequate to correctly identify the effects of smoking, with a sensitivity of 82.4% and a specificity of 85.3%. As expected, because of the smaller alterations in respiratory mechanics, the <20 pack–years group showed reduced AUC values (Figures 3 and 4, Table 4). Even in this adverse situation, R0 and Rm were able to obtain AUC values considered adequate for clinical use, while Crs,dyn reached the limit value (0.78). Among all the studied parameters, R0 was the best, showing a sensitivity of 73.5% and a specificity of 73.5%. These promising results suggest that the FOT may be useful in prevention of the adverse effects of the smoking habit, non-invasively detecting early smoking-induced respiratory abnormalities while the pathologic changes are still potentially reversible. This also suggests that the FOT may be useful as a screening tool in the management of smoking-induced lung disease.

Difference in AUC has become one of the most commonly used measures for comparing the performance of two diagnostic systems.[38] According to Metz,[31] when we have a number of ROC curves to compare, the AUC is usually the best discriminator. In smoking subjects with <20 pack–years, this analysis was clearly in favor of R0 and Rm (Figure 5A and C). The diagnostic accuracy of Crs,dyn was higher than all the spirometric parameters, except FEF$_{25-75\%}$ (Figure 5E). There were no statistically significant differences in AUC considering Xm, fr, and S and the spirometric parameters (Figure 5B, D and F). This suggests that R0, Rm, and Crs,dyn values could be more useful than spirometric parameters in detecting early changes associated with smoking.

The results obtained in the present study considering patients with 20–39 pack–years show that the area under the ROC curve was significantly larger for R0, Rm, and Crs,dyn than for FEV$_1$(%) and FEV$_1$(L) (Figure 5A, C and E). There were no differences in diagnostic accuracy taking into consideration the other spirometric parameters. On the other hand, several spirometric parameters presented significantly higher AUC values than S, fr, and Xm (Figure 5B, D and F).

Oostven et al.,[8] suggested that, in general, the clinical diagnostic capacity of respiratory impedance measurement by the FOT is comparable to that of spirometry. In line with this hypothesis, the comparison of diagnostic accuracy of the FOT and spirometric parameters in the group of patients with 40–59 pack–years revealed similar performances of R0, Rm, and Crs,dyn and spirometric parameters (Figure 5A, C and E). The majority of the parameters obtained by spirometric measurements were significantly more accurate than S, fr, and Xm (Figure 5B, D and F), which suggests that R0, Rm, and Crs,dyn are as useful as spirometry, and that spirometric parameters are more adequate than S, fr, and Xm as indices of smoking effects in this range of pack–years.

The spirometric parameters FEV$_1$(%) and FEV$_1$(L) are standard measures of lung function commonly used in the evaluation of patients with COPD.[39] The diagnostic performance of R0 (Figure 5A) and Crs,dyn (Figure 5E) was significantly higher than that of FEV$_1$(%) and FEV$_1$(L), and similar to that presented by other spirometric parameters in smoking subjects with >60 pack–years. Rm and S showed accuracies similar to those presented by the spirometric parameters (Figure 5B and C). In general, fr and Xm were less accurate than spirometric parameters (Figure 5D and F).

Spirometric measurements require good cooperation, are also effort dependent, and can lead to temporary alterations in bronchomotor tone due to the deep inspiration required, which can have implications for respiratory mechanics measurements. In contrast, the FOT is easy to perform, requires minimal cooperation from the patient, and no respiratory maneuvers are needed. These practical considerations, together with the results of the present study, indicate that R0, Crs,dyn, Rm, and S may be added to other conventional examinations to help with the clinical evaluation of patients with COPD who are not able to adequately perform spirometric measurements.

In conclusion, the smoking habit resulted in changes in respiratory mechanics that were proportional to pack–years. The FOT provided resistive and reactive parameters that were in close agreement with the involved pathophysiology. An important increase in respiratory system resistance and a reduction in dynamic compliance were observed in all the groups studied.

Accordingly, the parameters with the highest sensitivity and specificity for identifying smoking patients were R0,
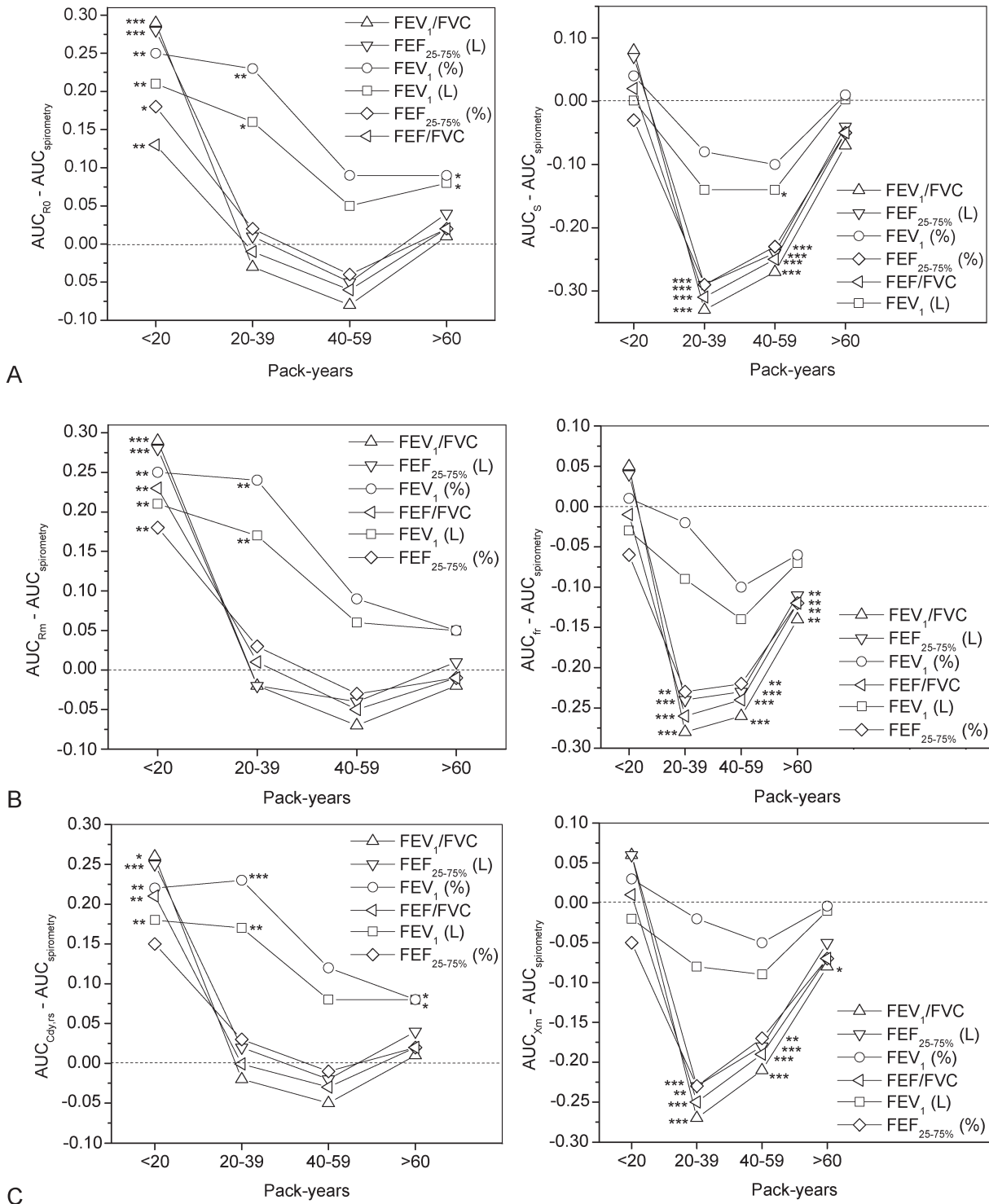
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Figure 5 - Comparisons of AUC among R0 (A), S (B), Rm (C), fr (D), Crs,dyn (D), Xm (E) and spirometric parameters according to the increase in pack-years. *** $p<0.001$; ** $p<0.01$; * $p<0.05$.

Rm, and Crs,dyn. Even in the group with the smallest alterations (<20 pack–years), R0 and Rm were able to obtain AUC values considered adequate for clinical use. Our data demonstrated that the FOT might be useful for early detection of obstructive disease related to the smoking habit, which agrees with the literature consensus that the mechanical modifications resulting from smoking should be

detected as early as possible in order to advise smoking cessation.

The comparison of the diagnostic accuracy of the FOT and spirometric parameters indicated that R0, Rm, and Crs,dyn were more accurate than spirometric indices in diagnosing smaller alterations (<20 pack–years). These parameters presented diagnostic performance similar to

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the spirometric parameters in groups with higher pack–years.

These results suggest that the FOT can be proposed as a complementary method to detect the harmful effects of smoking while they are still potentially reversible, contributing to COPD prevention, diagnosis, and treatment.

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