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Relationship between functional and X-ray alterations in patients with cystic fibrosis

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ABSTRACT

BACKGROUND: Cystic fibrosis (CF) is a disease marked by airway inflammation and airflow obstruction, resulting in air trapping in the lungs.
OBJECTIVE: To assess the associations between airflow limitation, pulmonary volume and X-ray findings in patients with cystic fibrosis.
METHOD: A cross-sectional retrospective study. Review of spirometric, plethysmographic, and chest X-ray findings of outpatients (age ³ 16 years). The airflow findings were classified as within normal limits or as airflow obstruction: mild, moderate or severe obstructive alteration.
RESULTS: A total of 23 patients (15 male and eight female; mean age, 21 ± 5.9 years) were studied. Six of them were within normal limits, four had a mild, five had a moderate, and eight had a severe obstructive alteration. There was an association between airflow limitation and the increase of residual volume ($p = 0.006$) and also with the Brasfield score ($p = 0.001$), but not with the total lung capacity ($p = 0.33$). There was a correlation between residual volume and Brasfield score ($r = 0,73$, $p = 0,002$), but not with the total pulmonary capacity. Moreover, according to X-ray criteria, the air trapping was correlated only with the residual volume ($p = 0.006$).
CONCLUSION: In patients with cystic fibrosis (age ³ 16 years), the progressive airflow limitation is accompanied by an increase in residual volume, while the total pulmonary capacity remains normal or tends to decrease. The X-ray score was associated with airflow limitation and residual volume, but not with total lung capacity.

Key words: Cystic fibrosis. Pulmonary disease. Lung volume measurements. Radiography, thoracic

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Abbreviations used in this study

CFTR – Cystic fibrosis transmembrane conductance regulator
TPC– Total pulmonary capacity
FVC – Forced vital capacity
MVD – Mixed ventilatory disturbance
NOVD – Non obstructive ventilatory disturbance
OVD – Obstructive ventilatory disturbance
SOVD – Severe obstructive ventilatory disturbance
MOVD – Mild obstructive ventilatory disturbance
ModOVD – Moderate obstructive ventilatory disturbance
CF – Cystic fibrosis
HCPA – Hospital de Clínicas de Porto Alegre
N – Normal
FEV_1 – Forced expiratory volume in one second
FEV_1/FVC – Ratio between forced expiratory volume in one second and forced vital capacity
RV – Residual volume
RV/TPC – Proportion between residual volume and total pulmonary capacity

Background

Cystic fibrosis (CF) is a recessive autonomic genetic disease. It is characterized by chronic pneumopathy, exocrine pancreatic failure and elevated electrolytes' concentration in the perspiration. [1] Its incidence varies from one in 2,500 to 3,200 of the alive newborns. [2] The diagnosis is still based on clinical findings (phenotype) associated to demonstration of high chlorine and sodium concentrations in the perspiration. [3 -5] There is a great phenotypical variability, that is, a great variability in organic commitment, severity and complications. [6,7]

This is an irreversible disease, whose evolution didn't allow, until some years ago, the patients to survive until adolescence. [1] In the last two decades, the research on this disease progressed importantly, leading to the institution of better therapies and increasing the mean survival up to 31 years. [8-10]

CF is marked by airways inflammation and the most important functional pulmonary alterations are air flow obstruction, air trapping and inadequate ventilation. The evolutive pattern of these alterations is characterized by a predominance of obstructive ventilatory disturbance (OVD) with early reduction of small airways flow and late commitment of forced vital capacity (FVC). [11] The CF patients differ from the usual pattern of other chronic airflow obstructions, in what regards total pulmonary capacity (TPC), which is frequently a little increased, normal or even reduced, even when measured by plethysmography. [12]

Of all the organs and systems involved, the pulmonary component is the one which presents the most varied and unpredictable phenotypical expression. Thus, the clinical, functional and radiological behavior of the disease may not be the same in different communities. [7] TPC behavior, its relation to OVD severity and correspondence with the radiological findings, which express the pulmonary lesion's magnitude in this disease, are not well characterized in our midst. [13]

The objective of this study is to define possible associations between air flow limitation, pulmonary volumes alterations and radiological abnormalities in CF patients above ³ 16 years of age.

Material and methods

Design

In a cross-sectional and retrospective study, the spirometric, plethysmographyc and radiological thoracic findings in the exams performed during the year 2001 in patients from the Adolescent's and Adult's CF Team at the HCPA were revised, aiming to establish associations between airflow limitation severity's degree, pulmonary volumes and capacities and radiological thorax score. The present investigation's protocol was previously approved by the Ethics Committees of HCPA.

Study population

Patients ³ 16 years of age and CF diagnosis established according to Consensus criteria, [14] under follow up at the Pneumology Department of HCPA, who had spirometry, plethysmography and conventional chest X-ray performed during the year 2001, and who were clinically stable (outside exacerbation periods).

CF diagnosis was based on the presence of one or more phenotypical characteristics, on CF history in a sibling or on a positive neonatal screening test, together with laboratory evidence of abnormality in the CF transmembrane conductance regulator (CFTR), documented by elevated concentrations of chlorine in perspiration (sweat test) or evidence of known mutations as cause of CF in each one of the CFTR genes (genotyping). [14]

During the year 2001, 40 CF patients were seen by the Adolescent's and Adult's CF team of the HCPA. 25 patients out of those 40 had spirometry, plethysmography and chest X-ray performed so that they were included in the study. Two patients were excluded; one for having non-obstructive ventilatory disturbance and another for having mixed ventilatory disturbance.

Of the studied patients, 15 (65.2%) were male and 8 (34.8%) were female. The mean age was 21.0 ± 6.2 years (range from 16 to 44 years).

Measures and procedures

The functional respiratory exams were performed at the Pulmonary Physiology Unit of the Pneumology Department of the HCPA.

The spirometric, pletysmographyc and radiological exams used in the study were the ones which were asked at the annual routine check-up and were concomitant in their performance.

Functional respiratory tests

Spirometry was performed with the patient seated, using *Jaeger –v 4.31a* (Jaeger, Wuerzburg, Germany) equipment and the technical acceptability criteria of the I Brazilian Consensus on Spirometry. [15] Three forced successive expiratory curves were performed, and the highest one was recorded. Forced expiratory volume in one second (FEV1), FVC and FEV_1/FVC ratio were measured. The values were expressed in percent of the predicted for gender, age and height. [16]

The absolute pulmonary volumes were obtained with whole body plethysmography with constant volume, performed with the patient in the sitting position, with the *Master Screen Body* equipment ((Jaeger, Wuerzburg, Germany). The values were expressed in percent of the predicted for gender, age and height. [16]

The air flows were analyzed according to the I Brazilian Consensus in Spirometry criteria. [15] For statistical analysis, the patients were stratified into four groups, according to the presence and severity of the obstructive ventilatory disturbance (OVD): a) group N, with spirometric evaluation within the normal range; b) group MOVD, with mild OVD; c) group ModOVD, with moderate OVD and group SOVD, with severe OVD.

Radiological exam

Conventional chest radiological exam at frontal and profile incidences was performed in all included subjects. The interpretation of the radiological exams was performed in blind mode (without clinical or pulmonary functional information), by the most graduate member in this research, using Brasfield et al [18] radiological scoring system. A score, according to increasing degrees of severity for each one the following characteristics: air trapping (0 -4), bronchial walls enhacement (0 – 4), small cystic or nodular lesions (0-4), extensive air space lesions (0-4) and general severity (0-5) ,was assigned. Also, a total score was obtained using the following formula: 25 – total number of points obtained from the five radiological characteristics examined. Thus, the score corresponding to the highest severity is four points and the least severity is 25 points.

Statistical analysis

The general, spirometric, plethysmographyc and radiological data are presented as mean ± standard deviation for all the patients. The established significance level was 5%. Kruskal – Wallis and Dunett C tests were used for the analysis of the plesthymographyc and radiological findings in the four studied groups (N, MOVD, ModOVD and SOVD). The Spearman correlation test was used to estimate the correlations between total radiological score, plethysmographyc findings and FEV_1/FVC ratio in all the patients. The Kendall Tau test was used to analyze the correlation between individual radiological characteristics (Brasfield scores), RV, TPC and FEV_1/FVC.

Results

The air flow evaluation showed that six patients had findings within the normal range (group N), 17 had (OVD) (four MOVD, five ModOVD and 8 SOVD). As it can be seen in Table 1, there was a statistically significant difference among the groups for the FVC, FEV_1, FEV_1/FVC, RV and RV/TPC variables.

TABLE 1
General data from patients in each pulmonary classification group

N	MOVD n = 5	ModOVD n = 4	SOVD n = 3	p n = 6	
Age (years)	19.6 2.1	18.8 2.2	17.7 1.2	21.7 3.8	0.21
Gender. male/fem	2/3	3/1	2/1	5/1	0.48
FVC					
litters	4.4 1.5	04.0 0.8	02.3 0.6	01.8 1.0	< 0.01*
% of predicted	96.4 12.2	90.8 9.6	60.9 2.2	40.4 18.5	< 0.01*
FEV_1					
littes	3.8 1.5	3.0 0.8	01.3 0.6	1.2 0.8	< 0.01*
% of predicted	73.0 35.1	76.4 11.3	43.7 0.2	27.2 12.1	< 0.01*
FEV_1/FVC					
%	085.6 4.6	70.5 3.7	61.7 3.1	58.0 4.8	< 0.01*
% of predicted	100.3 6.5	83.8 4.2	73.6 4.5	68.4 6.7	< 0.01*
TPC					
litters	006.8 1.5	006.8 1.3	005.0 0.0	06.0 1.9	0.53
%	115.6 8.9	126.0 7.7	115.8 4.0	107.7 23.3	0.41
RV					
litters	02.0 0.0	003.0 0.82	03.0 0.0	03.8 1.3	0.08
% of predicted	155.4 22.5	245.0 30.1	285.2 44.3	300.8 71.2	< 0.01*
RV/TPC					
%	30.2 3.6	42.5 5.0	61.0 0.0	60.4 8.0	< 0.01*
% of predicted	136.0 14.1	231.4 85.5	236.0 20.0	270.0 20.3	0.01*

Figure 1 presents a comparison between residual volumes values (RV) and TPC, expressed in a percentage of the predicted for each one of the four groups of functional pulmonary classification. We observed that, in the presence of increasing OVD's severity, there was no modification in TPC (p=0.178) where RV increased significantly (p=0.013). According to the contrast test, RV values for group N were significantly different from the SOVD group (p=0.004) whereas the groups MOVD and ModOVD didn't differ between themselves or in comparison with the groups N and SOVD.

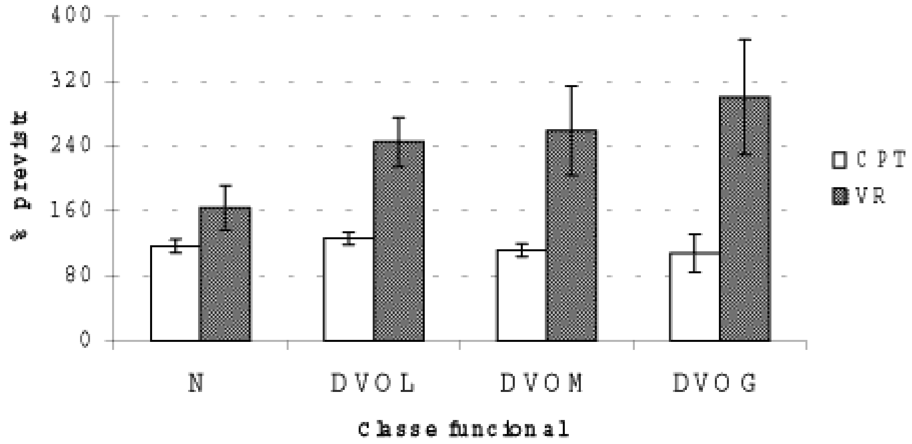

Figure 1 – TPC and RV evaluation according to the severity of the obstructive ventilatory disturbance N – normal;; SOVD – Severe obstructive ventilatory disturbance; MOVD – Mild obstructive ventilatory disturbance ; ModOVD – Moderate obstructive ventilatory disturbance.
**; RV –residual volume ; TPC –total pulmonary capacity*
** Statistically significant difference for $p < 0,05$.*

Table 2 shows the radiological scores values for each pulmonary classification group. There was a statistically significant difference for the total radiological score between the different groups (p=0.013). For the multiple comparison test, the total radiological score for the group N was statistically different from the scores of the groups with OVD, which were not statistically different between themselves. There was also a statistically significant difference for the nodular-cystic lesion (p=0.020) and general severity (p=0.009).

TABLE 2
Radiological score for each functional classification group

	N		MOVD		ModOVD		SOVD		p
Total radiological score	22.2	2.8^a	14.0	2.4^b	14.7	3.2^b	12.5	3.8^b	< 0.01*
Air trapping	00.6	0.8	02.2	2.2	02.3	0.5	02.7	1.6	0.140
Linear markings	01.0	1.0	02.2	0.9	02.3	1.1	02.5	1.3	0.169
Nodular-cystic lesions	00.2	0.4^a	02.0	0.8^b	01.3	$1.1^{a.b}$	01.2	2.0^b	0.020*
Extensive lesions	0.0		00.7	1.5	00.7	1.1	01.2	2.0	0.590
General severity	01.0	1.0^a	03.7	0.5^b	02.7	$1.1^{a.b}$	03.8	0.7^b	0.009*

N – normal; OVD – Obstructive ventilatory disturbance; SOVD – Severe obstructive ventilatory disturbance; MOVD – Mild obstructive ventilatory disturbance ; ModOVD – Moderate obstructive ventilatory disturbance.

Table 3 shows the result of the Spearman correlational analysis between Brasfiled radiological score, RV, TPC and FEV_1/FVC. There was a statistically significant correlation between RV and FEV_1/FVC with the total radiological score. Regarding the individual radiological characteristics, there was a significant correlation of RV with air trapping and general severity, whereas the FEV_1/FVC ratio was also correlated to the presence of linear markings and nodular-cystic lesions (p<0.01). TPC, in contrast, was not correlated to any specific or general radiological aspect (p>0.05).

TABLE 3
Correlation between total radiological score, RV, TPC e FEV_1/FVC

	RV		TPC		FEV_1/CFVC	
	r	p	r	p	r	p
FEV_1/FVC	–0.75	< 0.01*	0.30	0.28	–	–
Total radiological score	–0.54	0.04*	0.20	0.48	0.75	< 0.01*
Air trapping	0.57	0.006*	0.27	0.196	–0.39	0.049*
Linear markings	0.37	0.072	0.24	0.237	–0.44	0.025*
Nodular-cystic lesions	0.33	0.111	–0.20	0.329	–0.47	0.019*
Extensive lesions	0.26	0.222	–0.21	0.335	–0.34	0.106
General severity	0.60	0.004*	0.21	0.316	–0.53	0.008*

RV = residual volume; TPC = total pulmonary capacity; Ratio between forced expiratory volume in one second e forced vital capacity
$FE1_1$/FVC: Ratio between forced expiratory volume in one second e forced vital capacity =; r = correlation coefficient

Discussion

The results of the present study evinced the predominance of OVD in the functional evaluation of patients with CF (age ³ 16 years) followed up at the HCPA, which was in agreement with the previous literature data (11-13) The progressive severity of air flow limitation was accompanied by an increase in RV, but without significant alterations in TPC; additionally, RV was significantly associated to air trapping in chest X-ray (Brasfield score). These data show that obstruction to expiratory air flow in CF is characterized by the presence of air trapping, without pulmonary hyperinsuflation.

Pulmonary volumes have different determining factors. TPC is determined by the balance between inspiratory muscles' force and elastic resistance of the lungs-chest walls. If the muscular force and chest wall normality are maintained, it is the complacency variation that determines TPC. Thus, TPC will be increased in emphysema (greater distensibility) and reduced in pulmonary fibrosis (less distensibility).

In young individuals, RV is determined by the balance between expiratory muscular force and system compressibility, mainly the chest wall expansive recoiling forces. In elderly individuals and in patients with OVD, the air flows are very slow at low pulmonary volumes. Thus, the expiratory maneuver can be interrupted while the flow is still ongoing, that is, before the interruption occurs due to a balance between compression forces and system elasticity. In OVD patients, this dynamic mechanism is the main RV determinant, leading to dynamic hyperinsuflation and air trapping. (19-20)

In the obstructive processes. RV increase is associated to elastic pulmonary tissue loss and elastic recoiling reduction, which together, produce air-trapping and pulmonary hyperinsuflation. In these cases, RV increase is accompanied by TPC increase. (21)

On the other hand, the presence of sever air flow obstruction and normal or reduced TPC suggests the association of opposing physiopathological processes. This way, the patients will have a mixed ventilatory disturbance, that is, air flow obstruction and pulmonary restriction. (22-23) Patients with air flow obstruction, air-trapping and simultaneous parenchimal pulmonary injury or extra-pulmonary restriction will have mixed ventilatory disturbance, characterized by OVD and TPC reduction. (22)

In the present study, the severity of the radiological alterations, assessed by Brasfield et al scores, was significantly associated to air flow limitation. The total scores decreased and the severity scores increased together with the increase in air flow obstruction (Table 2). RV, but no TPC, was significantly correlated to air-trapping at chest X-rays. Such data demonstrated that air flow obstruction in CF is related to an isolated RV increase (air-trapping), that is, without concomitant pulmonary hyperinsuflation.

Despite pulmonary architecture being normal at birth, the basic defect in CFTR provokes alterations in the mucus which recover the airways, impairing mucocilliary function and predisposing to infections and inflammations. The primary pulmonary lesion that takes place then, is the small airways' obstruction by inflammation and mucous plug. The inflammatory and infectious process' progression leads to micro-abscesses formation, and through the years, to progressive derangement of airways architecture, due to its structural remodeling by fibrosis and scarring. [24] Functionally, these alterations are expressed initially by small airways flow disturbances, and as the disease progresses, by flow limitation in more central airways with appearance of progressive OVD, which can be associated to a restrictive pattern in various degrees. [11,12]

Rosenberg et al. [25] studied 27 CF adult patients, aged between 18 and 40 years, showing a good correlation between spirometric findings and Brasfield et al scores. [18] Analyzing the percentage of annual FEV_1 and radiological scores decrease, they suggested that a functional evaluation is more sensitive to detect early alteration in small airways, which are not observed in radiological evaluation, and is a more useful indicator to show respiratory deterioration leading, thus, to aggressive therapeutic intervention. The routine evaluation of CF patients should include spirometry every one or two months, leaving radiological chest evaluation for every 6 or 12 months. In our study, we also observed significant associations between the OVD degree and radiological severity evaluated by Brasfield et al scores. [18] Also, RV increase was correlated to greater radiological severity.

Ries et al's study [12] showed that the restrictive component in the functional pulmonary evaluation in CF patients is not infrequent. The restriction, detected by plethysmographic measures of pulmonary volumes may not be evident at radiological evaluation, suggesting the participation of the disease in the airways as a restrictive mechanism. The restriction observed can be revertible and does not indicate greater severity in CF patients.

Our study has added information on the association of air flow limitation, pulmonary volumes and radiological scores in CF patients (aged ³ 16 years) followed up at the HCPA. It also showed that in patients with OVD, TPC is not increased.

It is speculated that the non increase in TPC might be due to fibrosis or parenchymal lesions unidentified by simple chest radiological study. Nutritional state and inspiratory muscles' force could participate in the process which restricts TPC increase. However, the findings regarding these facts haven't been uniform, suggesting the necessity of complementary studies. [26,27]

Our study also evinced that air trappping, observed in radiological studies, is associated to RV, denoting good correlation functional-structural. This finding suggests that the radiological score may be used, without concomitant functional evaluation to predict air trapping with reasonable accuracy.

It should be noted that, in our study, the small sample size studied may have interfered with the results, leading to type b error (insufficient n), especially in what regards the absence of difference in air-trapping between the groups, presented on Table 2.

We conclude that in the functional evaluation of CF patients (aged > 15 years), the progressive expiratory flow limitation was accompanied by RV increase, but without TPC elevation. Additionally, only RV and FEV_1/FVC ratio were correlated with air trapping as defined by simple chest X-ray (Brasfield score). Such data demonstrate that obstructive phenomena associated to CF are characterized by isolated presence of air-trapping, that is, without concomitant pulmonary hypersinsuflation.

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