ASPECTS OF THE LUNG FUNCTION DETERIORATION IN A GROUP OF PATIENTS DIAGNOSED WITH CYSTIC FIBROSIS

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Abstract

Objectives. To assess the types of respiratory dysfunction and their relationship with functional severity, maximal expiratory flows at low lung volumes and prognosis, in patients with cystic fibrosis (CF).

Material and methods. We studied a group of children, adolescents and young adults diagnosed with CF, found in the records of the 2nd Pediatric Clinic of Emergency Hospital from Craiova, Children's Emergency Hospital "Maria Sklodowska Curie and the Institute for Maternal and Child, Alfred Rusescu (IOMC), both of Bucharest. All patients performed spirometry tests. They were classified as having normal respiratory function (N), obstructive lung disease (OLD), presumptive restrictive lung disease (RLD) and mixed obstructive and restrictive lung disease (MORLD). Maximal expiratory flows at low lung volumes were assessed using FEF25-75. The prognosis was assessed using a simplified cystic fibrosis scoring system (SCS), described by Cooperman. We also included 52 subjects without respiratory disease, as control group, tested spirometry.

Results. The group included 52 patients studied, 11 (21.15%) with normal respiratory function, 15 (28.84%) with OLD, 2 (3.84%) with presumptive RLD and 24 (46.15%) with MORLD. The FEV1 and the Cooperman Score (SCS) were significantly lower in the MORLD group then in the other groups ($p<0.0001$). In the group with normal respiratory function, FEF25-75 showed a decrease of up to 60% of predicted value, in 5 patients.

Conclusions. The respiratory types was impaired in 78.83% of the patients with CF. The most common type of respiratory dysfunction was MORLD. The degree of functional damage was significantly higher and the prognosis more reserved in the MORLD group then in the other groups. Even some patients, regarded as having normal respiratory function, showed a slight deterioration of FEF25-75.

Keywords: cystic fibrosis, respiratory patterns, spirometric tests, early diagnosis, prognosis.

Introduction

Cystic fibrosis (CF) or mucoviscidosis is the most common monogenic disease in people of caucasian origin, autosomal recessive, multisystemic disease, with chronic progressive evolution, potentially fatal, translating it in terms of pathophysiology by altering the transport of chloride in the serous and mucous glands, the primary abnormality is represented by CF gene (3, 8, 11). Because CF is characterized by wide phenotypic variability, there are significant clinical differences between patients in terms of severity and complications. A major clinical repercussion is given of the pulmonary and respiratory symptoms that are responsible for 90% of cases of morbidity and mortality, infection and chronic inflammation leading invariably to progressive respiratory failure (1, 11, 13). In the lung, the mechanisms to increase the rate of absorption of sodium and chloride excretion decreased, leading to a liquid periciliar thick, dehydrated, sticky and consequently to a decrease in mucociliary clearance (11) and the excretory ducts obstruction leading to atrophy, fibrosis, destruction (12). Studies conducted in the second trimester of pregnancy showed the accumulation of mucin in the glands tracheobronchitis. The histopathological aspects can be drawn from the first days of life, even before infection: the submucosal glands hypertrophy, secretory ducts obstruction and the mucous cells hyperplasia of the trachea and major bronchi (12). The retention of the thick mucus in bronchioles promotes the vicious cycle of inflammation, the bacterial infection, the destruction of architecture and the bronchiectasis (9, 15).

Due to improvements in the symptomatic therapies and the late decline in lung function, increased survival over the past 30 years (16, 17). Recent epidemiological data showed an average survival in Europe for over 22 years (11) and another study observed an average survival of 38.6 years in Germany, in 2006 (16). The regular assessment of the lung function in patients with CF and the early detection of alterations that occur in the airways, play an important role in treatment, helping to decrease the morbidity and mortality rate (17). Once the patient can cooperate, the pulmonary function tests are particularly useful for the evaluation of the bronchoalveolar performance and to assess the airways damage. The clinical studies recommended inspection every three months, and at times of exacerbation of the disease, providing the optimal therapy for clinically (11, 14, 18).

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Measuring and monitoring of the maximale expiratory flows at low lung volumes - FEF25-75 is particularly useful in the early diagnosis of the distal obstructive syndrome, because it reveals more sensitive than forced expiratory volume in one second (FEV1) and the ratio FEV1/VC, narrowing the small airways , allowing prevention of the major functional changes (5, 11). The objective of this study was to evaluate the spirometric types of the respiratory disorders and to determine their relationship with the functional severity, prognosis (assessed by Cooperman Score) and values of the end-expiratory air flow, in a group of patients diagnosed with CF.

Material and methods

The study design was a retrospective cross-sectional multicenter, conducted on a lot of children (older than 6 years), adolescents and young adults diagnosed with CF, which are found in the records of the 2nd Pediatric Clinic of Emergency Hospital from Craiova, Children's Emergency Hospital "Maria Sklodowska Curie and the Institute for Maternal and Child, Alfred Rusescu (IOMC), both of Bucharest. The case histories of the 52 patients have been updated. We used data from the last hospitalization of the patients, in 2008-2009. We included patients with definite diagnosis of CF, based on characteristic anamnestic clinical criteria and confirmed by the sweat test, and in some patients by the genetic test. They received a comprehensive treatment according to the management guidelines FC (2, 7, 8, 10). We selected a control group of the healthy patients with normal lung function from the database of the functional exploration laboratories of the medical centers, where this study was conducted. The control subjects were matched with the study subjects in terms of the age and sex.

The general characteristics of patients, weight, height and body mass index (BMI) were recorded from the case report forms and these values (expressed in kg, m, kg/m2) were converted into numbers standard deviation (SD) from average values correlated with the age and gender (Z Score).The data from the case report forms allowed to evaluate the five dimensions of the Cooperman Score, a simplified cystic fibrosis scoring system (SCS): the genelal activity, the aspects of the chest radiography, the digital hipocratism degree, the growth and development, the complications, which was obtained by adding an overall score for each patient. Each dimension is valued at 0, 1 or 2, the total score is the sum of the 5 points A patient with an excellent health may be of a score of 10 points (4). Spirometry tests were performed in the laboratories of functional exploration of the three medical centers to treat CF. It was measured vital capacity (VC), forced expiratory volume in one second (FEV1), forced expiratory flow between 25 and 75% of forced VC (FEF25-75) and FEV1/VC report. During the spirometry test was performed three forced expiration maneuvers, and were recorded the best results. All values were expressed in liters and percentage of predicted for age, height and sex. Respiratory disorders were classified in accordance with the guidelines of the pulmonary function investigations (5). For the statistical analysis patients were classified according to two directions:

1. by the type of the respiratory disorders: normal respiratory function (N), obstructive lung disease (OLD), presumptive restrictive lung disease (RLD) and mixed obstructive and restrictive lung disease (MORLD);
2. by the severity of respiratory disorder: normal spirometry results (FEV1≥80% of predicted), mild respiratory disorder (FEV1≥60-80% of predicted), moderate respiratory disorder (FEV1≥40-60% of predicted) and severe respiratory disorder (FEV1<40% of predicted) .

Data were expressed as number of cases (percentage) and mean ± SD. Anova test was used to compare variables between three or more groups.The statistical significance was set at $p < 0.05$.

Results

Of the 52 patients, 23 were female and 29 male. The average age of patients was 12.2 ± 4.7 years (range 6-29 years). Patients had a mean weight (Z score) of -1.9 ± 1.1 SD, a mean height (Z score) of -1.3 ± 0.9 SD and an average BMI (Z score) of -1.8 ± 1.4. Averages of the VC, FEV1 and FEF25-75 were 69.9 ± 21.8, 64 ± 24, respectively 52.8 ± 27.7, percent of the predicted value. The average of the Cooperman Score (SCS), which was considered the prognosis, was 3.7 ± 2.6. The average days of hospitalization per year was 20.9 ± 21.3 (Table 1).

Table 1 – General characteristics of the patients with cystic fibrosis

Variable	n=52
Gender (female/male), n	23/29
Age (years), mean±SD	12.2±4.7 (6 – 29)
BMI (Z score), mean±SD	-1.8±1.4
Weight (Z score), mean±SD	-1.9±1.1
Height (Z score), mean±SD	-1.3±0.9
VC (%),mean±SD	69.9±21.8
FEV1(%),mean±SD	64±24
FEF25-75(%), mean±SD	52.8±27.7
FEV1/VC, mean±SD	0.7±0.1
Cooperman Score, mean±SD	3.7±2.6
Number of hospital days/year, mean±SD	20.9±21.3

BMI – body mass index; **VC** – vital capacity; FEV1 – forced expiratory volume in one second; FEF25-75 – forced expiratory flow between 25 and 75% of VC.

Table 2 compares the spirometric variables depending on the type of the respiratory disorder. In our sample, 11 patients (21.15%) were classified as having normal spirometry results (N), 15 (28.84%) with OLD, 2 (3.84%) with RLD and 24 (46.15%) as being MORLD. FEV1 values were significantly lower in the MORLD, than the other groups (p<0.0001). Of the 11 patients classified as having preserved respiratory function, FEF25-75 showed a decrease of up to 60% of predicted, in 5 patients.

Table 2 – Comparison of the spirometric variables by respiratory disorder.

Variable	N	OLD	RLD	MORLD	p
	n=11	n=15	n=2	n=24	
Age (years)	11.8±4.2	9.3±2.5	9±2.8	14.4±5.1	p=0.004
VC (% of predicted)	96.1±8	81.7±6.6	70.5±3.5	50.5±13.7	p<0.0001
FEV1 (% of predicted)	95.7±13	68.2±3.7	79.5±2.1	45.5±18	p<0.0001
FEF25-75 (% of predicted)	84.3±19.2	52.5±9	108.5±17.7	34±18.9	p<0.0001
FEV1/VC	0.9±0	0.7±0	0.9±0.1	0.6±0.1	p<0.0001

N – normal respiratory function; OLD – obstructive lung disease; RLD – restrictive lung disease; MORLD – mixed obstructive and restrictive lung disease.

Figure 1 compares the values of FEV1/VC ratio (bronchial permeability index) in normal individuals and the patients with CF, grouped by the type of respiratory disorders. No statistically significant differences between the control group, the group with preserved respiratory function and the group with presumptive RLD, although these groups differ significantly from the OLD and MORLD groups, that did not differ among themselves (p<0.0001). Regarding the patients grouped according to severity of respiratory dysfunction, there are statistically significant differences of the bronchial permeability index, in the 4 classes of patients (p <0.0001), those with severe respiratory dysfunction were having lower value of this report (Table 3).

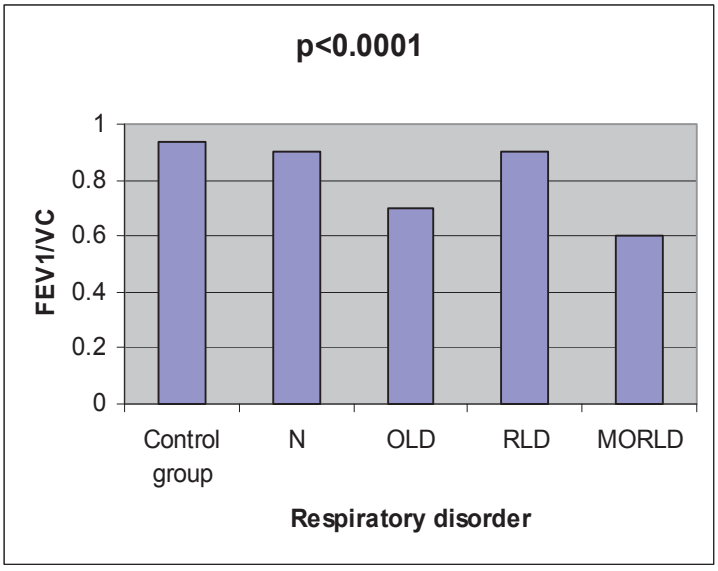

Figure 1 – Mean values of the airway permeability index (FEV1/VC) in the control group and in cystic fibrosis patients grouped by the type of respiratory disorder.

N – normal respiratory function; OLD – obstructive lung disease; RLD – restrictive lung disease; MORLD – mixed obstructive and restrictive lung disease; VC – vital capacity; FEV1 – forced expiratory volume in one second.

Figure 2 compares patients with CF, grouped by the type of respiratory disorders, according to the value of the Cooperman Score (SCS), which considers the prognosis. The group with preserved respiratory function differs significantly from the other three groups in terms of prognosis, and the Cooperman Score in patients with MORLD is significantly lower than in groups with OLD and presumptive RLD (p<0.0001).

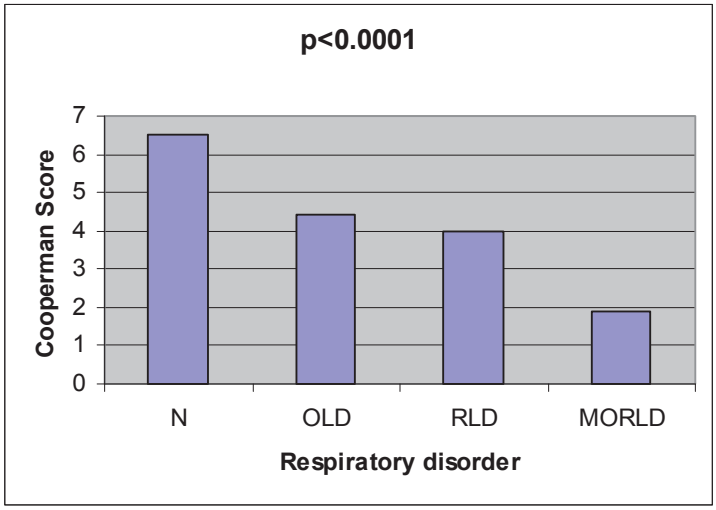

Figure 2 – Mean values of the Cooperman Score in the cystic fibrosis patients grouped by the type of respiratory disorder.

N – normal respiratory function; OLD – obstructive lung disease; RLD – restrictive lung disease; MORLD – mixed obstructive and restrictive lung disease.

Table 3 and Figure 3 examine spirometry variables and the Cooperman Score, according to the functional severity (value of FEV1). Of the 52 patients, 12 (23.07%) had FEV1 ≥ 80%, for 21 (40.38%), FEV1 was between 60 and 80%, 9 (17.30%), FEV1 was between 40 and 60% and 10 patients (19.23%) had an FEV1 <40%. There are significant differences between the four groups of patients, by the value Cooperman Score (p <0.0001).

Table 3 – Comparision of the spirometric variables by functional severity (value of FEV1).

Variable	**FEV1≥80**	**FEV1≥60-80**	**FEV1≥40-60**	**FEV1<40**	**p**
	n=12	n=21	n=9	n=10	
VC (% of predicted)	94.2±9.7	76.1±11.1	57.8±9.5	38.6±8.5	p<0.0001
FEV1 (% of predicted)	94.5±12.5	68.8±4.3	53.8±4.3	26.5±5.4	p<0.0001
FEF25-75 (% of predicted)	87.4±20.2	56.2±13.4	38.1±9.5	17.5±7.3	p<0.0001
FEV1/VC	0.9±0.1	0.7±0.1	0.6±0	0.5±0	p<0.0001
Cooperman Score	6.4±2.5	3.9±1.9	2.3±1.5	1.2±1	p<0.0001

VC – vital capacity; FEV1 – forced expiratory volume in one second; FEF25-75 – forced expiratory flow between 25 and 75% of VC.

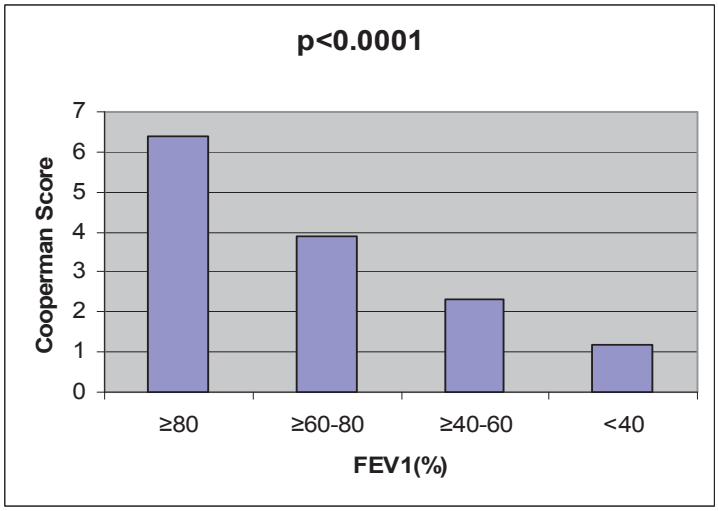

Figure 3 – Mean values of the the Cooperman Score in the cystic fibrosis patients grouped by the functional severity (value of FEV1).

FEV1 – forced expiratory volume in one second.

Discussion

In this retrospective cross-sectional study, we observed that out of 52 patients with CF, 41 (78.83%) showed deterioration in the respiratory function, as demonstrated by spirometry tests. The pulmonary function was preserved in 11 patients (21.15%). The most common type of the respiratory disorder was MORLD (46.15%), followed by OLD (28.84%). The average age of the MORLD group was significantly higher than other groups of patients, which shows the inherent progression of the disease and worsening lung function with age (p=0.004) (Table 2). If at first, inflammatory events, superimposed on obstruction, are reversible, their repetition leads to destruction of the lung parenchyma (12). The changes in the pulmonary function in patients with CF lung correlates with the severity of the structural changes and clinical manifestations. Our study showed a parallel trend in VC and FEV1 values (Table 3), which demonstrates the mixed character of the bronchoalveolar damage, at least in the stage where the endobronchial barrier is overcome. Thus, it becomes useful measure VC, as an indicator of the bronchoalveolar damage, to children who can not work for the determination of FEV1. The decline in the respiratory function is progressive, each exacerbation, representing another step toward the final moment (11).

There was a statistically significant association between the type of the ventilatory dysfunction, functional severity (FEV1 determination) and prognosis (Cooperman Score), MORLD patients had the highest degree of the functional deterioration and the more reserved prognosis. The average of the Cooperman Score for patients with MORLD was 1.9 ± 1.3 SD. Cooperman says in his article titled "A Simplified cystic fibrosis scoring system", that a score value of 4 or less has a serious prognosis (4). Although, CF is a multisystem disease, the prognosis is usually dependent on the degree of the respiratory impairment, some researchers agree that the pulmonary involvement is most responsible for morbidity and mortality (4). The evaluation of end-expiratory air flows, in patients with preserved lung function, showed a decrease in FEF25-75 to 60% of predicted value, in 5 patients. This shows narrowing of bronchial small pipes in a less advanced stage of disease, probably caused by the inflammatory process. Regarding the assessment of functional severity, as determination of FEV1, 40.38% of patients had mild pulmonary disease, 17.3% moderate damage and for 19.23% of the patients was severely impaired pulmonary function. 23.07% of patients had normal lung function. According to bibliographic data, it is considered that the value of FEV1 less than 30% mortality over the next two years is 50%, so the value of FEV1 may be useful in considering the optimal timing for heart-lung transplantation (6). In our study of 10 patients with severe pulmonary disease, 6 (11.53%) had a value of FEV1 below 30%. In agreement with the literature, this study highlights the value of marker stable of FEV1 in relation to prognosis (assessed by Cooperman Score), it is the more reserved (Cooperman Score lower value), as the value of FEV1 decreases. There were statistically significant differences Cooperman Score values in patients grouped according to severity of respiratory dysfunction (FEV1 value). Therefore, Cooperman Score is valuable for assessing pulmonary functional status (Figura 3).

Airway permeability index (FEV1/VC) was significantly lower in patients with OLD and MORLD, compared to other patients and its value decreased with the deterioration of the respiratory function (Figure 1 and Table 3). Particularly useful is monitoring the FEV1/VC ratio values, over time, for each patient. A study conducted in the Center of Mucoviscidosis from Timisoara showed that patients with clinical condition stabilized, despite the lower values of VC and FEV1, the values of the FEV1/VC report were acceptable. In contrast, in those that the FEV1/VC values curve became downward in parallel with decreased FEV1 and VC, the prognosis was infaust (11).

The main limit of this study was that respiratory tests did not include determining residual volume (RV) and total lung capacity (TLC), (TLC=VC+RV), which can not be assessed by spirometry. Thus, some patients diagnosed with MORLD, could have pure DVO, because of reduced VC (the restrictive component of MORLD) might be due to an excessive increase in RV. For these patients should be demonstrated decreased TLC, for the correct diagnosis of respiratory dysfunction (5).

Another limit of the present study was that it used a cross-sectional design, which does not provide sufficient evidence to establish a temporal link between the progression of disease severity and the patterns of alterations, as determineted by spirometry.

In **conclusion,** we observed that 78.83% of patients with CF taking the study had a lung function deterioration. MORLD has been the most common type of respiratory dysfunction due to the inherent disease progression with age. MORLD patients showed the greatest degree of severity funtion.

In CF, ventilatory exploration should include determination of RV and TLC, in addition to the usual tests, for correct diagnosis of respiratory dysfunction.

FEV1, VC and FEV1/VC report have demonstrated its important as prognostic factors. It is necessary to perform periodic spirometry for providing therapy to the clinical condition (including when necessary the heart-lung transplantation).

Analysis of end-expiratory flow parameters (FEF25-75) allowed the identification of respiratory disorders in some patients initially classified as having normal lung function, leading to early recognition of changes in peripheral airway levels.

The Cooperman Score is a simple tool which assesses both prognosis and effects of different drugs and treatments, used in the management of CF. The study highlighted the importance of this score for pulmonary functional status, responsible for the greatest morbidity and mortality in CF.

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