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Article *in* Revista Chilena de Pediatría · June 2018

DOI: 10.4067/S0370-41062018005000303

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DOI: 10.4067/S0370-41062018005000303
ORIGINAL ARTICLE

Spirometric caracterization of cystic fibrosis patients

Caracterización espirométrica de pacientes con fibrosis quística

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Received: 02-10-2017; Accepted: 15-01-2018

Abstract

Introduction: The prognosis of patients with cystic fibrosis (CF) has remarkably improved. The assessment of the disease progression is based on the measurement of the FEV_1 (Forced Expiratory Volume in one second). **Objectives**: 1. To describe forced expiratory flows and volumes and compare their interpretation according to different reference standards (Knudson, Gutiérrez, and multiethnic GLI); 2. To describe bronchodilator response. **Patients and Method**: The medical records and spirometries of all patients with CF controlled at the Dr. Sotero del Rio Hospital were reviewed. Demographic background, sweat test results, genetic study , and bacteriological study were obtained. In addition, Forced Vital Capacity (FVC) was recorded as well as FEV_1 and FEV_1/FVC ratio. **Results:** Data from 14 patients, were analyzed, seven males, aged 6-24 years, median 15 years, median BMI 18.15 (range 14.6-23.3), median sweat chloride test 76 mEq/l (range 50,2-119 mEq/l), seven patients with at least one F508del mutation. Using multi-ethnic and Gutierrez predictive formulas, lung function involvement occurred previously in relation to the use of Knudson equations. None of the patients had a significant bronchodilator response. **Conclusion:** The group of patients described mostly presents functional respiratory involvement and had no bronchodilator response. The interpretation of functional respiratory involvement varies according to the theoretical values used.

Keywords:
Cystic fibrosis; spirometry; pulmonary function tests; FEV_1

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Introduction

Cystic Fibrosis (CF) is the most common autosomal recessive lethal disease in Caucasians, caused by mutations in the gene that encodes the protein that regulates chlorine transport in the cell membrane[1]. In Chile, it is estimated a prevalence of approximately 1/8,000 to 1/10,000 live births[2]. It is a multisystemic disease in which pulmonary involvement represents 85% of mortality[3].

Lung damage is caused by airway obstruction due to dehydration and thickening of secretions, resulting in endobronchial infection, and an exaggerated inflammatory response leading to the development of progressive bronchiectasis and obstructive and restrictive disease[3]. Lung function tests play a central role in the management and treatment of CF patients of all ages[4-6]. The measurement of FEV_1 (Forced expiratory volume in one second) by spirometry is currently the essential parameter for monitoring lung function, assessing its severity and progression[7-12]. On the other hand, the choice of reference standard may have a determinant effect on the interpretation of pulmonary function impairment and consequently on therapeutic measures[11]. Currently, in our country, reference equations of Knudson[13], Gutiérrez[14], and multi-ethnic from the Global Lung Initiative (GLI)[15] are used. The objectives of this study are 1. To describe forced expiratory volumes in cystic fibrosis patients and to compare their interpretation according to different reference standards, 2. To compare the evolution of FEV_1 according to different reference standards, and 3. To describe the response to bronchodilator.

Patients and Method

Retrospective and descriptive study of CF patients controlled in the Pediatric Respiratory Care Unit of the Sótero del Rio Hospital. The clinical records were reviewed, recording the following data: age at diagnosis and date of the study, gender, anthropometry, nutritional status according to body mass index (BMI), sweat test, present mutation, number of hospitalizations and exacerbations, and bacterial colonization to date. The following nutritional diagnoses according to BMI were considered: Obesity ≥ p95, overweight: ≥ p85 - ≤ 94, eutrophy: ≥ p10 - ≤ 84 and low weight: < p10, according to recommendations for this disease[16,17].

In addition, the total spirometries of each patient were reviewed, recording Forced Vital Capacity (FVC), Expired Volume in one second (FEV_1), FEV_1/FVC ratio, and Forced Expiratory Flows between 25 and 75% of FVC (FEF25-75). The spirometry was performed according to established standards[18-20], meeting the criteria of acceptability and repeatability required for schoolchildren and adolescents. The spirometer used was MedGraphics Breeze Suite 6.4.144SPA, 510 version, 2009, St Paul, Minnesota, USA. Knudson[13], Gutierrez[14], and multi-ethnic of GLI[15] were used as reference values. The last spirometry recorded in each patient was interpreted, according to Knudson and Gutiérrez using the fifth percentile as the lower limit (both using the lower limit in percent, which varies according to gender, height, and age), and for GLI 1 z-score (lower limit 1 z-score, -1.64 SD), analyzing FEV_1, FVC and FEV_1/FVC ratio. In order to establish the severity degree, a percentage of the real value of FVC and FEV_1 was used with respect to the theoretical value[2].

The response to bronchodilator (salbutamol 400 ugr) was assessed, considering significant an increase of 12% in FEV_1[19]. The value of chlorine in sweat was obtained through the Gibson and Cooke method[1].

In order to illustrate the progression of FEV_1 over time and the theoretical curves of GLI, Knudson, and Gutiérrez, the free software R 3.3.1 version was used. This research was approved by the ethics committee of the Dr. Sótero del Río Hospital (waiver of informed consent).

Results

Out of the 17 patients controlled in this Unit, 14 had serial spirometry during a median follow-up time of nine years (range 1-17 years), seven men. The median age at the time of the study was 15 years (range 6 - 24 years), median weight 41 kg (range 19 - 61 kg). Table 1 shows the demographic characteristics, results of chlorine in sweat and genetic study.

Median follow-up time was ten years (range 1-17), exacerbations 12 (range 4-29). The median number of exacerbations calculated per year of follow-up was 1.8 (range 0.35 - 4/year) and hospitalizations 0.95 (range 0.14 - 3.5 / year). In three of our patients, no data were found due to the recent start of follow-up at our center.

Table 2 shows the interpretation of the last spirometry of each patient, according to Knudson[13], Gutiérrez[14] and GLI[15]. Seven patients had normal spirometry according to Knudson, six of them according to GLI, and four according to Gutierrez parameters. In six patients there was no agreement on interpretation. According to GLI, there was a greater tendency to find restrictive patterns, and according to Gutierrez, obstructive ones.

Table 3 shows the baseline values of FVC and FEV_1 and the response to the administration of 400 ugr of salbutamol, observing that when interpreting accor-

Table 1. Clinical characteristics of the study group

Patient	Gender	Actual age (y.o.)	Age at diagnosis	Weight (Kg)	Height (cm)	BMI	Nutritional status	Sweat chloride (mEq/L)	Mutations
1	M	6	5 a	22.5	113	17.6	Overweight	55.1	R117H/R1162X
2	F	7	4 m	35	125	22.4	Obesity	102	F508del/ -
3	M	7	9 m	19	114	14.6	Normal	77	-/-
4	F	8	3 m	30	126	18.9	Overweight	69.5	F508del / -
5	F	10	8 a	38	138	20.1	Overweight	117	F508del / -
6	M	11	3 m	24.4	128	14.9	Under weight	97	F508del / -
7	M	12	2 a	42	148	19.2	Normal	119	F508del / -
8	F	18	14 a	61	175	19.9	Normal	75	-/-
9	F	20	3 a	43.1	156	17.7	Under weight	58.1	-/-
10	F	21	5 a	58	158	23.3	Eutrofia	59	-/-
11	M	22	8 a	54	183	16.1	Under weight	55.9	F508del/-
12	M	22	14 a	51.3	168	18.2	Under weight	79.1	F508del/-
13	M	24	7 a	53	171	18.1	Under weight	50.2	-/-
14	F	24	7 a	40.7	155	16.7	Under weight	77.5	-/-

M: male; F: female; BMI: body mass indexl; y.o.: years old, m:month; -: unidentified mutation.

Table 2. Spirometric diagnosis according reference values

Patient	Knudson	GLI	Gutiérrez
1	N	N	MiOL*
2	Mild OL	Mild OL	Mild OL with low FVC*
3	Mild RL	Mild RL	Mild OL with low FVC*
4	Severe OL with low FVC	Severe OL with low FVC	Severe OL with low FVC
5	Mild OL	Mild OL	Mild OL
6	Moderate OL with low FVC	Moderate OL with low FVC	Moderate OL with low FVC
7	N	N	N
8	N	Mild RL	Mild RL *
9	Mild OL with low FVC	Mild RL	Mild OL with low FVC *
10	Mild RL	Mild RL	Mild RL
11	N	N	Mild OL *
12	N	N	N
13	N	N	N
14	N	N	N

N: normal, OL: Obstructive Limitation; RL: restrictive limitation; FVC: Forced Vital Capacity. *: Interpretation non concordant.

ding to guidelines[19,20], no patient showed a significant increase (≥ 12% in relation to the baseline) in this variable.

Figure 1 shows the evolution over time of the FEV_1 percentage in each patient interpreted according to Knudson, GLI, and Gutierrez, and projects the average age at which 30% of the predicted FEV_1 would be reached, being approximately 38 years if Knudson is used as a reference, and approximately 33 years using GLI and Gutierrez.

Table 3. Bronchodilator response

Patient	Basal FEV_1 (l)	Post B2 FEV_1 (l)	% change
1	1.44	1.56	7
2	1.76	1.82	3
3	1.25	1.28	3
4	1.97	1.97	0
5	1.73	1.86	7
6	1.12	1.12	1
7	1.75	1.85	5
8	0.62	0.66	5
9	2.49	2.46	-1
10	2.3	2.32	1
11	5.2	5.52	6
12	4	4.16	4
13	2.04	1.96	-4
14	2.39	2.38	0

FEV_1: Forced Espiratory Volume at 1 second. Post B2: 400 ugr Fesema® (salbutamol).

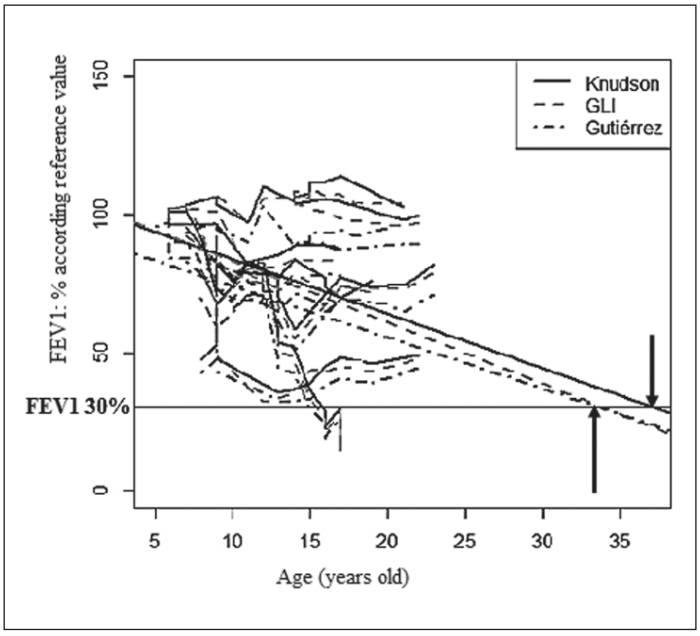

Figure 1. Percentaje of FEV_1 evolution of individual patients according Knudson, GLI and Gutiérrez reference values and its projection to 30% (arrows). FEV_1: Forced Expiratory Volume in the first second.

Discussion

In this series of 14 cystic fibrosis patients, our data indicate that the interpretation of functional respiratory involvement varies according to the theoretical values used, diagnosing greater involvement with theoretical values GLI and Gutierrez, and reaching the critical level of FEV_1 of 30% approximately five years earlier when using the latter as a reference compared to Knudson. In addition, there was no significant response to bronchodilator in any of the patients, consistent with the physiopathology of this disease[1,3].

The implementation of the CF ministry program in Chile[21,22] has contributed to the early diagnosis, highlighting the early diagnosis in our patients before the age of five in seven of them, and three before to the first year of life. It has also favored survival, which is why the current median age of our patients is 15 years.

The sweat test is the gold standard for the diagnosis of cystic fibrosis[1], five patients had intermediate results (30-59 mmol/l)[23] (Table 1). The patient with R117H and R1162X mutations have normal lung function, which would be consistent with the phenotypic prevalence of R117H, known to have mild manifestations[23,24]. In another patient, only one had F508del mutation; it is assumed that the other mutation would be a mild phenotype since the patient is 22 years old and his lung function is normal. No mutation was identified in the remaining three patients. In two of them, lung function is impaired. Discrepancies between mutations and expected clinical manifestations have been described[25].

With respect to nutritional status, Barja et al[26] report a close correlation between nutritional status and FEV_1 value. In our series, there were three overweight patients and one obese patient, due to the small number it is not possible to establish correlations. It is important to note that not only low weight but also overweight and excess fat mass are associated with impaired lung function, impaired metabolic function, and worse post-lung transplant outcomes[27-29].

In Chile, predictive values of Knudson are still used[13], which have been found to underestimate the results when interpreting spirometries[30]. The formulas of Gutierrez were obtained from healthy Chilean children living in Valparaiso[14]. The predictive formulas of GLI[15] were designed with data obtained from different countries and ethnic groups, with the great advantage of reflecting lung function as a continuum between the ages of two and 95[11,31]. In our series, there was a difference in the interpretation of spirometry in six of the 14 patients, with greater involvement diagnosed using the Gutierrez and GLI formulas. This means that if we use Knudson as a reference, some CF patients would present results apparently in the 'normal range', and incorrect treatments could be determined. There were more restrictive limitations when interpreting with GLI, which would indicate that these formulas are

more demanding for the FVC value, on the other hand, Gutiérrez would be for FEV_1 and FEV_1/CVF.

FEV_1 is the most commonly used variable to assess the severity and progression of the disease. Its percentage with respect to the theoretical value is used to decide on therapy changes, evaluate treatment efficacy, hospitalization decision, among others[9,11,32]. But in addition, the percentage of FEV_1 is related to the survival of CF patients; it was demonstrated that patients whose percentage of FEV_1 is less than 30% compared to the theoretical one, have a mortality higher than 50% at two years[7-10], and for this reason this is one of the criteria that is considered to decide the indication of lung transplantation[4,7,8,18,28].

Figure 1 shows different evolutionary patterns, including increased lung function in some patients. This could be explained by the known greater variability of spirometric parameters in these patients due to the permanent presence of bronchial secretions[4,7,33]. In our case, it is not due to the change in spirometric reference standards, as described in other cases[31]. A correlation between significant variability of lung function during one year of evolution with greater deterioration of FEV_1 fall has been seen, considering its variability a good predictor of disease progression[4,7,9].

What is expected of a healthy child is an increase in lung volumes until the pubertal growth spurt ends[6,34]. Most CF patients have an unavoidable characteristic which is a progressive decrease in lung function over time[10,11,34]. To evaluate this evolution, FEV_1 is used, describing a variable decrease between -0.65 and -2.52% per year according to various risk factors for loss of lung function, such as present mutation, pancreatic involvement, nutritional status, present infectious agent, number of annual exacerbations, etcetera[7,25]. In our patients, we see how the average percentage of FEV_1 decreases with age, regardless of the reference standard used.

As a result of this study, it should be noted that there is a relevant difference in the cut of FEV_1 of 30% according to the different reference parameters. This occurs with up to five years difference between the Knudson values and the Gutierrez and GLI values. This leads to a delay in decision making which could have a negative impact on the evolution of patients.

In relation to therapy, CF patients frequently receive bronchodilators, but their use has not always been justified[34-36]. The pathogenesis of wheezing in this disease involves several overlapping mechanisms: edema of the bronchial mucosa due to chronic infection and inflammation, obstruction due to secretions, autonomic pathways stimulation, bronchial smooth muscle contraction, and dynamic collapse of the airway due to the destruction of its walls[35]. In this case, we see that following the guidelines for spirometric interpretation no patient showed a significant change in FEV_1 with the use of bronchodilator, that is to say, FEV_1 did not increase 12% or more from baseline[19]. These findings are similar to those found by Ziebach et al[37] and Sánchez et al[38]. However, the latter authors report that a 6% increase over baseline FEV_1, would suggest the presence of bronchial hyperreactivity in CF patients with 83% sensitivity and 100% specificity. If Table 3 is analyzed, only three patients would have a change equal to or higher than 6%. In any case, it is difficult to define a cut-off point to consider a significant change due to the great variability that patients present of FEV_1 and FVC, with figures of 15-20% spontaneously, even on the day of spirometry[3]. The authors of a Cochrane review[39] suggest that prior to initiating permanent bronchodilator therapy, the response to bronchodilator should be assessed considering a reasonable increase in FEV_1 of 10% after the administration of the drug. In relation to forced flows (FEF 25-75), we do not consider showing it since its variability has been seen to be even higher, and it is proposed to omit it in the spirometric report[40], although other authors have found that these (FEF75) would serve as an early marker of small airway compromise[41].

We consider it a strength of this study to have had all the spirometries of each patient, which allowed to carry out functional respiratory follow-up for a considerable period of time, and thus define the individual trend of FEV_1, determining its prognosis. In addition, these tests were always performed with the same spirometer, which meets the required characteristics for reliable results.

The weaknesses of the study are the low number of patients, which is not enough to assume a representation of the Chilean population nor to obtain correlations of lung function with clinical or other laboratory parameters.

Conclusion

Pulmonary function measurements are fundamental for making therapeutic decisions in CF patients, where FEV_1 is the most commonly used variable to assess its severity and progression and to look for the presence of bronchial hyperreactivity.

We must be aware of the reference values used for spirometry since according to the chosen one, the respiratory functional diagnosis can be variable.

Ethical responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World

Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of interest

Authors declare no conflict of interest regarding the present study.

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