Lung function in patients with sickle cell anemia

Função pulmonar em portadores de anemia falciforme

Función pulmonar en portadores de anemia falciforme

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ABSTRACT

Objective: To evaluate the pulmonary function in children and adolescents with sickle cell disease (SCD) and to associate the findings with clinical and hematologic characteristics of the studied population.

Methods: Male and female SCD patients with ten or more years old, clinically stable and without acute clinical problems were tested by spirometry. At that time, total pulse oximetry values, hemoglobin and total white blood cell count were verified. Association between altered pulmonary function tests and demographic, clinical and laboratorial characteristics of the patients were assessed. Statistical analysis included chi-square and t-test, being significant $p<0.05$.

Results: Among the 51 studied patients, 40 (78%) had abnormal spirometric results: 20 (50%) had mixed or combined ventilatory disorders, 13 (33%) had classical restrictive profile and seven (18%), obstructive ventilatory disorder. Out of these seven patients, five (71%) had a positive response to bronchodilators. Increased total white blood cells count was associated with abnormal pulmonary function. Patients with previous acute pulmonary hospital admissions had lower forced expiratory volume in one second without bronchodilators, lower forced vital capacity before and after bronchodilators, and lower forced expiratory flow between 25 and 75% of the forced vital capacity after bronchodilators.

Conclusions: Most SCD patients presented abnormal pulmonary function, being predominant the mixed or combined type, followed by the classical restrictive pattern. Increased white blood cell count in the blood, without acute clinical events, was associated to abnormal pulmonary function.

Key-words: anemia, sickle cell; lung; spirometry; Pediatrics.

RESUMO

Objetivo: Avaliar a função ventilatória por meio de espirometria, em escolares e adolescentes com anemia falciforme (AF), relacionando os achados a parâmetros clínicos e hematológicos.

Métodos: Foram avaliados portadores de AF de ambos os gêneros, a partir dos dez anos, clinicamente estáveis, sem intercorrências agudas, que foram submetidos à espirometria e avaliados quanto à saturação transcutânea de oxigênio, níveis de hemoglobina e contagem de leucócitos. Verificou-se a associação de alterações à espirometria com as características demográficas, clínicas e laboratoriais dos pacientes analisados. Para a análise estatística, aplicou-se o teste do qui-quadrado e o teste *t* para amostras não pareadas, sendo significante $p<0,05$.

Resultados: Foram estudados 51 pacientes e, em 40 (78%), identificou-se comprometimento do perfil espirométrico, do quais 20 (50%) apresentaram distúrbio ventilatório misto ou combinado, 13 (33%) mostraram perfil restritivo clássico e sete (18%), distúrbio ventilatório obstrutivo. Dos

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Fonte financiadora: Programa Institucional de Bolsas de Iniciação Científica do Conselho Nacional de Desenvolvimento Científico e Tecnológico.
Conflito de interesse: nada a declarar

Recebido em: 23/11/2009
Aprovado em: 25/6/2010

sete, em cinco (71%) observou-se resposta broncodilatadora positiva. A contagem total de leucócitos associou-se à função pulmonar alterada. O volume expiratório forçado no primeiro segundo sem broncodilatador, a capacidade vital forçada antes e após broncodilatador e o fluxo expiratório forçado entre 25 e 75% da capacidade vital forçada após broncodilatador foram significativamente menores nos pacientes com relato de internação hospitalar prévia por doença pulmonar aguda.

Conclusões: A maioria dos pacientes apresentou alteração da função pulmonar, predominando o padrão misto ou combinado, seguido pelo restritivo clássico. Presença de leucocitose, na ausência de intercorrências agudas, associou-se a comprometimento de função pulmonar.

Palavras-chave: anemia falciforme; pulmão; espirometria; Pediatria.

RESUMEN

Objetivo: Evaluar la función ventilatoria, mediante espirometria, en escolares y adolescentes con Anemia Falciforme (AF), relacionando los hallazgos a parámetros clínicos y hematológicos.

Métodos: Fueron evaluados portadores de AF de ambos géneros, a partir de los 10 años, clínicamente estables, fuera de complicaciones agudas, que fueron sometidos a la espirometria y tuvieron verificados la saturación transcutánea de oxígeno, los niveles de hemoglobina y el recuento de leucocitos. Se verificó la asociación de alteraciones a la espirometria con las características demográficas, clínicas y laboratoriales de los pacientes analizados. Para el análisis estadístico, se usó el chi cuadrado y la prueba t para muestras no pareadas, siendo significante $p<0,05$.

Resultados: Fueron estudiados 51 pacientes, y en 40 (78,4%) se identificó comprometimiento del perfil espirométrico de los que: 20 (50%) presentaron disturbio ventilatorio mixto o combinado, 13 (32,5%) tuvieron perfil restrictivo clásico y siete (17,5%) disturbio ventilatorio obstructivo. De los siete, en cinco (71,4%) se observó respuesta broncodilatadora positiva. El recuento total de leucocitos se asoció a la función pulmonar alterada. El Volumen Espiratorio Forzado en el primer segundo sin broncodilatador, la Capacidad Vital Forzada antes y después del broncodilatador y el Flujo Espiratorio Forzado entre 25 y 75% de la Capacidad Vital Forzada después del broncodilatador fueron significativamente menores en los pacientes con relato de internación hospitalaria previa por enfermedad pulmonar aguda.

Conclusiones: La mayoría de los pacientes presentó alteración de la función pulmonar, predominando el estándar mixto o combinado, seguido por el restrictivo clásico. Presencia de leucocitosis, en la ausencia de intercurrencias agudas, se asoció al comprometimiento de función pulmonar.

Palabras-clave: anemia falciforme; pulmón; espirometria; pediatría.

Introduction

Sickle cell disease (SCD) is a genetic hemoglobinopathy first described in 1910[1]. In Brazil, data on the prevalence of the disease suggest a significant rate, albeit based on regional studies[2]. SCD is characterized by multisystem impairment, resulting in significant morbidity and mortality[3]. The occurrence of vaso-occlusive phenomena represents the crucial pathophysiological event causing ischemia, endothelial dysfunction, vascular proliferation, inflammation, and oxidative stress. These mechanisms result in proliferative vasculopathy, which may affect cerebral, renal, and even pulmonary circulations[4].

Previous studies[5] have identified chronic changes in the pulmonary function of patients with SCD, regardless of a history of acute chest syndrome (ACS); however, these studies did not include adolescents. Adults with SCD have impaired pulmonary function, most often showing the characteristics of restrictive ventilatory disorder (RVD)[6-8] caused by repeated episodes of vaso-occlusion, infection, and fat embolism, which have their onset during childhood[6,9,10]. Pulmonary complications are the leading cause of morbidity and mortality among patients with SCD. Such complications usually occur in the second decade of life and cause death in the fourth decade of life. Pulmonary lesions caused by upper airway obstruction, repeated lung infections, and chronic proinflammatory state lead to obstructive or restrictive ventilatory disorder, resulting in pulmonary hypertension and death. A multicenter study has listed more than 20% of fatal pulmonary complications in adults[11]. Pulmonary function abnormalities have also been described in young children whose restrictive pattern becomes more prominent as they get older, a factor possibly associated with pulmonary hypertension and chronic hypoxemia in adults. The development of pulmonary hypertension is another factor that increases mortality[9,10].

Pulmonary function tests appear to be the first tests to show abnormalities during the course of the lung disease;

therefore, all patients with SCD should undergo pulmonary function tests. Spirometry is easily administered, in addition to being inexpensive and fairly sensitive to detect and confirm lung disease, particularly in individuals at risk. Thus, the objective of the present study was to assess the pulmonary function in children and adolescents with SCD using spirometry as a diagnostic tool and investigate the association of abnormal results with some additional clinical and laboratory parameters used in the routine evaluation of these patients.

Method

The present study was conducted between July and September 2009. We investigated female and male patients, aged 10 years or older, with a diagnosis of SCD confirmed by hemoglobin electrophoresis, who were being followed up at the Department of Pediatric Hematology of the University Hospital of Universidade Federal de Sergipe for at least 12 months. Exclusion criteria were: having congenital or acquired heart disease not related to SCD and being asthmatic on corticosteroid or bronchodilator.

The guardians of the eligible patients were invited to participate in the study after reading and signing the written consent form. Data on respiratory symptoms (cough, "shortness of breath," "chest pain") during the month prior to the medical visit and previous diagnosis of asthma or respiratory allergy at any time during their lifetime were collected by means of an interview with the patients' guardians. Data related to previous hospitalization for acute chest syndrome were collected from medical records.

Heart rate and oxygen saturation were measured using a portable pulse oximeter (model 9500 Nonin Onyx, Nonin Medical, Inc., Plymouth, MN, USA) with measurements with an interval of one percentage point. Each patient had these measurements taken three times at each medical visit (in the beginning of the visit, before physical examination, and after delivery of prescription) during three consecutive elective visits when there were not acute intercurrent diseases or complaints. The sensor was placed on the second left finger and the arithmetic mean of the values was calculated. We also obtained the mean values of hemoglobin concentration and total white blood cell count during the same three consecutive visits.

Spirometry was always performed at the same time of day and by the same professional. The spirometer was coupled to a computer (model Spiro USB, manufactured by Micro Medical) to determine the volume-time and flow-volume curves. Patients were instructed to remain seated during the tests and use a nose clip. Bronchodilator testing was carried out (400 mcg of salbutamol sulfate spray). Three curves were built according to the acceptability and reproducibility criteria of the American Thoracic Society[12], and the best curve was selected. Based on this curve, we calculated values of forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and forced expiratory flow between 25% and 75% of FVC (FEF25-75%), all corrected for BTPS conditions (Body Temperature and Pressure Saturated). The results of the pulmonary function tests were analyzed and compared with reference ranges by the same pulmonologist, who was trained and experienced in performing spirometry in school-aged children, adolescents, and adults[13,14].

Results were analyzed using the computer program SPSS 13.0 for Windows. Variables were expressed as proportions, with a confidence interval of 95%. The proportions between groups were compared using the chi-square test and the means were compared by Student's *t* test for unpaired samples. The level of significance was set at 5% ($p < 0.05$).

This research project was approved by the Research Ethics Committee of Universidade Federal de Sergipe as part of the project "Clinical Studies in Sickle Cell Disease."

Results

We studied 51 patients, whose mean age was 15±4 years (ranging from 10 to 26). Fifty-seven percent of the participants were male. The most common current symptom was cough and duration of symptoms was 18 days on average. Fifty-seven patients reported two or more episodes of previous acute lung disease, requiring hospitalization. Of these, 12% were hospitalized for acute chest syndrome in the previous year. Only two patients had previous diagnosis of asthma, but none were on maintenance therapy (Table 1).

Mean oxygen saturation by transcutaneous oximetry was 93.7±4.5% (ranging from 84 to 100) and mean heart rate was 93±14 beats per minute (ranging from 56 to 120). Mean total white blood cell count was 10,979±3,959 leukocytes/mm^3 (ranging from 6,250-17,000) and mean hemoglobin concentration was 8.6±1.6 g/dL (ranging from 6.2 to 12.2).

The lung function tests administered to our sample showed the following values described as mean and standard deviation: forced expiratory volume in one second

Table 1 - General characteristics of patients with sickle cell disease according to spirometric profile

	Total (N = 51)	Normal spirometry (n = 11)	Abnormal spirometry (n = 40)	p-value
Age (years) [b]	14.8 (10-26)	14.0	14.9	0.48
Sex: Male	29 (57%)	6 (55%)	23 (58%)	0.99
Non-White	44 (86%)	11 (100%)	33 (82.5%)	0.32
PALD with H				0.41
- No episode	15 (29%)	5 (45.4%)	10 (25%)	
- One episode	7 (14%)	1 (10%)	6.15	
- ≥ 2 episodes	29 (57%)	5.50	24 (58.5%)	
Cough	32 (63%)	6 (54.5%)	26 (65%)	0.73
Chest pain	7 (14%)	3 (27.3%)	4 (10%)	0.16
Shortness of breath	5--|10	1 (9%)	4 (10%)	0.99
Duration of symptoms (days)[a]	17.8	14.7 ± 20.3	18.6 ± 13.3	0.54
Respiratory allergy	12 (23.5%)	4 (36.4%)	8 (20%)	0.26
Asthma	2 (4%)	1 (9%)	1 (2.5%)	0.39
ACS in the previous year	6.12	2 (18.2%)	4 (10%)	0.58
Outpatient SpO_2 [a]	93.71 ± 4.47	93.1 ± 3.6	93.9 ± 4.7	0.65
Outpatient HR [a]	92.98 ± 14.16	93.2 ± 14.3	92.9 ± 14.3	0.95
Outpatient Hb [a]	8.6 ± 1.64	8.0 ± 0.79	8.8 ± 1.77	0.14
Outpatient WC [a]	10,979 ± 3,950	10,206 ± 3,270	13,791 ± 5,023	0.006

[a]Mean ± Standard deviation; [b]Median (range); PALD with H: previous acute lung disease with hospitalization; ACS: Acute Chest Syndrome; SpO_2: oxygen saturation (%); HR: Heart rate (bpm); Hb: hemoglobin (g/dl); WC: total white blood cell count (/dl)

Table 2 - Values of ventilatory parameters of patients with sickle cell disease as mean ± standard deviation according to history of acute lung disease.

	Previous acute lung disease		P-value
	No (n = 15)	Yes (n = 36)	
FEV1 before [BD]	2.04 ± 0.79	1.65 ± 0.47	0.03
FEV1 [BD]	2.04 ± 0.78	1.71 ± 0.47	0.06
FVC before [BD]	2.25 ± 0.91	1.78 ± 0.54	0.02
FVC after [BD]	2.28 ± 0.88	1.84 ± 0.55	0.03
FEF 25-75 before [BD]	2.65 ± 1.09	2.18 ± 0.67	0.06
FEF 25-75 after [BD]	2.94 ± 1.13	2.36 ± 0.64	0.02

BD - bronchodilator; FEV1 - Forced Expiratory Volume in one second; FVC - Forced Vital Capacity; FEF 25-75% - Forced expiratory flow between 25 and 75% of Forced Vital Capacity

(FEV1) without bronchodilator 1.85±0.65 L; FEV1 after bronchodilator 1.86±0.64 L; forced vital capacity (FVC) without bronchodilator 1.99±0.75 L; FVC after bronchodilator 2.03±0.73 L; forced expiratory flow between 25 and 75% of forced vital capacity (FEF 25-75 %) without bronchodilator 2.39±0.90 L/s; FEF 25-75% after bronchodilator 2.61±0.92 L/s. That is, of the 51 patients, 40 (78.4%) showed evidence of altered respiratory function and, of these, 50% (20 patients) had mixed or combined respiratory disorder (MRD). We found classic restrictive ventilatory disorder (RVD) in 32.5% (13 patients) and 17.5% (seven patients) had obstructive lung disease (OLD). Among these seven patients, five (71.4%) had positive bronchodilator response. The values of FEV1 before

Table 3 - Values of ventilatory parameters of patients with sickle cell disease according to total count of white blood cells.

	Previous acute lung disease		P-value
	<15,000 mm ^{3} (n = 45)	≥ 15,000 mm ^{3} (n = 6)	
FEV1 before BD	1.88 ± 0.67	1.38 ± 0.26	0.08
BD FEV1	1.91 ± 0.65	1.42 ± 0.25	0.07
FVC before BD	2.05 ± 0.77	1.48 ± 0.29	0.08
FVC after BD	2.10 ± 0.77	1.49 ± 0.25	0.05
FEF 25-75 before BD	2.47 ± 0.92	1.78 ± 0.45	0.08
FEF 25-75 after BD	2.71 ± 0.93	1.89 ± 0.17	0.04

BD - bronchodilator; FEV1 - Forced Expiratory Volume in one second; FVC - Forced Vital Capacity; FEF 25-75% - Forced expiratory flow between 25 and 75% of Forced Vital Capacity

bronchodilator (BD), FVC before and after BD, and FEF 25-75 after BD were significantly lower in patients reporting previous acute lung disease (Table 2).

There was no statistically significant difference in the spirometric parameters when the patients were divided according to hemoglobin concentration. However, when they were divided according to leukocyte count, considering a cutoff point of 15,000/mm^3, we found that the value of FEF 25-75% after BD was significantly lower in the group of patients with a value equal to or higher than 15,000 mm^3. The values of FEV1 before and after BD, FVC before and after BD, and FEF 25-75% before BD show a tendency to be associated with leukocyte count, but without statistical significance (Table 3). No significant difference was found when the patients were stratified according to oxygen saturation and there was no difference between the parameters measured when compared according to the ventilatory pattern as well.

Discussion

Since 1886, based on the study by John Hutchinson[15], it has been considered that spirometric measures should be analyzed in comparison with values obtained for a standard population and that factors such as age, height, sex, and ethnicity may influence the results[16]. However, results are usually very similar between 15 and 25 years, except for large variations in height. The present study included patients 10 years old or older because it has been demonstrated that, in individuals older than 9 years, spirometric data can be interpreted based on the same criteria used in adults[16]. In a study of similar design[5] that evaluated 53 patients with SCD, those patients aged between 15 and 24 years showed higher percentage of normal results (62.5%) and the remaining 37.5% showed a restrictive pattern, while half of the patients older than 24 years showed a restrictive pattern. In the present study, mixed respiratory disorder was the most common pattern of abnormality in the pulmonary function even though our patients were younger than those studied by Enright *et al*[16].

The predominance of mixed respiratory disorder in the present study may be explained by the clinical spectrum that characterizes SCD involving chronic anemia, pulmonary infarction, and presence of mediators of the inflammatory response. The restrictive ventilatory disorders found in this population are probably caused by the occurrence of pulmonary infarction due to vaso-occlusion and fat pulmonary embolism, which may be followed by bone ischemia, with consequent replacement of lung parenchyma with fibrotic tissue. These events affect lung elasticity and chest wall expansion, causing limitations[5,9], a situation that worsens as individuals get older[9]. It is important to highlight that among 11 patients with normal spirometric reports, only four were older than 15 years. We should keep in mind that the spirometric pattern of pulmonary restriction can also result from ineffective inspiration caused by pain and structural impairment of the chest as a consequence of rib infarction during bone growth, vertebral osteoporosis or osteomalacia[17].

However, the restrictive pattern is not the only consequence of pulmonary function impairment that occurs over the long term in patients with SCD. Pulmonary hypertension, which seems to have a multifactorial etiology, has been increasingly detected in individuals with this hemolytic anemia[4]. Studies that have found high frequency of obstructive pattern suggested that the recurrence of ACS may promote obstructive disorders[18] and that bronchial hyperreactivity

is a major cause of abnormalities[6]. Another study cited the proinflammatory state, leading to leukocytosis, increase of adhesion molecules and elevation of cytokines, as probable causative agent of the reversible obstruction of the lower airways[4]. However, the pathogenesis of bronchial hyperreactivity has not been fully understood so far[19].

A study conducted in Jamaica[20] suggested that the administration of bronchodilators may be useful in the treatment of ACS in people with SCD because bronchial hyperresponsiveness may be a component of the syndrome, but this approach arouses controversy[19]. Although, in the present study, spirometry tests were performed in an outpatient setting in patients without evidence of SCD, five out of seven patients who had obstructive lung disease had a positive response to bronchodilators.

Previous studies have demonstrated a significant association between previous diagnosis of asthma and obstructive ventilatory pattern with ACS and painful crises[6,8,10]. Further studies might clarify the relationship between the findings of mixed or restrictive ventilatory pattern in childhood and adolescence and the severity of pulmonary function impairment in adults with SCD.

Some authors consider that pulse oximetry is little specific to determine the actual oxygen saturation; however, they recommend using this tool to screen cases at risk for chronic alteration in the pulmonary function[7]. Nevertheless, the present study found no association between spirometric alterations and values of percutaneous oxygen saturation.

The present findings relate to the cross-sectional evaluation of pulmonary function in a cohort of adolescents and young adults with SCD prospectively followed up with the purpose of better characterizing the severity of abnormalities and the impact at the medium and long term as well as analyzing the role played by some therapeutic measures, especially the use of bronchodilators, inhaled steroids, replacement blood transfusion, and hydroxyurea. Thus, we concluded that mixed respiratory disorder respiratory was the most frequent spirometric pattern in our patients. In order to define the relationship between dysfunctional spirometric pattern, specific constitutional and environmental variables of patients with SCD and the type and severity pulmonary function impairment at the long term it is necessary to conduct a longitudinal follow-up of this cohort.

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