Lung Function in Infants with Sickle Cell Anemia

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Lung volumes and forced expiratory flows were evaluated in 22 infants with sickle cell anemia and compared with a control group. Forced expiratory flows showed significantly lower values in the sickle cell group. The majority of infants had normal lung function, and obstruction was the most common pattern of abnormality. *(J Pediatr 2019;207:252-4).*

Pulmonary impairment is common in sickle cell anemia (SCA) and is one of the leading causes of morbidity and mortality.[1] The origins of lung alterations in SCA are still poorly known. Studies in adults and children of school age and older frequently reveal impaired lung function in patients with SCA with different patterns of ventilatory dysfunction.[2] Studies involving young children and infants are scarce.

The present study aimed to evaluate the pulmonary function of infants with SCA and compare the findings with a control group.

Methods

We performed a cross-sectional study of infants with SCA (SS genotype), age 6-18 months, with gestational age of ≥37 weeks and birth weight above 2.5 kg. The study was approved by the local ethics committee. All patients' parents provided written informed consent. The study excluded patients with chronic and pulmonary diseases, hemoglobin <7 g/dL, and those with a recent respiratory infection. Study results from the group of infants with SCA were compared with a control group of infants without SCA or pulmonary disease who were previously evaluated in the same laboratory.[3]

Before the examination, the infants received oral sedation with chloral hydrate (50-70 mg/kg) and remained sedated with continuous heart rate monitoring and pulse oximetry. The Infant Pulmonary Lab equipment (Collins-nSpire, Longmont, Colorado) was used for the analysis of forced expiratory flows (FEFs) and volumes (raised volume rapid thoracoabdominal compression technique) and for lung volumes (whole-body plethysmography) according to standard and laboratory recommendations.[4-6] The total lung capacity (TLC) and other lung volumes were calculated by integrating the 2 techniques.[7] The recorded measures were forced vital capacity (FVC); forced expiratory volume in the first half-second ($FEV_{0.5}$); FEF at 50%, 75%, 85%, and between 25% and 75% of FVC (FEF_{50}, FEF_{75}, FEF_{85}, FEF_{25-75}); residual volume (RV); TLC; and RV/TLC ratio. Values were recorded as a z score or percent of predicted.[7,8] Controls were evaluated exactly under the same conditions and by the same equipment.

Parents from all eligible infants with SCA were invited to the study (30 patients), and 22 agreed to participate in the study. Clinical, demographic, and laboratory data were obtained through interviews with the patients' guardians and from their medical records.

Results

Compared with the control group, the SCA group had a higher proportion of older and taller infants. Characteristics of patients with SCA (n = 22) and controls (n = 37) are shown in **Table I**. In patients with SCA, 50% had a single episode of wheezing with no cases of recurrent wheezing. No patient with SCA had a history of acute chest syndrome (ACS), and only 1 patient had a history of a painful vaso-occlusive crisis.

In infants with SCA, we observed significant variability in the values of forced flows and volumes. Pulmonary function values in both groups are shown in **Table II**. The comparative analysis of the SCA and control groups (adjusted for race, gestational smoking, and wheezing) showed that with the exception of FEF_{85} and the $FEV_{0.5}$/FVC, all forced flow and volume measures were significantly lower in the SCA group. Such differences were not found for lung volumes and capacities.

Normal pattern of lung function was observed in the majority of infants with SCA (77%). Restrictive pattern was found in only 1 (5%) infant characterized by reduction in TLC (<75%) and normal $FVC/FEV_{0.5}$. Four (18%) infants showed an obstructive pattern with $FVC/FEV_{0.5}$ below -2 z score and reduction in forced flows. A previous episode of wheezing was reported by only 1 of these infants.

Race did not affect lung function results among infants with SCA. We also did not find any demographic or clinical variable that significantly influenced lung function in infants with SCA.

ACS	Acute chest syndrome
FEF	Forced expiratory flows
$FEV_{0.5}$	Forced expiratory volume in half the first second
FVC	Forced vital capacity
RV	Residual volume
SCA	Sickle cell anemia
TLC	Total lung capacity

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Table I. Characteristics of patients with SCA (n = 22) and control group (n = 37)

	SCA group	Controls	*P*
Male infants*	12 (54%)	15 (41%)	.418
White infants*	5 (15%)	19 (51%)	.013
Gestational smoking*	0	7 (19%)	.039
Family history of asthma*	4 (18%)	15 (41%)	.091
Age (wk)†	55,5 (±14.2)	45.4 (±5.4)	.013
Height (cm)†	75,8 (±5.1)	71.6 (±5.4)	.003
Hemoglobin (g/dL)	8.6 (±0.8)	‡	
Reticulocytes (%)	6.9 (±4.4)	‡	
LDH (IU/L)	493 (±158)	‡	
Fetal hemoglobin (%)	30 (±11)	‡	

LDH, lactate dehydrogenase.
Controls results have been already showed in a previous study (Gonçalves et al[3]).
*Absolute number and percentage—Fisher exact test.
†Mean and SD—Student t test.
‡No laboratory tests were performed in the control group.

Only 1 out of the 22 patients had an adverse effect during sedation, which consisted of a brief respiratory pause with a decrease in oxygen saturation but with rapid improvement with tactile stimulation.

Discussion

The present study evaluated the lung function of infants with SCA and compared them with healthy infants. There was a reduction in FEFs of patients with SCA in relation to the control group, and no difference was observed in relation to lung volumes or capacities. Koumbourlis et al evaluated 20 infants with SCA but using different techniques from our study (partial expiratory curves and diffusion) and without a comparison/control group.[9] These pulmonary function assessment techniques used by Koumbourlis et al may be less sensitive and present greater variability in outcomes.[10]

Comparing the pulmonary function of the SCA and control groups, we observed significantly lower values in the SCA group for several FEFs. We did not observe significant differences between pulmonary volume and capacity measured by plethysmography. The substantial difference observed between the mean z scores of forced flows indicates a relevant variation, showing that patients with SCA already display compromised pulmonary function at this time of life. The pulmonary function changes observed in our study were measured prior to vaso-occlusive crises and ACS. Lung function alterations in older children may not always be associated with previous episodes of ACS[11] but may be predictive of future episodes.[12] The presence of early alterations in our study may indicate a population at higher risk for ACS.

Table II. Lung function values (mean ± SD) of infants with SCA (n = 22) and controls (n = 37)

	SCA group	Controls	*P**
FVCz	−0.48 (±0.7)	0.58 (±0.5)	<.001
$FEF_{50}z$	−0.24 (±0.8)	0.99 (±0.7)	<.001
$FEF_{75}z$	0.23 (±0.9)	0.80 (±0.8)	.024
$FEF_{85}z$	0.54 (±0.9)	0.74 (±0.9)	.399
$FEF_{25-75}z$	−0.15 (±0.9)	1.03 (±0.7)	<.001
$FEV_{0.5}z$	−0.62 (±0.8)	0.82 (±0.5)	<.001
$FEV_{0.5}$/FVCz	−0.21 (±1.4)	0.39 (±0.7)	.075
RV%†	119 (±17)	113 (±24)	.598
TLC%†	95 (±9)	96 (±9)	.703
RV/TLC%†	122 (±13)	113 (±19)	.284

%, percentage of predicted; *RV*, residual volume; *z*, z score.
*Tukey post hoc adjusted for smoking in gestation, race, and wheezing.
†Plethysmography (SCA, n = 20; controls, n = 35).

The reduction in expiratory flows indicates that the impairment is higher in the airways than in the lung parenchyma, exhibiting similar alterations to those observed in obstructive airway disorders. Our results showed that obstruction is the main pattern of abnormal lung function in SCA. This finding is in accordance with the 1 previous SCA infant study[9] and with research in the other pediatric age groups.[2] Prospective studies have suggested that the prevalence of restrictive alterations in lung function becomes more common with increasing age.[12]

The use of chloral hydrate sedation in our study was safe, with only 1 minor and easily resolved adverse event being observed. Chloral hydrate was the sedative used in the previous study of pulmonary function in infants with SCA[9] and is the standard sedative in our laboratory.[13]

This study had several limitations. First, there was the sample loss of 27% of the contacted patients, mostly because of nonattendance at different scheduled dates. There was no clinical, demographic, and laboratorial difference between these patients and the participants. Race did not influence lung function in our study. This result should be interpreted with caution because of the small number of white infants with SCA and because the ethnicity of patients and controls are different. We did not assess bronchodilator responsiveness in those with obstruction. Finally, there may be limitations of the existing normative data.

In conclusion, our study demonstrated that infants with SCA present reduced lung function in the first years of life, with a predominance of obstructive alterations and considerable variability in forced expiratory flow values being observed. The observed pulmonary damage was independent of prior vaso-occlusive crises and ACS. ■

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