PEDIATRIC ALLERGY, IMMUNOLOGY, AND PULMONOLOGY
Volume 00, Number 00, 2018

DOI: 10.1089/ped.2018.0870

ORIGINAL RESEARCH

Extensive Evaluation of Pulmonary Function Abnormalities by Different Techniques in Turkish Children and Young Adults with Sickle Cell Disease

Tugba Arikoglu, MD,[1] Melih Er, MD,[2] Selma Unal, MD,[3] Didem Derici Yildirim, PhD,[4] Funda Erkasar Çitak, MD,[5] Necdet Kuyucu, MD,[6] and Semanur Kuyucu, MD[1]

Pulmonary involvement in sickle cell disease (SCD) is a major cause of morbidity and mortality. Recent data about pulmonary function tests in children with SCD are conflicting. The objective of this study was to determine the pulmonary function abnormalities for the first time in Turkish children and young adults with SCD by different techniques such as plethysmography and impulse oscillometry (IOS). Fifty-eight patients with SCD and 51 healthy controls were included in the study. Spirometry, IOS, and plethysmography tests were applied. Lactate dehydrogenase (LDH) level as a hemolysis marker was measured. The median age was 15 years (min: 7, max: 22 years) in SCD group and 14 years (min: 7, max: 24 years) in healthy controls. The values of forced expiratory volume in 1 s (FEV1)% ($P < 0.001$) and forced vital capacity (FVC)% ($P < 0.001$) were lower in SCD patients than healthy controls, but FEV1/FVC was normal. The resistance at 5 Hz (R5)% ($P < 0.001$) and difference of resistance at 5 and 20 Hz (R5%–R20%) ($P = 0.001$) in IOS were higher in SCD group. In plethysmography, functional residual capacity (FRC)% ($P = 0.002$), residual volume (RV)% ($P = 0.043$), and total lung capacity (TLC)% ($P < 0.001$) levels were lower in SCD patients than healthy controls. RV% ($P = 0.020$) and RV/TLC ($P = 0.010$) levels were significantly lower in SCD patients with hydroxyurea usage than those without this therapy. Serum LDH levels were found to be negatively correlated with FVC% ($P = 0.042$) and TLC% ($P = 0.043$) levels in SCD group. This study suggested that both obstructive and restrictive pulmonary dysfunctions were present in children and young adults with SCD. In addition, the increased total and peripheral airway resistance in IOS may be a predictor of small airway disease in SCD patients, despite normal lower airway indices in spirometry.

Keywords: spirometry, impulse oscillometry, plethysmography, acute chest syndrome, sickle cell disease

Introduction

Sickle cell disease (SCD) is an inherited hemoglobin disorder that can result in life-threatening acute complications and chronic damage to various organs, with lung involvement being a major cause of mobidity and mortality.[1] Abnormalities in pulmonary function tests have been demonstrated as early objective signs of the development of chronic lung disease in SCD.[2]

Recent data about pulmonary function tests in children with SCD are conflicting regarding whether the major abnormality is restrictive or obstructive lung dysfunction.[3] Nevertheless, there is an increasing evidence that the obstructive pattern is the most commonly detected functional abnormality in children.[2] Restrictive pattern may represent the chronic progression of the disease from childhood to adulthood.[4] It is possible that the different patterns of lung function represent different stages of the disease or different phenotypes. Also, it must be taken into consideration that the onset of the lung function abnormalities occurs in early childhood in SCD. Despite a significant gap in our understanding of the pathophysiology of pulmonary conditions in SCD, previous studies highlighted the importance of pulmonary function testing in early diagnosis of chronic sickle cell lung disease in children.[2]

The major predisposing risk factor for sickle cell lung disease is acute chest syndrome (ACS).[5] Previous studies showed that patients with ACS episodes had higher respiratory resistance than those with no ACS episodes.[6] It was also reported that recurrent episodes of ACS contribute to fibrotic

Departments of [1]Pediatric Allergy and Immunology, [2]Pediatrics, [3]Pediatric Hematology, [4]Biostatistics, and [6]Pediatric Infectious Diseases, Faculty of Medicine, Mersin University, Mersin, Turkey.
[5]Department of Pediatric Hematology, Mersin Maternal and Child Health Hospital, Mersin, Turkey.

changes in the lungs leading to restrictive lung disease.[7] The purpose of this study was to determine every aspect of lung function abnormalities by different techniques such as plethysmography and impulse oscillometry (IOS) for the first time in Turkish children and young adults with SCD.

Materials and Methods

Study population

The current study was conducted at Pediatric Allergy and Immunology Department of Mersin University Hospital from January 2016 to January 2017. The children and young adults attending to Pediatric Hematology Departments in Mersin Province with steady state SCD and aged 6–24 years were enrolled. Forty-eight patients with SCD had HbSS genotype, whereas 10 patients had HbSβ. Those who had painful crisis or ACS or received blood transfusions in last 3 months or were unable to perform the respiratory maneuvers were excluded. Also, patients with a diagnosis of asthma by a physician or atopy, which was evaluated by skin prick testing, were not included in the study.

The healthy controls were those without SCD, chronic lung disease, asthma, or any other chronic disease.

Medical chart of the patients were reviewed to determine whether they were being treated with hydroxyurea and had an ACS and painful crisis ever or in the last 1 year.

The study was approved by Institutional Ethics Committee of Mersin University. All patients provided written informed consent before taking part in the study.

Evaluation of atopy

Atopy was evaluated by skin prick testing in SCD patients. The following inhalant antigens were applied in addition to histamine and saline controls: *Dermatophagoides pteronyssinus, Dermatophagoides farinae*, cat and dog dander, *Alternaria alternata*, cockroach, mixed grass, and tree pollen. Healthy controls did not undergo skin prick testing.

Evaluation of hemolysis

Serum lactate dehydrogenase (LDH) level was measured as a hemolysis marker.

Pulmonary function tests

Pulmonary function tests were performed in the order of IOS, spirometry, and plethysmography on the same day. Because the forced respiratory maneuvers in spirometry would affect the IOS results, pulmonary function tests were performed in this order. SCD patients were tested under steady state conditions defined as the absence of painful crisis and ACS in last 3 months. No subject was tested within 2 weeks of an upper respiratory tract infection.

Spirometry

Spirometry was performed by Master Screen Spirometry System (JaegerCO, Germany) according to American Thoracic Society (ATS) guideline.[8] The values of forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), the ratio of FEV1/FVC, and maximum mid-expiratory flow (MMEF) were recorded. Bronchodilator response was calculated by the percent change in FEV1 after 200 mcg salbutamol inhalation. Zapletal reference values were used for spirometric indices.[9]

Impulse oscillometry

IOS was performed according to the European Respiratory Society (ERS)/ATS guideline[10] by MasterScreen IOS system (JaegerCO). The IOS parameters obtained at the end of the application were resistances (R5, 20) at 5 and 20 Hz and reactance at 5 Hz (X5), R5–R20 (resistance at 5 Hz minus resistance at 20 Hz).

Plethysmography

Plethysmographic measurements were made using a MasterScope Body plethysmography system (JaegerCO) according to current recommendations.[11] The whole-body plethysmograph box is closed during measurement. One pressure transducer measured the pressure inside the box, another one recorded the mouth pressure during a shutter maneuver. Respiratory flow rate is recorded by pneumotachograph, which is calibrated regularly. Total lung capacity (TLC), residual volume (RV), the ratio of RV/TLC (ratio of RV to TLC), and functional residual capacity (FRC) were recorded and the results were expressed as the percent predicted for age, sex, and height. The default settings (E.J.Kids) of the software predmaker V4.30b-_JQM_SYR1 of the Jaeger Masterscope Body plethysmograph and Zapletal reference values were used as reference equations.[9]

Statistical analyses

Statistica 13.3.1 was used for statistical analysis. Descriptive analyses were performed using median (minimum–maximum) values for variables not distributed normally and means ± standard deviations (SDs) for normally distributed variables. The Shapiro–Wilk test was performed to test the normal distribution of continuous variables. Independent Sample *t*-test and Mann–Whitney *U* test were used for comparison of two groups according to the distribution assumption. The chi-square test was used for categorical endpoints. Spearman's rho correlation coefficient was used for the correlation analysis. A P value of less than 0.05 was considered statistically significant.

Results

A total of 109 children and young adults (58 patients with steady state SCD and 51 patients with healthy controls) aged 6–24 years were enrolled. The median age was 15 years (min: 7, max: 22 years) in SCD group and 14 years (min: 7, max: 24 years) in healthy controls. Seventeen patients with SCD and 14 healthy subjects were ≥18 years of age. There was no significant difference between SCD and healthy group in terms of age and body mass index. Forty-two of the patients with SCD (72.4%) and 20 (39.2%) of the healthy group were male. There was a significant difference in gender between SCD patients and healthy controls ($P = 0.001$) (Table 1). Forty-one (70.7%) of the SCD patients were being treated with hydroxyurea. Thirty (51.7%) of the patients had a history of ACS ever. Twenty (34.5%) patients had ACS and 42 (72.4%) had painful crisis in the last year (Table 1).

Serum LDH levels were significantly higher in SCD group ($P < 0.001$) (Table 1).

The values of FEV1% ($P < 0.001$) and FVC% ($P < 0.001$) were lower in SCD patients than healthy controls but FEV1/FVC was normal (Table 2). The R5Hz% ($P < 0.001$) and

Table 1. The Demographic and Clinical Characteristics and Hemolysis Marker of Patients with Sickle Cell Disease and Healthy Controls

	Sickle cell disease, n = *58*	*Healthy controls,* n = *51*	P
Age (year)	15.0 (7.0 to 22.0)	14.0 (7.0 to 24.0)	0.315
Male gender	42 (72.4%)	20 (39.2%)	0.001
Body mass index	18.1 (13.8 to 29.4)	19.9 (13.4 to 32.0)	0.191
LDH (U/L)	528.0 (202.0 to 1,652.0)	200.0 (124.0 to 376.0)	<0.001
Hydroxyurea therapy	41 (70.7%)	—	
History of ACS ever	30 (51.7%)	—	
ACS history in last year	20 (34.5%)	—	
Painful crisis in last year	42 (72.4%)	—	

Results in median (minimum–maximum) or number (%).
ACS, acute chest syndrome; LDH, lactate dehydrogenase.

(R5%–R20%) ($P = 0.001$) values in IOS were found to be higher in patients with SCD than the healthy group (Table 2). There was no significant difference in the magnitude of change in spirometric and IOS indices following bronchodilator administration between SCD patients and healthy controls. In plethysmography, FRC% ($P = 0.002$), RV% ($P = 0.043$), and TLC% ($P < 0.001$) levels were lower in SCD patients than healthy controls (Table 2).

The values of FVC% were significantly lower in the SCD group with ACS ever than the patients without any ACS ($P = 0.022$). There was no significant difference between SCD patients with and without ACS history in terms of IOS indices. RV% ($P = 0.020$) and RV/TLC ($P = 0.010$) levels were significantly lower in SCD patients with hydroxyurea therapy than those without this therapy (data not shown).

Serum LDH levels were found to be negatively correlated with FVC% (rho: –0.27, $P = 0.042$) and TLC% (rho: –0.28, $P = 0.043$) levels (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/ped).

Discussion

SCD is a genetic blood disorder with acute and chronic effects on many organ systems. The effects of SCD on pulmonary functions and eventually the chronic lung complications have begun to be thoroughly investigated in recent

Table 2. The Comparison of Pulmonary Lung Function Tests (Spirometry, Impulse Oscillometry, and Plethysmography) of Patients with Sickle Cell Disease and Healthy Controls

	Sickle cell disease, n = *58*	*Healthy controls,* n = *51*	P
Spirometry			
FVC%	94.8 ± 14.5	105.7 ± 13.3	<0.001
FEV1%	97.3 ± 14.7	108.5 ± 14.5	<0.001
ΔFEV1%	4.1 (–7.3 to 16.7)	3.8 (–10.7 to 14.1)	0.599
FEV1/FVC	102.3 ± 5.4	103.1 ± 8.3	0.597
MMEF%	90.9 ± 19.6	99.4 ± 29.4	0.086
Impulse oscillometry			
R5%	133.7 (86.8 to 372.8)	107.3 (57.1 to 216.2)	<0.001
ΔR5%	–15.3 (–42.0 to 18.0)	–18.0 (–67.0 to 24.0)	0.644
R20%	120.1 (70.6 to 260.6)	110.9 (53.3 to 204.2)	0.196
ΔR20%	–7.7 (–35.0 to 66.0)	–13.0 (–37.0 to 74.0)	0.325
R5–R20%	16.7 (–37.4 to 112.3)	–3.8 (–33.5 to 49.3)	0.001
X5	–0.2 (–0.4 to –0.1)	–0.1 (–0.5 to –0.1)	0.858
Plethysmography			
FRC%	92.9 (45.9 to 176.3)	103.6 (73.7 to 165.7)	0.002
RV%	84.8 (9.6 to 233.3)	91.9 (35.1 to 259.5)	0.043
TLC%	92.9 ± 15.6	102.8 ± 11.9	<0.001
RV/TLC	86.7 (26.1 to 189.2)	90.6 (38.7 to 195.1)	0.518

Results in median (minimum–maximum) or mean ± SD.
ΔR5%: the ratio of difference between the absolute value of R5 obtained before and after salbutamol inhalation to the absolute value of R5 before salbutamol and the result was multiplied by 100.
ΔR20%: the ratio of difference between the absolute value of R20 obtained before and after salbutamol inhalation to the absolute value of R20 before salbutamol and the result was multiplied by 100.
ΔFEV1%: the ratio of difference between the absolute value of FEV1 obtained before and after salbutamol inhalation to the absolute value of FEV1 before salbutamol and the result was multiplied by 100.
FEV1, forced expiratory volume in 1 s; FEV1/FVC, the ratio of forced expiratory volume in 1 s to forced vital capacity; FRC, functional residual capacity; FVC, forced vital capacity; MMEF, maximum mid-expiratory flow; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5–R20, resistance at 5 Hz minus resistance at 20 Hz; RV, residual volume; RV/TLC, ratio of residual volume to total lung capacity; SD, standard deviation; TLC, total lung capacity; X5, reactance at 5 Hz.

years.[2,12] However, previous studies regarding pulmonary functions in children with SCD are conflicting.[2,3,12–14] A greater understanding of pulmonary abnormalities in SCD may allow for early diagnosis and effective interventions to reduce the morbidity and mortality.

The present study showed that the values of FEV1% and FVC% were lower in SCD patients than healthy controls and FEV1/FVC% levels were similar. The R5Hz% and (R5%–R20%) values in IOS were found to be higher in patients with SCD than the healthy group. In plethysmography, FRC%, RV%, and TLC% levels were lower in SCD patients than healthy controls. In addition, FVC% levels were significantly lower in the SCD group with ACS ever than the patients without any ACS episode. Furthermore, RV% and RV/TLC levels were significantly lower in SCD patients with hydroxyurea usage than those without this therapy. LDH levels were found to be negatively correlated with FVC% and TLC% levels.

It has traditionally been reported for many years that SCD has been associated with the development of restrictive pulmonary defects.[4,13] However, it has been recently understood that not only restrictive but also obstructive lung dysfunction can be observed in children with SCD.[2] A study conducted by Koumbourlis et al.[14] suggested that SCD itself may be associated with chronic inflammation that initially affects the smaller airways even in the absence of other clinical symptoms. Restrictive pattern may indicate the chronic progression of the disease at older children and adults.[15] Our data were in agreement with the findings of Pianosi et al.,[16] who reported that children with SCD had significantly lower FEV1 and FVC than controls, but similar FEV1/FVC% pointing out to restrictive defect. They also showed that the children with SCD had significantly lower TLC.

IOS can be easily applied even to young children as it only requires passive cooperation.[17,18] The resistance at 5 Hz (R5) reflects the total airway resistance, and the resistance at 20 Hz (R20) reflects the large airways resistance in IOS. The resistance at 5 Hz minus the resistance at 20 Hz (R5–R20) represents the small airway function.[18,19] A previous study found that SCD children had a significantly higher mean R5% predicted than the healthy controls indicating that they had a higher respiratory system resistance. Their results also suggested that the raised pulmonary capillary blood volume seen in SCD children may explain their increased airway resistance.[20] In the present study, although the difference between MMEF% values in spirometry did not reach statistical significance between groups, R5Hz% and R5%–R20% values of SCD group were found to be significantly higher than healthy group in IOS. Our results suggested that the total and peripheral airway resistance were increased in SCD group, and this may be a predictor of small airway disease despite normal lower airway indices in spirometry. Also, this finding supports the notion that IOS is a more sensitive technique in detecting the subtle changes in the lung function.[21]

In the present study, there was no significant difference in the magnitude of change in spirometric and IOS indices (ΔR5% and ΔR20%) following bronchodilator administration between SCD patients and healthy controls. Consistent with our results, Wedderburn et al., showed that there was no significant difference in the magnitude of change in lung function and reduction in R5% predicted between SCD children and the controls.[20] However, Koumbourlis et al., demonstrated a high number of patients with a positive bronchodilator response (54%) and suggested that airway reactivity was an important factor in the pathophysiology of SCD.[14]

Recurrent ACS has been suggested as a risk factor for chronic lung dysfunction in SCD.[6,22] The SCD children with ACS have been reported to have poorer lung function, as indicated by lower FEV1, FEV1/FVC ratio, and TLC.[22] Also, a previous study reported that the adults with SCD and recurrent ACS had lower FVC, FEV1, and TLC levels than SCD adults who had one or no ACS episode. The greater the number of ACS episodes, the greater the reduction in lung function.[23] Santoli et al.,[6] demonstrated that recurrent ACS may contribute specific obstructive defects. They showed that respiratory resistance, measured using the forced oscillation technique, increased with the number of ACS episodes. The increase in respiratory resistance associated with ACS was shown to be accompanied by an increase in diffusion capacity, suggesting that it may have been related to an increase in lung blood volume. The present study revealed that FVC% levels were significantly lower in SCD group with ACS ever than the patients without any ACS episode indicating the role of ACS in the development of restrictive lung disease. However, there was no significant difference between SCD patients with and without ACS history in terms of IOS indices.

Hydroxyurea is widely recommended for the treatment of individuals with SCD regardless of the disease severity. It has demonstrated favorable effects on vaso-occlusion through multiple mechanisms, the most significant of which is the stimulation of fetal hemoglobin.[24] Hydroxyurea therapy might lessen the severity of airway hyperreactivity in children with SCD.[25] Mclaren et al.,[26] examined the effect of hydroxyurea therapy on longitudinal pulmonary function changes in children with SCD. They suggested that hydroxyurea therapy in children with SCD leads to improvement in annual pulmonary function decline. The potential mechanisms of hydroxyurea-related effects on lung function are likely multifactorial and may include reduced damage due to less frequent vaso-occlusive events.[24] A previous study showed that mean FVC and FEV1 values improved significantly on hydroxyurea therapy, when compared with initial pulmonary function test and to those without hydroxyurea therapy.[27] Arteta et al. demonstrated that hydroxyurea therapy was associated with higher FEV1/FVC level.[28] The present study showed that RV% and RV/TLC levels which reflect air trapping were significantly lower in SCD patients with hydroxyurea therapy than those without. These results suggest that hydroxyurea therapy may modulate pulmonary functions and reduce air trapping.

A greater degree of hemolysis as reflected by LDH concentration was found to be associated with airway obstruction in children and adolescents with SCD.[28] Higher LDH concentration was found to be significantly associated with lower FEV1/FVC level and hence, obstructive disease.[28] The current study revealed that LDH levels were negatively correlated with FVC% and TLC% levels, which pointed out a close relationship between hemolysis and restrictive lung disease in SCD.

The limitation of our study was the relatively small number of subjects analyzed. Despite the discrepancy for gender between controls and cases, this was not a problem since we used percent of predicted values to compare the lung function tests, not the absolute values. Although we did not use Global Lung Function Initiative (GLI) reference values,[29] the algorithm by Zapletal et al.,[9] which we used in

the present study, included gender and standing height of patients for prediction equations. The strengths of the present study were the evaluation of SCD patients with simultaneous multiple lung function tests, including spirometry, IOS, and plethysmography, for the first time in Turkish children and young adults with SCD and revealing the pulmonary function abnormalities that are not evident in conventional spirometry.

Conclusions and Clinical Implications

Besides the restrictive type abnormalities in spirometry and plethysmography, peripheral airway resistance values in IOS were significantly higher in patients with SCD. These results suggested that both obstructive and restrictive lung dysfunctions were present in Turkish children and young adults with SCD. In addition, the increased airway resistance in IOS may be a predictor of small airway disease in SCD patients despite normal lower airway indices in spirometry. Furthermore, the early identification of pulmonary function defects may reduce morbidity and mortality in the long-term by appropriate treatment.

Acknowledgments

The research was granted by TÜBİTAK (The Scientific and Technological Research Council of Turkey) ARDEB (Research Support Programs Directorate). Grant No. 215S154.

Author Disclosure Statement

No competing financial interests exist.

References

1. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet 2017; 390:311–323.
2. Koumbourlis AC. Lung function in sickle cell disease. Paediatr Respir Rev 2014; 15:33–37.
3. Vieira AK, Alvim CG, Carneiro MC, Ibiapina CD. Pulmonary function in children and adolescents with sickle cell disease: have we paid proper attention to this problem? J Bras Pneumol 2016; 42:409–415.
4. Klings ES, Wyszynski DF, Nolan VG, Steinberg MH. Abnormal pulmonary function in adults with sickle cell anemia. Am J Respir Crit Care Med 2006; 173:1264–1269.
5. Powars D, Weidman JA, Odom-Maryon T, Niland JC, Johnson C. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. Medicine (Baltimore) 1988; 67:66–76.
6. Santoli F, Zerah F, Vasile N, Bachir D, Galacteros F, Atlan G. Pulmonary function in sickle cell disease with or without acute chest syndrome. Eur Respir J 1998; 12: 1124–1129.
7. Vij R, Machado RF. Pulmonary complications of hemoglobinopathies. Chest 2010; 138:973–983.
8. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force. General considerations for lung function testing. Eur Respir J 2005; 26:153–161.
9. Zapletal A, Samanek M, Paul T, et al. Lung function in children and adolescents: methods, reference values. Basel: Karger, 1997, pp. 114–218.
10. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, Bisgaard H, Davis GM, Ducharme FM, Eigen H, Gappa M, Gaultier C, Gustafsson PM, Hall GL, Hantos Z, Healy MJ, Jones MH, Klug B, Lødrup Carlsen KC, McKenzie SA, Marchal F, Mayer OH, Merkus PJ, Morris MG, Oostveen E, Pillow JJ, Seddon PC, Silverman M, Sly PD, Stocks J, Tepper RS, Vilozni D, Wilson NM. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med 2007; 175: 1304–1345.
11. Criée CP, Sorichter S, Smith HJ, Kardos P, Merget R, Heise D, Berdel D, Köhler D, Magnussen H, Marek W, Mitfessel H, Rasche K, Rolke M, Worth H, Jörres RA; Working Group for Body Plethysmography of the German Society for Pneumology and Respiratory Care. Body plethysmography—its principles and clinical use. Respir Med 2011; 105:959–971.
12. Miller AC, Gladwin MT. Pulmonary complications of sickle cell disease. Am J Respir Crit Care Med 2012; 185: 1154–1165.
13. Sylvester KP, Patey RA, Milligan P, Dick M, Rafferty GF, Rees D, Thein SL, Greenough A. Pulmonary function abnormalities in children with sickle cell disease. Thorax 2004; 59:67–70.
14. Koumbourlis AC, Zar HJ, Hurlet-Jensen A, Goldberg MR. Prevalence and reversibility of lower airway obstruction in children with sickle cell disease. J Pediatr 2001; 138: 188–192.
15. Shilo NR, Lands LC. Asthma and chronic sickle cell lung disease: a dynamic relationship. Paediatr Respir Rev 2011; 12:78–82.
16. Pianosi P, D'Souza SJ, Charge TD, Esseltine DE, Coates AL. Pulmonary function abnormalities in childhood sickle cell disease. J Pediatr 1993; 122:366–371.
17. Shirai T, Kurosawa H. Clinical application of the forced oscillation technique. Intern Med 2016; 55:559–566.
18. Brashier B, Salvi S. Measuring lung function using sound waves: role of the forced oscillation technique and impulseoscillometry system. Breathe (Sheff) 2015; 11:57–65.
19. Desiraju K, Agrawal A. Impulse oscillometry: the state-of-art for lung function testing. Lung India 2016; 33:410–416.
20. Wedderburn CJ, Rees D, Height S, Dick M, Rafferty GF, Lunt A, Greenough A. Airways obstruction and pulmonary capillary blood volume in children with sickle cell disease. Pediatr Pulmonol 2014; 49:716–722.
21. Frantz S, Nihlén U, Dencker M, Engström G, Löfdahl CG, Wollmer P. Impulse oscillometry may be of value in detecting early manifestations of COPD. Respir Med 2012; 106:1116–1123.
22. Sylvester KP, Patey RA, Milligan P, Rafferty GF, Broughton S, Rees D, Thein SL, Greenough A. Impact of acute chest syndrome on lung function of children with sickle cell disease. J Pediatr 2006; 149:17–22.
23. Knight-Madden JM, Forrester TS, Lewis NA, Greenough A. The impact of recurrent acute chest syndrome on the lung function of young adults with sickle cell disease. Lung 2010; 188:499–504.
24. National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services. Evidence-based management of sickle cell disease: expert panel report, 2014. Available from: https://www.nhlbi.nih.gov (Last accessed October 21, 2017).
25. Shilo NR, Alawadi A, Allard-Coutu A, Robitaille N, Pastore Y, Bérubé D, Jacob SV, Abish S, Dauletbaev N, Lands

LC. Airway hyperreactivity is frequent in non-asthmatic children with sickle cell disease. Pediatr Pulmonol 2016; 51:950–957.
26. McLaren A, Klingel M, Behera S, Odame I, Kirby-Allen M, Grasemann H. Effect of hydroxyurea therapy on pulmonary function in children with sickle cell anemia. Am J Respir Crit Care Med 2017; 195:689–691.
27. Record E, New T, Brown R, Graham L, Brown RC. Pulmonary function in children with sickle cell anemia following treatment with hydroxyurea. Blood 2008; 112:1435.
28. Arteta M, Campbell A, Nouraie M, Rana S, Onyekwere OC, Ensing G, Sable C, Dham N, Darbari D, Luchtman-Jones L, Kato GJ, Gladwin MT, Castro OL, Minniti CP, Gordeuk VR. Abnormal pulmonary function and associated risk factors in children and adolescents with sickle cell anemia. J Pediatr Hematol Oncol 2014; 36:185–189.
29. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 2012; 40: 1324–1343.

Address correspondence to:
Tugba Arikoglu, MD
Department of Pediatric Allergy and Immunology
Faculty of Medicine
Mersin University
Ciftlikkoy Kampusu
Mersin 33343
Turkey

E-mail: arikoglutugba@yahoo.com

Received for publication January 9, 2018; accepted after revision March 27, 2018.