Published in final edited form as:
Pediatr Pulmonol. 2009 March ; 44(3): 290. doi:10.1002/ppul.20998.

Lower Airway Obstruction Is Associated With Increased Morbidity in Children With Sickle Cell Disease

Jessica H. Boyd, MD, MPH[1,*], **Michael R. DeBaun, MD, MPH**[2], **Wayne J. Morgan, MD, CM**[3], **Jingnan Mao, MS**[4], and **Robert C. Strunk, MD**[1]

[1]Division of Allergy and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri.

[2]Division of Genetics, Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri.

[3]Division of Pulmonology, Department of Pediatrics, University of Arizona, College of Medicine, Tucson, Arizona.

[4]Division of Patient Oriented Research, Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri.

Summary

Rationale—The association between pulmonary function and morbidity in children with sickle cell disease (SCD) has not been previously evaluated. Our objective was to study the relationship between abnormalities in pulmonary function and morbidity as represented by the rate of hospitalizations for pain or acute chest syndrome (ACS) in children with SCD.

Methods—Results of pulmonary function tests obtained for clinical indications in children ages 6–18 years were classified as lower airway obstruction (forced expiratory volume in 1 sec/forced volume capacity <95% confidence interval adjusted for age, gender, race, and height), restriction (total lung capacity <80% predicted adjusted for gender, age, race, and height), and normal lung function. Incidence rates of pain or ACS were compared between children with lower airway obstruction or restriction and children with normal lung function.

Results—A total of 102 children, mean age at evaluation 12.0 years with follow-up of 3.8 years, were included. Children with lower airway obstruction had twice the rate of morbidity compared to children with normal lung function (2.5 vs. 1.2 hospitalizations for pain or ACS per patient-year, $P = 0.003$) (Risk ratio: 2.0; 95% CI: 1.3–3.3). Children with restriction did not have different rates of future morbidity compared to children with normal lung function (1.4 vs. 1.2 hospitalizations for pain or ACS per patient-year, $P = 0.68$) (Rate ratio: 1.1; 95% CI: 0.6–2.1).

Conclusions—We conclude that children with SCD who have lower airway obstruction should have increased surveillance for future morbidity.

Keywords

sickle cell disease; pulmonary function; lung disease

*Correspondence to: Dr. Boyd Jessica, Washington University School of Medicine in St Louis, 660 S. Euclid Avenue, CB 8116, St Louis, MO, 63110. boyd_j@kids.wustl.edu .

None of the authors have a conflict of interest that may have a perceived influence on the results of this research.

INTRODUCTION

Acute and chronic lung disease is a major contributor to morbidity and mortality in individuals with sickle cell disease (SCD).[1–3] Acute chest syndrome (ACS) is a common pulmonary complication in children with SCD,[1,4] while chronic lung disease predominates in adults.[3,5] Among the SCD population in St. Louis as well as in a national sample, ~17% of children with SCD also carry a diagnosis of asthma, which has previously been shown to be associated with increased incidence rates of pain and ACS.[4,6–9] Additionally, both asthma and ACS are independent risk factors for death in this population.[2,10]

Asthma, an airway disease characterized by episodes of recurrent wheezing and cough, is often diagnosed clinically; lower airway obstruction is the characteristic pulmonary function pattern found in children with asthma.11 Several studies have demonstrated that children and adults with SCD have abnormalities in lung function including lower airway obstruction, restriction, and airway hyperresponsiveness.[5,12–16] Among children with SCD, 5–35% had an obstructive pattern whereas only a small percentage (6–8%) have a restrictive pattern of lung function.[12,16–19] In contrast to the predominantly obstructive pattern in children, restrictive lung defects are present in the majority of adults although obstructive lung disease also occurs.5 Restrictive lung disease represents one characteristic of the spectrum of sickle cell chronic lung disease (SCLD).[5,16,19] Limited data exist about the impact of restrictive lung disease on future SCD events; however, SCLD is associated with a greater than twofold increased risk of death.[19]

Despite the significant morbidity associated with pulmonary complications among individuals with SCD, the association between specific pulmonary function abnormalities and the incidence and severity of SCD-related morbidity is not clear. Given the findings that suggest an association between asthma and SCD-related morbidity and the prevalence of pulmonary function abnormalities in this population, we hypothesized that abnormal pulmonary function, restrictive or obstructive, is associated with an increased rate of future hospitalizations for pain or ACS in children with SCD. To test this hypothesis, we retrospectively reviewed a cohort of children who underwent pulmonary function evaluation, classified their lung disease based on spirometry and lung volumes, and investigated their subsequent rates of hospitalization for pain or ACS during the study period.

PATIENTS AND METHODS

The Institutional Review Board at the Washington University School of Medicine approved the study protocol. Written consent was not obtained as a part of this study as all data collected were part of standard clinical care.

Study Design

A retrospective cohort study of children with SCD who completed pulmonary function testing for clinical indications at St. Louis Children's Hospital was conducted. The study population included children with all sickle hemoglobinopathy types (hemoglobin SS, SC, S beta thalassemia), ages 6–18 years, who completed both a lung volume and spirometry evaluation at any time during the study period, January 1, 1995 to August 31, 2006. The first lung volume evaluation and spirometry done on the same day were taken as the index pulmonary function tests used to classify pulmonary function. Medical records were reviewed to determine the frequency and cause of hospitalizations, with determination of incidence rates of pain or ACS from the time of pulmonary function assessment to the end of the study period or follow-up.

Only children who were routinely followed in the hematology clinic and received all inpatient and outpatient care at St. Louis Children's Hospital were included, assuring that all morbidity

episodes were available. Children who were followed for <6 months following their pulmonary function evaluation were excluded from the analysis. Prior to 2004, children received pulmonary function testing at the discretion of the treating physician. Following the development of a joint SCD and pulmonary clinic, all children were recommended to have at least one pulmonary function test to define status of pulmonary physiology. All pulmonary function testing sessions were done when the children were clinically stable (no current pain, no recent discharge from hospital for either a pain or ACS episode) and at least 4 hr after taking a short acting bronchodilator and 12 hr after taking a long acting bronchodilator.

Pulmonary Function Evaluation

Spirometry and lung volume evaluations were completed using Vmax® by Sensormedics equipment (Sensormedics Corp.; Yorba Linda, CA) in the clinical pulmonary function laboratory at St. Louis Children's Hospital in accordance with American Thoracic Society criteria.[20,21] Maximal expiratory flow-volume loops were measured, and at least three reproducible maneuvers were performed with each test.20 Lung volumes were measured by whole body plethysmography in all study participants.21 All tests were analyzed for validity of results by attending pediatric pulmonologists. Predicted values were determined using reference equations for lung volumes[22] and spirometry[23] accounting for age, race, height, and gender. Lung volume equations were corrected for race using a 12% correction. We retrospectively collected pulse oximetry data on all children in the cohort from the medical record. From one to three pulse oximetry measurements obtained during well visits nearest to the time of the pulmonary function evaluation were averaged to determine a baseline value.

Classification of pulmonary function abnormalities was based on a cross-sectional assessment. The first lung volume evaluation after 6 years of age and spirometry evaluation done on the same day were used as the index test in this analysis to determine cases with pulmonary function abnormalities and controls with normal lung function. Lower airway obstruction was defined as forced expiratory volume in 1 sec/forced volume capacity (FEV_1/FVC) <95% confidence interval adjusted for age, gender, race, and height.[23] A restrictive defect was defined as total lung capacity (TLC) <80% predicted adjusted for gender, age, race, and height.[22] One child had evidence of obstruction on spirometry and restriction on lung volumes and was classified as having both obstruction and restriction and included in both analyses. A subset of patients also had a bronchodilator response evaluation; a positive bronchodilator response was defines as an increase in the FEV1 by 12% or greater following administration of inhaled albuterol. Normal pulmonary function was defined as FEV_1/FVC ≥95% confidence interval, a TLC ≥80% of predicted.

Outcome Measures

The primary outcome measure for this study was rate of hospitalization for pain and ACS combined. The total number of hospitalizations for each participant was ascertained through retrospective medical record review. All hospitalizations were then examined and ICD-9 codes were used to identify episodes of pain (282.62, 282.64, 282.69, 282.42) or ACS (480–487, 517.3). Hospitalizations within 2 weeks of a previous admission were considered re-admissions and not counted as a distinct event. Length of stay was also determined for each hospitalization for pain or ACS and reported as hospital days per patient-year. Pain rates and ACS rates were also examined separately as secondary outcome measures. Follow-up was accrued from the date of the lung volume and spirometry evaluation to the end of the study period (September 1, 2006), the date of last follow-up in SCD clinic, or date at bone marrow transplant or death. A physician-diagnosis of asthma at anytime in the child's life was determined for all children through medical record review. As asthma is considered a lifetime diagnosis; once a participant was identified as having asthma they were always defined as having asthma. Hematological variables were also extracted from the medical chart. White blood cell count (k/mm^3) and

hemoglobin (g/dl) were determined by averaging the values obtained at three well clinic visits that were closest in time to the lung volume evaluation. Percent hemoglobin F levels were determined by averaging up to three hemoglobin F levels obtained at visits closest to the lung volume evaluation.

Data Analysis

Data analysis was completed using a comparison of rates program, Rates2 (PEPI), SPSS 12.0, and SAS 9.0. In the primary analysis, incidence rates of hospitalizations for pain or ACS were compared between children with abnormal pulmonary function (restrictive or obstructive) and children with normal pulmonary function. Secondary analyses were done comparing pain rates, ACS rates, and the total hospital days for pain or ACS. Additional analyses to examine the impact of bronchodilator responsiveness and baseline pulse oximetry on morbidity were also completed. Incidence rates of combined pain and ACS events and the 95% confidence intervals were estimated using general linear models assuming the counts of events followed a negative binomial distribution with scale parameter estimated by maximum likelihood and a log link function. Both negative binomial regression models and poisson regression models with deviance scale adjustment were used to estimate the incidence rate and compare them between the restrictive or obstructive group, and normal group, using P-value <0.05 as the significance. We chose to report negative binomial P-values because this was most conservative and the data best fit a negative binomial distribution.

Two sub-group analyses were conducted as a part of this study. We analyzed patients with HbSS as a sub-group. The second analysis was designed to control for asthma in the regression analysis. These results are reported below.

RESULTS

Cohort Demographics and Characteristics

A total of 102 children were included in the study cohort. The mean age of first lung volume evaluation was 12.0 years (median: 11.8 years, range: 6.4–18.7 years). The mean length of follow-up was 3.8 years (median: 3.1 years, range: 0.6–9.6 years). The cohort was 45% male and the majority of patients were diagnosed with hemoglobin SS (73%).

Pulmonary function testing was normal in 75% of the cohort; 13% (n = 13) had lower airway obstruction and 13% (n = 13) had restriction (one met criteria for both obstruction and was considered in both groups). Doctor diagnosis of asthma was common in the cohort affecting 53% of children with normal lung function, 38% with restriction, 77% obstruction. No significant differences existed when comparing age, gender, hemoglobin phenotype, or length of follow-up between patients with normal pulmonary function testing and patients with restrictive or obstructive patterns of lung function, Table 1. Hematologic variables were not different between the normal, restricted, or obstructed.

Lower Airway Obstruction Is Associated With Increased SCD Morbidity

Children with SCD and lower airway obstruction had a higher incidence rate of hospitalizations for pain or ACS (2.50 hospitalizations per patient-year) compared to children with normal lung function (1.23 hospitalizations per patient-year, $P = 0.025$), Table 2. Children with lower airway obstruction also spent more than twice as many days per year in the hospital for pain or ACS as those with normal lung function (17.9 vs. 6.2 days per patient-year, $P = 0.007$). When examining pain and ACS event rates separately, children with lower airway obstruction had a significantly higher rate of pain (Rate ratio: 2.16 (1.08–4.26); $P = 0.027$), but not ACS (Rate Ratio: 1.38 (0.64–2.97); $P = 0.40$). Laboratory values previously correlated with morbidity in SCD were not different between children with and without obstructive lung

disease (Table 2). When controlling for asthma, lower airway obstruction was associated with increased rates of pain or ACS (2.50 vs. 1.22 events per patient-year, $P = 0.02$) and increased rates of pain alone (2.22 vs. 1.01 events per patient-year, $P = 0.02$).

Restrictive Defects Are Not Associated With Subsequent SCD Morbidity

A restrictive pattern of lung function was not associated with a difference in hospitalization rates for pain or ACS. Children with restriction had similar hospitalization rates for pain or ACS when compared to children with normal pulmonary function (1.32 vs. 1.23 events per patient-year, Rate Ratio = 1.07, 95% CI: 0.56–2.08; $P = 0.68$). The number of hospital days per year for pain or ACS were also similar in the two groups (7.5 vs. 6.2, Risk Ratio = 1.2, 95% CI: 0.6–2.6; $P = 0.60$). Pain and ACS rates were also similar in both groups when examined separately, Table 2. Laboratory values previously correlated with morbidity in SCD were not different between children with and without restrictive lung disease.

Bronchodilator Responsiveness and Baseline Pulse Oximetry Are Not Associated With Increased Morbidity

SCD-related morbidity was not found to be significantly different between children with and without bronchodilator responsiveness. Among all children in the study cohort who had a bronchodilator response evaluation during the study period (n = 77), children who had a positive bronchodilator response did not have significantly different rates of pain or ACS when compared to children without bronchodilator responsiveness (1.76 vs. 1.43 episodes per patient-year; $P = 0.28$). Among children with lower airway obstruction, 50% (6/12) had a positive bronchodilator response; 9% (1/11) of children with restriction and 15% (8/54) of children with normal lung function had a positive bronchodilator response. No differences in rates of SCD-morbidity exist when the effect of bronchodilator response was examined among children in each group. In the cohort, the mean oxygen saturation levels were not statistically different among children with normal (mean: 96.1%, range: 87–100%), restricted (mean: 97.4%, range: 92–100%) and obstructed (mean: 96.8%, range: 90–100%) lung function ($P = 0.26$).

Pulmonary Function Is Associated With Morbidity in Children With Hemoglobin SS

In a sub-group analysis of children with hemoglobin SS, children with lower airway obstruction had increased rates of pain or ACS (2.84 vs. 1.23 events per patient-year, $P = 0.025$) when compared to children with normal lung function. Pain events were also significantly different in children with HbSS and lower airway obstruction (2.48 vs. 1.03 events per patient-year, $P = 0.04$). Among children with HbSS, ACS rates tended to be higher in children with lower airway obstruction, but did not reach statistical significance (0.36 vs. 0.21 events per patient-year, $P = 0.14$). There were no statistically significant differences for pain or ACS events, pain events, or ACS events when comparing children with restrictive lung disease and normal lung function. A positive bronchodilator response was not associated with increased SCD-related morbidity (1.99 vs. 1.51 events per patient-year, $P = 0.26$) when compared to children with a negative bronchodilator response.

DISCUSSION

In previous studies, our group and others have demonstrated that asthma is associated with an increased rate of pain, ACS, and death when compared to individuals without asthma.[4,6–8,10] We hypothesized that abnormal pulmonary function, restrictive or obstructive, is associated with an increased rate of future hospitalizations for pain or ACS in children with SCD. In this study, we demonstrate that lower airway obstruction is associated with an increased rate of hospitalization for pain or ACS. Data examining the impact of other lung function

abnormalities on SCD morbidity suggest that a restrictive pattern of lung function is not associated with a higher rate of hospitalizations for pain or ACS.

The strong association between lower airway obstruction and pain or ACS rates suggests that children with lower airway obstruction may have ventilation-perfusion mismatch which in turn predisposes to either acute or chronic regional hypoxia that promotes vaso-occlusive pain episodes and ACS. Alternatively, the inflammatory processes present in the airways of children with asthma may accentuate the systemic inflammation in SCD and predispose to increase morbidity. Our secondary analysis examining the impact of pulmonary function on pain rates alone strengthens this association because pain alone avoids a clinical overlap with respiratory symptoms due to asthma and ACS. This is further supported by evidence that in children with asthma and SCD respiratory symptoms are temporally associated with painful episodes.[24] It is important to note that the association of lower airway obstruction and pain persists even among children without asthma. The etiology of lower airway obstruction in the children in the study without asthma is not clear, but it is possible that the children actually had a physiologic process consistent with asthma but had not been diagnosed. This suggests that a clinical diagnosis of asthma alone may not be sufficient to determine who is at risk of increased future morbidity.

A restrictive pattern of lung disease was not associated with future SCD-morbidity in this study. While it may be difficult to determine if the result is a true negative, the point estimate of the rate ratio of hospitalizations for children with restriction compared to children with normal lung function is 1.1 and the confidence interval is relatively narrow (0.6–2.1). When comparing hospital days per year between the groups, the point estimate of the rate ratio was 1.2 and the confidence intervals were also narrow (0.6–2.6). These findings suggest that children with restrictive lung disease do not have a higher rate of sickle cell-related events in the near future, but the impact of restriction on acute morbidity beyond the mean follow-up of ~3.8 years is unclear.

Bronchodilator responsiveness may contribute to air-way limitation and ventilation-perfusion mismatch, but its impact on SCD-morbidity is not demonstrated in this study. Bronchodilator responsiveness evaluation was not completed in all patients in the cohort at the onset of the study period and the analysis does not take into account the effect of current treatment. Further evaluation of airway responsiveness among children with SCD in relation with morbidity is warranted, particularly in light of the reported prevalence in this population.[12,15] Our findings regarding pulse oximetry are consistent with previous reports in the literature which demonstrated that a single daytime pulse oximetry measurement does not predict future morbidity.[25]

Inherent limitations exist in this cohort study. First, the cohort was comprised of a convenience sample of children with SCD who had undergone a lung volume evaluation. Therefore, prevalence estimates cannot be established from this cohort, and the proportion of patients with known lung disease, such as asthma, was greater in the cohort when compared to the general SCD population. Given the high prevalence of asthma in this cohort, children included in the study more likely exhibited clinical symptoms and had some underlying lung disease than children who did not have a pulmonary function evaluation required for inclusion in the analysis. This study, however, compares children with confirmed pulmonary function abnormalities to those with normal pulmonary function as determined by both spirometry and lung volumes. Inclusion of patients with a doctor diagnosis of asthma in the normal pulmonary function group would bias the results towards the null hypothesis. Additionally, some patients without respiratory symptoms were selected for a full pulmonary function evaluation based on a history of multiple pain episodes; this would also suggest that patients classified as normal

were sicker than the larger sickle cell population and would bias the results toward the null hypothesis.

The second major limitation of this study is the cross-sectional assessment of pulmonary function tests in the children included in this study. Given the episodic nature of asthma, some children may have episodic lower airway obstruction that is not captured in this study. Additionally, children may have developed an abnormality in lung function after the index pulmonary function evaluation, which could potentially impact future rates of pain and hospitalization. Unfortunately, this cannot be accounted for in this study. The findings of this study suggest that even a single assessment of lung function in a child can identify pulmonary function abnormalities that significantly impact the risk for subsequent SCD-related morbidity.

In conclusion, lower airway obstruction in children with SCD is associated with increased rates of pain or ACS. Lower airway obstruction is often associated with asthma and both are common among children with SCD. Current therapy guidelines exist for treating asthma and improving lower airway obstruction; appropriate management may impact future morbidity. Additionally, some children in the cohort without a doctor diagnosis of asthma were identified as having lower airway obstruction by pulmonary function testing. It may be that some of these children have asthma that has been unrecognized, but there may be other reasons for development of lower airway obstruction in children with SCD. Treatment of lower airway obstruction in the absence of asthma has not been evaluated. These results suggest that even children without a diagnosis of asthma should be evaluated for pulmonary function abnormalities and that children with lower airway obstruction should be more closely evaluated for the presence of asthma symptoms. Further research in an unselected population with a longitudinal assessment of lung disease is warranted to elucidate risk factors for abnormal lung function and to determine the temporal relationships between lung disease and recurrent events.

Acknowledgments

This work was supported in part by the National Institutes of Health, National Heart, Lung and Blood Institute, contract N01-HB-47110, RO1 HL079937 (M.R.D., R.C.S.), T32 HL07873 (J.H.B.)

REFERENCES

1. Castro O, Brambilla DJ, Thorington B, Reindorf CA, Scott RB, Gillette P, Vera JC, Levy PS. The acute chest syndrome in sickle cell disease: incidence and risk factors. The cooperative study of sickle cell disease. Blood 1994;84:643–649. [PubMed: 7517723]
2. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg M, Klug P. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994;330:1639–1644. [PubMed: 7993409]
3. 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. [PubMed: 3336282]
4. Boyd JH, Moinuddin A, Strunk RC, DeBaun MR. Asthma and acute chest in sickle-cell disease. Pediatr Pulmonol 2004;38:229–232. [PubMed: 15274102]
5. 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. [PubMed: 16556694]
6. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. Blood 2006;108:2923–2927. [PubMed: 16690969]
7. Nordness ME, Lynn J, Zacharisen MC, Scott PJ, Kelly KJ. Asthma is a risk factor for acute chest syndrome and cerebral vascular accidents in children with sickle cell disease. Clin Mol Allergy 2005;3:2. [PubMed: 15663785]
8. Knight-Madden JM, Forrester TS, Lewis NA, Greenough A. Asthma in children with sickle cell disease and its association with acute chest syndrome. Thorax 2005;60:206–210. [PubMed: 15741436]

9. Sylvester KP, Patey RA, Broughton S, Rafferty GF, Rees D, Thein SL, Greenough A. Temporal relationship of asthma to acute chest syndrome in sickle cell disease. Pediatr Pulmonol 2007;42:103–106. [PubMed: 17186507]
10. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with increased mortality in individuals with sickle cell anemia. Haematologica 2007;92:1115–1118. [PubMed: 17650441]
11. National Heart L, and Blood Institute. , editor. National Institutes of Health. National asthma education and prevention program. Expert panel report 2: guidelines for the diagnosis and management of asthma. 1997.
12. 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. [PubMed: 11174615]
13. Ozbek OY, Malbora B, Sen N, Yazici AC, Ozyurek E, Ozbek N. Airway hyperreactivity detected by methacholine challenge in children with sickle cell disease. Pediatr Pulmonol 2007;42:1187–1192. [PubMed: 17960821]
14. Strunk RC, Brown MS, Boyd JH, Bates P, Field JJ, DeBaun MR. Methacholine challenge in children with sickle cell disease: a case series. Pediatr Pulmonol 2008;43:924–929. [PubMed: 18671275]
15. Leong MA, Dampier C, Varlotta L, Allen JL. Airway hyper-reactivity in children with sickle cell disease. J Pediatr 1997;131:278–283. [PubMed: 9290616]
16. 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. [PubMed: 9864008]
17. Pianosi P, D'Souza JA, Charge TD, Esseltine DE, Coates AL. Pulmonary function abnormalities in childhood sickle cell disease. J Pediatr 1993;122:366–371. [PubMed: 8441089]
18. 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. [PubMed: 14694252]
19. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltimore) 2005;84:363–376. [PubMed: 16267411]
20. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–338. [PubMed: 16055882]
21. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CP, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511–522. [PubMed: 16135736]
22. Zapletal A, Samanek M, Paul T. Lung function in children and adolescents: methods, reference values. Prog Respir Res 1987;22:114–218.
23. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG Jr. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol 1993;15:75–88. [PubMed: 8474788]
24. Glassberg J, Spivey JF, Strunk R, Boslaugh S, DeBaun MR. Painful episodes in children with sickle cell disease and asthma are temporally associated with respiratory symptoms. J Pediatr Hematol Oncol 2006;28:481–485. [PubMed: 16912587]
25. Uong EC, Boyd JH, DeBaun MR. Daytime pulse oximeter measurements do not predict incidence of pain and acute chest syndrome episodes in sickle cell anemia. J Pediatr 2006;149:707–709. [PubMed: 17095349]

TABLE 1

Demographic and Characteristics of Pulmonary Function in Children with Sickle Cell Disease With Normal, Restricted, or Obstructed Pulmonary Function

	In all subjects		
	Normal (n = 77)	**Restrictive (n = 13)**	**Obstructive (n = 13)**
Mean age at PFT (years)	11.9	12.4	12.9
Mean follow-up (years)	3.7, Median = 3.1 (0.8–9.6)	3.8, Median = 3.0 (0.6–7.9)	3.9, Median = 2.6 (1.8–8.0)
Male (%)	44.2%	53.8%	38.5%
Hemoglobin SS (%)	77.6%	58.3%	61.5%
FEV_1/FVC (%)	88.7	88.3	75.2
FEV_1 (percent predicted)	92.1	68.5	72.1
FVC (percent predicted)	91.3	66.6	84.2
TLC (percent predicted)	95.5	72.6	94.8
Asthma diagnosis (%)	53.2%	38.5%	76.9%

FEV_1/FVC, forced expiratory volume in 1 sec/ forced vital capacity; FEV_1, forced expiratory volume in 1 sec; TLC, total lung capacity.

TABLE 2

Comparison of Event Rates for Sickle Cell Disease (SCD) Hospitalizations, Length of Stay, and Hematologic Variables for Children SCD With Abnormal, Pulmonary Function Abnormalities When Compared to Children With Normal Pulmonary Function, Detected From a Cross-Sectional Assessment

	In all subjects		
	Normal (n = 77) (95% CI)	**Restrictive (n = 13) (95% CI)**	**Obstructive (n = 13) (95% CI)**
Rate of pain or ACS (events per patient-year)	1.23 (0.0–3.3)	1.32 (0.69–2.56), *P* = 0.82	2.5 (1.5–3.9), *P* = 0.025
Pain rate (events per patient-year)	1.02	1.08, *P* = 0.88	2.20, *P* = 0.027
ACS rate (events per patient-year)	0.21	0.23, *P* = 0.78	0.28, *P* = 0.40
Length of stay (hospital days per patient-year)	6.2 (1.3–11.1)	7.5 (3.5–16.2), *P* = 0.92	17.9 (10.5–30.7), *P* = 0.007
White blood cell count (k/mm^3)	11.8	13.0	11.1
Hemoglobin (g/dl)	8.4	8.6	8.7
Fetal hemoglobin (%)	5.9	5.6	4.4

Using the poisson model with deviance scale adjustment and negative binomial (NB) method for the incidence estimation and comparison test, using normal group as the reference group.