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Progression and Prognostic Indicators of Bronchial Disease in Children with Sickle Cell Disease

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Abstract

Purpose The pulmonary complications of sickle cell disease (SCD) are a leading cause of morbidity and mortality (MacLean et al. *Am J Respir Crit Care Med* 178:1055–1059, 2008; Klings et al. *Am J Respir Crit Care Med* 173:1264–1269, 2006; National Heart, Lung, and Blood Institute, 2009). Despite this recognition, predictive markers of lung dysfunction progression remain elusive (Klings et al. *Am J Respir Crit Care Med* 173:1264–1269, 2006; Platt et al. *N Engl J Med* 330:1639–1644, 1994; Caboot et al. *Curr Opin Pediatr* 20:279–287, 2008; Field et al. *Am J Hematol* 83:574–576, 2008; Shirlo et al. *Pediatr Respir Review* 12:78–82, 2011). This study was designed describe the longitudinal progression and identify specific markers that influence bronchial disease in SCD. **Methods** A retrospective, chart review of 89 patients with SCD was conducted. All patients underwent spirometry in conjunction with body plethysmography as part of routine care. Eleven lung function variables were assessed, five of

which were selected to establish patterns of normal, obstructive, restrictive, or mixed obstructive-restrictive physiology (Klings et al. *Am J Respir Crit Care Med* 173:1264–1269, 2006; Field et al. *Am J Hematol* 83:574–576, 2008).

Results In the unadjusted model, forced expiratory volume in one second (FEV1)% of predicted trended downward with age, while total lung capacity (TLC)% of predicted showed a bimodal distribution and carbon monoxide diffusion capacity corrected for hemoglobin (DLCO_{cor})% of predicted remained stable. Adjusting for acute chest syndrome (ACS) episodes, medication status, and growth velocity (GV), the final model demonstrated that the downward trend between FEV1% of predicted with age was further influenced by the latter two factors.

Conclusions Initial decline in FEV1% of predicted is associated with worsening pulmonary dysfunction over time. Independent of ACS episodes, the factors most influential on the progression of FEV1% predicted include the introduction of medications as well as the promotion of adequate prepubertal growth. Efforts to ensure normal prepubertal GV and treatment with bronchodilators, such as short-acting beta₂ agonists and inhaled corticosteroids (ICS), should be considered at an early age to delay progression of pulmonary dysfunction.

Keywords Sickle cell disease · Pulmonary function testing · Inhaled corticosteroids · Acute chest syndrome

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Abbreviations

ACS	Acute chest syndrome
ATS	American Thoracic Society
DLCO	Carbon monoxide diffusion capacity
DLCO _{cor}	Carbon monoxide diffusion capacity corrected for hemoglobin

DL/VA	Diffusion capacity corrected for alveolar volume
FEF25-75	Forced expiratory flow between 25 and 75 percent of forced vital capacity
FEV1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
GV	Growth velocity
HbSS	Homozygous inheritance of hemoglobin S in sickle cell disease
ICS	Inhaled corticosteroids
MCH	Miller Children's Hospital
MGC	Medgraphics Cardiopulmonary Diagnostics
PH	Pulmonary hypertension
RV	Residual volume
SCD	Sickle cell disease
SCLD	Sickle cell lung disease
TLC	Total lung capacity
VA	Alveolar volume
VOC	Vaso-occlusive crisis
WHO	World Health Organization

Introduction

Sickle cell disease (SCD) is a group of genetic disorders identified primarily by homozygosity of hemoglobin S (HbSS) [1–3]. SCD affects approximately 70,000–100,000 people within the United States [3]. SCD life expectancy has doubled since 1972 with advances, including transfusion protocols and administration of hydroxyurea [3]. However, pulmonary complications, including pulmonary hypertension (PH), acute chest syndrome (ACS), and sickle cell chronic lung disease (SCLD), remain a leading cause of morbidity and mortality in adults [4–11].

Several studies characterize SCD lung manifestations [5, 6, 8–11]. The presence of a restrictive lung pattern have been reported in adults [2, 6, 12–16]. An obstructive pattern has been reported in pediatric studies, with increased prevalence over time approximating a 3 % loss in forced expiratory volume in one second (FEV1)% of predicted/year [7]. Together, the data suggest SCD lung disease progresses from airway obstruction to a restrictive pattern of impairment. Nevertheless, there is a paucity of studies that measure and correlate lung function in children with adult lung disease morbidity and mortality. Consequently, the underlying mechanisms of lung physiology and disease progression are not completely understood [2, 6, 7].

There also are limited data on the prevalence of asthma in SCD children and the role of respiratory medications, including bronchodilators, such as short-acting beta₂

agonists (i.e., albuterol) and inhaled corticosteroids (ICS) on SCD-related pulmonary complications. Subsequently, the clinical utility of lung function testing for directing therapy and the utility of respiratory medications are unclear [2, 6, 7].

Our study primarily was designed to describe the longitudinal progression of pulmonary dysfunction from 6–20 years of age, with particular focus on bronchial disease as manifested by FEV1% of predicted. The trends for 11 lung function variables, including the percent predicted and actual values of FEV1, forced vital capacity (FVC), FEV1/FVC, forced expiratory flow between 25 and 75 percent of FVC (FEF25-75), total lung capacity (TLC), residual volume (RV), RV/TLC, carbon monoxide diffusion capacity corrected for hemoglobin (DLCO_{cor}), alveolar volume (VA), diffusion capacity corrected for alveolar volume (DL/VA), and functional residual capacity (FRC) were all assessed with age. Additionally, a subset of variables inclusive of FVC% of predicted, FEV1% of predicted, FEV1/FVC, TLC% of predicted, and DLCO_{cor}% of predicted were selected based on the American Thoracic Society (ATS) criteria to define pulmonary function status of normal, obstructive, restrictive, or mixed obstructive-restrictive physiology [2, 17, 18].

We also sought to identify characteristics that may independently predict or influence the relationship between lung function variables and bronchial disease progression. Delineating the course of pulmonary dysfunction and identifying other markers of airway disease may allow for earlier intervention to prevent poor pulmonary status in adulthood.

Methods

A retrospective cohort study initially of 93 pediatric patients with SCD who completed lung function testing at Miller Children's Hospital (MCH) was conducted. The institutional review board at MCH approved the study protocol. Written consent was not obtained as part of this study, because all data collected were part of standard medical care.

All patients between the ages of 6 to 20 years at first recorded visit to MCH outpatient Sickle Cell Clinic from 1993–2011, diagnosed with SCD and with lung function measurements recorded for at least two clinical visits, were eligible for inclusion in this study. Nearly all study patients were African American, with exception of four Hispanic children who were then excluded from analysis due to potential influence of race and limited sample size to power examination of this factor in the analysis (final sample size = 89).

Table 1 Patient characteristics

Variable	Patients baseline <i>N</i> = 89
Male (%)	55.1
Age, year (range 6–18 at baseline)	8.2 ± 2.79
Weight (kg)	31.11 ± 12.36
Height (cm)	131.54 ± 15.2
Stature percentile <25th	18.2 %
BMI	17.31 ± 3.13
BMI percentile ≥85th (at risk or overweight ^a)	15.7 %
History of ACS (before baseline visit)	38.2 %
Episode of ACS (ever) thru end of follow-up	48.3 %
History of VOC (prior to baseline visit)	80.9 %
Episode of VOC (ever) thru end of follow-up	95.5 %
Diagnosis of asthma	35.9 %
Smoking history	2.2 %
Smoking exposure	19.1 %
On transfusion protocol	15.7 %
Medication	
None	43.8 %
Hydroxyurea	24.7 %
Albuterol ± ICS	15.7 %
Both (hydroxyurea and albuterol ± ICS)	15.7 %
On medication (ever) thru end of follow-up	63.1 %
On medication and diagnosis of asthma	12.3 %

Distribution of continuous variables presented as mean ± SD

^a In patients ≥20 years of age, at risk or overweight based on CDC criteria of BMI ≥25 defined as overweight or obese

Lung function testing was performed and best maximal effort selected according to ATS criteria [17, 18]. Maximal expiratory flow-volume loops were measured and at least three reproducible maneuvers were performed with each test, with the best results reported. Lung volumes were measured by whole body plethysmography and variables included the percent predicted and actual values of FEV1, FVC, FEV1/FVC, FEF25-75, TLC, RV, RV/TLC, DLCOcor, VA, DL/VA, and FRC. Testing was completed using Medgraphics Cardiopulmonary (MGC) Diagnostics (Medgraphics, St. Paul, MN).

Values for FVC, FEV1, FEF25-75, VC, TLC, RV, VA, DLCOcor, and FRC were expressed as percentage of the predicted values based on normal values. The values were adjusted for African Americans according to Morrison–Polgar equations and adjusted for height. The absolute carbon monoxide diffusion capacity (DLCO) was first corrected for the hemoglobin value, obtained within a three month period to the lung function testing and was reported as DLCOcor and then normalized for VA (DL/VA) [17–20].

Information regarding episodes of vaso-occlusive crisis (VOC) and of ACS was obtained. ACS was defined by

fever, respiratory distress, and radiographic findings consistent with pulmonary infiltrates [6, 21]. The diagnosis of VOC was based on the onset of pain unexplained by injury or infection [6, 21]. In addition, each chart was reviewed for recording of the following: age, sex, race, height, medications, and diagnosis of asthma. Growth velocity (GV) at each age was determined based on World Health Organization (WHO) stature percentile and trajectory that matched their growth from age at prior visit and defined by six categories: 1) baseline visit stature ≥25th %; 2) baseline visit stature <25th %, and at follow-up when GV from prior visit determinable: 3) GV ≥5th % trajectory, stature ≥25th %, 4) GV ≥5th % trajectory, stature <25th %, 5) GV <5th % trajectory, stature <25th %, 6) GV <5th % trajectory, stature <25th. [22]

Statistical Analysis

Patient characteristics in our study population were described in terms of valid percent of patients with defined trait for categorical variables and as average (mean, standard deviation [SD]) observed in population for continuous variables (Table 1). The pattern of each continuous factor (lung function variables and BMI) with age (linear, quadratic, or bimodal) was assessed by mixed effects modeling (PROC MIXED in SAS 9.2). Restricted maximum likelihood estimation was applied and first-order autoregressive correlation structure assumed, which indicates two observations taken close in time within an individual tend to be more highly correlated than two observations taken far apart.

Multivariable analyses using stepwise forward selection identified the combination of factors with consideration to age dependencies and potential interaction effects that influence the course of FEV1% of predicted across time (age, years). LSmeans function was utilized in the final predictive model to assess differentials in average FEV1% of predicted for specified pulmonary function status and patient characteristics in order to identify prognostic indicators of worsening disease. Influential lung function variables were evaluated in range signifying normal lung function, which was the pattern observed most often in our population with respect to significant predictors (e.g., FVC% of predicted ≥80 %, FEV1/FVC ≥70 %, and TLC% ≥80 % of predicted) and restrictive lung physiology (e.g., FVC% of predicted <80 %, FEV1/FVC ≥70 %, and TLC% <80 % of predicted) [2]. Specifically, normal lung function values were defined by using the OM option as average values followed a normal course in study population (coefficients proportional to those found in the input data set ~ outcome evaluated under assumed distribution of patient characteristics). Analyses were performed using SAS v9.2.

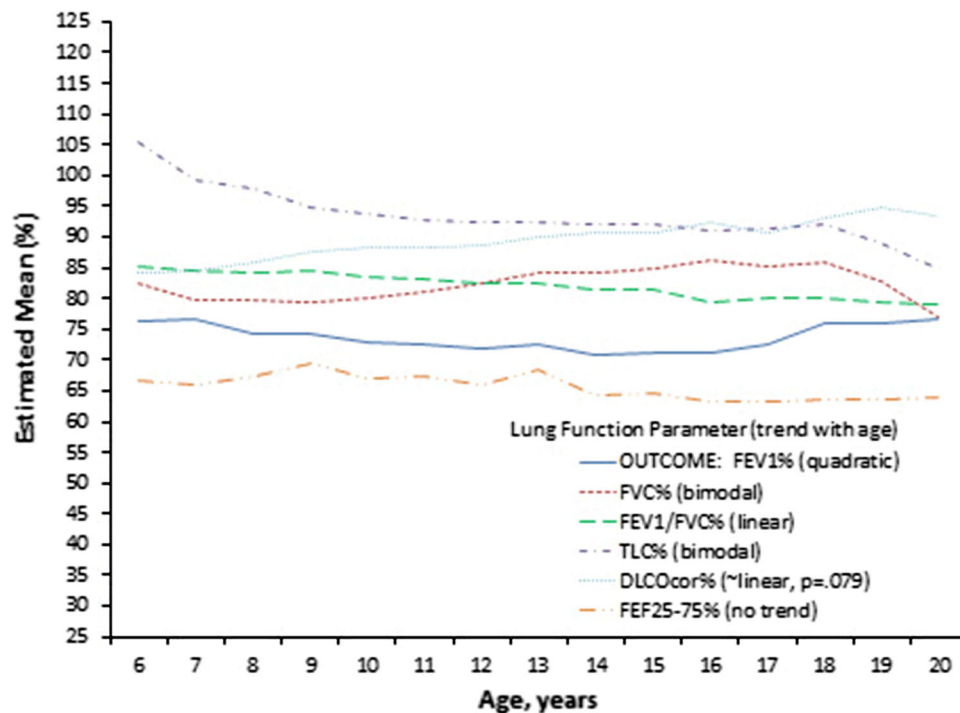


Fig. 1 Trend of each lung function variable with age, unadjusted for other factors

Results

Study Population

Patient age at entry averaged 8.2 years (SD = 2.8), Table 1. Male patients accounted for 55.1 % and average BMI at baseline was 17.3 (SD = 3.1). Before baseline, 38 % of patients had a history of ACS, which increased to 48 % when evaluated through the last visit. Approximately 63.1 % of patients were on therapy during one or more annual cycles. Two patients were self identified as smokers and 17 other patients where smoking exposure was documented in the medical chart. Of the 89 patients included in the study, 35.9 % had a diagnosis of asthma. Of 32 patients identified as asthmatics, 17 had a documented bronchodilator response.

Longitudinal Pattern of Lung Function

Figure 1 displays the trend of each lung function variable with age, unadjusted for other factors. Average FEV1% of predicted trended below normal and typically in range of 70–79 % across time with lowest levels observed around early adolescence (11–13 years of age). FVC% of predicted and TLC% of predicted followed a bimodal distribution with higher average levels observed in early childhood (6–7 years of age) and late adolescence (15–18 years of age). FEV1/FVC, FRC% of predicted, and

RV/TLC trended downward with age, whereas average DLCOcor% of predicted and FEF25-75% of predicted remained fairly stable across time.

Figure 2A displays longitudinal pattern of normal versus abnormal lung function. Figure 2B displays further subdivision of the longitudinal pattern of pulmonary physiology in terms of restrictive, obstructive, mixed obstructive-restrictive, or variations of normal. Restrictive physiology was rare in the first decade of life with slightly increased percent of visits classified as restrictive during the second decade of life. Obstructive physiology was rare in patients during early childhood and again rarely observed during adolescence.

Characteristics Influencing Longitudinal Pattern of FEV1% of Predicted

Table 2 shows the relationship between patient characteristics and FEV1% of predicted across time (age, years). In patients whose stature was in the lower 25th percentile, average FEV1% of predicted was 6.13 percentage points lower (standard error [SE] = 2.17) when their GV followed a normal trajectory ($p = 0.005$). Medication status showed an age dependent relationship to FEV1% of predicted ($p \leq 0.05$). Unadjusted for other factors, patients who were treated versus nontreated had lower average FEV1% of predicted during early childhood (6–7 years of

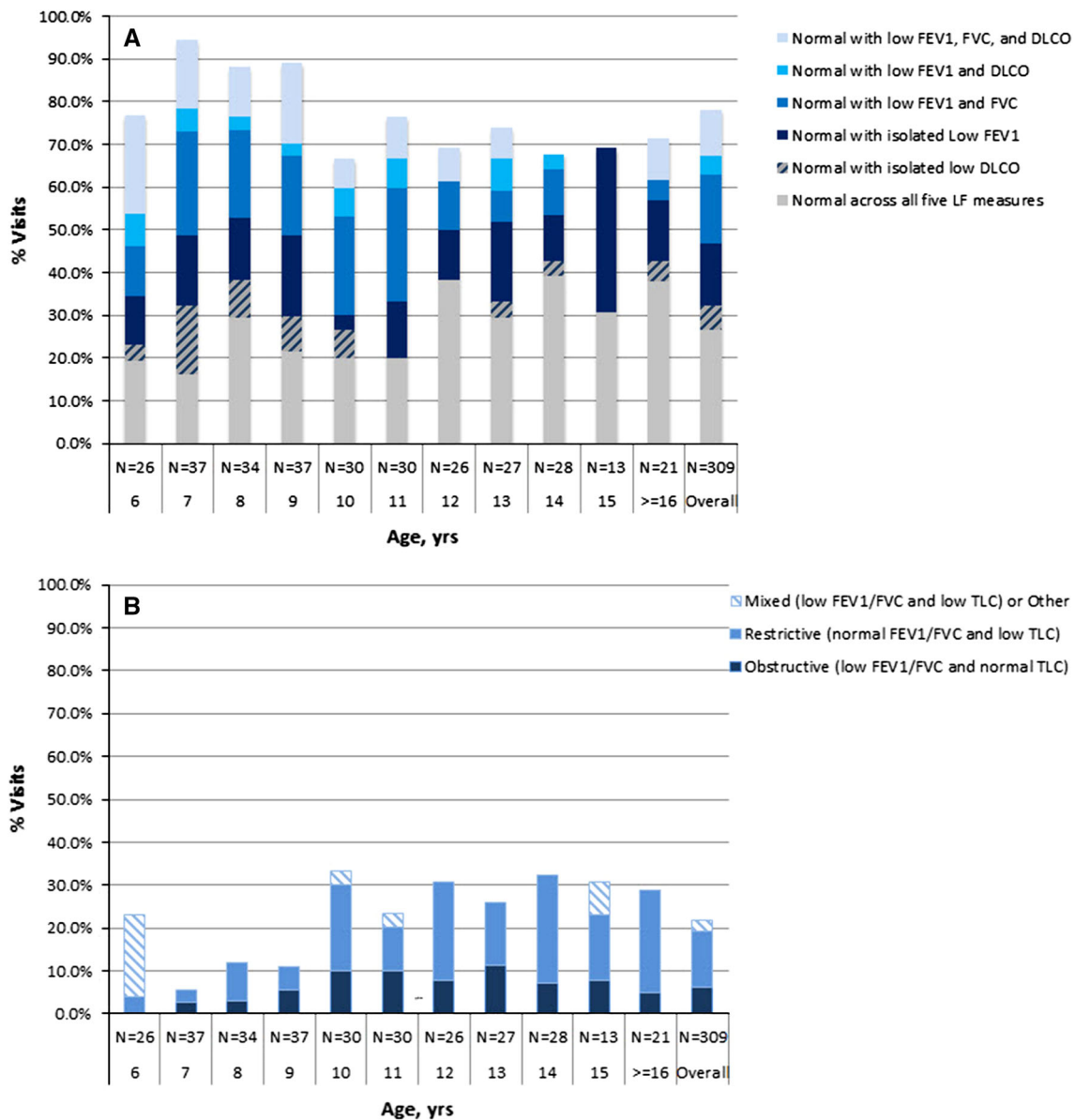


Fig. 2 a Longitudinal pattern of normal versus abnormal lung function. **b** Subdivision of the longitudinal pattern of pulmonary physiology in terms of restrictive, obstructive, mixed obstructive-restrictive or variations of normal

age) and in late adolescence when the differential reached significance after 16 years of age ($p \leq 0.05$).

In the final adjusted model, patient characteristics influencing FEV1% of predicted included ACS history prior to visit, medication status, and GV. All lung function variables with exception of DLCOcor% of predicted showed an age dependent association with FEV1% of predicted in the adjusted model. Effect estimates for each contributing patient characteristics were evaluated under the assumption of normal and restrictive physiology in the final adjusted model. When lung function fell in the normal range, ACS history differentials in average FEV1% of predicted were not observed ($p > 0.05$).

Influence of medication status on average FEV1% of predicted also was associated with FVC% of predicted, VA% of predicted, and additionally on FEF25-75% of predicted and RV/TLC. Compared with nontreated patients, patients who were treated showed higher average FEV1% of predicted, which was more pronounced when restrictive pattern of impairment was additionally present. This effect reached significance under the scenario FVC <74 % of predicted and VA ≥ 80 % of predicted (effect size = 1.16 (SE = 0.53) percentage points higher in treated versus nontreated patients, $p = 0.048$). The observed beneficial effect of medication in patients with restrictive physiology diminished with decreased VA% of predicted.

Table 2 Impact of each characteristic on lung function (FEV1% predicted) trajectory across time (age, years), unadjusted for other factors ($N = 89$ patients, $N = 309$ visits)

Factors	Effect size (SE) ^d	<i>p</i> value
Male versus female	2.59 (2.32)	0.268
Factors measured at each time point		
Growth velocity ^a		0.045
1 = Baseline stature ≥ 25 %	-2.54 (2.33)	0.279
2 = Baseline stature < 25 %	-1.18 (3.08)	0.702
3 = Fup: GV ≥ 5 % trajectory for height, stature ≥ 25 %	-3.28 (2.2)	0.138
4 = Fup: GV ≥ 5 % trajectory for height, stature < 25 %	-6.13 (2.17)	0.005
5 = Fup: GV < 5 % trajectory for height, stature ≥ 25 %	-0.49 (2.23)	0.826
6 = Fup: GV < 5 % trajectory for height, stature < 25 %	Reference	
BMI (per 1 unit increase) ^b	0.66 (0.27)	0.014
BMI percentile ≥ 85 th versus BMI < 85 %	1.25 (2.01)	0.542
ACS history (no vs. yes)	1.2 (2.15)	0.59
VOC history (no vs. yes)	-3.89 (2.55)	0.153
Off vs. on medication (presented for ages 6–18 years) ^c	(Age dependent trend)	‡
Age 6 years	6.93 (3.78)	0.088
Age 7 years	3.12 (2.83)	0.289
Age 8 years	0.18 (2.37)	0.942
Age 9 years	-1.91 (2.28)	0.417
Age 10 years	-3.12 (2.34)	0.204
Age 11 years	-3.47 (2.39)	0.169
Age 12 years	-2.96 (2.39)	0.236
Age 13 years	-1.58 (2.42)	0.525
Age 14 years	0.66 (2.67)	0.808
Age 15 years	3.77 (3.33)	0.276
Age 16 years	7.74 (4.44)	0.103
Age 17 years	12.58 (5.99)	0.054
Age 18 years	18.28 (7.91)	0.037

Linear and quadratic effects for age included in each model

^a Growth velocity at baseline reflects stature percentile as prior stature unknown to measure growth velocity at that time

^b In patients ≥ 20 years of age, at risk or overweight based on CDC criteria of BMI ≥ 25 defined as overweight or obese

^c On medication in concurrent time period (hydroxyurea and/or albuterol)

^d Estimated average difference in FEV1% predicted between groups at any age (or per 1 unit increase for continuous factors)

‡ Significant age dependency on relationship between factor and FEV1% predicted found ~ model effects: Meds_on ($p = 0.088$), age ($p = 0.003$), age*age ($p = 0.003$), meds_on*age ($p = 0.008$), meds_on*age*age ($p = 0.006$)

In patients with normal lung function, average FEV1% of predicted tended to be higher in nontreated patients, particularly when FVC was ≥ 85 % of predicted. This may reflect disease severity as well as the decision regarding initiation of therapy.

Impact of GV on FEV1% of predicted depended on patient age and FVC% of predicted. Due to multiple comparisons across GV categories, the Tukey–Kramer adjustment was applied in assessment of intercategory differences. Interestingly, average FEV1% of predicted in patients at 8 years of age whose growth trajectory normal

and stature < 25 th percentile was 2.38 points higher (SE = 0.679) than in patients whose growth trajectory delayed and stature ≥ 25 th percentile ($p = 0.008$). These differentials were not detectable by 10 years of age.

We did record the response of airway obstruction to inhaled bronchodilators and observed significant reversibility in approximately 44.9 % of our patient population, of which less than 50 % had a documented diagnosis of asthma. When analyzing the FEV1% of predicted between those who did and did not demonstrate postbronchodilator reversibility, there was no significant difference seen in the

FEV1% of predicted trend. We did however note that the group that demonstrated reversibility had initial lower FEV1% of predicted levels, which averaged around 71 %.

Discussion

Earlier studies emphasize chronic vascular injury and parenchymal disease as an important baseline factor in determining the progression of pulmonary dysfunction in children with SCD [23–26]. However, our study demonstrates earlier signs of bronchial disease and airway obstruction as reflected by declining FEV1% of predicted has a stronger correlation with disease progression. Previously not reported, our study clinically and statistically revealed that FEV1% of predicted was the first parameter to show decline and the only parameter that remained influential across all ages, therefore making it an early and sensitive lung function variable to follow in regards to assessing pulmonary disease severity and further dysfunction.

Prior studies have suggested changes in lung function measurements are an early marker of sickle cell lung disease [1, 12, 27]. Many of these studies showed that unlike a normal nonsmoking individual, where pulmonary function is expected to increase during childhood, in SCD there was a progressive decline in pulmonary function [1, 6, 12, 27]. Our study affirmed this data and showed that average FEV1% of predicted trended below normal with the lowest levels observed during the early adolescent period [1, 2, 6, 12]. This was seen even in the 70 patients where a clearly documented smoking history or exposure was absent and may be a reflection of chronic subclinical inflammation resulting in chronic lung injury. FEV1% of predicted also was the variable serving as the strongest predictive factor for overall lung decline over time once adjusted for ACS episodes, medication status, and GV.

The trend of TLC% of predicted and FRC% of predicted is consistent with previous studies revealing increased prominence of restrictive abnormalities with age [2, 6]. However, although there was an overall shift in prevalence from obstructive physiology in childhood to restrictive physiology in adulthood, our study did not find individualized transition from obstruction to restriction in each SCD patient. Those with a restrictive pattern of impairment either presented with isolated restrictive physiology during childhood or had a mixed obstructive-restrictive physiology, which shifted to a purely restrictive physiology over time. The remaining children showed a pattern that fluctuated between normalcy and obstruction, which may reflect multiple factors, including initiation of medication and GV.

Impact of Medication Status, GV, and ACS

The recognition of bronchial disease and airway inflammation as a key factor in progression of lung disease have been limited [27, 28]. Our study analyzed the impact on FEV1% of predicted by hydroxyurea use alone or in combination with albuterol to promote bronchodilation and ICS to control airway inflammation. At baseline, 43 % of patients did not receive such medications. By the end of the study period included in analysis, 37 % of patients remained untreated. The largest increase in treatment was attributed to the group started on both hematologic and respiratory medications. Studies on SCD children additionally diagnosed with asthma have suggested a beneficial role of treatment with albuterol and ICS [29–35]. In our study, approximately 35.9 % of the study population had a concurrent diagnosis of asthma, but an improvement in FEV1% of predicted was seen in all groups started on medications regardless of a concurrent diagnosis. It is suggestive that ongoing inflammatory processes aside from inflammatory asthma may be responsible for progressive dysfunction and may be solely reflected by abnormalities in pulmonary function testing with specific presentation of declining FEV1% of predicted [35].

Growth may be another factor contributing to pulmonary abnormalities in children with SCD as seen by its impact on FEV1% of predicted trend [36–40]. Our data showed those with delayed GV not only experienced a faster rate of decline in FEV1% of predicted but also were unable to regain the normalcy of lung growth and lung function. Earlier studies attributed this impact to structural changes of the rib cage with data showing that adults with SCD have delayed epiphyseal closure and smaller thoraces [36, 40]. However, our results indicate that aside from thoracic restriction, those with normal GV parameters, particularly during the prepubertal period, have better lung function and slower progression of pulmonary dysfunction.

Lastly, an important factor revealed in our study is that the decline in FEV1% of predicted and subsequently in both TLC% of predicted and FRC% of predicted were independent of ACS episodes. This is contrary to several earlier studies suggesting a link between prior lung injury resulting from ACS episodes and progressive decline in lung function. In our study, no influence by ACS episodes was noted unless VA% of predicted was also previously affected. This was not surprising, because ACS impacts primarily smaller airways and would be expected to present as declining VA% of predicted measurements. However, in the absence of deteriorating VA% of predicted and by extension, recurrent ACS episodes, lung volume, and lung function decline still persisted.

There are a few studies, including Koumbourlis et al., that validate related findings of the presence of abnormal

lung function in infants with SCD long before the onset of ACS episodes [41]. Similarly, no discernible association between lung function and prior ACS episodes existed in adolescents with SCD [42]. A study by Tassel et al. did identify leukocytosis as a risk factor for declining lung volumes [43]. They proposed that the stimulation of the vascular endothelium by leukocytes results in an inflammatory cascade that favors further vessel occlusion. This subclinical obstruction of capillaries mediated by leukocyte overabundance is what leads to the declining lung volumes and the presence of a restrictive physiology [43].

Study Limitations

Our study has several limitations. First, it lacks the validity of a prospective cohort study, because no clear control group was isolated. Nonetheless, few previous studies attempted to analyze comprehensively, isolate, and corroborate a singular lung function parameter over childhood into adulthood in SCD [1, 2, 6]. Second, the ethnic and racial demographics of this study limits extrapolation to other populations. Third, the SCD therapies deployed were not controlled for dosing, commencement of therapy, adherence, adverse effects, or dose adjustment for weight. The authors substantiate that further studies will stem from the novel findings presented, analyzing these parameters of treatment in its effect on lung function in SCD. Lastly, a thorough investigation of smoking history and exposure to smoking and other airborne environmental factors was not performed as part of this initial study. As this is likely an independent contributing factor to lung function decline, data regarding this parameter is being analyzed and included as part of a follow up study currently being conducted on the same patient population.

Conclusions

Our study confirmed previous reports of SCD association with progressive lung function decline [1]. More notably, our study demonstrates that initial decline in FEV1% of predicted is associated with worsening pulmonary status over time. Independent of ACS episodes, the factors most influential on FEV1% of predicted progression include the introduction of medications as well as the promotion of adequate prepubertal growth. Treatment at an early age with evidence of FEV1% of predicted decline, even in the absence of an absolute diagnosis of asthma, may be warranted in attempt to prevent and/or delay pulmonary dysfunction [35]. Future interventional studies should assess potential benefits of these treatment options and employ medical strategies designed to promote growth of children with SCD [40].

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Conflicts of interest None.

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