Abnormal Pulmonary Function in Adults with Sickle Cell Anemia

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Rationale: Pulmonary complications of sickle cell anemia (Hb-SS) commonly cause morbidity, yet few large studies of pulmonary function tests (PFTs) in this population have been reported.

Objectives: PFTs (spirometry, lung volumes, and diffusion capacity for carbon monoxide [DL_{CO}]) from 310 adults with Hb-SS were analyzed to determine the pattern of pulmonary dysfunction and their association with other systemic complications of sickle cell disease.

Methods: Raw PFT data were compared with predicted values. Each subject was subclassified into one of five groups: obstructive physiology, restrictive physiology, mixed obstructive/restrictive physiology, isolated low DL_{CO} , or normal. The association between laboratory data of patients with decreased DL_{CO} or restrictive physiology and those of normal subjects was assessed by multivariate linear regression.

Measurements and Main Results: Normal PFTs were present in only 31 of 310 (10%) patients. Overall, adults with Hb-SS were characterized by decreased total lung capacities ($70.2 \pm 14.7\%$ predicted) and DL_{CO} ($64.5 \pm 19.9\%$). The most common PFT patterns were restrictive physiology (74%) and isolated low DL_{CO} (13%). Decreased DL_{CO} was associated with thrombocytosis ($p = 0.05$), with hepatic dysfunction (elevated alanine aminotransferase; $p = 0.07$), and a trend toward renal dysfunction (elevated blood urea nitrogen and creatinine; $p = 0.05$ and 0.07 , respectively).

Conclusions: Pulmonary function is abnormal in 90% of adult patients with Hb-SS. Common abnormalities include restrictive physiology and decreased DL_{CO} . Decreased DL_{CO} may indicate more severe sickle vasculopathy characterized by impaired hepatic and renal function.

Keywords: airway obstruction; dyspnea; restrictive disease

Sickle cell anemia (Hb-SS) results from homozygosity for a point mutation in the β -globin gene (*HBB*; Glu6Val) causing the resultant sickle hemoglobin (Hb S) to be less soluble when deoxygenated than normal hemoglobin (1). Even with improved treatment, including the early use of prophylactic antibiotic regimens, judicious transfusions, and the administration of hydroxyurea in selected patients, mortality remains high for this population. The median age at death is 42 yr for males and 48 yr for females with Hb-SS. Pulmonary complications, including acute chest syndrome (ACS), pulmonary hypertension (PH), and pulmonary fibrosis, account for 20–30% of deaths in the Hb-SS population and are often underrecognized by the health care community (2, 3).

Dyspnea is a frequent complaint amongst patients with sickle cell disease, the etiology of which is unclear and likely multifactorial (4, 5). Studies of lung function to date in this population have been of modest size, often involving fewer than 50 patients (4, 6–11) and largely inconclusive. Their results have yielded a spectrum of abnormalities, including restrictive lung disease, abnormal diffusion capacity for carbon monoxide (DL_{CO}), obstructive disease, and hypoxemia (4, 6, 7, 9, 12). No definitive profile for pulmonary function in sickle cell disease has emerged. As a result, clinicians find pulmonary function tests (PFTs) difficult to interpret in this population and their clinical utility for directing further investigation and therapy has not been well evaluated.

Of growing concern is the link between obstructive lung disease and ACS, particularly in children (7, 13, 14). The few published studies suggest that obstructive lung disease, in some cases, plays a role in the pathogenesis of ACS (7, 13, 15). Moreover, obstructive lung disease could be a long-term sequela of recurrent episodes of ACS (6, 9). Larger scale studies are necessary to elucidate more clearly the interaction between lung function and ACS. In addition, certain findings on PFTs might be a marker of other complications of sickle vasculopathy. For example, isolated decreased DL_{CO} is a well-established finding associated with PH (16, 17). However, its role as a marker or predictor of PH in the Hb-SS population is unknown. The purpose of this study is to evaluate the relation of the demographic, clinical, and laboratory characteristics to lung function in the sickle cell disease (SCD) population. PFTs were done on subjects recruited as part of the Cooperative Study of Sickle Cell Disease (CSSCD), a cross-sectional epidemiologic study. Some of the results of these studies have been previously presented in the form of an abstract at the American Society of Hematology 47th Annual Meeting (18).

METHODS

Patient Database

PFTs were collected as part of the CSSCD, which enrolled and monitored more than 4,000 patients with SCD evaluated at 1 of 23 participating clinical centers across the United States between 1978 and 1998 (19, 20). One of the primary goals of the CSSCD was to collect data on the clinical course of SCD from birth to death. From the original study population, only the 2,061 (51%) subjects with sickle cell anemia were included in this study. The study population was further limited by inclusion of only those subjects who were African American and over the age of 18 yr. A history of ACS was assessed as part of the original data collection. ACS was defined as (1) a new infiltrate on chest radiograph or (2) pleuritic chest pain and/or dyspnea in addition to an abnormal ventilation-perfusion scan. As part of the standard protocol established by the CSSCD, each subject underwent pulmonary function testing three times to ensure reproducibility. If the results from the three studies differed by more than 2%, the study was considered to be of poor quality. Before entering into the database, all PFTs were reviewed for quality by pulmonologists at either Harlem Hospital (New York, NY) or Howard University Medical Center (Washington, DC) as part of the standard protocol. On our review of the data, we considered data insufficient if the evaluation was considered poor quality or if more than 25% of the data for a subject were missing, suggesting an inability to perform the tests correctly; these cases were subsequently

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removed from our database. Review of these data was approved by the Institutional Review Board of Boston University/Boston Medical Center (Boston, MA).

Pulmonary Function Testing

PFTs were obtained from patients clinically in the steady state (at least 4 wk after a vasoocclusive crisis). Each subject underwent spirometry (FVC, FEV₁, and FEV₁/FVC), lung volumes (total lung capacity [TLC] and residual volume [RV]), and DL_{CO} according to the standard protocols employed by each of the 23 centers of the CSSCD. DL_{CO} values were corrected for the serum hemoglobin concentration obtained at the time of PFT testing, using previously published formulas (21). They were not corrected for alveolar volumes as these data were not available. Predicted values for FEV₁, FVC, FEV₁/FVC, TLC, RV, and DL_{CO} were calculated on the basis of algorithms that accounted for sex, age, and height in the African American population (STATA, version 9; Stata-Corp, College Station, TX); data are presented as percent predicted values (22–24).

Classification of Pulmonary Function

The pulmonary function of each subject was classified into one of five categories based on American Thoracic Society criteria (25). The five categories were as follows: (1) normal, (2) obstructive, (3) restrictive, (4) mixed obstructive and restrictive, and (5) isolated low DL_{CO}, based on the following criteria:

1. Normal: FEV₁, FVC, TLC, RV, and DL_{CO} within the normal range (at least 80% predicted) with FEV₁/FVC at least 70%
2. Obstructive: An FEV₁/FVC ratio less than 70%, associated with decreased FEV₁ and FVC (less than 80% predicted). TLC and RV either normal or elevated (at least 120% predicted). DL_{CO} normal (at least 80% predicted)
3. Restrictive: (1) FEV₁, FVC, and TLC decreased (no more than 80% predicted) with normal FEV₁/FVC ratio (at least 70%) and a decrease in DL_{CO} (no more than 80% predicted) or (2) TLC and RV decreased (no more than 80% predicted) with normal DL_{CO}, FEV₁, FVC, and FEV₁/FVC, suggestive of low lung volumes, or (3) reduced TLC and DL_{CO}
4. Mixed obstructive and restrictive: FEV₁/FVC ratio reduced, suggestive of obstructive disease. TLC and RV reduced, suggestive of restrictive disease. DL_{CO} normal
5. Isolated low DL_{CO}: DL_{CO} decreased with normal FEV₁, FVC, FEV₁/FVC, TLC, and RV

Statistical Analysis

Sociodemographic and laboratory measures are presented as means $\pm$ SD. PFT data are presented as means $\pm$ SD, and medians according to their percent predicted values. The association of selected laboratory measures was determined by comparing those patients with isolated low DL_{CO} and restrictive disease with those patients with normal DL_{CO} measures and normal PFTs, respectively. Analysis of variance was used to calculate both the unadjusted and age-adjusted means for each laboratory measure and these means were compared using an F test (SAS software, version 8.2; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 310 adult subjects were eligible for this study after subjects who were not African American, not homozygous for Hb S, and without complete PFTs were excluded. The average age of the subjects was 30.7 $\pm$ 10.3 yr (range, 20–67 yr) and 41% were males (Table 1). Subjects had a normal body habitus as reflected by a body mass index of 21.3 $\pm$ 4.2 kg/m². ACS was common in this population, with 37% of subjects reporting a history of ACS before enrollment in the study and an additional 38% reported an incident episode during the follow-up period.

TABLE 1. PATIENT CHARACTERISTICS

	All Patients (n = 310)
Clinical and demographic characteristics	
Age, yr	30.72 $\pm$ 10.34
Males, %	41
Height, cm	170.07 $\pm$ 9.56
Weight, kg	61.28 $\pm$ 12.20
BMI	21.25 $\pm$ 4.22
History of ACS, %	37
Episode of ACS during study, %	38
ACS episodes during study	2.48 $\pm$ 1.23
History of chronic transfusions, %	17
Summary of laboratory values	
WBC, cells/L/mm ³	11.75 $\pm$ 2.64
Hb, g/dl	8.25 $\pm$ 1.44
Platelet count, $\times$ 100,000/ml	410.96 $\pm$ 113.46
Hematocrit, %	24.76 $\pm$ 3.91
BUN, mg/dl	10.00 $\pm$ 6.63
Creatinine, mg/dl	0.87 $\pm$ 0.60
LDH, U/L	497.39 $\pm$ 166.67
Bilirubin, mg/dl	3.62 $\pm$ 2.13
AST, U/L	47.24 $\pm$ 23.93
ALT, U/L	44.90 $\pm$ 52.31

Definitions of abbreviations: ACS = acute chest syndrome; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; Hb = hemoglobin; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; WBC = white blood cell count.

Values represent means $\pm$ SD unless indicated otherwise.

Laboratory Values

The hematologic profile of the subjects was reflective of adults with Hb-SS (Table 1). Anemia (Hb, 8.25 $\pm$ 1.44 g/dl), leukocytosis (white blood cell count [WBC], 11.75 $\pm$ 2.64 cells/L/mm³), and thrombocytosis [platelet count, 410.96 ($\pm$ 113.46) $\times$ 10⁵/ml] were present. There was evidence of ongoing hemolysis characterized by an elevation in lactate dehydrogenase (497.39 $\pm$ 166.67 U/L; normal, 100–250 U/L), aspartate aminotransferase (47.24 $\pm$ 23.93 U/L; normal, 5–40 U/L), and bilirubin (3.62 $\pm$ 2.13 mg/dl; normal, 0.3–1.2 mg/dl) concentrations (26). There was a mild elevation of the hepatic enzyme alanine aminotransferase (ALT, 44.90 $\pm$ 52.31 U/L). Renal function as assessed by serum creatinine concentration was within normal laboratory ranges in this population; however, creatinine is now known to be an insensitive measure of glomerular filtration rate in Hb-SS (27).

Pulmonary Function in Patients with Hb-SS

Abnormal pulmonary function was observed in 90% (279 of 310) of the subjects (Table 2). Overall, the population was characterized by restrictive physiology with decreased TLC (70.20 $\pm$ 14.69% predicted) and DL_{CO} (56.57 $\pm$ 20.11%). Although the spirometry was technically within the normal range, the means for FEV₁ (83.03 $\pm$ 16.06% predicted) and FVC (84.37 $\pm$ 16.01% predicted) were considered to be low-normal, with an FEV₁/FVC of 98.36 $\pm$ 9.15%. The decreased DL_{CO} persisted after adjustment for the patients' hemoglobin concentration (64.54 $\pm$ 19.93% predicted). Subcategorization of the patients revealed that the most common PFT abnormalities observed were restrictive disease (74%) and isolated low DL_{CO} (13%). Obstructive disease, either alone or in conjunction with restrictive disease, was relatively uncommon, occurring in 3% of the patients.

Effect of ACS on Lung Function

Two hundred and twenty-one of the 310 subjects (71.3%) had at least one episode of ACS before obtaining pulmonary function studies (Table 3). Overall, this group was characterized by a

TABLE 2. SUMMARY OF PULMONARY FUNCTION TEST RESULTS

	All Patients (n = 310)
Summary of PFT results	
FEV ₁	
Median	82.80
Mean ± SD	83.03 ± 16.06
FVC	
Median	83.62
Mean ± SD	84.37 ± 16.01
FEV ₁ /FVC, %	
Median	98.61
Mean ± SD	98.36 ± 9.15
TLC	
Median	69.79
Mean ± SD	70.20 ± 14.69
RV	
Median	78.04
Mean ± SD	88.60 ± 60.88
DL _{CO}	
Median	53.74
Mean ± SD	56.57 ± 20.11
Adjusted DL _{CO} *	
Median	61.74
Mean ± SD	64.54 ± 19.93
Subclassification based on PFTs	
Normal, n (%)	31 (10)
Isolated low DL _{CO} , n (%)	40 (13)
Mixed O/R, n (%)	5 (2)
Obstructive, n (%)	4 (1)
Restrictive, n (%)	230 (74)

Definition of abbreviations: DL_{CO} = diffusion capacity for carbon monoxide; O/R = obstructive/restrictive; PFT = pulmonary function test; RV = residual volume; TLC = total lung capacity.

* Adjusted for hemoglobin concentration.

trend toward lower TLC (69.17 vs. 72.83%; $p = 0.06$) and adjusted DL_{CO} (63.32 vs. 67.81%; $p = 0.10$) compared with those without a history of ACS. The patterns of pulmonary function abnormalities observed in those with a history of ACS were similar to those without a history of ACS with restrictive disease and an abnormal diffusion capacity predominating.

Decreased DL_{CO} Is Associated with Increasing Age

As our population did not have a predominance of obstructive disease as observed in other studies of the pediatric population

TABLE 3. COMPARISON OF PULMONARY FUNCTION TEST RESULTS ACCORDING TO HISTORY OF ACUTE TEST SYNDROME

	History of ACS (n = 221)	No History of ACS (n = 89)	p Value
PFT results*			
TLC, %	69.17 ± 1.01	72.83 ± 1.62	0.06
DL _{CO} , %	55.32 ± 1.43	59.94 ± 2.36	0.10
Adjusted DL _{CO} , %	63.32 ± 1.43	67.81 ± 2.34	0.10
Subclassification based on PFTs			
Normal, n (%)	20 (9)	11 (12)	(0.6073)
Isolated low DL _{CO} , n (%)	27 (12)	13 (15)	
Mixed O/R, n (%)	3 (1)	2 (2)	
Obstructive, n (%)	2 (1)	2 (2)	
Restrictive, n (%)	169 (77)	61 (69)	

Definition of abbreviations: ACS = acute chest syndrome; DL_{CO} = diffusion capacity for carbon monoxide; O/R = obstructive/restrictive; PFT = pulmonary function test; TLC = total lung capacity.

* PFT results are presented as means ± SD.

(7, 13–15), we evaluated the effects of age on TLC and DL_{CO} (Figure 1). Interestingly, a negative linear correlation existed between DL_{CO} and age, suggesting that in adults with Hb-SS, disruption of alveolar–capillary gas exchange may be a potential mechanism for hypoxemia in older adults with Hb-SS. There was no association between TLC and age in this population (data not shown).

Association of Restrictive Lung Disease with Severity of Hb-SS

The multivariate regression analysis adjusting for age resulted in a trend toward association between the presence of restrictive lung disease and a more severe Hb-SS phenotype (Table 4). This phenotype is characterized by more severe anemia (Hb concentration, 8.3 vs. 8.7 g/dl [$p = 0.08$]; hematocrit, 24.7 vs. 26.2% [$p = 0.05$]) and leukocytosis (WBC, 11.93×10^3 vs. 10.95×10^3 cells/mm³; $p = 0.06$), compared with Hb-SS patients with normal PFTs. Additional linear regression analysis revealed a negative correlation between TLC and WBC ($r = -0.15$, $p = 0.01$; data not shown).

Association of Decreased DL_{CO} with Systemic Disease

After adjustment for age, the presence of low DL_{CO} was associated with an increase in platelet count (441,000 vs. 391,900; $p = 0.05$) and blood urea nitrogen (BUN) concentration (10.9 vs. 8.3 mg/dl; $p = 0.05$), compared with those with normal DL_{CO} or normal PFTs (Table 4). There was a trend toward increased ALT (59.2 vs. 31.1 U/L; $p = 0.08$) and creatinine concentrations (1.11 vs. 0.8 mg/dl; $p = 0.07$) in the patients with decreased DL_{CO} compared with those with normal DL_{CO}. In addition, linear regression revealed a negative correlation between DL_{CO} and both BUN ($r = -0.22$, $p = 0.0002$) and creatinine ($r = -0.22$, $p = 0.0003$) concentrations, suggesting that worsening diffusion capacity may be a marker for systemic vasculopathy. Interestingly, there was no correlation between DL_{CO} and the severity of anemia. Uncorrected DL_{CO} had a positive linear association with Hb concentration (Figure 2), as would be expected in a non-SCD population, suggesting that correcting the DL_{CO} for the level of anemia in our study did not falsely modify the results.

DISCUSSION

Pulmonary complications of adult Hb-SS are responsible for 20–30% of the mortality observed in this population (2, 3, 8). Although PH occurs in about one-third of patients with Hb-SS (28), it is not the only etiology of dyspnea observed in this population. We and others have found that at least one-half of adults with sickle cell disease are at least mildly dyspneic and that dyspnea, in some cases, is not associated with echocardiographic evidence of PH ([4]; and E. S. Klings, unpublished observations). Prior studies have suggested that abnormal pulmonary function tests are the first objective sign of chronic sickle cell lung disease and that they could be helpful in patient management (8). Previously, multiple small studies have demonstrated a spectrum of PFT abnormalities in adult sickle cell disease including restrictive physiology, decreased DL_{CO}, hypoxemia, and obstructive disease (4, 5, 8, 10, 12, 26). Our analysis is the first large-scale multicenter effort to report PFTs in adults with Hb-SS. Pulmonary function was abnormal in 90% of our cases and PFTs may allow clinicians to objectively assess dyspnea in this population.

The most common PFT abnormality observed was restrictive disease. According to the American Thoracic Society guidelines, the best diagnostic test for the presence of restrictive disease is a TLC less than 80% predicted (25). When we examined the group of patients with restrictive disease, an interesting pattern emerged. Of the 230 subjects with restrictive disease, only 111

Figure 1. Adjusted diffusion capacity for carbon monoxide (DL_{CO}) compared with age (yr). DL_{CO} was adjusted for hemoglobin concentration before this analysis. There was a decrease in DL_{CO} associated with increasing age.

(48.3%) had the full constellation of low TLC, abnormal spirometry (reduced FEV_1 and FVC, with an FEV_1/FVC of at least 70%) and reduced DL_{CO} . The remaining subjects were characterized by low lung volumes with normal spirometry. The categorization of these subjects together reflects the fact that low TLC alone is enough to make a diagnosis of restriction (25). Our population demonstrates a divergence of spirometry and lung volumes, contradicting other studies in the literature. Previously, in a large-scale study of a healthy white population, only 2.4% of subjects with a normal FVC had restrictive disease and it was recommended that spirometry alone was sufficient to exclude the presence of restriction unless a high degree of clinical suspicion was present (29). In Hb-SS, it appears clear that spirometry alone is not sufficient to predict the presence of restrictive lung disease.

One explanation for this may be racial differences inherent to the sickle cell population. Race is an important determinant of lung function. Previous studies have demonstrated that, on average, equations for predicted values of PFT data based on data generated in white subjects overestimate the TLC, FEV_1 , and FVC by 12% and the RV and FRC by 7% (25). Although all our data were corrected for race before analysis, there may

still be a differential pattern present. Another possible explanation may stem from extrapulmonary causes of restrictive physiology. In the Hb-SS population, one extrapulmonary mechanism of restriction would be ineffective inspiration due to chest wall pain related to peripheral vasoocclusion, prior rib infarctions, or vertebral disease (30). Although the PFTs obtained in this study were done while the subjects were clinically at their baseline, even when clinically well, patients with Hb-SS may have subacute vasoocclusion (31). The amount of chest wall discomfort experienced by the subjects at the time of their testing is unknown but could have contributed to the low lung volumes observed. In addition, there may be differences in chest wall and vertebral structure among adults with Hb-SS contributing to the restrictive physiology. This could be due to repeated bony infarctions during growth and development and the spinal osteoporosis and osteomalacia typical of Hb-SS (32–34). Non-SCD-specific etiologies of extrapulmonary restriction such as obesity may be playing a role in the restrictive physiology observed in a subset of the subjects observed. The presence of restrictive physiology was associated with a trend toward more severe clinical disease, as exemplified by lower total hemoglobin concentrations and hematocrits, leukocytosis, and renal dysfunction (elevated BUN and creatinine; Table 4). The association of leukocytosis with a decrease in the TLC supports the notion that restrictive lung disease occurs as a result of repeated episodes of ACS and may be a risk factor for mortality (2). The occurrence of more frequent episodes of ACS may be a risk factor for the development of pulmonary fibrosis, a common etiology of restrictive physiology on PFTs. In addition, this suggests that the patients with restrictive lung disease have a greater propensity toward vasoocclusion, placing them at increased risk for the development of bony infarcts. Interestingly, we noted an association between chronic organ dysfunction of the lungs and the kidneys in our population, confirming findings of prior studies and suggesting an etiologic link between these two entities (35).

An equally interesting finding is the presence of decreased DL_{CO} in adults with Hb-SS. In 13% of subjects, this was the only PFT abnormality observed. Isolated decreased DL_{CO} can be a marker for early interstitial lung disease (36) or, more commonly, is associated with the presence of PH. In patients with systemic sclerosis, DL_{CO} not exceeding 55% predicted may be observed in patients up to 5 yr before the diagnosis of PH and is thought to be an early screening tool in this population (17, 37). Moreover, in patients with idiopathic pulmonary arterial hypertension, low DL_{CO} is not only a marker of PH but is also an independent predictor of mortality (16). Unfortunately, as the CSSCD was designed before the determination of the importance of PH

TABLE 4. ASSOCIATION OF LABORATORY MEASURES WITH SUBCLASSIFICATIONS OF PULMONARY FUNCTION TEST RESULTS

Significant Variables ($\alpha = 0.1$)		p Value	Case Mean (n = 40)	Control Mean (n = 64)
Low DL_{CO} versus Normal DL_{CO}				
Unadjusted	Creatinine	0.07	1.11	0.8
	BUN	0.0002	11.9	7.7
	ALT	0.06	55.8	33.1
Age adjusted	Creatinine	0.07	1.11	0.8
	BUN	0.05	10.9	8.3
	Platelets	0.05	441.0	391.9
	ALT	0.08	59.2	31.1
Restrictive Disease versus Normal PFTs				
			(n = 230)	(n = 31)
Unadjusted	Hb	0.08	8.3	8.7
	Creatinine	0.08	0.9	0.7
	BUN	0.07	9.9	7.7
	HCT	0.05	24.7	26.2
Age adjusted	Hb	0.08	8.3	8.7
	WBC	0.06	11.93	10.95

Definition of abbreviations: BUN = blood urea nitrogen; Hb = hemoglobin; HCT = hematocrit; WBC = white blood cell count.

Figure 2. Unadjusted DL_{CO} compared with serum hemoglobin concentrations (mg/dl). There was a trend toward decreased DL_{CO} with increasing anemia.

in the natural history of SCD, echocardiographic data are not available for the majority of the study subjects. Because of this, a definitive conclusion about the relationship between reduced DL_{CO} and the presence of PH cannot be made. We recognize that this is a shortcoming of the current study and recommend a longitudinal study evaluating pulmonary function tests and echocardiograms in adults with Hb-SS to clarify this issue.

Age-adjusted multivariate analysis revealed a link between the presence of low DL_{CO} and markers of hepatic and renal dysfunction and with thrombocytosis. Prior studies of PH in Hb-SS have revealed an association of PH with a history of renal dysfunction and an elevation in ALT (28, 38). In addition, platelets appear to have an important role pathogenically in the development of PH, both as mediators of serotonin metabolism and in their role in thrombosis. These observations support the notion that decreased DL_{CO} may be associated with PH in the SCD population. Unfortunately, the lack of correlative echocardiographic data limits our ability to draw definitive conclusions about the link between decreased DL_{CO} and PH in this population.

Limitations of the current analysis stem from the study design. As this was a cross-sectional study of pulmonary function data, it is impossible to assess the longitudinal effects of Hb-SS disease on pulmonary function. The lack of a non-SCD control group also limits the interpretability of this study somewhat. It would be interesting to determine whether the apparent obstructive disease observed in the pediatric Hb-SS population undergoes a transition to a more restrictive pattern in adulthood. In addition, testing for airway hyperreactivity, such as response to inhaled bronchodilators or methacholine challenge testing, was not done. It is possible that subjects with coexistent asthma may not have been detected in the current study as airflow typically normalizes in these patients between acute exacerbations. A large-scale prospective study of patients with Hb-SS would be helpful in determining the association of asthma with Hb-SS, the role of asthma in the development of sickle cell lung disease, and the usefulness of the presence of decreased DL_{CO} as a marker for PH. In addition, further work needs to be performed to more clearly delineate the etiologies of restrictive disease in Hb-SS, the potential role that parenchymal lung disease plays in the pathogenesis of hypoxemia in this population, and the extent and severity of PFT abnormalities in Hb-SC disease (compound heterozygosity for Hb S and Hb C [*HBB*, Glu6Lys]), another common genotype of sickle cell disease.

In conclusion, pulmonary function is abnormal in 90% of adults with Hb-SS. It is likely that abnormal pulmonary function reflects intrinsic lung disease in these patients and that the mechanisms of dyspnea are more complex in this population than originally appreciated. Greater understanding of the diagnostic utility of pulmonary function testing in this population is paramount as it could lead to a more comprehensive appraisal of the mechanisms responsible for dyspnea and hypoxemia.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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