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The Impact of Recurrent Acute Chest Syndrome on the Lung Function of Young Adults with Sickle Cell Disease

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Abstract The aim of this study was to assess the impact of recurrent acute chest syndrome (ACS) episodes on the lung function of young adults with sickle cell disease (SCD). Our prospective study included 80 SCD adults [26 with recurrent acute chest syndrome (ACS)] and 80 ethnically matched controls aged between 18 and 28 years. Lung function (spirometry and lung volumes) was measured and the results were expressed as the percentage predicted for height. Bronchial hyperresponsiveness (BHR) was assessed by the response to either a bronchodilator or an exercise challenge. The adults with recurrent ACS (two or more ACS episodes) had lower median forced vital capacity (74 vs. 83%, $p = 0.03$), forced expiratory volume in 1 s (79 vs. 90%, $p < 0.03$), and total lung capacity (69 vs. 81%, $p = 0.04$) than SCD adults who had one or no ACS episodes. The greater the number of ACS episodes, the greater the reduction in lung function ($p = 0.001$). The adults with SCD had lower median forced vital capacity (81 vs. 106%), forced expiratory volume in 1 s (85 vs. 107%), and total lung capacity (80 vs. 87%) than the controls ($p < 0.001$). Similar numbers in each group had BHR ($p = 0.2$). The prevalence of restrictive ventilatory defect in the patients with SCD was almost double that of the controls ($p = 0.004$). Young adults with SCD have worse lung function than ethnically matched controls, particularly if they have suffered recurrent ACS episodes.

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Introduction

Adults with sickle cell disease (SCD) can develop sickle chronic lung disease (SCLD). SCLD is characterized by progressively worsening restrictive lung disease, pulmonary hypertension, hypoxemia, and chest pain [1]. SCLD is associated with sudden death in young adults with SCD; this can be due to a sudden episode of pulmonary hypertension. The most important risk for SCLD is acute chest syndrome (ACS), with a relative risk of 16.92 in one series [1]. It would then seem likely, and it is our hypothesis, that even in young adulthood, SCD patients who had suffered recurrent ACS episodes would have significantly worse lung function than those who had one or no ACS episodes. Surprisingly, there are few data about the effect of ACS episodes on the lung function of SCD patients, and those available are conflicting. In one study [2], the number of ACS episodes correlated with increased respiratory system resistance using the forced oscillation technique, and in another study [3], exercise capacity was significantly reduced in children and young adults with a history of recurrent episodes. In contrast, Klings et al. [4] found only a nonsignificant trend between a lower total lung capacity (TLC) and the number of ACS episodes. In addition, Sen et al. [5] found no significant difference in the lung function results of patients with and without ACS episodes, but they did find a significant correlation between airway hyperresponsiveness (AHR), using a metacholine challenge, and recurrent ACS episodes. Sen et al. [5], however, reported a mixed population of SCD patients: 21 had

Sβ-thalassaemia and only 10 had haemoglobin (Hb)SS. The latter group are more at risk of severe disease and worse outcomes. We have reported that restrictive abnormalities become more common in HbSS patients with increasing age [6], and AHR is significantly more common only in young SCD children (mean age = 6.9 years) [7] but not in older children (mean age = 10 years) [6] versus controls. Therefore, it is important to determine whether there is impairment of lung function in young adulthood in the highest-risk SCD patients (i.e., HbSS) who have had recurrent ACS episodes and determine the nature and magnitude of such abnormalities. Such data would not only inform immediate treatment but also highlight whether long-term lung function would be an important outcome measure to assess the efficacy of treatments for ACS episodes. The aim, therefore, of this study was to assess the impact of recurrent ACS episodes on the lung function of young adults with SCD (HbSS) by comparing the results of patients with SCD who had recurrent episodes to those of patients who had one or no ACS episodes. In addition, to determine the magnitude of any effect, the results of the SCD patients were compared to those of contemporaneously assessed, ethnically matched controls.

Methods

Study Subjects

Eighty patients with homozygous SS disease (HbSS) (SCD group) and 80 ethnically matched (HbAA) controls from the Jamaican Sickle Cell Cohort Study (JSCCS) [8], who gave informed written consent, were recruited (see Sample Size). The names of 90 of the remaining 183 HbSS disease adults were randomly selected using a computer programme. They were contacted in the order in which they appeared in the list. Seventy-nine of the 90 HbSS adults agreed to take part and an additional HbSS adult from an additional three names also randomly selected agreed to take part. Of the 11 who did not take part, seven refused, two were pregnant, one was enrolled in another study, and one had died. As attempts were made to recruit the controls, it became apparent that few controls were available; 69 had emigrated and 31 no longer took part in the cohort study. Thus, an attempt was made to contact all remaining controls. The controls were less likely than the SCD adults to agree to take part in this study (25 refused). Twenty-seven controls were untraceable and 10 had died. Other reasons for nonrecruitment included living too far from the clinic ($n = 2$), unable to miss work or school ($n = 3$), in prison ($n = 1$), and medical conditions precluding participation ($n = 2$). The control group, therefore, included all surviving subjects in the cohort except those who had emigrated, were untraceable, or did not consent to involvement in this study. The cohort, particularly those with HbSS, has been closely followed since birth. The SCD patients were seen every 3-6 months during childhood and then every 6 months in adulthood. The controls were seen regularly until they were 18 years of age. Their clinical history was documented in the clinic records and many of the chest radiographs obtained during acute respiratory episodes remain available.

Study Design

The subjects were seen in the Pulmonary Function Laboratory where they were weighed and their height measured and they then underwent pulmonary function testing. Spirometry was performed in keeping with the European Respiratory Standards [9].

Lung volume was measured using a helium gas dilution technique (Morgan TLC Test Mk 11, Morgan Scientific, Haverhill, MA). The lung function results were expressed as the percentage predicted for height using prediction equations [10] for FEV_1, FVC, and TLC for Jamaicans.

Subjects with a baseline FEV_1 less than 75% of that predicted for height were remeasured 15 min after administration of the bronchodilator challenge of albuterol 200 mcg (Ventolin, GlaxoSmithKline, Aranda de Duero, Spain) which was delivered via a metered dose inhaler with a spacer (Ace Spacer®, DHD Healthcare, Canastota, NY). Those with a baseline FEV_1 of at least 75% predicted undertook an exercise test on a treadmill (True S.O.F.T., True Fitness Technology Inc., O'Fallon, MO). The exercise test lasted at least 6 min. Acceptable tests were those in which the heart rate remained less than 10 beats per minute below the desired maximal heart rate [(220 − age) × 0.80)] for more than 3 min. Spirometry was repeated 1, 5, 10, 15, and 20 min after exercise. BHR was diagnosed if there was an increase of at least 10% in FEV_1 after the bronchodilator challenge [11] or a decrease of at least 10% in FEV_1 after the exercise challenge [12].

Classification of the pulmonary function abnormalities was undertaken using the criteria published by Klings et al. [4], modified by use of the lower limits of normal [where the lower limits of normal = predicted value − 1.645 × SD (SD of the reference range) [13]]. In those individuals in whom TLC measurements were not available ($n = 11$), classification was made on the basis of the spirometry results. Restrictive ventilatory defect was diagnosed if either FEV_1, FVC, or TLC were less than the lower limits of normal and the FEV_1/FVC ratio was in the normal range. Obstructive lung function was diagnosed if the FEV_1/FVC ratio was less than 70% of that predicted, FEV_1 and FVC

were less than the lower limit of normal, and the TLC was either in the normal or elevated range. Individuals were diagnosed as having a mixed, obstructive and restrictive abnormality if the FEV_1/FVC ratio and FEV_1 were less than 70% of that predicted and FVC and TLC were less than the lower limit of normal.

The medical records were examined to identify whether the SCD patients had had ACS episodes. An ACS episode was diagnosed if the patient had suffered an acute onset of abnormal respiratory signs and/or symptoms in association with a new infiltrate on a chest radiograph [14]. SCD patients were classified as having recurrent ACS episodes if they had two or more episodes of ACS and as having nonrecurrent ACS episodes if they had one or no ACS episodes. Subjects were classified as smokers or nonsmokers by self report.

Analysis

Differences between groups were assessed for statistical significance using the Mann–Whitney U or χ^2 test as appropriate. Multiple linear regression analysis was used to determine whether ACS episodes were independently related to any reduction in lung function when adjusted for age, height, weight, and gender. Analysis was performed using SPSS v10.0 for Windows (SPSS Inc., Chicago, IL).

Sample Size

Recruitment of 80 SCD patients and 80 controls allowed us to detect, with at least 80% power at the 5% level, a difference equivalent to 0.5 SD in the results of each of the measurements between the two groups.

Results

Forty-six of the SCD adults had had 135 ACS episodes: 20 had a single episode, 5 had two episodes, 7 had three episodes, 12 had four to six episodes, and 2 had 10 or more episodes. SCD patients who had had recurrent ACS episodes ($n = 26$) had worse lung function than those who had not had recurrent episodes, with lower FEV_1 ($p = 0.03$), lower FVC ($p = 0.03$), and lower TLC ($p = 0.04$) (Table 1). Regression analysis demonstrated that the number of ACS episodes was significantly and independently related to reduced lung function (Table 2).

The patients with SCD were of similar height but weighed less and were younger ($p < 0.0001$) than the controls. The median FEV_1, FVC, and TLC of the SCD patients were lower than that of the controls ($p < 0.001$) (Table 3, Fig. 1a–c). Of those completing the tests for BHR, 3 of 73 (4.1%) SCD adults and 5 of 54 (9.3%) controls had BHR ($p = 0.2$). Similar proportions in the two

Table 1 Demographics and lung function of SCD patients with recurrent ACS episodes versus one or no ACS episodes

	Recurrent ACS episodes	One or no ACS episodes	p value
N	26	54	
Age (years)	24.1 (19.0–27.3)	21.9 (19.4–27.6)	0.06
Height (cm)	168.1 (150.2–189.6)	171.5 (155.1–190.5)	0.4
Weight (kg)	55.2 (41.2–83.2)	56.4 (42.2–86.9)	0.4
Males (n)	12 (46%)	26 (48%)	0.9
FEV_1 (% pred)	78.6 (46.2–121.0)	89.8 (61.0–139.8)	0.03
FVC (% pred)	73.7 (46.2–121.0)	83.5 (57.1–136.4)	0.03
TLC (% pred)	68.7 (53.0–92.7)	80.9 (57.8–115.5)	0.04
FEV_1/FVC	87.0 (69.6–97.1)	88.3 (68.5–100.0)	0.3

Data are presented as median (range)

Table 2 Results of regression analysis

	FVC	FEV_1	TLC
R^2	0.70	0.70	0.67
Age (years)	0.001 (0.9)	−0.001 (0.9)	0.03 (0.2)
Gender	−0.43 (<0.001)	−0.37 (<0.001)	−0.56 (0.001)
Height (cm)	0.04 (<0.001)	0.03 (<0.001)	0.05 (<0.001)
Weight (kg)	0.01 (0.08)	0.009 (0.06)	0.009 (0.3)
Number of ACS episodes	−0.08 (<0.001)	−0.09 (<0.001)	−0.08 (0.001)

Except for R^2, all values are β coefficient (p value)

Table 3 Demographics and lung function by SCD status

	SCD patients	Controls	*p* value
n	80	80	
Age (years)	23.0 (19.0–27.6)	26.2 (24.8–27.8)	<0.001
Height (cm)	170.8 (150.2–190.5)	170.0 (155.3–188.3)	0.9
Weight (kg)	55.8 (41.2–86.9)	66.4 (46.8–119.9)	<0.001
Males (*n*)	38	40	0.9
FEV_1 (% pred)	85.1 (46.2–139.8)	107.0 (68.7–174.2)	<0.001
FVC (% pred)	80.5 (45.0–136.4)	105.1 (65.4–157.1)	<0.001
TLC (% pred)	79.5 (27.6–115.5)	86.5 (58.6–133.0)	<0.001
FEV_1/FVC	87.5 (68.5–100.0)	88.1 (69.5–99.5)	0.9

Data are presented as median (range)

groups admitted to smoking (SCD, 8; controls, 10; $p = 0.6$). A greater proportion of the SCD patients had a restrictive lung function abnormality than the controls ($p = 0.004$) (Table 4).

Discussion

The SCD individuals who had had recurrent ACS episodes had significantly worse lung function than those who had had one or no ACS episodes. In addition, we found a significant association between the number of ACS episodes and reduction in lung function. We have demonstrated that the lung function (FEV1, FVC, and TLC) of young adults with SCD was significantly lower than that of contemporaneously assessed, ethnically matched controls and was particularly reduced in those SCD patients who had had recurrent ACS episodes. Miller et al. [15] reported lower mean vital capacity and TLC values and Akgul et al. [16] reported lower mean FEV_1 and FVC values in patients with SCD compared with controls. Smoking can adversely affect the lung function of young adults [17]. Similar proportions in each of our two groups admitted to smoking. A limitation of our study is that we relied on self-reporting rather than urinary cotinine analysis. Previous studies [15, 16], however, did not assess smoking status.

The prevalence of restrictive ventilatory defects (RVD) in adults with SCD is reported to vary from 24 to 74% [18]. Many studies that have demonstrated a high prevalence of RVD, however, have not included a control group [2, 4, 19]. Klings et al. [4] and MacLean et al. [19] compared their results to reference ranges derived for a Caucasian population and Santoli et al. [2] to reference ranges derived for Jamaican adults [2]. An aim, therefore, of this study was to compare lung function in young adults with SCD to that of contemporaneously assessed, ethnically matched controls and determine whether the prevalence of restrictive ventilatory defects was higher in the adults with SCD.

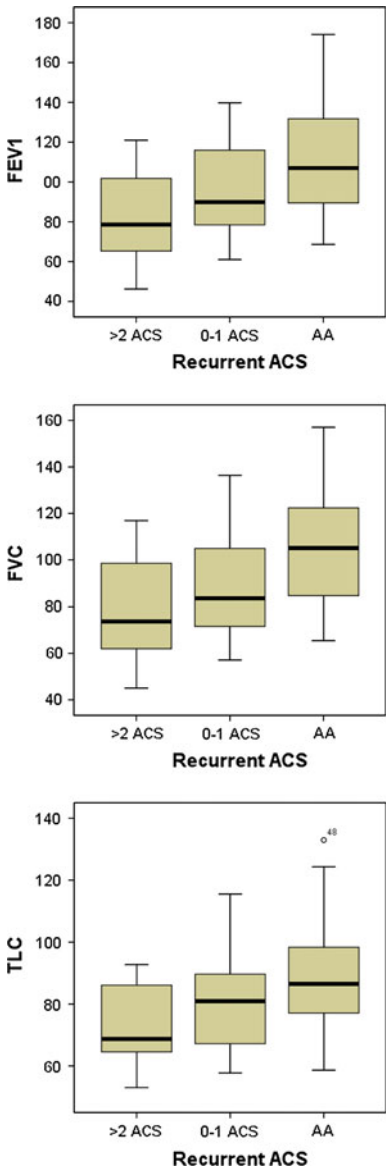

Fig. 1 Pulmonary function in controls and in patients with SCD by recurrent ACS status. Data are shown as percent predicted. Each plot shows the median (*line within box*), interquartile range (*horizontal lines at either end of the box*), and 10th and 90th centiles (*I line*) within a category. Outliers are shown as 0

Restrictive lung function abnormalities were more common in our SCD patients than in the controls. Vendramini et al. [18] reported a RVD prevalence rate of 24% in a group of 26 Brazilians with a mixture of SCD genotypes and Santoli et al. [2] reported a rate of 41% in a group of 49 adults also with a mixture of SCD genotypes. Klings et al. [4] reported a RVD prevalence rate of 74% in 310 adults with HbSS. In this study of 80 adults with HbSS disease aged 19-28 years, the prevalence rate of RVD was 60%. Those data [2, 4, 18] and our findings suggest that RVD may be more prevalent in patients with a more severe

Table 4 Lung function abnormality by SCD status

	Controls	SCD patients	One or no ACS episodes	Recurrent episodes
n	80	80	54	26
Normal	50 (63%)	30 (38%)	23 (42%)	7 (27%)
Restrictive	29 (36%)	48 (60%)	30 (56%)	18 (69%)
Obstructive	1 (1%)	1 (1%)	0 (0%)	0 (0%)
Mixed	0 (0%)	1 (1%)	1 (2%)	1 (4%)

Data are presented as the number of individuals (%)

genotype (HbSS) than in those with a mild genotype (HbSC). We also found that a high proportion (36%) of the controls were diagnosed as having RVD, which is surprising given that the occurrence of RVD was only between 4.9 and 6.8% amongst 40-69-year-old healthy Korean adults [20]. The reference range we used was constructed from results from Jamaicans and has been used in other studies [2, 10]. Others have used prediction equations generated for Caucasian populations with a correction factor [4, 21], or they have failed to state which reference equations were used to define normal values [16, 22]. Our findings emphasize the importance of having a control group, even when an ethnically appropriate reference range is used in the analysis of the results. Our results also highlight that current reference ranges may be inappropriate for comparative purposes.

We demonstrated that the prevalence of RVD was twice as high in the SCD patients compared to contemporaneously assessed, ethnically matched controls. The most likely explanation regarding the restrictive ventilatory defect is acute on chronic inflammation, hastened by episodes of ACS which lead to fibrosis over time. Findings at postmortem include pulmonary thromboembolism, fat emboli, pulmonary hypertension, and microvascular occlusive thrombi [23]. Somatic growth, which could be affected by muscular and skeletal factors, does not predict changes in lung function [21]. We are not aware of any data on the possible influence of pleural factors on lung function.

One of the SCD patients had an obstructive lung function abnormality and one had a mixed pattern. This is in keeping with the findings of Klings et al. [4] who reported only 3% of their subjects had an obstructive abnormality, but Santoli et al. [2] reported that 57% of 49 patients with any SCD genotype had obstructive abnormalities, despite no concurrent asthma or bronchitis. To some extent, these differences are explained by the use of different definitions of obstructive lung disease: Santoli et al. [2] defined obstructive lung disease as a FEV_1/FVC ratio of less than 80%, whereas we and Kling et al. [4] used a cutoff of 70%.

Similar proportions of our two groups had bronchial hyperresponsiveness; indeed very few of our study population were so affected ($n = 3$ SCD; $n = 5$ controls; $p = 0.2$). Sen et al. [5] reported a higher proportion of SCD adults (48%) than controls (16%), with a mean age 28 years, to have BHR. Sen et al. [5] patients, however, underwent a metacholine challenge, whereas we assessed BHR by using either an exercise test or a bronchodilator challenge. It has recently been reported that metacholine challenge can have an adverse effect in SCD patients [24, 25]. Hence, it would not be appropriate to determine whether the prevalence of BHR might vary according to whether a metacholine or an exercise challenge was undertaken in SCD patients.

In conclusion, young adults with SCD had worse lung function than contemporaneously assessed, ethnically matched controls, particularly if they had suffered recurrent ACS episodes. These results emphasize the importance of trying to identify an effective method of preventing ACS episodes.

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