PAEDIATRIC LUNG DISEASE

Pulmonary function abnormalities in children with sickle cell disease

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Background: Adults with sickle cell disease (SCD) have restrictive lung function abnormalities which are thought to result from repeated lung damage caused by episodes of pulmonary vaso-occlusion; such episodes start in childhood. A study was therefore undertaken to determine whether children with SCD have restrictive lung function abnormalities and whether the severity of such abnormalities increases with age.

Methods: Sixty four children with SCD aged 5–16 years and 64 ethnic matched controls were recruited. Weight and sitting and standing height were measured, and lung function was assessed by measurement of lung volumes and forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and peak expiratory flow (PEF) before and after bronchodilator.

Results: Compared with the control subjects, the children with SCD had lower mean (SD) sitting height (69 (6.3) cm *v* 73 (7.7) cm; p = 0.004), sitting:standing height ratio (0.50 (0.02) *v* 0.51 (0.01); p<0.0001), weight (33 (10.9) kg *v* 41 (14.9) kg; p = 0.001), functional residual capacity measured by a helium gas dilution technique (1.2 (0.3) l *v* 1.3 (0.4) l; p = 0.04), FEV_1 (1.5 (0.5) l *v* 1.9 (0.7) l; p = 0.0008), FVC (1.7 (0.6) l *v* 2.1 (0.8) l; p = 0.001), and PEF (3.9 (1.3) l/s *v* 4.8 (1.5) l/s; p = 0.0004). The effect of age on lung function differed significantly between the children with SCD and the controls for total lung capacity and vital capacity measured by plethysmography and functional residual capacity measured by helium gas dilution.

Conclusion: Lung function differs significantly in children with SCD compared with ethnic matched controls of a similar age. Our results suggest that restrictive abnormalities may become more prominent with increasing age.

Sickle cell disease (SCD) is the most common inherited disorder affecting African and Caribbean populations. Each year 200 000–250 000 children are born with SCD. Young adults have restrictive lung function abnormalities[1] which are thought to be the result of repeated lung damage caused by episodes of pulmonary vaso-occlusion.[1 2] Such episodes start in childhood, so it is likely that restrictive lung function abnormalities might be found in children with SCD and that the severity of such abnormalities would increase with age. It is important to test this hypothesis because, if proven, it would have implications regarding the age at which to start aggressive treatment aimed at preventing chronic lung damage. To date, however, studies of lung function in children with SCD have yielded conflicting results. Only one study has shown restrictive abnormalities,[3] while others have found either obstructive abnormalities[4 5] or no abnormalities.[6] The key to accurate documentation of lung function abnormalities is comparison with the results from ethnic matched controls of a similar age; both age[7] and ethnicity[8 9] affect lung function.

This study was therefore undertaken to compare lung function in children with SCD and in age and ethnic matched controls, and to determine whether any abnormalities found were influenced by age.

METHODS

Children aged 5–16 years homozygous for sickle haemoglobin (HbSS) were recruited from two specialist clinics. School children of similar age and the same ethnic origin and siblings without HbSS were recruited as controls but were not individually matched. The study was approved by the King's College Hospital research ethics committee and parents gave informed written consent for their children to take part.

Children were seen in the paediatric lung function laboratory where a detailed history was taken, the child examined, and respiratory function tests undertaken. No child was tested within 2 weeks of an upper respiratory tract infection and children with SCD were not tested within 1 month of a vaso-occlusive crisis. Short acting bronchodilators were withheld for at least 4 hours before testing. Standing and sitting heights were measured using a wall mounted stadiometer (Holtain Ltd, Crymmych, UK); standing height was measured without footwear and sitting height with the child sitting on a rigid topped stool. The sitting to standing height ratio was then calculated. Weight was measured using Avery scales (Avery Berkel, UK).

Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and peak expiratory flow (PEF) were measured using a dry rolling seal spirometer (Morgan TLC, Morgan Medical, Rainham, UK), and FEV_1/FVC was calculated and expressed as a percentage. A minimum of three flow-volume loop results within 10% of each other were recorded and the flow-volume loop with the highest FEV_1

Abbreviations: FEV_1, forced expiratory volume in 1 second; FRCHe, functional residual capacity measured by helium gas dilution; FRCpleth, functional residual capacity measured by whole body plethysmography; FVC, forced vital capacity; PEF, peak expiratory flow; RV, residual volume measured by whole body plethysmography; SCD, sickle cell disease; TLCpleth, total lung capacity measured by whole body plethysmography; VCpleth, vital capacity measured by whole body plethysmography

Table 1 Comparison of patient characteristics and lung volumes between children with SCD and controls

	SCD (n = 64)	Control (n = 64)	Mean difference (95% CI)	p value
Age (years)	10 (2.4)	10 (2.5)	−0.1 (−0.9 to 0.8)	0.7
Standing hight (cm)	139 (13.9)	142 (16.2)	3.3 (−2.0 to 8.5)	0.2
Sitting hight (cm)	69 (6.3)	73 (7.7)	3.7 (1.2 to 6.1)	0.004
Weight (kg)	33 (10.9)	41 (14.9)	7.6 (3.0 to 12.2)	0.001
Sitting:standing height	0.50 (0.02)	0.51 (0.01)	0.02 (0.01 to 0.02)	<0.0001
TLCpleth	2.7 (0.6)	2.8 (0.8)	0.2 (−0.1 to 0.4)	0.3
RVpleth	0.8 (0.3)	0.8 (0.3)	0.0 (−0.1 to 0.1)	0.5
VCpleth	1.8 (0.6)	2.0 (0.7)	0.2 (0.0 to 0.4)	0.1
FRCpleth	1.5 (0.4)	1.6 (0.5)	0.1 (−0.1 to 0.2)	0.4
FRCHe	1.2 (0.3)	1.3 (0.4)	0.1 (0.0 to 0.3)	0.04
FRCHe:FRCpleth	0.8 (0.2)	0.8 (0.2)	0.0 (0.0 to 0.1)	0.3

Data are presented as mean (SD) unless stated otherwise.

analysed. Lung volume was assessed by measurement of functional residual capacity using a helium gas dilution technique (FRCHe) (Morgan TLC, Morgan Medical) and by whole body plethysmography (FRCpleth). Total lung capacity (TLCpleth), vital capacity (VCpleth), and residual volume (RVpleth) were also measured by whole body plethysmography. Measurements were performed at least twice and the mean of values within 10% of each other recorded. The ratio between FRCHe and FRCpleth (FRCHe:FRCpleth) was calculated to determine the presence of airway gas trapping.[7] Following completion of the tests, a bronchodilator (200 µg salbutamol administered via a Volumatic spacer device (Allen & Hanburys, UK)) was given and FEV_1, FVC, FEV_1/FVC, and PEF were remeasured after 20 minutes. All results were corrected to body temperature, pressure, saturated conditions. The lung function test results were expressed as a percentage of that predicted for height using the data of Rosenthal *et al*.[10 11]

Children were diagnosed as having a restrictive abnormality if TLCpleth, FEV_1 and FVC were at least 1.64 standardised residuals below the reference range but FEV_1/FVC was in the normal range, and an obstructive abnormality if FEV_1 but not FVC was at least 1.64 standardised residuals below the normal range. A standardised residual is calculated by dividing the observed value minus the predicted value by the residual standard deviation of the predicted value. Children were diagnosed as having a positive response to bronchodilator if FEV_1 increased by at least 15% in response to the administration of a bronchodilator.

Analysis of data

Data were tested for normality using Kolmogorov-Smirnov and found to be normally distributed. Differences were assessed for statistical significance using the independent samples *t* test. Analysis of variance was performed with sickle cell status as a factor, height and age as covariates, and the interactions of sickle cell status with height and age in the model. Non-significant terms were removed one at a time from each model in backwards elimination. Statistical analysis was performed using SPSS software (SPSS Inc, Illinois, USA).

Sample size

Recruitment of 64 children into each group allowed detection, with 80% power at the 5% level, of a difference in the lung function results between the two groups of 0.5 standard deviations of each measurement. The standard deviations of FEV_1 were 0.06 l, FVC 0.06 l, FEV_1/FVC 2.4%, FRCHe 0.08 l, PEF 0.3 l/s, TLCpleth 0.1 l, RVpleth 0.1 l, and FRCpleth 0.1 l.

Patients

Sixty four children with SCD (34 girls) and 64 controls (34 girls) of mean age 10 years (range 5–16) were recruited. Thirty one of the children were aged between 10 and 16 years. Six of the children with SCD and 12 of the controls were known asthmatics; five and seven, respectively, were taking regular anti-asthma medication. Seven of the children with SCD had been previously admitted to hospital because of an acute chest syndrome.

Table 2 Comparison of spirometric measurements before and after bronchodilator in children with SCD and controls

	SCD	Controls	Mean difference (95% CI)	p value
FEV_1				
Prebronchodilator	1.5 (0.5)	1.9 (0.7)	0.4 (0.2 to 0.6)	0.0008
Postbronchodilator	1.6 (0.5)	2.0 (0.7)	0.4 (0.1 to 0.6)	0.002
% change	5 (11.5)	4 (10.0)	−0.8 (−4.7 to 3.1)	0.7
FVC				
Prebronchodilator	1.7 (0.6)	2.1 (0.8)	0.4 (0.2 to 0.7)	0.001
Postbronchodilator	1.8 (0.6)	2.1 (0.8)	0.4 (0.1 to 0.6)	0.004
% change	2 (8.9)	3 (8.2)	0.9 (−2.1 to 3.9)	0.5
FEV_1/FVC (%)				
Prebronchodilator	89 (7.4)	90 (6.8)	1.2 (−1.3 to 3.7)	0.3
Postbronchodilator	90 (8.5)	91 (8.3)	0.6 (−2.4 to 3.6)	0.7
% change	2 (7.0)	1 (7.1)	−1.5 (−4.0 to 1.1)	0.3
PEF				
Prebronchodilator	3.9 (1.3)	4.8 (1.5)	0.9 (0.4 to 1.4)	0.0004
Postbronchodilator	4.3 (1.4)	5.0 (1.7)	0.7 (0.2 to 1.3)	0.009
% change	11 (21.0)	6 (11.7)	−4.5 (−10.5 to 1.5)	0.1

Data are presented as mean (SD) unless stated otherwise.

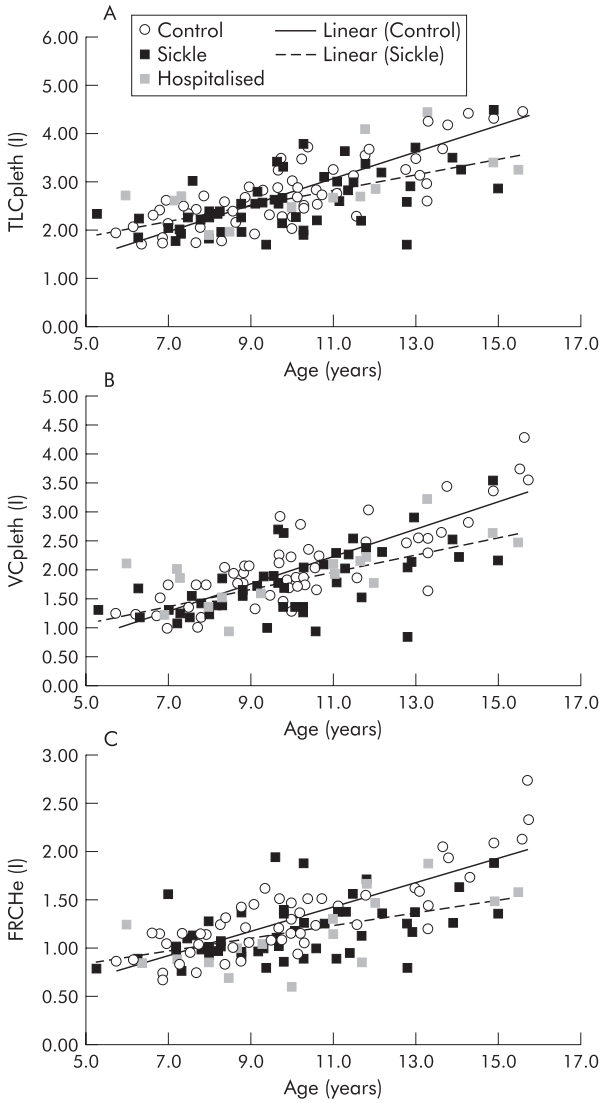

Figure 1 Relationship between age and TLCpleth, VCpleth, and FRCHe in children with sickle cell disease (SCD), children with SCD previously hospitalised, and controls. Repression lines are shown for SCD children (- - -) and controls (—).

RESULTS

Compared with the controls, the children with SCD had lower sitting height ($p = 0.004$), sitting:standing height ($p<0.0001$), and weight ($p = 0.001$, table 1). The children with SCD had lower FRCHe ($p = 0.04$, table 1), FEV_1 ($p = 0.0008$), FVC ($p = 0.001$) and PEF ($p = 0.0004$), but their FEV_1/FVC ratios were not significantly different from those of the controls (table 2). These significant differences remained after bronchodilator treatment, but the changes in FEV_1, FVC and PEF in response to bronchodilator did not differ significantly between the two groups (table 2).

Restrictive and/or obstructive abnormalities were only found in children over 10 years of age. Four children had a restrictive abnormality, three an obstructive abnormality, and two mixed restrictive/obstructive abnormalities. Two of the children with abnormalities (one with an obstructive abnormality) had a positive response to treatment with a β agonist bronchodilator.

The effect of age on lung function differed significantly between children with SCD and controls with regard to TLCpleth, VCpleth, and FRCHe (fig 1, table 3).

Table 3 Results of the analysis of variance: all factors in the final models are shown.

Lung function measurement	Terms in final model	p value
TLCpleth	SS/AC	0.03
	Height	<0.001
	SS/AC*Age	0.03
	Age	0.7
RVpleth	Height	0.001
VCpleth	SS/AC	0.07
	Height	<0.001
	SS/AC*Age	0.03
	Age	0.2
FRCpleth	Height	<0.001
FRCHe	SS/AC	0.05
	Height	<0.001
	SS/AC*Age	0.01
	Age	0.2
FEV_1	SS/AC	<0.001
	Height	<0.001
FVC	SS/AC	<0.001
	Height	<0.001
	Age	0.02
FEV_1/FVC	Height	0.01
PEF	SS/AC	<0.001
	Height	<0.001

SS/AC = sickle cell children/African-Caribbean controls; SS/AC*Age = interaction of age with disease status.

DISCUSSION

We have shown that, compared with control children of a similar age and ethnic origin, children with SCD had significantly lower mean FRCHe, FEV_1, FVC, and PEF. All the patients included in this study were homozygous HbSS, the commonest and most severe form of SCD.[12 13] However, the mean results for the children with SCD were not outside the normal range and very few had sufficiently impaired lung function to be classified as having obstructive or restrictive abnormalities. It should be noted that, to diagnose restrictive and obstructive abnormalities, comparison was made with reference ranges established using the results of children of white ethnic origin. Use of such reference ranges may have resulted in underdiagnosis or misdiagnosis of lung function abnormalities.

It has previously been reported that children with SCD may have increased hyperreactivity when assessed by cold air challenge.[14] However, we did not find that the children with SCD had significantly greater bronchodilator responsiveness than controls. In response to bronchodilator administration there was only a small non-significant improvement in lung function in the children with SCD, and their post-bronchodilator results remained significantly lower than those of the controls (table 2). The results of this study therefore suggest that the children with SCD had mild restrictive defects. Our data agree with the findings of Pianosi *et al*[3] who showed that children with SCD had significantly lower FEV_1 and FVC than controls matched for sex, race and height, but similar FEV_1/FVC. They also reported that the children with SCD had significantly lower TLCpleth, but they were on average older than those included in the present study.

It is important to compare the results of SCD children with those of ethnic matched controls. We have previously shown that 3–9 year old children of African or Caribbean origin were taller, heavier, and had a higher body mass index than white children of a similar age.[15] In this study we therefore recruited controls matched for ethnic origin and related their results and those of the SCD children to the same reference ranges. The body configuration of the children with SCD differed significantly from that of the matched controls, and these differences were

particularly marked if only the older children were considered. This finding is consistent with the suggestion that the effect of SCD becomes greater with increasing age. However, children with SCD enter puberty later than those without SCD.[16 17] Pubertal staging was not undertaken in this study so we cannot exclude the possibility that the greater differences in body configuration noted in the older children were the result of delayed puberty in the children with SCD.

To determine whether the effect of age on lung function differed significantly between children with SCD and controls, analysis of variance was carried out with height and age as covariates and the interactions of sickle cell status with height and age in the model. This showed that the effect of age differed significantly for TLCpleth, VCpleth, and FRCHe. These findings are consistent with restrictive abnormalities becoming more prominent with increasing age.

In conclusion, the lung function of children with SCD differed significantly from that of controls matched for age and ethnic origin. These results have implications for the timing of commencement of treatment aimed at reducing chronic pulmonary morbidity in patients with SCD.

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