Lung function in children with sickle cell disease from Central Africa

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ABSTRACT

Lung function in patients with sickle cell anaemia (SCA) living in sub-Saharan Africa is largely unknown. Anthropometry and spirometry were cross-sectionally evaluated in patients with SCA (HbSS) aged 6–18 years and in schoolchildren from the Democratic Republic of the Congo. The Global Lung Initiative 2012 spirometry reference values were used. A total of 112 patients and 377 controls were included. Twenty-six per cent of patients with SCA had spirometry findings suggestive of a restrictive pattern and 41% had a FEV_1 z-score <5th percentile. Wasting, increasing age and female sex were independently associated with increased risk of restrictive spirometry pattern in patients with SCA. Longitudinal studies could clarify the prognostic meaning of these findings.

BACKGROUND

Despite the high burden of respiratory disease in sickle cell anaemia (SCA), there is a paucity of data on lung function in patients with SCA living in sub-Saharan Africa.[1] Paediatric patients with SCA generally have a decline of lung function with age,[2] resulting in a high prevalence of restrictive lung disease in adults.[3] Most children and adolescents with SCA from high-income countries, however, have a normal or obstructive pattern.[4]

In this cross-sectional study, we compared lung function, using spirometry, in children and adolescents with SCA from the Democratic Republic of the Congo (DRC) and local controls. We hypothesised that paediatric patients with SCA would have a high frequency of restrictive spirometry pattern, reflecting SCA-related cumulative lung injury. We also aimed to investigate risk factors for spirometry results suggesting restrictive physiology in patients with SCA from DRC.

METHODS

Study design

Patients with SCA (haemoglobin SS) aged 6–18 years underwent spirometry, anthropometry and pulse oximetry (Nellcor Oximax N-65; Medtronic, Minneapolis, MN, USA) during a follow-up appointment at Monkole Hospital (secondary care centre), Kinshasa, DRC, and in two primary care clinics of Kinshasa, in April–May 2015. Patients' caregivers were interviewed about a history of asthma and frequency of pain crises in the last 12 months (details in online supplementary data). Other information regarding clinical history of the patients was taken from medical records. A control group of pupils aged 6–12 years was enrolled in four schools of different areas of Kinshasa (details in online supplementary data). Exclusion criteria valid for every participant were the presence of respiratory symptoms or feeling unwell on the test day and a low-quality spirometry.[5 6] Patients were excluded if they had experienced SCA-related acute events (eg, pain crises) in the last month. Controls with current asthma or known chronic conditions that could affect spirometry were excluded (details in online supplementary data).

Assessments

Height and weight were measured (details in online supplementary data). Z-scores for height (zHeight) and body mass index (zBMI) were derived.[7] Wasting was defined as zBMI <-2 and stunting as a zHeight <-2. Spirometry tests were performed using a Pony FX spirometer (Cosmed, Rome, RM, Italy) (details in online supplementary data).[5] Spirometry z-scores and percentage predicted for FEV_1, FVC and FEV_1/FVC were based on the Global Lung Initiative 2012 (GLI-2012) reference values, which take into account age, sex, height and ethnic group.[8] The lower limit of normal (LLN) for spirometry was established at −1.64 z-scores (5th percentile) of the reference population. Spirometry patterns were classified as normal (FEV_1 and FVC ≥LLN), obstructive (FEV_1/FVC <LLN), restrictive (FVC <LLN) or mixed (FEV_1/FVC and FVC <LLN). Whenever available, a full blood cell count from a blood test perfomed at steady state in the last 6 months was also reported in patients with SCA not on hydroxyurea.

Statistical analyses

Details on statistical analysis and sample size calculation are provided in online supplementary data.

RESULTS

A total of 143 patients with SCA and 459 controls were initially enrolled. After exclusions (figure 1), data of 112 patients with SCA and 377 controls were analysed.

Around half of the patients (57/112, 50.8%) were followed at the secondary care centre for SCA. Frequency of clinical variables in patients with SCA is reported in online supplementary table E1. Asthma prevalence was 7.1% among patients with SCA (details in online supplementary data). Spirometry and anthropometry z-scores were markedly lower in children with SCA than in controls (table 1).

A restrictive spirometry pattern was detected in 26.8% of patients (1.0% in controls), an obstructive

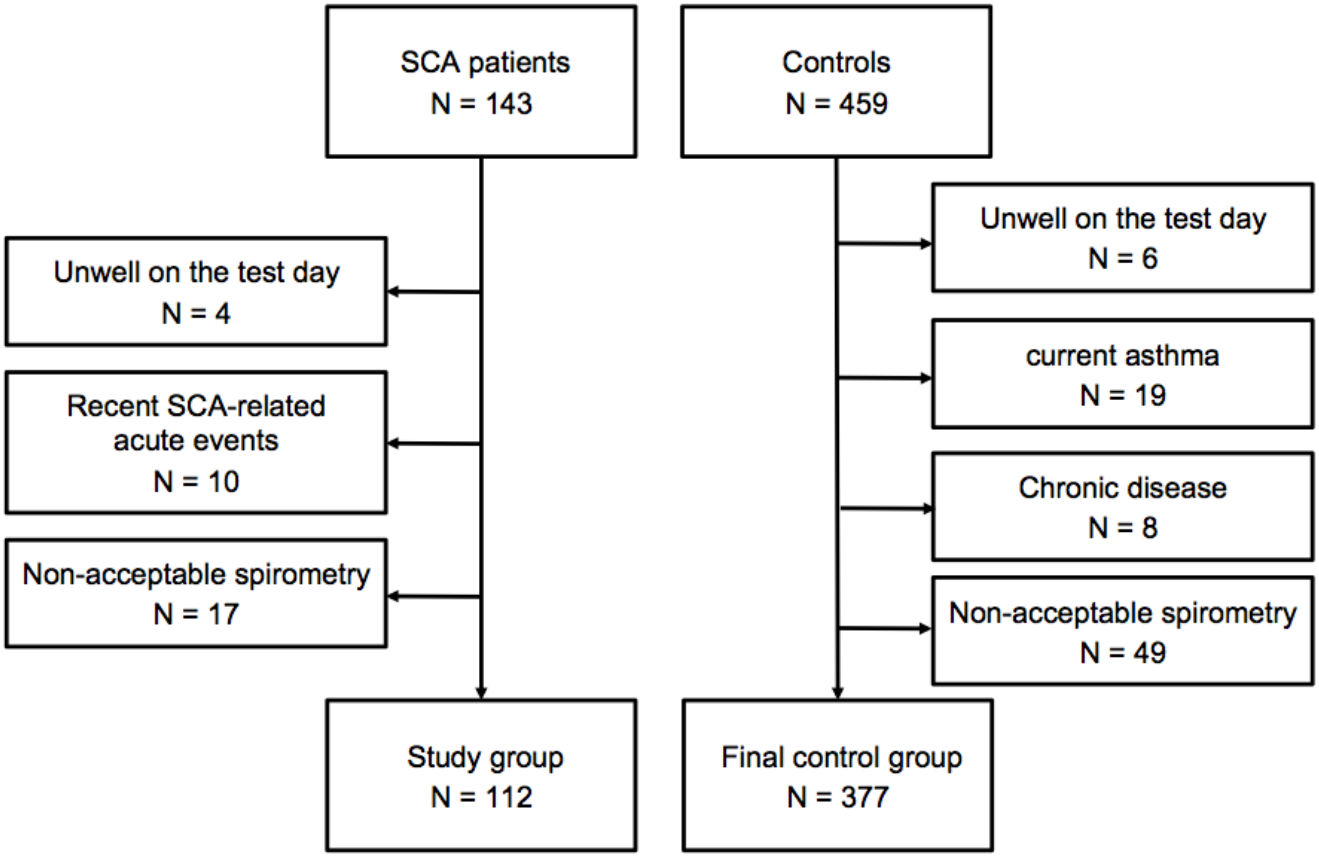

Figure 1 Study population. Patients with sickle cell anaemia (SCA) aged 6–18 years and apparently healthy controls aged 6–12 years from Kinshasa, DR Congo.

spirometry in 4.5% (1.9% in controls) and a mixed one in 6.2% (0% in controls). A $zFEV_1$ <LLN was present in 41.0% of the patients and in 1.9% of the controls.

Wasting and stunting affected, respectively, 26.7% and 25% of the patients versus 5% and 2.6% of controls (p<0.0001 for both indices).

Female sex, the annual increase of age and zBMI <−2 was significantly associated with a restrictive spirometry pattern in patients with SCA (table 2).

Median (1st–3rd quartile) values for Hb, white blood cell (WBC) and platelet count in 42 patients with SCA were, respectively, 73 g/L (66–82 g/L), 12.45×10⁹/L (9.2–16.2 ×10⁹/L) and 374×10⁹/L (329–466 ×10⁹/L). There were no significant differences in the frequency of pathological spirometry patterns

Table 1 Anthropometric and spirometric z-scores in patients with sickle cell anaemia (SCA) aged 6–18 years from the DR Congo and local controls aged 6–12 years

Index	SCA group	Controls	Mean difference (95% CI) SCA–controls
N (% male)	112 (59%)	377 (55%)	
Age (years)	11.2 (3.3)	9.5 (1.6)	1.6* (1.2 to 2.1)
Height z-score	−1.16 (1.41)	0.33 (1.11)	−1.50* (−1.75 to −1.25)
BMI z-score	−1.47 (1.07)	−0.20 (1.10)	−1.28* (−1.51 to −1.04)
FEV_1 z-score	−1.48 (1.01)	−0.16 (0.79)	−1.33* (−1.51 to −1.15)
FEV_1% predicted	80.2 (13.1)	97.9 (10.2)	−17.7%* (−20.0 to −15.3)
FVC z-score	−1.35 (1.03)	−0.09 (0.83)	−1.26* (−1.44 to −1.07)
FVC% predicted	83.0 (13)	98.8 (10.7)	−15.8* (−18.3 to −13.5)
FEV_1/FVC z-score	−0.50 (0.80)	−0.17 (0.71)	−0.33** (−0.48 to −0.18)

Results are presented as mean (SD), unless otherwise specified.
BMI and height z-scores based on WHO 2007 growth charts.[7]
Spirometry z-scores and % predicted values based on Global Lung Function Initiative 2012 equations for African Americans.[8]
*p<0.0001; **p<0.01.
BMI, body mass index.

Table 2 Multivariable logistic regression for restrictive spirometry pattern (vs normal spirometry) in 100 patients with sickle cell anaemia aged 6–18 years from the DR Congo

	Restrictive spirometry pattern*		
Predictor	OR	95% CI	P value
Female sex	3.8	1.2 to 11.6	0.02
Annual increase of age, years	1.3	1.1 to 1.5	0.005
Frequent pain crises†	0.4	0.1 to 1.4	0.16
zBMI <−2	5.4	1.6 to 17.6	0.006

ZBMI and zHeight values based on WHO growth charts.[7]
Spirometry z-scores based on Global Lung Function Initiative 2012 equations for African Americans.[8]
*Restrictive pattern=FVC <LLN and FEV_1/FVC ≥LLN; only covariates with p value <0.20 were included in the final model.
†At least three episodes in the last 12 months. Pain crisis defined as bone pain in the chest, extremities or other areas that required at least 24 hours of analgesic therapy.
zBMI, z-score body mass index; zHeight, z-score height.

between the lowest and highest quartile of Hb and WBC count, nor differences related to the number of platelets or to hydroxyurea therapy (data not shown).

DISCUSSION

Paediatric patients with SCA from DRC showed markedly lower dynamic lung volumes than local healthy controls. Prevalence of a restrictive spirometry in Congolese patients with SCA was 26.8%, higher than recently reported in their counterparts from high-income countries.[9 10] This difference probably reflects more severe chronic lung injury in paediatric patients with SCA from sub-Saharan Africa.

Asthma and an obstructive spirometry were less frequent in the study group than previously found in patients with SCA from Malawi[1] and from high-income countries.[9 10]

Factors associated with lung function impairment in Congolese patients with SCA

Previous episodes of ACS and the rate of pain crises were not associated with abnormal lung function, consistently with evidence from high-income countries.[9]

Every additional year of age was associated with a 30% increased risk of restrictive spirometry pattern in patients with SCA (p=0.005), indicating a decline of lung function over childhood and adolescence, probably due to the progression of chronic lung injury.

Wasting was common in the study group and was associated with 4.4-fold increased risk of restrictive spirometry pattern in patients with SCA (p=0.006). Wasting may have a negative impact on chest dimension and expiratory muscle strength, and could reflect increased metabolic demands due to higher rates of complications, including more severe lung injury.

The higher frequency of a restrictive spirometry pattern in girls with SCA (OR 3.8, p=0.02) requires further confirmation in sub-Saharan Africa.

As regards limitations, static lung volumes, whose measure is necessary for diagnosing restrictive lung disease, were not assessed. The healthy controls had a narrower age range than the patients (up to 12 years vs 18), although similar results can be expected also in the adolescent age (range, 13–18 years). Some potential confounders (ie, differences in exposure to outdoor and indoor pollution) were not included in the logistic regression.

A strength of this study is that it provided new data on lung function in African paediatric patients with SCA and that different risk factors for lung function impairment were investigated. Moreover, the control group size fulfilled the requirements for validating the GLI-2012 reference values in a population.[8]

In conclusion, this study showed that spirometry findings suggestive of a restrictive pattern are common in paediatric patients with SCA from DRC. Malnutrition, increasing age and female sex were all associated with increased risk of a restrictive spirometry pattern. Future studies should clarify whether a poor lung function is tracked over time in African paediatric patients with SCA and its prognostic meaning.

Correction notice This article has been corrected since it was published Online First. There was an error to the percentage stated in the 'Discussion' section.

Contributors MA conceived the study, performed data collection, interpreted data and wrote the manuscript. RK and PN performed data collection and contributed to the manuscript. LC performed statistical analysis, interpreted data and contributed to the manuscript. VB contributed to statistical analysis, interpreted data and contributed to the manuscript. PC interpreted data and contributed to the manuscript. LT conceived the study, interpreted data and contributed to the manuscript.

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