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Original Article

Exercise-induced haemoglobin oxygen desaturation in patients with SCD

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Abstract: Background: Patients with sickle cell disease (SCD) may experience severe clinical complications when there is low tissue oxygenation due to the increased risk of the polymerization of haemoglobin S in deoxygenated environment. The predictors of oxygen desaturation after exercise is not clear in patients with SCD. The current study compared lung function and six-minute walk test (6MWT) between SCD patients with oxygen desaturation after exercise and those without oxygen desaturation. Methodology: A cross-sectional study was conducted among adults with SCD (with HbSS and HbSC genotypes) at a large tertiary hospital in Accra, Ghana. Lung function and exercise tolerance (using the 6MWT) were performed for all the study subjects (n=119). Venous blood was collected from all the study subjects for determination of some haemolytic markers. Oxygen saturation was assessed before and after the 6MWT for all the study subjects, and individuals who had oxygen desaturation of ≥3% after the 6MWT were considered as having exercise-induced haemoglobin oxygen desaturation (EIHOD). The lung function and 6MWT were compared between these two groups. Predictors of EIHOD were determined in both HbSC and HbSS patients. Results: The prevalence of EIHOD in the HbSS and HbSC adults were 41% and 36.1% respectively. Haemoglobin, aspartate amino transaminase, indirect bilirubin, lactate dehydrogenase and six-minute walk distance did not differ in both HbSS and HbSC patients. Decreasing haemoglobin is a predictor of EIHOD in HbSC adults but not HbSS patients. Lung function abnormalities did not predict EIHOD in both HbSS and HbSC patients. Conclusion: The study demonstrates that SCD patients with EIHOD have similar degree of haemolysis and lung function when compared to those without EIHOD.

Keywords: Sickle cell disease, lung function, six-minute walk test, oxygen desaturation

Introduction

Sickle cell disease (SCD) is an inherited disease caused by single mutation in the beta-globin gene which leads to the formation of abnormal haemoglobin S (HbS) [1, 2]. The HbS can polymerize when in deoxygenated environment, leading to red blood cell (RBC) sickling [2, 3]. The sickled red blood cell contributes to episodes of painful crisis (vaso-occlusive crisis), chronic haemolysis and end-organ damage [4-7]. The frequent destruction of the abnormal RBCs leads to the production of free haeme which scavenges nitric oxide (a potent vasodilator), leading to impaired blood flow [8, 9].

The impaired blood flow, coupled with the prevailing anaemia reduces tissue oxygenation [10-12], which may cause damage to important organs of the body including the muscles [13]. Adults with sickle cell anaemia have been reported to have reduced tolerance to exercise in a six-minute walk test (6MWT) compared to their healthy counterparts [14]. The distance covered was significantly lower compared to their healthy counterparts [14]. A number of independent predictors of reduced exercise tolerance have been reported in patients with SCD in earlier studies [15-19]. Exercise-induced haemoglobin oxygen desaturation (EIHOD) could trigger acute sickle cell complications since there is an increased tendency for the

HbS to polymerize in hypoxemic conditions [16, 20].

The independent predictors of EIHOD is not known in adults with SCD in the sub-region. It is also not clear whether haemolysis with its attendant anaemia, lung function abnormalities or baseline oxygen saturation predicts EIHOD among adult SCD patients living in sub-Saharan Africa. The current study aimed at comparing lung function parameters, markers of haemolysis and 6MWT between adults SCD patients with EIHOD and those without EIHOD. It also aimed to determine the predictors of EIHOD among the SCD patients.

Methodology

Study design, subject recruitment and data collection

The study was conducted at the center for clinical genetics of the Korle-Bu Teaching Hospital. This was a cross-sectional study involving adult patients (>18 years) with SCD (Haemoglobin SS and SC) who consented to the study and were in a steady state. Steady state was defined as absence of VOC, blood transfusion, infection, stroke, priapism and acute chest syndrome at least 3 months prior to study recruitment [8]. The cellulose acetate electrophoresis was used to determine the genotype of all the study subjects and sickle cell patients with genotypes other than SS and SC were excluded. Data on anthropometry were collected from all the study subjects (n=119). Venous blood was drawn from all the study subjects into EDTA and gel separator tubes. Full blood count was done for all samples in the EDTA tubes and the samples in the gel separator tubed were centrifuged. The sera were kept in Eppendorf tubes and stored at -80°C prior to analyses.

Laboratory analysis

The haemolytic markers (aspartate aminotransaminase, indirect bilirubin and lactate dehydrogenase) were measured using the MINDRAY BS-200 benchtop automated chemistry analyzer, following the manufacturer's protocol.

Spirometry

Lung function tests using vitalograph was performed for all study subjects according to American Thoracic Society/European Respiratory Society guidelines (ATS) [13] and parameters such as FVC, FEV_1 and FEV_1/FVC were recorded. Lung function results were categorized as normal lung function, obstructive lung disease, restrictive lung disease or mixed obstructive and restrictive lung disease using the percentage predicted values.

6 minute-walk test

All the study subjects were taken through six-minute walk test (6MWT) according to ATS guidelines. The 6MWT is an exercise test often used to determine functional capacity in patients with SCD. The test was done on a flat surface and peripheral oxygen saturation (SpO_2) was measured before and after the test using the pulse oximeter. The difference in SpO_2 before and after the 6MWT was computed and a reduction in SpO_2 of ≥3 was defined as exercise-induced haemoglobin oxygen desaturation [12, 15].

Data analyses

The data was entered into SPSS version-22 software (IBM SPSS Statistics, Chicago, IL, USA). Frequency tables were generated for nominal and ordinal variables. The results were expressed as means plus or minus standard deviation (mean ± SD). The unpaired Student's t-test was used to compare the different parameters between the two subgroups; non-EIHOD versus EIHOD for patients with HbSS and HbSC genotypes. A logistic regression model was developed to determine independent predictors of a decline in oxygen saturation of three points or more during the six-minute walk test. Statistical significance was considered at $P<0.05$.

Ethical statement

Ethical approval for the study was sought from the Korle-Bu Teaching Hospital Scientific and Technical Committee/Institutional review board. The protocol identification number given was STC/IRB/00045/2019. Blood samples and demographic data were obtained from study participants following their consent to partake in the study.

Table 1. Laboratory and spirometry parameters in relation to EIHOD in the HbSS group

Parameter	Non-EIHOD (n=49)	EIHOD (n=34)	*P*-value
Age	25.49±9.72	28.91±9.24	0.112
SpO_2 (%) baseline	97.57±2.23	97.38±2.27	0.706
SpO_2 (%) after 6MWT	97.53±2.03	91.76±5.12	<0.001
WBC	10.33±4.29	11.12±4.05	0.402
PLT	419.82±171.07	444.12±163.82	0.519
Haemolytic parameters			
Hb	8.76±1.57	8.22±1.46	0.117
AST	23.46±11.30	25.50±14.25	0.470
IBIL	19.23±24.63	27.65±27.99	0.152
LDH	351.86±250.61	334.55±177.89	0.730
6MWD	434.60±64.35	427.50±80.92	0.658
Lung function test			
Normal	20 (41.7)	16 (47.1)	0.578
Obstructive Lung disease	5 (10.4)	6 (17.6)	
Restrictive Lung disease	15 (31.2)	9 (26.5)	
Mixed obstructive and restrictive Lung disease	8 (16.7)	3 (8.8)	

SpO_2: Peripheral Oxygen Saturation; WBC: White blood count; PLT: Platelet; Hb: Haemoglobin; LDH: Lactate dehydrogenase; IBIL: Indirect bilirubin; AST: Aspartate aminotransferase; 6MWD: Six-minute walk distance. P<0.005 represents significance.

Results

Clinical characteristics of HbSS patients based on exercise-induced haemoglobin oxygen desaturation

The prevalence of exercise-induced haemoglobin oxygen desaturation (EIHOD) in the HbSS patients was 41%. No significant difference was observed between HbSS patients with exercise-induced haemoglobin oxygen desaturation and those without exercise-induced haemoglobin oxygen desaturation with regards to age, WBC, PLT, Hb, AST, LDH, IBIL, 6MWD, as well as lung function (P>0.05). The SpO_2 (%) after 6MWT was however, significantly lower in the EIHOD group (P<0.001) (**Table 1**).

From **Table 2**, the prevalence of EIHOD in the HbSC patients was 36.1%. Patients' age, WBC, PLT, Hb, AST, IBIL, LDH, 6MWD and lung function were similar in the two groups (Non-EIHOD versus EIHOD) (P>0.05).

Predictors of exercise induced haemoglobin oxygen desaturation

From the logistic regression analyses, none of the variables entered into the model (age, sex, BMI, height, Hb, FEV1 percentage predicted, baseline SpO_2, AST, IBIL, LDH) predicted exercise induced haemoglobin oxygen desaturation in the patients with HbSS genotype. In patients with HbSC however, reduced Hb, was the only predictor of EIHOD (OR=0.549; 95% CI=0.313-0.962; *p*-value=0.036) (**Table 3**).

Discussion

This study provides the first baseline data on exercise-induced haemoglobin oxygen desaturation in Ghana and the predictors of oxygen desaturation of ≥3% after 6 minute walk test in patients with SCD. Sickle cell disease has been associated with a number of complications due to the frequently encountered chronic intravascular haemolysis and episodes of vaso-occlusive crises. Lower oxygen saturation may also result in ventilation-perfusion mismatching and contribute to sickle cell related complications [15]. Most of the studies done to explain changes in SpO_2 after exercise have been in the developed countries. These studies were conducted mainly in children and adolescents but not adults. In a recent study, Brousse *et al*. (2020) [19] reported that about 18% of patients (mean age 11.9±3.8 years) with sickle cell anaemia (SCA) experience EIHOD after exercise, lower than what was observed in this current study (41%). The prevalence obtained in this current study was also higher than what

Table 2. Clinical characteristics of HbSC patients based on exercise-induced haemoglobin oxygen desaturation

Parameter	Non-EIHOD (n=23)	EIHOD (n=13)	*P*-value
Age	29.91±12.38	37.92±16.81	0.111
SpO_2 (%) at baseline	98.65±1.58	98.38±1.98	0.656
SpO_2 (%) after 6MWT	98.00±1.54	91.62±5.72	<0.001
WBC	7.64±2.60	7.85±3.42	0.837
PLT	334.04±119.08	291.54±137.58	0.338
Haemolytic parameters			
Hb	10.12±1.76	11.32±1.59	0.05
AST	31.08±24.09	27.64±26.34	0.693
IBIL	20.31±16.86	13.23±7.40	0.162
LDH	356.03±164.10	379.14±319.16	0.775
6MWD	455.04±61.28	435.00±46.19	0.313
Lung function test			
Normal	13 (59.1)	5 (38.5)	0.298
Obstructive Lung disease	3 (13.6)	2 (15.4)	
Restrictive Lung disease	3 (13.6)	4 (30.8)	
Mixed obstructive and restrictive Lung disease	3 (13.6)	2 (15.4)	

SpO_2: Peripheral Oxygen Saturation; WBC: White blood count; PLT: Platelet; Hb: Haemoglobin; LDH: Lactate dehydrogenase; IBIL: Indirect bilirubin; AST: Aspartate aminotransferase; 6MWD: Six-minute walk distance. P<0.005 represents significance.

Table 3. Predictors of exercise induced haemoglobin oxygen desaturation

	HbSC (n=36)	HbSS (n=83)
	OR 95% CI, *P*-value	OR, 95% CI, *P*-value
Age	0.939 (0.873-1.011), 0.094	0.964 (0.912-1.019), 0.199
sex	0.730 (0.054-9.812), 0.812	0.374 (0.111-1.261), 0.113
BMI	1.151 (0.931-1.423), 0.194	1.131 (0.947-1.350), 0.175
height	1.003 (0.875-1.150), 0.961	1.012 (0.944-1.084), 0.735
Hb	0.549 (0.313-0.962), 0.036*	1.253 (0.882-1.778), 0.208
FEV1 pp	0.983 (0.933-1.037), 0.533	0.979 (0.955-1.004), 0.103
Baseline SpO_2	0.937 (0.569-1.541), 0.797	1.018 (0.808-1.282), 0.881
AST	0.976 (0.926-1.027), 0.348	0.994 (0.952-1.038), 0.791
IBIL	1.046 (0.973-1.124), 0.227	0.988 (0.968-1.009), 0.263
LDH	1.001 (0.995-1.006), 0.778	1.000 (0.998-1.002), 0.977

BMI: Body mass index; Hb: Haemoglobin; FEV1 pp: Forced expiratory volume in one second percentage predicted; SpO_2: Peripheral Oxygen Saturation; LDH: Lactate dehydrogenase; IBIL: Indirect bilirubin; AST: Aspartate aminotransferase. P<0.005 represents significance. *indicates significant difference.

was reported in other studies [17-19]. It is possible that age (32.81±14.44 and 26.89±9.62 for HbSC and HbSS respectively) may have influenced the observed differences in prevalence. Unlike the earlier studies, this current study was conducted in adult patients with SCD.

The higher prevalence of EIHOD in the HbSS patients (41%) compared to those with the HbSC genotype (36.1%) suggest at least in part that, the complications that may arise in HbSS patients after exercise may be greater. The lower mean Hb observed in the HbSS patients may have contributed to the higher prevalence of EIHOD compared to the HbSC patients. Findings from this study also suggest that, sickle cell genotype may predict higher EIHOD. The HbSS patients are associated with increased risk of sickling compared to HbSC, and this could affect oxygen saturation after exercise. Nevertheless, having about 36% of HbSC patients experiencing EIHOD needs attention since a significant number of these patients may have exercise-related complications. The 36% prevalence of EIHOD in the HbSC patients is a surprise since this group has relatively normal mean Hb. In the event of hypoxemia or hypoxia after 6MWT, blood rheology may be impaired and several endothelial cells may be activated. These processes may interfere with blood flow, promote arterio-

venous shunts and lead to impaired microcirculation [19]. One limitation of this study worth mentioning was the inability to assess blood rheology.

Compared to a previous study [16], the prevalence of EIHOD in the HbSC patients was higher in this study. The study of Waltz et al. [16] was however conducted among children with SCD.

Although a previous large study [15] has reported the contribution of haemolysis in EIHOD in patients with SCD, this current study did not find any association in the HbSS patients. Markers of intravascular haemolysis herein assessed in our cohort included (AST, LDH and IBIL) but failed to predict EIHOD in the logistic regression model. Therefore in our patients, intravascular haemolysis did not influence oxygen desaturation after exercise. Future studies may consider the use of integrated haemolytic markers [21] in predicting EIHOD in a large population of SCD patients. Haemoglobin was the only predictor of EIHOD in patients with HbSC genotype similar to what was reported by Campbell and colleagues (2009) [15]. Recently, associations between blood rheological alterations and decreased tissue oxygenation, both at the muscle and cerebral level, have been described in sickle cell patients [14, 19]. Based on these previous studies, one could suggest that the degree of hemorheological abnormalities, in association with the degree of anemia, could affect the 6MWT performance in SCA population due to decreased tissue oxygen at the level of the muscle.

Lung function done on all patients with SCD before the 6MWT was not a predictor of EIHOD, similar to results obtained from previous studies done in children with SCD [15, 16, 19]. Although a large study coupled with lung function test after the 6MWT are recommended to confirm this observation, these findings suggest in part that, lung function abnormalities may not explain oxygen desaturation after an exercise in both children and adults with SCD.

Hydroxyurea (HU) has been noted to improve the synthesis of fetal haemoglobin as well as RBC deformability and could positively affect exercise capacity among SCD [16, 22, 23]. A significant proportion of the patients in the earlier studies were on HU, which is thought to modify sickle cell phenotype. None of our patients were on HU and this may explain the higher prevalence of EIHOD observed among our SCD cohort. We propose a longitudinal study to ascertain the role of HU in EIHOD in patients with SCD.

Conclusion

In conclusion, EIHOD is common in patients with SCD, particularly in those with the HbSS genotype. Lung function and exercise tolerance (using the 6MWT) was comparable in SCD patients with EIHOD and those without EIHOD. Reduced haemoglobin is a risk factor for EIHOD in HbSC patients. Lung dysfunction and markers of intravascular haemolysis (AST, IBIL, LDH) are not predictors of EIHOD in patients with SCD.

Disclosure of conflict of interest

None.

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