Deterioration of lung diffusion capacity during childhood in sickle cell disease

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To the Editor,

The American Society of Hematology guidelines, 2019, recommended obtaining pulmonary function tests (PFTs) in patients with sickle cell disease (SCD) with various respiratory symptoms even if they are at their steady state.¹ These guidelines acknowledged that the usefulness of routine PFT is unknown because of the lack of research. However, this society further suggested that if the PFTs are obtained, it should be a comprehensive study including lung volumes and lung-diffusing capacity for carbon monoxide (DLCO), in addition to spirometry.¹ A large study in adult patients (n=310) with SCD showed that pulmonary function is abnormal in 90% of adult patients with Hb-SS.² Common abnormalities included restrictive physiology and decreased DLCO. In this study, decreased DLCO indicated more severe sickle vasculopathy characterized by impaired hepatic and renal function, and a negative linear correlation existed between DLCO and age, suggesting that in adults with Hb-SS, disruption of alveolar–capillary gas exchange progressively deteriorated with time.² Two recent cross-sectional studies of children with SCD showed that pulmonary function, including DLCO, worsened with age and showed correlations with biological markers of inflammation (induced sputum IL-6 levels or blood neutrophilia).³,⁴

Overall, these studies highlight the potential interest of DLCO measurement in SCD. The DLCO is the product of KCO (carbon monoxide coefficient of transfer) and alveolar volume (VA) and these two latter indices need to be interpreted separately since the decrease in DLCO is often mitigated by a preserved KCO or even increased KCO in SCD. It has been demonstrated that when corrected for hemoglobin levels, the children with SCD compared to controls of similar age had elevated KCO_corrected. The determination of alveolar-capillary membrane conductance (Dm) and pulmonary capillary blood volume (Vc) from the lung diffusing capacity for carbon monoxide (DLCO) or for nitric oxide (DLNO) has been done in SCD since the seventies, demonstrating an increase in Vc in SCD. KCO is mathematically linked to both Dm and Vc (1/KCO = VA/Dm + VA/θVc); thus, the increase in KCO is related to Vc increase, but since DLCO has been shown to worsen with age, the changes of DLCO, VA and KCO over time in children with SCD deserve to be studied.

The objectives of our study were to describe the evolution of DLCO and its determinants, KCO and VA, and to further assess the initial risk factors of the decrease in DLCO in children/adolescents with SCD. To this end, we retrospectively recorded the routine follow-up PFTs of children with SCD who were included in a prospective cross-sectional study that included the measurement of both DLCO and DLNO with the calculation of Dm and Vc.⁵
Material and Methods

Patients
Sixty children/adolescents of Sub-Saharan African or Caribbean ethnicity were prospectively included in the DrepaSympa trial. Among them, 43 had subsequent PFTs as part of their routine follow-up (without DLNO measurement). These 43 participants are described in this retrospective study and the 17 non-included children are described in the online supplement. This study was approved by our local Ethics Committee (PHENOB: N° 2018-430). The parents were informed of the collection of the prospective data for research purposes and they could request that their child be exempted from this study in accordance with French law (non-interventional observational research).

Pulmonary function tests (PFTs)

First visit: Children underwent spirometry and DLCO/DLNO measurement (Medisoft, Hyp’Air Compact, Belgium) to calculate the membrane diffusion (Dm) and capillary blood volume (Vc), as recommended (a finite specific conductance in the blood for NO (θNO) was assumed), as previously described. The breath-hold time of this DLCO/DLNO measurement was 4 seconds.

Second visit: Children underwent spirometry and DLCO measurement (without DLNO) according to international recommendations. The breath-hold time of this DLCO measurement was 10 seconds.

The predicted values were those of Global Lung Initiative, taking into account ethnicity for spirometry, and those of Caucasians for DLCO. The results of KCO and DLCO are given without and with correction (KCO_corrected, DLCO_corrected) for hemoglobin concentration, as recommended. The changes in DLCO and KCO from visit 1 to visit 2 were calculated as visit 1, % predicted value minus % predicted value of visit 2.

Statistical analyses
The results were expressed as median (25–75th percentiles) since most indices followed a non-normal distribution. Comparisons between the visits were performed using Wilcoxon signed-rank test. Correlations were evaluated using Pearson’s correlation coefficient. A p value <0.05 was deemed significant. All statistical analyses were performed with StatView 5.0 software (SAS Institute, Cary, NC, United States).

Results
The characteristics of the 43 children/adolescents at their initial evaluation are described in Table 1. At their second visit, the adolescents had a median age of 14.9 [13.5; 16.2] years. The figure 1 describes the change in DLCO and its components between the two visits. Overall, a significant decrease in DLCO indices is evidenced that is also true for spirometry indices with the exception of FEV1/FVC: at the second evaluation, the FEV1 % predicted was 87 % [77; 94] (versus visit 1, see Table 1, p=0.0004), the FVC % predicted was 91 % [84; 98] (versus visit 1, p=0.0011) and the FEV1/FVC % predicted was 96 % [90; 99] (versus visit 1, p=0.0656).

The median decrease from visit 1 to visit 2 in DLCO_corrected % predicted was 46% [31; 70]; in KCO_corrected % predicted was 43% [29; 59] and in VA % predicted was 14% [4; 25]. The conditional change scores of DLCO indices are provided in the online supplement further demonstrating the decrease in VA, KCO, KCO_corrected and DLCO_corrected. The decrease in DLCO_corrected was independently related to both KCO and VA decreases in a multiple regression (r^2=0.92; p<0.0001). The DLCO_corrected % predicted change negatively correlated with serum LDH while the KCO_corrected % predicted change positively correlated with baseline Vc/VA (R=-0.33, p=0.036 and R= 0.34, p=0.037; respectively, see figure in the online supplement). These decreases also positively correlated with their baseline (visit 1) % predicted values (R= 0.85; p<0.0001 for DLCO and R= 0.58; p=0.0002 for KCO, respectively).

The decrease in KCO_corrected % predicted was more severe in boys than in girls: 56% [41; 64] versus 37 % [20; 56], p=0.0189.

Discussion
Our original finding is to show that DLCO indices deteriorate but from elevated values to normal values during childhood in SCD. The elevated values of DLCO in childhood are related to a frank increase in KCO due to the increase in Vc. This increase in Vc is at least partly related to the increase in cardiac output due to anemia, thus related to vasodilation that is further limited on exercise. The decrease in KCO that is observed with age is probably related to a decrease in vasodilation or even related to pulmonary vascular bed remodeling.

The increase in Vc and KCO change correlated since the more the KCO was elevated at baseline (visit 1) and the more was its subsequent decrease. Thus, the deterioration that was evidenced is related to the loss of an adaptive process. Persistent intravascular hemolysis over decades leads to chronic vasculopathy, with 10% of patients developing pulmonary hypertension. Thus, follow-up of DLCO may help to detect at risk patients, which warrants further studies. Moreover, DLCO has been correlated with both exertional dyspnea and performance (6 minute walked distance) in adult SCD further emphasizing its usefulness.6

A frank deterioration of DLCO_corrected and KCO_corrected % predicted was observed only 2-3 years apart. Nevertheless, at a median fifteen years of age, the KCO predicted values were still into the normal range (z-scores -1.645 to +1.645) for almost all participants. This result is consistent with the finding of only slightly reduced KCO values (’80% predicted) of young adult patients (’30 years) with SCD. The more severe deterioration of KCO_corrected in men could be consistent with the fact that NO bioavailability and NO responsiveness are greater in women than in men with SCD, allowing the preservation of capillary vascular bed in women.

Elevated level of serum LDH is a marker of nonspecific tissue damage and its negative correlation with subsequent decrease in DLCO_corrected may seem counterintuitive. Nevertheless, those patients who had the lesser degree of DLCO decrease over time and the higher levels of LDH were those with normal baseline DLCO, which may traduce the lack of compensatory vasodilation already present in the patients with more severe disease.

Our study has inherent limitations related to its design. Seventeen (28%) participants had no follow-up PFTs; logically they were older explaining their loss of follow-up in a pediatric center. Finally, DLCO measurement was made with two different breath-hold durations between visit 1 (4 seconds) and visit 2 (10 seconds). The reduced breath-hold time of the first measurement could have lowered the baseline alveolar volume; nevertheless, a significant decrease was subsequently observed, as expected from the decrease in FVC, which argues against a bias.

In conclusion, our retrospective study shows that DLCO indices significantly decrease in adolescents with SCD from elevated values to normal values and that the decrease in KCO was proportional to the baseline increase in capillary blood volume, while the decrease in DLCO was inversely proportional to baseline LDH concentration.

References


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**Table 1**. Clinical, biological and functional characteristics of the 43 patients with SCD at their initial evaluation.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n Age, years</th>
<th>Sex, female / male</th>
<th>n Height, cm</th>
<th>n Weight, kg</th>
<th>VOC#, n last year</th>
<th>At least one ACS, n patients</th>
<th>ACS, total number / child</th>
<th>Cerebral vasculopathy*, n</th>
<th>Hydroxyurea / Chronic transfusion, n</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical characteristics</td>
<td>12.6 [10.4; 13.6]</td>
<td>23 / 20</td>
<td>149 [140; 161]</td>
<td>39.0 [33.2; 47.5]</td>
<td>0 [0; 1]</td>
<td>13</td>
<td>0 [0; 1]</td>
<td>17</td>
<td>26 / 12</td>
<td></td>
</tr>
<tr>
<td>Biological characteristics</td>
<td>SS / SB-thalassemia / SC, n</td>
<td>35 / 2 / 6</td>
<td>Deficit G6PD, n</td>
<td>2</td>
<td>Hemoglobin, g/dL</td>
<td>8.5 [8.0; 9.6]</td>
<td>Leucocyte count, x 10^9/L</td>
<td>8.14 [7.14; 10.58]</td>
<td>Lactic dehydrogenase, IU/L</td>
<td>193.2 [148.9; 295.2]</td>
</tr>
<tr>
<td>PFTs characteristics</td>
<td>FEV₁, % predicted</td>
<td>93 [80; 104]</td>
<td>FEV₁, z-score</td>
<td>-0.54 [-1.51; 0.34]</td>
<td>FVC, % predicted</td>
<td>98 [85; 104]</td>
<td>FVC, z-score</td>
<td>-0.13 [-1.22; 0.35]</td>
<td>FEV₁/FVC, % predicted</td>
<td>98 [93; 101]</td>
</tr>
<tr>
<td>KCO, % predicted</td>
<td>158 [152; 173]</td>
<td>KCO, z-score</td>
<td>3.35 [3.01; 4.70]</td>
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<tr>
<td>DLCO, % predicted</td>
<td>138 [120; 167]</td>
<td>DLCO, z-score</td>
<td>2.23 [1.33; 3.34]</td>
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<tr>
<td>DLCO corrected</td>
<td>17.9 [16.8; 20.0]</td>
<td>DLCO corrected, z-score</td>
<td>0.76 [0.34; 1.18]</td>
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<tr>
<td>DmCO/VA, mL.min⁻¹.mmHg</td>
<td>25.6 [20.8; 28.1]</td>
<td>Vc/VA, mL/L</td>
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#: is vaso-occlusive crisis (VOS) requiring hospitalization

ACS is acute chest syndrome

*: cerebral vasculopathy (any time) has been defined as high stroke risk as previously done

$:$ predicted values are those of Caucasians

**Figure 1**. Description of the changes in DLCO and its components between the two visits.

The individual changes (lines) and population changes (box and whisker plots show median, 25 and 75th percentiles, and 10 and 90th percentiles) from visit 1 to visit 2 of KCO, % predicted (upper left panel), of corrected KCO, % predicted (upper right panel), of VA, % predicted (lower left panel) and corrected DLCO, % predicted (lower right panel). The bold dotted lines are medians.