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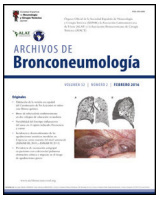

Scientific Letter

Reduced Lung Diffusion Capacity Caused by Low Alveolar Volume and Restrictive Disease Are Common in Sickle Cell Disease

To the Director,

Pulmonary complications are among the most common causes of morbidity and mortality in patients suffering from homozygous sickle cell disease (SCD; i.e., HbSS).[1] Dyspnea is a frequent reported symptom and closely linked to reduced diffusion lung capacity for carbon monoxide (DLCO).[2] Prior studies have suggested that abnormal pulmonary function tests are the first objective sign of chronic sickle cell lung disease and that it could be helpful to perform them on a regular basis, in order to improve clinical management.[3] More than a predictive factor for chronic lung complications, impaired lung function could lead to sickle cell complications. Pulmonary complications of HbSS patients are responsible of 20% of the mortality observed in this population.[1] Ventilatory defect could lead to hypoxemia, which may promote red blood cell (RBC) sickling.[4] In turn, impaired RBC rheology may play a key role in the severity of hemolytic anemia and the occurrence of vaso-occlusive crises.[5] Pulmonary function is abnormal in 90% of SCD adults with 74% suffering from restrictive lung disease, and 13% exhibiting reduced DLCO.[6] Despite a high prevalence of acute chest syndrome (ACS) in patients suffering from homozygous SCD, the association between ACS and lung dysfunction remains uncertain.[7] The first aim of the present study was to characterize the pulmonary function of patients suffering from homozygous SCD, and to investigate potential determinants of altered lung diffusion capacity. Secondly, we aimed to test putative associations between ACS and pulmonary function in SCD patients.

Seventy height prospectively recruited homozygous SCD patients (36 men and 42 women; ages ranging from 15 to 62 yrs.) underwent pulmonary function testing (spirometry, lung volumes, and DLCO). DLCO was assessed using the single breath method with values corrected for hemoglobin concentration.[8] The single breath method was used to determine alveolar volume (AV) and derive the carbon monoxide transfer coefficient (KCO), which represents an index of the alveolar transfer of carbon monoxide efficiency.[8] The pulmonary function of each subject was classified according to the American Thoracic Society criteria.[9] They were all considered as being in their usual steady-state, i.e., without any transfusion or acute event requiring hospitalization in the 2 months preceding their visit. ACS was defined as chest pain, dyspnea, cough, abnormal lung auscultation, and the presence of a new radiologic lung infiltrate. Recurrent ACS was defined as 2 or more ACS in the patient history medical files. The study was approved by the ethics committee of the CPP-OUEST V (2017-A03352-51) and performed according to the Declaration of Helsinki.

Table 1
Pulmonary function test results according to restrictive lung defect status.

	Restrictive lung defect ($n=25$)	No restrictive lung defect ($n=53$)	p
Age (years)	29.8 ± 8.9	28.6 ± 8.8	0.483
BMI (kg/m^2)	22.6 ± 4.4	23.1 ± 2.9	0.551
Smoking (%)	16	7.5	0.427
HU treatment (%)	76	64	0.436
SpO2 (%)	97.2 ± 1.6	98 ± 1	0.047
FVC (L)	3.06 ± 0.7	3.45 ± 0.8	<0.001
%FVC	76.6 ± 8.9	91.6 ± 9.3	0.691
FEV1/FVC	82.4 ± 5.2	83 ± 6.2	0.44
%FEV1/FVC	99.4 ± 6.8	100.7 ± 7.1	0.04
FEV1 (L)	2.53 ± 0.6	2.84 ± 0.7	<0.001
VR (L)	1.39 ± 0.3	1.52 ± 0.4	0.001
%VR (%)	86.2 ± 16.1	101.4 ± 20.2	0.543
VR/TLC	31.3 ± 7	30.4 ± 6.2	0.703
VR/TLC (%)	115.21 ± 18	113 ± 17.6	0.038
DLCO	21.48 ± 5.2	22.63 ± 6.3	0.012
DLCO (%)	68.3 ± 11.4	76.9 ± 14.7	0.103
KCO	5.53 ± 0.8	5.2 ± 0.8	0.03
KCO (%)	107.3 ± 14.4	98.8 ± 16.6	0.05
AV	3.87 ± 0.7	4.36 ± 1	<0.001
AV (%)	63.4 ± 6.1	76.2 ± 8	0.028

BMI: body mass index; HU: hydoxyurea; FVC: forced vital capacity; % FVC: percentage of predicted FVC values; FEV1: forced expiratory volume in one second, % FEV1: percentage of predicted VEF1 values; RV: Residual Volume; % RV: percentage of predicted RV values; TLC: Total Lung Capacity; KCO = DLCO/AV; %KCO: percentage of predicted KCO values; AV: Alveolar Volume; % AV: percentage of predicted AV values.

Only 2 of the subjects suffered from an obstructive ventilatory defect (i.e., 2.5%) while twenty-five participants had evidence of restrictive lung disease (i.e., 32%). The definition of obstructive pulmonary disease used in previous studies was rather heterogeneous, which could be of the underlying source of the highly variable prevalence of obstructive lung disease in SCD. For instance, a high prevalence of obstructive lung disease was described when airway hyperresponsiveness[10] or lower airway obstruction[11] served as the criteria used. Our results are consistent with the study by Klings and colleagues[6] who evaluated 310 homozygous SCD patients, and found that only 4 had evidence of an obstructive respiratory pattern.

Restrictive ventilatory defect is the most frequent pulmonary abnormality in patients suffering from SCD.[6] The non-restrictive group was composed of all the others subjects of the study (only 2 obstructive, the others had normal pulmonary function tests). The decreased lung volume reported in SCD (Table 1) could be a consequence of the increase in cardiac volumes and output elicited by the underlying chronic anemia. SCD patients frequently manifest elevated cardiac-to-thoracic ratio on chest radiography, which could be an important determinant of reduced lung volumes.[12] Moreover, lung volumes and respiratory muscle

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Table 2
Pulmonary function test results according to lung diffusion capacity status.

	Low diffusion ($n=36$)	Normal diffusion ($n=42$)	p
Age (years)	31.1 ± 8.5	27.1 ± 8.7	0.042
BMI (kg/m^2)	22.9 ± 4.5	23 ± 2.3	0.907
Smoking (%)	22	0	0.002
HU treatment (%)	79	58	0.05
SpO2 (%)	97.4 ± 1.2	97.7 ± 1.4	0.013
FVC (L)	2.98 ± 0.5	3.62 ± 0.9	<0.001
%FVC	83.4 ± 11.5	89.4 ± 11.1	0.031
FEV1/FVC	82.5 ± 6.4	83.1 ± 5.4	0.667
%FEV1/FVC	100.2 ± 7	100.4 ± 7.1	0.911
FEV1 (L)	2.45 ± 0.5	3 ± 0.7	<0.001
TLC (L)	4.43 ± 0.6	5.25 ± 1.1	<0.001
%TLC (%)	80.5 ± 8.3	87.6 ± 9	0.001
VR (L)	1.39 ± 0.3	1.55 ± 0.4	0.046
%VR (%)	90.2 ± 20.6	102 ± 18.4	0.009
VR/TLC	31.6 ± 6.4	30 ± 6.4	0.276
VR/TLC (%)	109.8 ± 19.3	117.6 ± 15	0.137
DLCO	18.1 ± 3.5	25.8 ± 5.3	<0.001
KCO	4.86 ± 0.8	5.7 ± 0.7	<0.001
KCO (%)	92.4 ± 14.2	109.3 ± 13.8	<0.001
AV	3.75 ± 0.6	4.59 ± 1	<0.001
AV (%)	67.7 ± 9.7	75.6 ± 8	<0.001

BMI: body mass index; HU: hydoxyurea; FVC: forced vital capacity; % FVC: percentage of predicted FVC values; FEV1: forced expiratory volume in one second, % FEV1: percentage of predicted VEF1 values; RV: Residual Volume; % RV: percentage of predicted RV values; TLC: Total Lung Capacity; KCO = DLCO/AV; %KCO: percentage of predicted KCO values AV: Alveolar Volume; % AV: percentage of predicted AV values.

strength have been reported to be associated in SCD children.[13] A small Brazilian study focusing on respiratory muscle strength in 21 SCD patients showed decreased maximal inspiratory and expiratory pressures that were also below normative range values.[14] Patients suffering from a restrictive lung pattern also exhibited lower DLCO, values that were lower than the normative range (Table 1). The lower DLCO values were attributable to the reduced alveolar volume (AV), while KCO did not significantly differ between the two groups (Table 1).

The most prominent pulmonary function problem noted in this study (thirty-six subjects (46.1%)) was the presence of a low DLCO (i.e., <75%) (Table 2). These patients were slightly older than those with a normal diffusing capacity (Table 2). They also had lower SpO_2, TLC, RV and KCO, all of which remained in the normal range. AV was lower in patients suffering from a low DLCO, and values were below the normative range values. The proportion of patients treated by hydroxyurea was higher in those with low DLCO compared to those without ($\chi^2 = 4.116$, $p = 0.05$). Only 8 subjects were smokers but all of them exhibited low DLCO. In the normal population, smoking is known to decrease lung diffusion capacity[15] and this is also probably the case in SCD individuals. Nevertheless, the exclusion of smokers from the low DLCO group did not affect the results (data not shown). The single-breath DLCO is the product of the rate of carbon monoxide uptake from alveolar gas to pulmonary capillary blood (i.e., KCO), by the "accessible" AV, which approaches total lung capacity TLC in normal subjects.[16] Reduced TLC and reduced AV could therefore share the same pathophysiological mechanisms.[17] Incomplete alveolar expansion (respiratory muscle weakness), a local loss of alveolar units and/or a diffuse loss of alveolar units (interstitial lung disease) could explain the low AV.[16]

Our study also showed that thirty-nine patients had a positive history of ACS (50%), of whom 18 had only one episode (23%) and 20 had recurrent ACS episodes (27%). Compared to those who never had ACS, patients with recurrent ACS exhibited lower RV, although RV values remained in the normal range of the predicted values for both groups (1.58 L ± 0.4 vs. 1.34 L ± 0.3 in patients with recurrent ACS and patients with no history of ACS, respectively; $p = 0.034$). The other parameters reflecting lung function did not differ between SCD patients with a positive history of ACS (recurrent or not) and those without. The proportion of patients treated by hydroxyurea did not differ between those with a positive history of ACS and those without ($\chi^2 = 0.059$, $p = 1$). Our results contrast with previous studies inferring that obstructive ventilatory defects and ACS would be associated.[18] We found no evidence supporting an association with hydroxyurea treatment, but we should also point out that half of our subjects received hydroxyurea treatment, which reduces ACS frequency.[19] However, the direct effects of hydroxyurea treatment on lung function remain unknown, and will need to be evaluated.

In conclusion lung diffusing capacity is decreased in 46.1% of patients suffering from homozygous SCD. The reductions in diffusing capacity may be primarily explained by a low alveolar volume, and are significantly more frequent in patients with evidence of restrictive lung disease. Further studies are needed to determine the mechanisms underlying these lung functional abnormalities in order to prevent the emergence of dyspnea in patients suffering from homozygous SCD.

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