Cerebrovascular Reserve Capacity is Impaired in Patients with Sickle Cell Disease

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Abstract

Sickle cell disease (SCD) is associated with a high incidence of ischemic stroke. SCD is characterized by chronic hemolytic anemia, resulting in reduced nitric oxide (NO)-bioavailability, and by impaired cerebrovascular hemodynamics. Cerebrovascular CO$_2$ responsiveness is NO dependent and has been related to an increased stroke risk in microvascular diseases. We questioned whether cerebrovascular CO$_2$ responsiveness is impaired in SCD and related to hemolytic anemia. Transcranial Doppler-determined mean cerebral blood flow velocity ($V_{\text{mean}}$), near-infrared spectroscopy-determined cerebral cortical oxygenation and end-tidal CO$_2$ tension ($P_{\text{ETCO}_2}$) were monitored during normocapnia and hypercapnia in 23 patients and 16 control subjects. Cerebrovascular CO$_2$ responsiveness was quantified as $\Delta\% V_{\text{mean}}$ and $\Delta\mu$mol/L cerebral oxyhemoglobin, deoxyhemoglobin and total hemoglobin per mmHg change in $P_{\text{ETCO}_2}$. Both ways of measurements revealed lower cerebrovascular CO$_2$ responsiveness in SCD patients than in controls ($V_{\text{mean}}$: 3.7(3.1–4.7) vs. 5.9(4.6–6.7)$\Delta\% V_{\text{mean}}$/mmHg, $P=0.0001$; oxyhemoglobin: 0.36(0.14–0.82) vs. 0.78(0.61–1.22)$\Delta\mu$mol/L/mmHg, $P=0.025$; deoxyhemoglobin: 0.35(0.14–0.67) vs. 0.58(0.41–0.86)$\Delta\mu$mol/L/mmHg, $P=0.033$; total-hemoglobin: 0.13(0.02–0.18) vs. 0.23(0.13–0.38)$\Delta\mu$mol/L/mmHg, $P=0.038$). Cerebrovascular CO$_2$ responsiveness was not related to markers of hemolytic anemia. In SCD patients, impaired cerebrovascular CO$_2$ responsiveness reflects a reduced cerebrovascular reserve capacity, which may play a significant role in the pathophysiology of stroke.
Introduction

Cerebral infarction is one of the most devastating complications of sickle cell disease (SCD), occurring in approximately 10% of patients in the first two decades of life.\(^1\)\(^-\)\(^3\) Furthermore, silent cerebral infarctions occur in about 17% of pediatric patients,\(^4\)\(^,\)\(^5\) and are associated with poor educational and cognitive functioning.\(^6\) SCD is characterized by chronic hemolytic anemia and ongoing vaso-occlusion with exacerbations often requiring medical care.\(^7\)\(^-\)\(^9\) The vaso-occlusive process in SCD is of a complex nature mediated by red cell and leukocyte adhesion, inflammation, oxidative stress, and a hypercoagulable state, all resulting in endothelial injury and dysfunction.\(^8\) In addition, by reducing the nitric oxide (NO) bioavailability and by damaging the endothelium through the catalyzation of oxidative reactions in endothelial cells, chronic hemolysis leads to vascular complications.\(^10\)\(^-\)\(^12\)

Elevated cerebral blood flow velocity (≥ 200 cm.s\(^{-1}\)), measured by transcranial Doppler (TCD), has been identified as a risk factor for stroke in SCD.\(^13\) However, little is known about the mechanism of (ischemic) stroke in SCD patients and it has not been elucidated whether the increased cerebral blood flow velocity plays a causative role in stroke or whether it is a result of SCD related hemodynamic disturbances.

Cerebral blood flow (CBF) is tightly regulated to maintain constancy of cerebral perfusion in the face of varying systemic blood pressures by both local mechanisms and autonomic control (cerebral autoregulation).\(^14\)\(^-\)\(^16\) Recently, we demonstrated that dynamic cerebral autoregulation is impaired in SCD.\(^17\) Independent from cerebral autoregulation, the influence of the partial arterial carbon dioxide (CO\(_2\)) tension on CBF is of importance. Under normal conditions, increments and decrements of the partial arterial and thus end-tidal CO\(_2\) tension (\(P_{ET}CO_2\)) increase and decrease CBF by cerebral vasodilatation and vasoconstriction respectively.\(^18\) This phenomenon is known as the cerebrovascular CO\(_2\) responsiveness and reflects the vasodilatatory capacity of the cerebral vasculature or cerebrovascular reserve capacity.\(^19\)\(^-\)\(^22\) A reduced cerebrovascular reserve capacity
has been demonstrated to be an independent predictor of cerebrovascular ischemic events.\textsuperscript{23-25}

Cerebrovascular CO₂ responsiveness has been demonstrated to be impaired in patients with endothelial dysfunction and cerebral microangiopathy possibly due to a reduced NO bioavailability.\textsuperscript{26-28} Since SCD is associated with increased risk of stroke and characterized by low NO bioavailability due to its decreased generation (endothelial dysfunction)\textsuperscript{29} and increased scavenging by cell-free heme (chronic hemolysis),\textsuperscript{10, 11} we tested the hypothesis that the cerebrovascular CO₂ responsiveness is impaired in SCD and may be related to the degree of hemolysis.

The cerebrovascular CO₂ responsiveness can be quantified by relating changes in TCD determined middle cerebral artery (MCA) mean cerebral blood flow velocity ($V_{\text{mean}}$) or near-infrared spectroscopy (NIRS) determined changes in frontal cortical hemoglobin concentrations to artificially increased $P_{\text{ET}}$CO₂ as an estimate of arterial CO₂ tension ($P_{\text{a}}$CO₂).\textsuperscript{30, 31} In this study we evaluated cerebrovascular CO₂ responsiveness in SCD patients by simultaneously recording changes in both MCA $V_{\text{mean}}$ and frontal cortical concentrations of oxygenated- (oxyhemoglobin, $[O_2\text{Hb}]$), deoxygenated- (deoxyhemoglobin, [dHb]) and total hemoglobin ([t-Hb]) in response to hypercapnia.\textsuperscript{28, 30}

**Materials and Methods**

**Study population**

Consecutive SCD patients of the outpatient clinic of the department of Clinical Hematology, Academic Medical Center, Amsterdam and age-, gender- and ethnicity-matched healthy HbAA controls were recruited for the study. Inclusion criteria for SCD patients were age $\geq$ 18 years and homozygous sickle cell anemia (HbSS) confirmed by high performance liquid chromatography. Exclusion criteria were history of stroke, hypertension (systolic $>140$ mmHg
and/or diastolic >90 mmHg), use of cardiovascular medication, blood transfusion in the preceding four months and acute vaso-occlusive events (painful crises, acute chest syndrome, sequestration crises or priapism) in the preceding four weeks. All participants received verbal and written explanation of the objectives and procedure of the study and subsequently provided written informed consent. The study was approved by the AMC Medical Ethical Commission and experiments were performed in accordance with the Declaration of Helsinki.

**Recordings**

The TCD (DWL Multidop X4, Sipplingen, Germany) derived cerebral blood flow velocity was measured in the proximal segment of the MCA and insonated through the posterior temporal window. Once the optimal signal-to-noise ratio was obtained, the probe was secured with a headband (Marc 600, Spencer Technologies, Seattle, USA). Middle cerebral artery \( V_{\text{mean}} \) was used for evaluation of changes in CBF assuming that changes in MCA \( V_{\text{mean}} \) are representative of those in CBF. TCD monitors blood flow velocity rather than blood flow and changes in the diameter of the insonated vessel could modulate velocity independently of flow. However the MCA is a conductance rather than a resistance vessel and changes in mean arterial pressure and CO\(_2\) have negligible effects on its luminal diameter.\(^{32, 33}\)

Changes in cerebral oxygenation were monitored using NIRS (Oxymon, Artinis Medical Systems BV, Zetten, The Netherlands) which, based on the transparency of tissue to light in the near-infrared region, detects changes in tissue chromophores, i.e. mainly \( O_{2}\text{Hb} \) and \( d\text{Hb} \). With the use of a modified Lambert-Beer law changes in light absorption at different wavelengths are measured, and tissue oxygenation is monitored. To estimate changes in \([O_{2}\text{Hb}]\) and \([d\text{Hb}]\), a differential path length factor of 6.0 was applied to account for the scattering of light in the tissue. Changes in regional cerebral tissue oxygenation were followed by NIRS at wavelengths of 775 and 850 nm. \([O_{2}\text{Hb}]\) and \([d\text{Hb}]\) were recorded at 10-Hz with the light source and sensing optodes
positioned on the ipsilateral side of the TCD insonation above the supra-orbital ridge below the hairline, with an interoptode distance of 5.0 cm, and secured with a lightproof holder attached to a headband. NIRS determined brain capillary oxygenation is functionally related to the balance between arterial and jugular venous oxygen saturation. Changes in cerebral blood volume are reflected by changes in total hemoglobin concentration [t-Hb] expressed as the sum of [O₂Hb] and [dHb]. Changes in [O₂Hb] and [dHb] in µmol/L are calculated with baseline (normocapnic resting) values as reference set at 0 µmol/L.

$P_{ET}CO_2$ was measured by a sampling infrared capnograph (Tonocap, Datex-Ohmeda, Madison, USA). Brachial arterial blood pressure (BP) was measured with an automated non-invasive device (HEM-705CP, Omron, Kyoto, Japan). Peripheral transcutaneous O₂ saturation (SpO₂) was measured using a pulse oximeter (Novametrix 515A, Wallingford, Connecticut, USA).

Protocol and Measurements

Measurements were performed in supine position in a quiet environment with an ambient temperature of 22° C. All participants were asked to abstain from caffeinated beverages for at least 12 hours prior to measurement. After instrumentation volunteers started breathing through a standard spirometry mouth-piece, with the lips sealed tightly around its edge to prevent air leakage. A nose peg was applied during the measurements to prevent nasal breathing. Following 5 minutes of baseline normocapnic measurements, the mouth-piece was attached to a gas mixture of 5% CO₂ and 95% O₂. Changes in $P_{ET}CO_2$ provided a continuous quality check of breathing through the mouth-piece. The participants continued breathing this hypercapnic gas mixture until the rising cerebral blood flow velocity and cerebral [O₂Hb], [dHb] and [t-Hb] signals reached a steady state.

Blood samples

Blood samples were drawn via venipuncture. Standard blood counts (hemoglobin (Hb), hematocrit
(Ht), leucocytes, platelets and reticulocyte %) were performed in EDTA blood (Cell-Dyn 4000, Abbott, Illinois, USA). Lactate dehydrogenase (LDH) and total bilirubin levels were measured in heparinized plasma with spectrophotometry (P800 Modular, Roche, Basel, Switzerland).

**Data Analysis**

Signals of MCA blood flow velocity and PETCO₂ were collected and analog-to-digital (AD) converted with a sampling frequency of 100 Hz. NIRS data were AD converted with a sampling frequency of 10 Hz. All data were stored on hard disk for off-line analysis. Beat-to-beat values for MCA V<sub>mean</sub> were derived as the integral over one beat divided by the corresponding beat interval. Cerebrovascular CO₂ responsiveness was expressed as percentage change of MCA V<sub>mean</sub> per mmHg change in PETCO₂ and as changes in [O₂Hb], [dHb] and [t-Hb] per mmHg change in PETCO₂ between normocapnia and hypercapnia.

**Statistics**

Based on the study of Lavi et al.,<sup>27</sup> (with a calculated standard deviation of 0.4, a difference in population means of 0.4 and type 1 error of 0.05) 19 patients and 14 controls had to be included in the study to attain 80% power for the difference in cerebrovascular CO₂ responsiveness as determined by the TCD measured V<sub>mean</sub>. Data are presented as medians with interquartile range (IQR), unless stated otherwise. Mann-Whitney U-test was applied to test differences between the groups. The Spearman Rank (rₚ) correlation coefficient was calculated for correlation studies. P-values < 0.05 were considered statistically significant (SPSS 16.0, SPSS Inc., Chicago, IL, USA).
Results

Patient data

Of 45 consecutive eligible homozygous (HbSS) SCD patients who visited our out-patient clinic, 23 (14 women; aged 26 (21 – 42) years) agreed to participate in the study. Sixteen age-, gender- and ethnicity-matched healthy controls [9 women; aged 33 (24 – 40) years] were also included in the study. NIRS data of 9 patients and 3 controls were excluded from analysis due to an insufficient noise to signal ratio (sudden and recurrent spikes during the measurements). SCD patients had lower BMI, diastolic BP, SpO2, Hb and Ht and higher MCA Vmean, reticulocyte percentage, LDH and total bilirubin levels (Table 1). Age, gender ratio and systolic BP were comparable between groups.

Cerebrovascular CO2 responsiveness

The cerebrovascular CO2 responsiveness determined with both TCD (Figure 1A) and NIRS (Figure 1B) was lower in SCD patients than in controls. Representative examples of continuous PETCO2 and cerebral blood flow velocity recordings of a healthy control (A) and a sickle cell patient (B) are depicted in Figure 2.

During normocapnia Vmean correlated to Ht (r = -0.46, P=0.004; Figure 3A). When analyzed for the SCD and control group separately, the correlations between normocapnic resting cerebral blood flow velocity and Ht were r = -0.40, P=0.068 and r = -0.01, P=0.98 respectively (Figure 3B). Neither Ht nor Vmean at normocapnia were related to cerebrovascular CO2 responsiveness (Figure 4, A and B respectively). Other indicators of hemolytic anemia, including Hb, reticulocyte percentage and LDH, were not related to cerebrovascular CO2 responsiveness either (data not shown). Cerebrovascular CO2 responsiveness was not related to age. Within the SCD group, patients using hydroxyurea tended to have a higher cerebrovascular CO2 responsiveness than those not on hydroxyurea, but only statistically
different for [dHb] (Figure 5). Hemoglobin levels between SCD patients using and those not using hydroxyurea were comparable (9.1 (8.5 – 9.6) vs. 9.0 (8.1 – 9.8). Hemoglobin F (HbF) levels, available from earlier laboratory controls, were not related to cerebrovascular CO₂ responsiveness (data not shown).

**Discussion**

The results of this study provide new insights regarding cerebrovascular control in sickle cell disease. The main finding of the study is that cerebrovascular CO₂ responsiveness in young adult SCD patients was reduced implying that the vasodilatatory capacity of the cerebral vasculature is impaired. The defect in cerebrovascular CO₂ responsiveness appeared not to be related to the hematocrit or normocapnic resting $V_{\text{mean}}$. Reduction of cerebrovascular CO₂ responsiveness is thought to play an important role in the pathogenesis of cerebral microangiopathy which may contribute to the increased susceptibility to cerebrovascular ischemic events, particularly upon increased metabolic requirements or during episodes of hypoperfusion, e.g. SCD-related cerebral vaso-occlusion and hypotension.

SCD is characterized by a reduced NO bioavailability which may contribute to the reduced cerebrovascular CO₂ responsiveness in this disease. Elevated levels of cell-free heme as a result of chronic hemolysis induce increased NO scavenging thereby reducing NO bioavailability in SCD. However, in the present study, the impaired cerebrovascular CO₂ responsiveness was not related to the standard biomarkers of hemolysis. As more specific indicators of hemolysis (eg cell-free heme) were not available, a causative relation between hemolysis and cerebrovascular CO₂ responsiveness can not be ruled out. Of interest, whereas cerebrovascular CO₂ responsiveness was not related to HbF levels, the use of hydroxyurea seemed to relate to a higher cerebrovascular reserve capacity in SCD patients, even though
hemoglobin levels between these two patient groups were comparable. Although the study was not designed to assess the effect of hydroxyurea on cerebrovascular reserve capacity, this observation suggests that hydroxyurea may have a beneficial influence on the endothelial function and consequently the cerebrovascular reserve capacity.

A possible role of hyperemia related cerebral vasodilatation as a cause of reduced cerebrovascular reserve capacity also needs to be considered. The hyperemia related cerebral vasodilatation might be induced by an increased cerebral blood flow demand as a compensation for anemia. However, in the present study, while finding a weak correlation between Ht and \( V_{\text{mean}} \) at normocapnia, neither Ht nor the normocapnic resting \( V_{\text{mean}} \) was related to cerebrovascular CO\(_2\) responsiveness, rendering a major role of hyperemia as a cause of reduced cerebrovascular reserve capacity in adult SCD patients less likely. While we do not exclude a role of hyperemia related cerebral vasodilatation in the reduced cerebral reserve capacity, as suggested by Prohovnik et al.,\(^{37}\) we would also like to call attention to other contributing factors, including chronic endothelial damage by repeated vaso-occlusion (ischemia-reperfusion),\(^{38}\) inflammation,\(^{8}\) and intravascular hemolysis\(^{10,11}\) and a reduced NO bioavailability.\(^{29,36}\) It should be taken into account that the study by Prohovnik et al., measuring global cerebral blood flow by the \(^{133}\)Xe inhalation method in SCD patients, was performed in a heterogeneous group of SCD patients ranging from HbSS children with high \( V_{\text{mean}} \) to adults with the less severe heterozygous HbSC and patients receiving blood transfusions with consequently higher Ht and lower \( V_{\text{mean}} \). In the present study only adult homozygous HbSS SCD patients without blood transfusions in the preceding 4 months were included. Furthermore, the normocapnic resting \( V_{\text{mean}} \) in SCD patients of the present study (79 (69 – 98)cm/s) was well below the hyperemic values normally observed in pediatric SCD patients.
The second important influence on CBF consists of cerebral autoregulation that maintains CBF more or less stable within a range of mean arterial pressure between 60 and 150 mmHg. In a previous study we demonstrated that SCD patients also have an impaired dynamic cerebral autoregulation. Together with the findings of the present study, these results imply that in SCD both mechano- and chemoregulation as the two major operative mechanisms responsible for maintaining CBF are impaired, rendering SCD patients susceptible to ischemic episodes. Based on the highly sensitive control of the cerebral vasculature via changes in $P_{\text{ET}}\text{CO}_2$ and the inverse relationship between CBF and ventilation, the alteration in CBF regulation has been proposed to contribute to breathing instability. This was recently verified in healthy subjects where pharmacological reduction of brain CO$_2$ responsiveness increased breathing instability and apneas during sleep. Whether this is of influence in SCD patients is unknown where the impact of the combined disarrangement of mechano- and chemo brain blood flow regulation is as yet largely unidentified and data regarding overnight pulse oximetry of the study patients were unavailable.

In the present study, the middle cerebral artery $V_{\text{mean}}$ was used for evaluation of changes in CBF. Since MCA is a conductance rather than a resistance vessel, changes in MCA $V_{\text{mean}}$ are representative of those in CBF. NIRS is based on a different physical principle and tracks changes in cerebral frontal oxygenation with a comparable time-resolution as TCD determined $V_{\text{mean}}$. In humans NIRS has been shown as an adequate measure of cerebral oxygenation. Simultaneous assessment of cerebrovascular CO$_2$ responsiveness by TCD and NIRS have shown correlating results in patients with cerebrovascular disease. This was also observed in the present study, where parallel changes of NIRS-determined cerebral blood oxygen concentrations to those in TCD determined $V_{\text{mean}}$ in response to CO$_2$ affirmed the observed differences between patients and controls. A potential influence of anemia on NIRS data in the patient group has to be considered. However, to our knowledge the effect of
reduced Hb concentration on changes in [O$_2$Hb], [dHb] and [t-Hb] as determined by NIRS has not been investigated yet. Therefore we can only speculate on the influence of anemia on the NIRS results, whereas the TCD results confirm the impairment of cerebrovascular CO$_2$ responsiveness in SCD patients.

Although a history of symptomatic stroke was an exclusion criterion, the presence of silent cerebral infarcts in the study patients can not be ruled out. Interestingly in patients with type 2 diabetes, regional white matter hyper-intensities were associated with reduced cerebrovascular CO$_2$ responsiveness. Despite the relatively small sample size, further limited by missing NIRS data in 9 patients and 3 controls, the strongly significant decreases in cerebrovascular CO$_2$ responsiveness in the SCD patients suggest an important role for impaired cerebrovascular CO$_2$ responsiveness in the increased susceptibility to stroke in SCD, regardless of the presence or absence of silent cerebral infarcts. However whether silent cerebral infarcts are related to cerebrovascular CO$_2$ responsiveness, needs to be elucidated in a larger study with cerebrovascular CO$_2$ responsiveness measurements combined with cerebral MRI.

Currently, pediatric SCD patients with high stroke risk are identified by TCD screening. Even though this is an effective strategy, many of these patients are exposed to the risks of long-term transfusion programs while not all patients will experience stroke. A better understanding of the pathophysiology of SCD related stroke is needed in order to identify new management strategies and to further optimize stroke risk assessment. Whether the degree of cerebrovascular CO$_2$ responsiveness could be of additional diagnostic and prognostic value in SCD related strokes in pediatric patients is subject of further study.

In conclusion, we demonstrated that homozygous sickle cell patients without a history of symptomatic stroke have an impaired cerebrovascular CO$_2$ responsiveness suggesting a reduced cerebrovascular reserve capacity that might play a role in the pathophysiology of
stroke in SCD. The impaired cerebrovascular CO₂ responsiveness was not related to the
degree of hemolysis. Whether cerebrovascular CO₂ responsiveness measurement could be of
additional prognostic value next to TCD screening in identifying patients at high risk for
stroke,⁴⁴,⁴⁵ remains to be elucidated.

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Authorship Contributions

E.N. designed and performed research, analyzed data and wrote the manuscript; Y.K.
designed and performed research, participated in data analysis and edited the manuscript; J.T.
performed research and participated in data analysis; E.J.v.B. designed and performed
research; S.C.A.T.D. performed research; D.P.B. participated in data analysis and edited the
manuscript; B.J.B. and J.J.v.L designed research and edited the manuscript.

Conflict of Interest Disclosures

All authors declare no conflicts of interest.

For a complete list of CURAMA Study Group participants, see the Supplemental
Appendix.
Reference List


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Table 1: Patient characteristics and hemolytic parameters.

<table>
<thead>
<tr>
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<th>Patients (n = 23)</th>
<th>Controls (n = 16)</th>
<th>P-value</th>
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<tr>
<td>Age (median + range)</td>
<td>26 (21 – 42)</td>
<td>33 (24 – 40)</td>
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<tr>
<td>Male: Female</td>
<td>9:14</td>
<td>7:9</td>
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<tr>
<td>BMI</td>
<td>21.2 (20.4 – 23.9)</td>
<td>23.5 (21.4 – 26.6)</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>121 (112 – 130)</td>
<td>125 (120 – 127)</td>
<td>0.25</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>71 (66 – 77)</td>
<td>78 (77 – 82)</td>
<td>0.003</td>
</tr>
<tr>
<td>MCA $V_{\text{mean}}$, cm·s$^{-1}$</td>
<td>79 (69 – 98)</td>
<td>69 (55 – 77)</td>
<td>0.021</td>
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<tr>
<td>SpO$_2$ (mmHg)</td>
<td>97 (96 – 97)</td>
<td>98 (97 – 98)</td>
<td>0.016</td>
</tr>
<tr>
<td>Hb (gm/dL)</td>
<td>9.0 (8.5 – 9.7)</td>
<td>12.9 (12.3 – 14.0)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Ht (L/L)</td>
<td>0.25 (0.24 – 0.29)</td>
<td>0.39 (0.37 – 0.41)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Reticulocyte %</td>
<td>7.8 (6.4 – 11.3)</td>
<td>0.9 (0.8 – 1.6)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>LDH (U/L)</td>
<td>380 (336 – 469)</td>
<td>155 (131 – 171)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Total bilirubin (mg/dL)</td>
<td>2.7 (2.0 – 4.5)</td>
<td>0.7 (0.4 – 1.7)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Values are medians with interquartile ranges (IQR); age is median with range. BMI body mass index; BP blood pressure; MCA middle cerebral artery; SpO$_2$ transcutaneous peripheral oxygen saturation; Hb hemoglobin; LDH lactate dehydrogenase;
Legends to figure:

Figure 1

Cerebrovascular CO₂ responsiveness (CCR) in SCD patients (SCD; black bars) and healthy controls (CTRL; black bars) use. (A) Cerebrovascular CO₂ responsiveness expressed as relative change in cerebral mean blood flow velocity (% ΔV mean) per mmHg change in PETCO₂ (CCR-TCD) was lower in SCD patients (n=23) than in healthy controls (n=16). (B) Cerebrovascular CO₂ responsiveness expressed as absolute changes (Δμmol/L) in cerebral [O₂Hb], [dHb] and [t-Hb] per mmHg PETCO₂ (CCR-NIRS) were also significantly lower in SCD patients (n=14) than in healthy controls (n=13). Mean ± SEM.

Figure 2

Representative continuous recordings of partial end-tidal CO₂ tension (PETCO₂) and cerebral blood flow velocity (CBFV) of a healthy subject (A) and a sickle cell patient (B). In the patient the increase in CBFV is less pronounced. Early leveling off for a comparable change in PETCO₂ indicates a reduced cerebrovascular CO₂ responsiveness.

Figure 3

Spearman Rank correlation between hematocrit (Ht) and resting cerebral blood flow velocity (V mean) at normocapnic conditions (rₙ=-0.46, P=0.004; n = 38) across all participants (A) and in the SCD (●; rₙ=-0.36, P=0.098; n = 23) and control (Δ; rₙ=-0.01, P=0.96; n = 16) groups separately (B).
Figure 4

A. Spearman Rank correlation between normocapnic resting cerebral blood flow velocity ($V_{\text{mean}}$) and cerebrovascular CO$_2$ responsiveness (CCR) in SCD patients (●; $r_s=0.07$, $P=0.8$; $n=23$) and controls (▲; $r_s=-0.05$, $P=0.9$; $n=16$).

B. Spearman Rank correlation between hematocrit and cerebrovascular CO$_2$ responsiveness (CCR) in SCD patients (●; $r_s=-0.18$, $P=0.4$; $n=23$) and controls (▲; $r_s=0.07$, $P=0.8$; $n=16$).

Figure 5

Cerebrovascular CO$_2$ responsiveness (CCR) in SCD patients with (Hydroxy+; gray bars) and without hydroxyurea (Hydroxy-; black bars) use. (A) Cerebrovascular CO$_2$ responsiveness expressed as relative change in cerebral mean blood flow velocity ($\% \Delta V_{\text{mean}}$) per mmHg change in $P_{\text{ET}}$CO$_2$ (CCR-TCD) was higher in SCD patients using hydroxyurea (n=10) than in those not using hydroxyurea (n=13), though the difference was not statistically significant. (B) Cerebrovascular CO$_2$ responsiveness expressed as absolute changes ($\Delta \mu$mol/L) in cerebral [O$_2$Hb], [dHb] and [t-Hb] per mmHg $P_{\text{ET}}$CO$_2$ were also higher in SCD patients using hydroxyurea (n=7) than in those not using hydroxyurea (n=7), though the difference was only statistically significant for dHb derived cerebrovascular CO$_2$ responsiveness. Mean ± SEM.
Figure 1
Figure 2
Figure 3
Figure 4
Figure 5
Cerebrovascular reserve capacity is impaired in patients with sickle cell disease

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