Dynamic Cerebral Autoregulation in Homozygous Sickle Cell Disease

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Background and Purpose—Sickle cell disease (SCD) is associated with cerebral hyperperfusion and an increased risk of stroke. Also, both recurrent microvascular obstruction and chronic hemolysis affect endothelial function, potentially interfering with systemic and cerebral blood flow control. We addressed the question whether cerebrovascular control in patients with SCD is affected and related to hemolysis.

Methods—Systemic and cerebrovascular control were studied in 18 patients with SCD and 10 healthy subjects. Dynamic cerebral autoregulation was evaluated by transfer function analysis assessing the relationship between mean cerebral blood flow velocity and mean arterial pressure.

Results—Normal baroreflex sensitivity and postural cardiovascular reflex responses indicated integrity of systemic cardiovascular control. In the low- (0.07 to 0.15 Hz) frequency region, mean arterial pressure variability was comparable for both groups, but a larger mean cerebral blood flow velocity variability in SCD (6.1 [4.6 to 7.0] versus 4.2 [2.6 to 5.2] [cm·s⁻¹]·Hz⁻¹; P<0.05) indicated a reduced capacity to buffer the transfer of blood pressure surges to the cerebral tissue. Impairment of dynamic cerebrovascular control was confirmed by a reduced mean arterial pressure-to-mean cerebral blood flow velocity transfer function phase lead in SCD versus healthy subjects (32±17° versus 50±19°, P<0.05) that was unrelated to the severity of hemolysis.

Conclusions—In patients with SCD, dynamic cerebral autoregulation is impaired but appears unrelated to hemolysis.

Key Words: baroreflex sensitivity ■ brain circulation ■ cerebral blood flow ■ hemodynamics ■ transcranial Doppler

Sickle cell disease (SCD) exhibits coexistence of contrasting perfusion profiles with microcirculatory hyperperfusion and systemic circulatory hyperperfusion with increased regional blood flow.¹ Patients with SCD are proposed to have a lower systemic vascular resistance² and blood pressure (BP)³ compared with healthy subjects, yet cerebral infarction with acute neurological deficits affects 5% to 17% of patients with SCD by 15 years of age.⁴–⁶ Silent cerebral infarctions are present in approximately one third of homozygous patients with SCD without clinically apparent neurological events,⁷ but whether control of cerebral blood flow (CBF) functions normally is unknown.

Generally, BP is a determinant of the risk of ischemic stroke. Although in patients with SCD BP is within the so-called cerebrovascular autoregulatory range, where constancy of CBF is maintained for a wide range of BP, patients may be nevertheless exposed to cerebral hyperperfusion⁸ reflected by an increased CBF and cerebral blood flow velocity (CBFV).⁹–¹⁰ Cerebral hyperemia is assumed to be a consequence of the anemic state and a relationship with a higher incidence of stroke in patients with SCD has been proposed.¹ This questions the efficacy of cerebrovascular autoregulatory capacity to protect the brain against hyperperfusion.

Furthermore, SCD is characterized by recurrent microvascular obstruction and chronic hemolysis. Both affect endothelial function and are associated with a reduced nitric oxide (NO) bioavailability as the result of reduced formation of NO and increased scavenging of NO by cell-free circulating hemoglobin (Hb) released due to chronic hemolysis. Cerebrovascular endothelium plays an important role in the regulation of CBF,¹¹ and endothelial dysfunction may interfere with cerebral autoregulation.

We questioned whether cerebrovascular control in patients with SCD is affected and related to hemolysis, and therefore set out to evaluate systemic cardiovascular and cerebral blood flow control in patients with SCD in relation to the degree of hemolysis.
Table 1. Group Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CTRL (n=10)</th>
<th>SCD (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>3/7</td>
<td>5/13</td>
</tr>
<tr>
<td>Age, years</td>
<td>35 (9)</td>
<td>33 (12)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.6 (4.6)</td>
<td>22.1 (3.0) †</td>
</tr>
<tr>
<td>History of hypertension*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>120 (9)</td>
<td>120 (11)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76 (6)</td>
<td>72 (7) †</td>
</tr>
<tr>
<td>Mean</td>
<td>92 (6)</td>
<td>88 (8)</td>
</tr>
<tr>
<td>Spo₂, %</td>
<td>97.4 (0.8)</td>
<td>96.3 (1.3) †</td>
</tr>
<tr>
<td>Hb, mmol/L</td>
<td>8.0 (7.6–8.3)</td>
<td>5.7 (5.3–6.1) †</td>
</tr>
<tr>
<td>Hematocrit, L/L</td>
<td>0.39 (0.03)</td>
<td>0.26 (0.04) †</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>154 (24)</td>
<td>392 (328–454) †</td>
</tr>
<tr>
<td>Reticulocyte, %</td>
<td>1.4 (0.8–1.7)</td>
<td>7.1 (6.4–9.5) †</td>
</tr>
<tr>
<td>Organ damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Folic acid</td>
<td>0</td>
<td>18</td>
</tr>
</tbody>
</table>

*Defined as BP >140/90 mm Hg. †P<0.05 and ‡P<0.01 versus CTRL. Data are presented as means (SD) or medians (interquartile range). Spo₂ indicates O₂ saturation.

Subjects and Methods

Subjects

Afro-Caribbean black subjects with SCD and age- and ethnicity-matched healthy subjects (CTRL) were consecutively recruited from the outpatient clinic at the Academic Medical Center. Group characteristics are presented in Table 1. All subjects gave their written informed consent as approved by the Academic Medical Center Medical Ethical Committee and experiments were performed in accordance with the Declaration of Helsinki. Only patients with SCD with genotype HbSS or HbSβ thalassemia, confirmed by high-performance liquid chromatography, were included in the study. Exclusion criteria consisted of: a sickle cell crisis in the preceding 4 weeks, history of symptomatic cerebral vascular disease, clinical manifestation of heart failure or other cardiovascular diseases, uncontrolled hypertension (BP >160/100 mm Hg), orthostatic hypotension, use of medication with potential influence on autonomic cardiovascular function, or a blood transfusion in the preceding 4 months. The studies were performed in morning sessions in a room at 22°C. Subjects were requested to abstain from caffeinated beverages for at least 12 hours before measurements.

Blood Samples

Degree of hemolysis was represented by Hb, reticulocyte count, lactate dehydrogenase (LDH), and haptoglobin plasma levels. Venous blood samples were drawn from all subjects and centrifuged immediately at 3000 g for 15 minutes and then stored at −80°C. Complete blood counts (Hb, hematocrit, leukocyte, reticulocyte percentage) were determined (Cell-Dyn 4000; Abbott) and LDH was analyzed using spectrophotometry (Roche Hitachi Modular P800, Basel, Switzerland).

Hemodynamic Parameters

Continuous BP was measured noninvasively by a servo-controlled finger photoplethysmograph (Portapres; FMS, Amsterdam, The Netherlands) with the cuff placed on the middle phalanx of the left middle finger kept at heart level. Changes in BP measured by photoplethysmography are not different from intra-arterial BP measurements both at rest and during orthostatic stress. An automated noninvasive BP measuring device (HEM-705CP; Omron, Kyoto, Japan) was used to calibrate the finger BP measurements. Stroke volume was determined by pulse wave analysis using the Modelflow method (BeatScope 1.0 software; BMEye, Amsterdam, The Netherlands). Heart rate (HR) was the inverse of the interbeat interval. Cardiac output was the product of HR and stroke volume, and systemic vascular resistance was mean arterial pressure (MAP) divided by cardiac output. The transcranial Doppler- (DWL Multi-dop X4, Sipplingen, Germany) derived CBFV was measured in the proximal segment of the right middle cerebral artery (MCA) and the MCA was sonomated 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, Wash). Arterial CO₂ tension influences CBF independently of cerebral autoregulation. To account for the cerebrovascular effects of CO₂, end-tidal CO₂ tension was measured by a sampling infrared capnograph (Tonocap; Datex-Ohmeda, Madison, Wis). Transcutaneous O₂ saturation was measured using a pulse oximeter (Novametrix 515A; Wallingford, Conn). The signals of BP, spectral envelope of MCA velocity, and end-tidal CO₂ tension were analog/digital converted at 100 Hz and stored on a hard disk for offline analysis.

Systemic Cardiovascular Control

The MAP, HR, and systemic vascular resistance responses to orthostatic stress assessed efferent sympathetic vasomotor function. Afferent, central, and vagal efferent baroreceptor reflex pathways were evaluated by quantifying baroreflex sensitivity using the sequential method. Beat-to-beat values of systolic BP and interbeat interval were interpolated and resampled at 1 second. Cross-correlations were calculated using a 10-second window containing systolic BP for delays in the interbeat interval window of 0 to 5 seconds. The highest coefficient of correlation was selected and accepted if P<0.01. Baroreflex sensitivity was the slope of the regression line between changes in interbeat interval versus systolic BP, expressed as ms · mm Hg⁻¹.

Cerebral Blood Flow Control

The steady-state response of mean MCA velocity (MCA Vmean) to postural change was assessed from steady-state arterial pressure and CBFV sampled from 1 minute before standing up to 5 minutes upright. With standing, the positioning of the head approximately 30 cm above heart level within a few seconds results in an abrupt reduction in cerebral perfusion pressure of approximately 20 mm Hg, with a decrease in cerebral tissue oxygenation, and reflected by the transcranial Doppler determined CBFV. Such steady-state reductions in cerebral perfusion take place even though the cerebral perfusion pressure remains within, what is considered to be, its autoregulatory range. Static cerebral autoregulation limits the steady-state postural reduction in MCA Vmean to approximately 15%, Beat-to-beat values for MCA Vmean and MAP were derived as the integral over one beat divided by the corresponding beat interval. MAP at brain level (MAPbrain) was calculated from MAP measured at heart level and the vertical finger-to-transcranial Doppler probe distance. Cerebrovascular resistance was the ratio of MAPbrain and MCA Vmean. The Gosling pulsatility index of the MCA was taken as an index of cerebral microangiopathy expressed as the amplitude of CBFV divided by time-averaged CBFV.

Frequency domain analysis quantified the counterregulatory capacity of dynamic cerebral autoregulation from spontaneous BP oscillations in the upright position. A 4-minute tracing of beat-to-beat data of MAP and MCA Vmean was spline interpolated and resampled at 4 Hz. To quantify the variability of BP and CBFV, the power spectra of the 2 variables were estimated by transforming the time series of BP and CBFV with discrete Fourier transformation to the frequency domain. From the cross-spectrum, transfer function phase shift and gain were derived. According to the high-pass filter...
model of cerebral autoregulation, autoregulatory capacity is reflected by the positive phase relation between oscillations of BP (input function) and CBFV (output function). At high frequencies, less cerebral attenuation of MAP surges to MCA Vmean implies that the cerebral autoregulation cannot respond fast enough to rapid changes in MAP. Results were expressed as the integrated area in the low-frequency range (0.07 to 0.15 Hz). The gain as the ratio of the amplitudes of MCA Vmean and MAP was taken to reflect the effective cerebral attenuation of BP fluctuations. To examine the strength of the relationship between MAP and MCA Vmean, coherence was used to signify that the 2 cardiovascular signals covary significantly in the low-frequency range.20

### Table 2. Cerebrovascular and Cardiovascular Response to Postural Change

<table>
<thead>
<tr>
<th>Groups</th>
<th>Supine</th>
<th>Standing 5 Minutes</th>
<th>Δ</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPmean mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTRL</td>
<td>83 (10)</td>
<td>93 (10)</td>
<td>+13%*</td>
<td>0.28</td>
</tr>
<tr>
<td>SCD</td>
<td>80 (7)</td>
<td>91 (11)</td>
<td>+14%*</td>
<td></td>
</tr>
<tr>
<td>MCA Vmean cm/s^-1</td>
<td>CTRL</td>
<td>64 (13)</td>
<td>-14%*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>SCD</td>
<td>87 (16)</td>
<td>-13%*</td>
<td></td>
</tr>
<tr>
<td>CVR, mm Hg.cm^-1.s^-1</td>
<td>CTRL</td>
<td>1.35 (0.23)</td>
<td>-4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>SCD</td>
<td>0.94 (0.16)</td>
<td>-5%</td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTRL</td>
<td>72 (13)</td>
<td>81 (4)</td>
<td>+13%*</td>
<td>0.34</td>
</tr>
<tr>
<td>SCD</td>
<td>75 (8)</td>
<td>86 (12)</td>
<td>+14%*</td>
<td></td>
</tr>
<tr>
<td>SV, mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTRL</td>
<td>96 (14)</td>
<td>68 (9)</td>
<td>-29%*</td>
<td>0.57</td>
</tr>
<tr>
<td>SCD</td>
<td>96 (16)</td>
<td>73 (12)</td>
<td>-25%*</td>
<td></td>
</tr>
<tr>
<td>CO, L.min^-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTRL</td>
<td>6.8 (1.2)</td>
<td>5.5 (0.8)</td>
<td>-19%*</td>
<td>0.13</td>
</tr>
<tr>
<td>SCD</td>
<td>7.1 (1.1)</td>
<td>6.0 (0.9)</td>
<td>-15%*</td>
<td></td>
</tr>
<tr>
<td>SVR, dyn.s.m^-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTRL</td>
<td>731 (182)</td>
<td>1022 (229)</td>
<td>+40%*</td>
<td>0.012</td>
</tr>
<tr>
<td>SCD</td>
<td>638 (78)</td>
<td>871 (135)</td>
<td>+37%*</td>
<td></td>
</tr>
<tr>
<td>PeCO2, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTRL</td>
<td>39.8 (2.7)</td>
<td>37.3 (2.3)</td>
<td>-6%*</td>
<td>0.72</td>
</tr>
<tr>
<td>SCD</td>
<td>39.3 (2.6)</td>
<td>37.5 (2.4)</td>
<td>-4%</td>
<td></td>
</tr>
<tr>
<td>Pulsatility index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTRL</td>
<td>0.78 (0.15)</td>
<td>0.75 (0.14)</td>
<td>-4%</td>
<td>0.90</td>
</tr>
<tr>
<td>SCD</td>
<td>0.78 (0.10)</td>
<td>0.78 (0.10)</td>
<td>-1%</td>
<td></td>
</tr>
<tr>
<td>BRS, ms.mm Hg^-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTRL</td>
<td>19 (8)</td>
<td>10 (5)</td>
<td>-49%*</td>
<td>0.93</td>
</tr>
<tr>
<td>SCD</td>
<td>19 (12)</td>
<td>10 (4)</td>
<td>-47%*</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.01 versus supine. P, probability value represents overall difference between CTRL and SCD groups. Data are given in means (SD) for n=10 (CTRL) versus n=18 (SCD).

CVR indicates cerebrovascular resistance; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance; PeCO2, end-tidal CO2 tension; BRS, baroreflex sensitivity.

### Results

#### Group Characteristics and Baseline Measurements

Eighteen Afro-Caribbean black subjects (5 male and 13 female) with SCD (17 patients with HbSS and one with HbSβ0 thalassemia) and 10 age- and ethnicity-matched healthy subjects (3 male and 7 female, CTRL) were included. Among the SCD versus CTRL groups, there were no differences with regard to gender ratio and age, whereas body mass index, O2 saturation, diastolic BP (P<0.05; Table 1), and systemic vascular resistance (P=0.012) were lower in SCD. In the SCD group, plasma LDH and reticulocyte count were higher and Hb lower (P<0.01), whereas haptoglobin was undetectably low. A limited (<15%) variation of these values in the preceding 2 years conformed to a relatively stable level of hemolysis. Baseline MAP, HR, stroke volume, cardiac output, end-tidal CO2 tension, and pulsatility index were comparable between groups (Table 2). MCA Vmean was higher (87±16 versus 64±13 cm/s^-1, P<0.01) and cerebrovascular resistance lower (0.94±0.16 versus 1.35±0.23 mm Hg.cm^-1.s^-1; P<0.01) in SCD.
A normal orthostatic increase in systemic vascular resistance confirmed intact efferent sympathetic vasomotor function in SCD (Figure 1). The postural reduction in stroke volume and cardiac output did not differ between groups. A normal orthostatic HR response together with normal baroreflex sensitivity indicated intact parasympathetic HR control in SCD.

Cerebral Blood Flow Control

The postural decline in MAP$_{\text{brain}}$ (−15%), MCA $V_{\text{mean}}$ (−13% versus −14%), and end-tidal CO$_2$ tension (−4% versus −6%) was comparable. In one subject from the CTRL group and in 2 subjects from the SCD group, coherence was <0.5 and these data were excluded from further analysis. MAP low-frequency power was comparable for both groups (Table 3), whereas MCA $V_{\text{mean}}$ low-frequency power was higher in the SCD group (6.1 [4.6 to 7.0] versus 4.2 [2.6 to 5.2] [cm·s$^{-1}$]²·Hz$^{-1}$; $P=0.043$). Representative examples of individual recordings are given in Figure 2. In the SCD group, the transfer function phase lead between MCA $V_{\text{mean}}$ and MAP was lower (32° [23° to 38°] versus 50° [44° to 60°]; $P<0.05$; Figure 3) with phase lead lower than 40° in 83% of the patients. MAP-to-MCA $V_{\text{mean}}$ transfer function phase did not relate to Hb, LDH, hematocrit, reticulocyte count, age, systolic and diastolic BP, body mass index, use of hydroxyurea or folic acid, and presence of chronic organ damage. Also, no relationship was found between Hb levels and MCA $V_{\text{mean}}$.

Discussion

The present study provides novel information regarding the control of CBF in patients with SCD. We found evidence for impairment of dynamic cerebral autoregulation in SCD that appeared unrelated to the degree of hemolysis, whereas systemic cardiovascular control was unaffected.

Impaired cerebral autoregulation has been linked to an increased risk for stroke, particularly in severe obstructive

![Figure 1. Cerebro- and cardiovascular response to postural change. The steady-state hemodynamic response to standing was comparable between the SCD group (n=18, gray line) and the CTRL group (n=10, black line). Bar indicates standing.](http://stroke.ahajournals.org/)

![Figure 2. Representative continuous recordings of BP and CBFV. A, Healthy control subject and (B) a patient with SCD. BP variability is comparable, whereas CBFV variability is enhanced in the patient with SCD indicating a reduced capacity to buffer the transfer of BP fluctuation to the cerebral circulation.](http://stroke.ahajournals.org/)
carotid artery disease. Silent cerebral infarctions are present in approximately one third of homozygous patients with SCD. The observation in the present study that cerebrovascular autoregulatory capacity was affected in the majority of consecutively recruited patients with SCD with asymptomatic cerebrovascular disease supports that impairment of dynamic CBF control precedes cerebral ischemic events. Our data represent the findings in adult patients and may therefore not be applicable in young children with homozygous SCD. However, although the clinical presentation of stroke appears to differ between children and adult patients with SCD, it seems likely that these clinical forms represent the same pathophysiological process. Both homozygous SCD and low Hb are major risk factors for both ischemic and hemorrhagic stroke in SCD. In addition, many patients with SCD present with secondary hemorrhagic stroke after a previous ischemic stroke. Future long-term follow-up studies in both young and adult patients with SCD are needed to strengthen these assumptions.

Impairment of dynamic cerebral autoregulation in patients with SCD puts forward a potential linkage to cerebral small vessel disease. This notion is supported by the finding that cerebral autoregulation is equally impaired in patients with Type 2 diabetes. The higher variability in CBFV in the SCD group indicated a reduced capacity to buffer the transfer of BP surges to the cerebral tissue. Impairment of dynamic cerebrovascular control was confirmed by a reduced phase lead of the BP-to-CBFV transfer function in SCD. In a previous study, the cerebral arterial pulsatility index has been proposed as an indicator of cerebral microangiopathy in patients with diabetes. However, this was not substantiated in the present study, questioning its applicability in patients with SCD.

SCD is characterized by an ongoing state of vascular inflammation with endothelial activation resulting in microvascular damage. This process is enhanced by the elevated oxidative stress associated with chronic hemolysis added to ischemia–reperfusion injury due to transient vaso-occlusive events. Both result in reduced NO bioavailability due to NO scavenging by cell-free hemoglobin and reduced NO formation due to increased arginase levels. We did not measure NO concentrations, but consider that the relationship between hemolysis and NO bioavailability is well established. Controversies exist regarding the role of NO in dynamic cerebral autoregulation in humans. We acknowledge that in the present study, indirect markers of hemolysis were used based on a small sample size; however, no relationship was found between dynamic cerebral autoregulatory capacity and severity of hemolysis. Larger studies are needed to establish the functional significance of this observation.

An inverse relationship between CBF and hematocrit level has been reported under physiological conditions both in animal models and in humans. In the present study, no relationship was found between either CBFV or dynamic cerebral autoregulatory capacity and Hb, rendering a role for anemia as an independent factor in the impairment of dynamic cerebral autoregulation unlikely. The finding of an elevated CBFV in the SCD group does not in itself imply affected dynamic cerebral autoregulation. For instance, in healthy subjects, CBFV changes in response to postural stress, exercise, and hyperglycemia independently of cerebral autoregulatory capacity.

Hydroxyurea has been demonstrated to reduce CBFV in children with SCD. Although hydroxyurea may reduce cellular adhesion of leukocytes and erythrocytes to endothelial cells, there are no data indicating an effect of folic acid or hydroxyurea on dynamic cerebral autoregulation. In the present study, all patients were treated with folic acid and 6 patients received hydroxyurea, whereas no correlation was found between the use of hydroxyurea or folic acid and transfer function phase.

The finding of comparable cardiac output but lower systemic vascular resistance and diastolic blood pressure in SCD versus CTRL is consistent with earlier observations. In contrast to an earlier report, we found intact baroreflex cardiovascular control and no signs of cardiovascular autonomic dysfunction in the SCD group. Thus, integrity of cardiovascular control contrasts to impairment of dynamic cerebrovascular control in patients with SCD.

Figure 3. Cross-spectral analysis of the entire spectrum from 0 to 0.30 Hz. Group averaged MAP and $V_{\text{mean}}$ variability, coherence, phase, and normalized gain between MAP and $V_{\text{mean}}$ are shown for SCD (n=16, gray line) versus CTRL groups (n=9, black line). Lines indicate low-frequency (0.07 to 0.15 Hz) range.

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Hydroxyurea has been demonstrated to reduce CBFV in children with SCD. Although hydroxyurea may reduce cellular adhesion of leukocytes and erythrocytes to endothelial cells, there are no data indicating an effect of folic acid or hydroxyurea on dynamic cerebral autoregulation. In the present study, all patients were treated with folic acid and 6 patients received hydroxyurea, whereas no correlation was found between the use of hydroxyurea or folic acid and transfer function phase.

The finding of comparable cardiac output but lower systemic vascular resistance and diastolic blood pressure in SCD versus CTRL is consistent with earlier observations. In contrast to an earlier report, we found intact baroreflex cardiovascular control and no signs of cardiovascular autonomic dysfunction in the SCD group. Thus, integrity of cardiovascular control contrasts to impairment of dynamic cerebrovascular control in patients with SCD.
Sickle cell disease is associated with an increased CBFV assessed by transcranial Doppler ultrasonography.4 Blood flow velocity rather than blood flow was monitored and it could be considered that changes in the diameter of the insonated vessel by enhanced sympathetic activity modulate blood flow velocity independently of flow. However, the large cerebral arteries are conductance rather than resistance vessels and moderate sympathetic activation does not modify the luminal diameter of a systemic conduit artery.16 Thus, CBF increases in proportion to changes in MCA mean blood flow velocity,44–46 or in internal carotid flow,47 and constancy of the diameter links changes in CBFV to changes in flow.48 An increased blood flow velocity may reflect intracranial stenosis in the MCA at the background of an unchanged global CBF, but it also may indicate cerebral hyperperfusion as a compensatory response to a SCD-associated reduced O2-binding capacity. Recently, an increased CBFV in patients with SCD has been attributed to hyperperfusion rather than intracranial stenosis,7 which conforms to earlier studies reporting an increased CBF as determined by \(^{133}\)Xe and MRI.10 In conclusion, the capacity to buffer the transfer of blood pressure surges to the cerebral tissue is reduced in patients with SCD but appears unrelated to hemolysis. Whether a hampered dynamic cerebral autoregulation plays a role in the high incidence of cerebrovascular complications in SCD remains to be elucidated.

Appendix

The CURAMA study group is a collaborative effort studying sickle cell disease in The Netherlands Antilles and The Netherlands. Participating centers are: the Red Cross Blood Bank Foundation, Curaçao, Netherlands Antilles; the Antillean Institute for Health Research, Curaçao, Netherlands Antilles; the Department of Internal Medicine, Slotervaart Hospital, Amsterdam, The Netherlands; the Department of Vascular Medicine and the Department of Hematology, Academic Medical Center, Amsterdam, The Netherlands; the Department of Hematology, Erasmus Medical Center, Rotterdam, The Netherlands; the Department of Pathology, Groningen University Hospital, The Netherlands; the Department of Internal Medicine, the Laboratory of Clinical Thrombosis and Hemostasis, and the Cardiovascular Research Institute, Academic Hospital Maastricht, The Netherlands.

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Disclosures

None.

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