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Cerebral Tissue Hemoglobin Saturation in Children with Sickle Cell Disease

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Abstract

Background—Desaturation of hemoglobin (Hb) in cerebral tissue, a physiologic marker of brain vulnerable to ischemic injury, can be detected non-invasively by transcranial oximetry. Absolute cerebral oximetry has not been studied in sickle cell disease (SCD), a group at very high risk of cerebral infarction in whom prevention of brain injury is key.

Procedure—We measured absolute Hb saturation in cerebral tissue (S_{CTO_2}) in children with SCD using near-infrared spectrophotometry and investigated the contributions of peripheral Hb saturation (SpO_2), hematologic measures, cerebral arterial blood flow velocity, and cerebral arterial stenosis to S_{CTO_2} . We also assessed the effects of transfusion.

Results—We studied 149 children with SCD (112 HbSS/ $S\beta^0$; 37 HbSC/ $S\beta^+$). S_{CTO_2} was abnormally low in 75% of HbSS/ $S\beta^0$ and 35% of HbSC/ $S\beta^+$ patients. S_{CTO_2} (mean $\pm$ SD) was 53.2 ± 14.2 in HbSS/ $S\beta^0$ and $66.1\pm9.2\%$ in SC/ $S\beta^+$ patients. S_{CTO_2} correlated with age, sex, Hb concentration, reticulocytes, Hb F, and SpO_2 , but not transcranial Doppler arterial blood flow velocities as continuous measures. In multivariable models, SpO_2 , Hb concentration, and age were significant independent determinants of S_{CTO_2} . Cerebral vasculopathy was associated with ipsilateral cerebral desaturation. Transfusion increased S_{CTO_2} and minimized the inter-hemispheric differences in S_{CTO_2} due to vasculopathy.

Conclusions—Cerebral desaturation, a physiologic marker of at-risk brain, is common in SCD, more severe in HbSS/ $S\beta^0$ patients, and associated with peripheral desaturation, more severe anemia, and increasing age. Cerebral oximetry has the potential to improve the identification of children with SCD at highest risk of neurologic injury and possibly serve as a physiologic guide for neuroprotective therapy.

Keywords

sickle cell disease; desaturation; hypoxemia; brain; risk factor; stroke

INTRODUCTION

Peripheral hemoglobin (Hb) desaturation is a common finding in sickle cell disease (SCD) that is associated with abnormally increased cerebral arterial blood flow velocities and central nervous system complications such as overt stroke. [1-4] Hb desaturation in SCD is

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the product of a combination of several known and suspected factors, including a compensatory rightward shift of the oxy-hemoglobin dissociation curve due to chronic anemia, physiochemical properties of sickle Hb in solution, ventilation-perfusion mismatching, possible cardiopulmonary shunts, and the confounding presence of dyshemoglobins. [5-7] Although a causal link has not been established, Hb desaturation might predispose to stroke by decreasing arterial oxygen content and limiting bulk delivery of oxygen to the brain, especially given SCD patients' chronic moderate to severe anemia, cerebral arterial stenosis, decreased cerebrovascular reserve, altered oxygen extraction, and periodic acute anemic or hypoxemic events. [8-11]

Cerebral oximetry is a non-invasive, near-infrared spectroscopic technique to measure Hb saturation in the brain. Cerebral oximetry measurements have been reported in patients with SCD previously. [12-15] However, these studies used an early-generation oximeter that did not measure the actual or absolute value of cerebral Hb saturation. Rather, it provided a relative value that helps to monitor changes in regional cerebral Hb saturations (rSO_2) from a known baseline state (e.g., following induction of anesthesia). This trending oximeter is also susceptible to interference by dark skin pigmentation because it uses only two wavelengths. [16,17] These early data suggested that cerebral Hb saturation is decreased in patients with SCD, but surprisingly no associations between peripheral and cerebral Hb saturation were found across studies. [12-15]

We wished to determine whether peripheral Hb desaturation is associated with Hb desaturation in the brain, because this could provide a mechanistic link between peripheral Hb desaturation and stroke. Therefore, we used a new-generation cerebral oximeter that measures the actual or absolute Hb oxygen saturation in cerebral tissue (S_{CTO_2}). By using four wavelengths, this oximeter is insensitive to interference by dark skin pigmentation. [16,17] We hypothesized that S_{CTO_2} was highly correlated with peripheral Hb oxygen saturation as measured by simultaneous pulse oximetry (SpO_2). We also explored the relationships between S_{CTO_2} and clinical, laboratory, and neurophysiological characteristics as well as the response to transfusion.

DESIGN AND METHODS

Study Overview and Participants

We performed a cross-sectional study of the Dallas Newborn Cohort (DNC) [18,19] to describe the distribution of S_{CTO_2} in children with SCD and to test the primary hypothesis that S_{CTO_2} correlated with SpO_2 . We studied all forms of SCD, including sickle cell anemia (HbSS), and sickle- β^0 -thalassaemia (HbS β^0), sickle-hemoglobin C disease (HbSC) and sickle- β^+ -thalassemia (HbS β^+). Participants with HbSS and HbS β^0 were analyzed as a single group (HbSS/S β^0), as were those with Hb SC and Hb S β^+ (HbSC/S β^+). Chronic transfusions were an exclusion from the main study. Response to single, simple transfusions was observed in a separate group of 10 chronically transfused participants. The local institutional review board approved this study. Parents or legal guardians of minors provided written informed consent. Minors ≥ 10 years of age also provided assent.

Oximetry

We used the FORE-SIGHT® cerebral oximeter (CAS Medical Systems, Inc., Branford CT, USA) to measure S_{CTO_2} with bi-frontal probes. S_{CTO_2} is measured mainly in gray matter (near the gray-white junction) in the frontal lobes, providing separate readings for each hemisphere. The probe overlays the watershed zone between the anterior and middle cerebral arteries. S_{CTO_2} is a measurement of a mix of arterial (~30%) and venous (~70%) blood, [20] reflecting the balance between cerebral tissue oxygen supply and demand. The

normal range of $S_{CT}O_2$ values in normal, normoxic individuals breathing room air is approximately 60-85%. [16,21,22].

We used the Nellcor N-395 pulse oximeter (Nellcor Puritan Bennett Inc., Pleasanton CA, USA) to measure SpO_2 . For the main study, we obtained single or “spot” measurements of cerebral tissue Hb saturation ($S_{CT}O_2$) and peripheral Hb saturation (SpO_2) during steady-state (“well”) clinic visits. In a separate analysis, intermittent or continuous $S_{CT}O_2$ monitoring was performed in 10 participants who received a simple transfusion as part of a chronic transfusion program for primary or secondary stroke prophylaxis. All transfused packed red blood cells were stored for 7 or fewer days before transfusion. All measurements of $S_{CT}O_2$ and SpO_2 were taken during the day in participants who were awake and breathing room air.

Clinical Imaging and Laboratory Studies

Transcranial Doppler ultrasonography (TCD) examinations were performed as part of an institutional screening program. We chose the TCD closest to the time of cerebral oximetry for analysis. TCD examinations were performed according to the stroke prevention in sickle cell anemia (STOP) study protocol [23] by a STOP-certified technician using a non-imaging system (2-Mhz pulsed Doppler ultrasonograph, model TC8080; Nicolet Viasys Healthcare, Madison, WI, USA). We collected the time-averaged maximum mean velocities (TAMMV) in the right and left middle cerebral arteries (RMCA, LMCA), the right and left anterior cerebral arteries (RACA, LACA), the right and left distal internal carotid arteries (RdICA, LdICA), and the vertebrobasilar system (VB). We used the highest TAMMV in each artery for analysis, consistent with clinical care, and the MCA:VB and ACA:VB ratios as a proxies for degree of stenosis. [4] The following laboratory studies were obtained during steady-state clinic visits: complete blood count, percent reticulocytes, and percent fetal Hb (Hb F). If not performed on the same day as the oximetry, we chose the values closest in time for analysis.

Sample Size and Statistical Analysis

We first validated the normal range of $S_{CT}O_2$ in a convenience sample of children without SCD or anemia, selecting the upper and lower limits to include at least 2 standard deviations (S.D.) above and below the mean. The control subjects were not race-matched because the cerebral oximeter we used is insensitive to interference by dark skin pigmentation, and racial differences in $S_{CT}O_2$ have not been reported. [16,17,21,22]

The sample size for the main study was estimated in advance to detect a minimum correlation of 0.25 (r) between $S_{CT}O_2$ and SpO_2 ($\alpha=0.05$; $1-\beta=0.8$) in the HbSS/ $S\beta^0$ group. Summary statistics were calculated for variables of interest. Differences between groups were tested by the Mann-Whitney U or Kruskal-Wallis tests, where appropriate, and paired data by the Wilcoxon matched-pairs signed rank test. We used Spearman correlation to test the two pre-specified primary hypotheses that both right- and left-sided $S_{CT}O_2$ directly correlated with SpO_2 . Spearman correlation was also used to test for monotonic relationships between $S_{CT}O_2$ and these pre-specified independent variables: age, sex, genotype, Hb concentration, percent Hb F, percent reticulocytes, TAMMV in all interrogated vessels, MCA:VB, and ACA:VB. We performed multivariable linear regression of $S_{CT}O_2$ in the HbSS/ $S\beta$ group only, because of the small size of the HbSC/ $S\beta^+$ group. We chose independent variables for inclusion in multivariable models, one model for each hemisphere, if bivariate correlation with $S_{CT}O_2$ (the dependent variable) was significant at a conventional $p<0.20$ level. From these, we built the final models using independent variables that were significant at $p<0.05$ by forced entry. Sex was coded by an indicator variable. We then used binary logistic regression to model the odds of a low $S_{CT}O_2$ defined

as a value less than the 25th percentile for the study population using the independent variables from the final multiple linear regression models. For all models we performed appropriate diagnostics to ensure that assumptions were met.

Individuals could participate only once in this study, but each provided a right- and left-sided value of $S_{CT}O_2$. Subjects with missing measurements were excluded from each analysis; no data were imputed. For the two pre-specified primary hypothesis tests, we considered $p < 0.025$ to be statistically significant. Other statistical hypothesis tests were considered exploratory, for which we considered $p < 0.05$ to be nominally significant. We used G*Power version 3.1 for Mac to calculate sample size, [24] SPSS version 19 statistical software for Mac (IBM Corp., Somers NY, USA) to analyze the data, and Prism 5.0d for Mac (GraphPad Software, Inc., La Jolla, CA, USA) to generate figures.

RESULTS

Validation of Normal Range of $S_{CT}O_2$

We validated the reported normal range of $S_{CT}O_2$ (60-85%) in 29 children without blood disorders (e.g., healthy siblings of patients or children in remission and off therapy for leukemia; $N=17$) or with a non-anemic blood disorder verified by concurrent hemoglobin measurement (e.g., hemophilia or neutropenia; $N=12$). The mean $S_{CT}O_2$ was 76.1% (median 76.4, range 68 – 90.8, standard deviation 4.8, mean $\pm$ 2 S.D. 66.8 – 86.0). Thus, we used a reference range of 65 – 90% for $S_{CT}O_2$ in healthy children for this study.

Characteristics of Participants with SCD

We studied 149 participants with a mean age of 6.6 years (S.D. 4.7, median 5.5). Almost all were African-American (98.3%); two (1.7%) were Caucasian. Table I provides characteristics by genotype group (HbSS/ $S\beta^0$, $N=112$; HbSC/ $S\beta^+$, $N=37$). Twenty-two participants were taking (prescribed) hydroxyurea at the time of oximetry (21 HbSS, 1 HbSC). We separately evaluated an additional ten participants with HbSS who were receiving chronic transfusions for secondary stroke prophylaxis (mean age 11.2 years, 50% male).

Distribution of $S_{CT}O_2$

The distribution of $S_{CT}O_2$ was skewed to the left (lower) for both genotype groups in both hemispheres, and approximately 35% and 75% of HbSC/ $S\beta^+$ and HbSS/ $S\beta^0$ participants, respectively, had values below the lower limit of normal that we validated (Figure 1 A-B). $S_{CT}O_2$ was significantly lower in the HbSS/ $S\beta^0$ group than the HbSC/ $S\beta^+$ group for both hemispheres (right $S_{CT}O_2$: median 54.3 vs 66, $p < 0.001$; left $S_{CT}O_2$: median 52.3 vs. 64.7, $p < 0.001$; Figure 1 C). For the HbSS/ $S\beta^0$ group, $S_{CT}O_2$ decreased with increasing age group ($p < 0.001$; Figure 2). The trend for $S_{CT}O_2$ decreasing with age in the HbSC/ $S\beta^+$ group was not statistically significant (data not shown). We then compared the $S_{CT}O_2$ of the HbSS/ $S\beta^0$ group to a separate group of patients with other forms of anemia (other than SCD) and found that the SCD group had lower $S_{CT}O_2$ than the non-SCD group even after adjusting for the difference in Hb concentration between groups (52.1 vs. 62.2%; $p = 0.023$; Supplemental Figure 1).

Correlates of $S_{CT}O_2$

Table II shows the bivariate correlations between $S_{CT}O_2$ and the pre-specified clinical and laboratory variables by genotype group. Consistent with our pre-specified primary hypotheses, both right-sided $S_{CT}O_2$ ($\rho = 0.40$, $p < 0.001$) and left-sided $S_{CT}O_2$ ($\rho = 0.32$, $p < 0.001$) were directly correlated with S_pO_2 in the HbSS/ $S\beta^0$ group (Figure 3). Also directly (positively) correlated with $S_{CT}O_2$ were Hb concentration, percent HbF, and sex.

Age and percent reticulocytes were inversely correlated with $S_{CT}O_2$. For the smaller HbSC/ $S\beta^+$ group, correlations between $S_{CT}O_2$ and the pre-specified variables were weak or absent (Table II). $S_{CT}O_2$ did not correlate with TAMMV in any ipsilateral vessel, the MCA:VB, or ACA:VB in either genotype group (data not shown).

Multivariable Modeling of $S_{CT}O_2$

We found a significant linear relationship between $S_{CT}O_2$ (right- and left-sided) and SpO_2 , Hb concentration, and age (Table III). As expected, lower SpO_2 and Hb concentration were associated with lower $S_{CT}O_2$. Higher age was associated with lower $S_{CT}O_2$. Female sex, encoded as a binary indicator variable, was associated with higher $S_{CT}O_2$ for right-sided $S_{CT}O_2$ only. Percent reticulocytes and percent Hb F did not have a significant linear relationship with $S_{CT}O_2$ when controlling for the other variables. These multivariable models explained a little less than half of the variability in $S_{CT}O_2$, while SpO_2 alone explained only 5-10% of the variability in $S_{CT}O_2$.

We then modeled the odds of having a value of $S_{CT}O_2$ that was less than the 25 percentile in the study population (45% on the right and 40.5% on the left) using binary logistic regression. Simultaneously controlling for Hb concentration, age and sex (right only), each unit decrease in SpO_2 gave an odds of 1.5 (95% C.I.: 1.004 – 1.8) and 1.4 (95% C.I.: 1.05 – 1.9) for a low $S_{CT}O_2$ in the right and left hemispheres, respectively. The area under the receiver-operating characteristic curves for both models was 0.84 ($p<0.001$).

Relationship of $S_{CT}O_2$ to TCD Abnormalities

The median time between TCD and $S_{CT}O_2$ measurements was 172.5 days. $S_{CT}O_2$ was not correlated to TAMMV in any vessel when TAMMV was considered as a continuous measurement (HbSS/ $S\beta^0$; N=70; Supplemental Figure 2). Two tentative relationships were seen when TAMMVs were grouped by STOP categories in exploratory analyses. First, right-sided $S_{CT}O_2$ was lower when there were abnormal or conditional TAMMVs in ipsilateral dICA (Supplemental Figure 2). Second, left-sided $S_{CT}O_2$ was numerically lower when there were abnormal TAMMVs in ipsilateral dICA (Supplemental Figure 2).

Response to Transfusion

Ten participants with SCD who were chronically transfused for secondary stroke prophylaxis had intermittent or continuous $S_{CT}O_2$ monitoring during a simple transfusion. $S_{CT}O_2$ increased after transfusion, significantly on the left (Figure 4). Twenty percent (2/10) of $S_{CT}O_2$ measurements were normal ($\geq 65\%$) before transfusion, increasing to 40% and 50% normal on the left and right, respectively, after transfusion. Two of these participants had known severe unilateral cerebral vasculopathy, demonstrated by magnetic resonance angiography, and had continuous $S_{CT}O_2$ monitoring during a transfusion (Figure 5). Patient 1 had severe stenosis of the left internal carotid artery, and patient 2 had a completely occluded right internal carotid artery. Both participants had a lower pre-transfusion $S_{CT}O_2$ on the side of the stenosis or occlusion. The right-left difference in $S_{CT}O_2$ was 5% (absolute) and for patient 1 and 20% (absolute) for patient 2. The $S_{CT}O_2$ rose during the course of transfusion (10-30% absolute rise in $S_{CT}O_2$), and by the end of the transfusion the right- and left-sided saturations appeared to equalize.

DISCUSSION

In this largest study of cerebral oximetry in children with SCD to date, and the only report of absolute cerebral oximetry in this population, we find that cerebral Hb desaturation is a common and sometimes severe neurophysiologic abnormality, especially in HbSS/ $S\beta^0$ patients. We confirmed our primary, pre-specified hypothesis that cerebral desaturation is

directly correlated with peripheral Hb desaturation and further showed that cerebral desaturation (decreased $S_{CT}O_2$) is associated with lower Hb concentration and increasing age. Our findings are consistent with the important prior observation that a lower Hb concentration is associated with a higher risk of overt stroke. [25] Males also had lower cerebral saturation than females, consistent with the prior observation that males with SCD have a lower peripheral Hb saturation than females. [2] We also found evidence that cerebral vasculopathy is associated with ipsilateral cerebral desaturation and that transfusion improves cerebral saturation.

There are four previous reports of cerebral oximetry in SCD, [12-15] all of which used early-generation oximeters (INVOS® 1400 or 5100, Somanetics Corp., Troy MI, USA) that do not measure the absolute or actual value of $S_{CT}O_2$. Instead, these INVOS devices report a relative value of regional brain saturation (called rSO_2), which is not the actual saturation, whose purpose is to monitor changes or trends in cerebral saturation from a known baseline state (e.g., following the induction of anesthesia). These prior studies showed that cerebral Hb saturation is decreased in patients with SCD, but no associations between rSO_2 and SpO_2 or Hb concentration were identified. The relationship between cerebral artery blood flow velocity measured by TCD and $S_{CT}O_2$ was not assessed in these prior studies. By measuring the absolute or actual saturation in cerebral tissue ($S_{CT}O_2$) in this study using the CASMED FORE-SIGHT oximeter (CAS Medical Systems, Inc., Branford CT, USA), we clearly show that cerebral Hb saturation is related to both peripheral Hb saturation (directly) and Hb concentration (inversely). Perhaps these relationships were not discerned in previous investigations [12-15] because an arbitrary value for cerebral saturation was used (rSO_2 , not absolute $S_{CT}O_2$), which may have been too inaccurate to resolve the relatively small overall contributions of Hb concentration and SpO_2 to cerebral saturation that we found.

Given the findings of this study and our past related studies, [3,4] we suggest that Hb desaturation predisposes to stroke and other neurologic morbidity by limiting bulk delivery of oxygen to the brain. Arterial oxygen content comprises mainly oxygen bound to Hb as well as a small component of dissolved oxygen [$(Hb \times 1.36 \times S_AO_2) + (0.0031 \times P_AO_2)$]. This is significant, because both Hb and S_AO_2 , the main determinants of oxygen content, are often low in SCD. Desaturation in SCD is partly the result of a compensatory rightward shift of the oxy-hemoglobin dissociation curve due to chronic anemia, which serves to preserve oxygen delivery in normal physiologic conditions. However, this shift may be insufficiently protective in SCD, in which there may be severe anemia, cerebral arterial stenosis, decreased cerebrovascular reserve, altered oxygen extraction, and periodic acute anemic or hypoxemic events [8-11] The lower $S_{CT}O_2$ in SCD patients compared to anemic patients without SCD, even after adjustment for degree of anemia, suggests that something about SCD, in addition to the anemia, also accounts for the desaturation (e.g., vasculopathy, microvascular vaso-occlusion, disordered cerebral autoregulation, and/or altered Hb oxygen affinity).

Given that cerebral Hb saturation has limited associations with TCD findings and is only partially explained by peripheral saturation, measurements of $S_{CT}O_2$ provide additional, new information that is not provided by TCD or pulse oximetry. $S_{CT}O_2$ is a measurement of a mixture of cerebral arterial (30%) and venous (70%) blood. Decreased $S_{CT}O_2$, therefore, is the result not only of arterial desaturation, as reflected by pulse oximetry, but also a larger component of venous desaturation due to cerebral oxygen extraction. Decreased $S_{CT}O_2$ indicates a marginal blood supply to regions of the brain as well as a higher risk of intravascular sickling from deoxygenation in the brain. Because $S_{CT}O_2$ reflects the balance between cerebral tissue oxygen supply and demand, it may be considered a physiologic biomarker for brain at risk of ischemic injury. Cerebral Hb desaturation, which worsens with age and severity of anemia, might also be a mechanistic link between the decline in

cognitive performance that has been observed in older (adult) SCD patients with more severe anemia. [26]

We propose that cerebral oximetry, a rapid and non-invasive technique, might help to identify children with SCD at highest risk of neurologic injury and, possibly, guide neuroprotective therapy. For example, Figures 4 and 5 show that transfusion can improve cerebral saturation and minimize inter-hemispheric differences in cerebral saturation associated with unilateral vasculopathy. As such, S_{CTO_2} should be studied as a patient-specific physiologic monitoring parameter for transfusion therapy. Currently, transfusion is guided mainly by an imperfect laboratory goal of maintaining the percentage of Hb S at 30% or less.

Our study has several limitations. First, we did not measure the partial pressure of oxygen (PO_2) in cerebral or jugular vessels, because this would require prohibitively invasive sampling, so we cannot necessarily infer that desaturation is associated with hypoxemia (low dissolved oxygen content). Nevertheless, desaturation is likely a morbid condition given the neurophysiology of SCD outlined above. Second, given the cross-sectional study design, we cannot conclude that cerebral desaturation precedes and causes neurologic injury. Although this is a reasonable pathophysiologic conjecture, further prospective studies will need to confirm this link. Third, the mean interval between measurement of S_{CTO_2} and TCD studies was long (278 days), and this may have obscured important relationships. Fourth, we could only measure S_{CTO_2} in a limited region of mainly gray matter in the watershed zone between the anterior and middle cerebral arteries of the frontal lobes due to the requirements of probe placement on glabrous skin. We were not able to interrogate other important vascular territories or deep white matter. Fifth, excessive skull thickness could interfere with some measurements of S_{CTO_2} by erroneously providing measurements of bone marrow Hb saturation (instead of or in addition to cerebral tissue Hb saturation). We did not measure skull thickness in these patients, so we can not exclude this possibility; however, our findings of right-left differences in S_{CTO_2} within patients and the minimization of right-left differences with transfusion argues against this possibility in all patients (because the medullary compartment of the frontal bone is a contiguous space). Moreover, a measurement of S_{CTO_2} that included (erroneously) bone marrow would give an apparently *higher* value of S_{CTO_2} than the true S_{CTO_2} , because Hb saturation is normally higher in bone marrow than cerebral tissue, [27] indicating that we might have under-estimated the degree of desaturation in some individuals. Finally, stored packed red blood cells (PRBCs) lose 2,3-bisphosphoglycerate with time and consequently develop increased Hb oxygen affinity. As such, the increases in S_{CTO_2} that we observed following transfusion could, at least in part, be explained by abnormally increased oxygen affinity (which would actually impair oxygen delivery to tissues). However, we transfused PRBCs stored for 7 days or less to minimize this effect. Serial post-transfusion sampling including measurements of the PO_2 in blood will be needed to address this question fully. The main strengths of this study, different from past reports, include the use of absolute cerebral oximetry, large sample size, and a pre-specified sample size and analysis plan.

In conclusion, cerebral desaturation is a common neurophysiologic abnormality in children with SCD. Cerebral desaturation is associated with peripheral desaturation, more severe anemia, and increasing age. Because S_{CTO_2} reflects the balance between cerebral tissue oxygen supply and demand, it is a physiologic biomarker for brain at risk of ischemic injury. This biomarker, which is measured by a rapid non-invasive technique, should be studied further to establish whether it can improve the identification of children with SCD at highest risk of neurologic injury and possibly serve as a physiologic monitoring parameter for neuroprotective therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Distribution of cerebral tissue hemoglobin saturation (S_{CTO_2}) by genotype group
 Histograms of S_{CTO_2} by right (Panel A) and left (Panel B) hemispheres, respectively, for the entire study population. Participants with sickle cell anemia and sickle- β^0 -thalassaemia (HbSS/ $S\beta^0$) are differentiated from those with sickle-hemoglobin C disease and sickle- β^+ -thalassemia (HbSC/ $S\beta^+$). Participants with HbSS/ $S\beta^0$ had lower S_{CTO_2} than HbSC/ $S\beta^+$ participants in both hemispheres (Panel C). Box-plots depict Tukey's hinges (box: 25-75th percentiles with median; whiskers: 1.5 times the interquartile range) and outliers. Dotted lines indicate the upper (90%) and lower (65%) limits of S_{CTO_2} for healthy children.

Figure 2. Cerebral tissue hemoglobin saturation (S_{CTO_2}) decreases with age
 Distribution of S_{CTO_2} by age groups of uniform width in participants with sickle cell anemia and sickle- β^0 -thalassaemia (HbSS/ $S\beta^0$) in the right (Panel A) and left (Panel B) hemispheres, respectively. Box-plots depict Tukey's hinges (box: 25-75th percentiles with median; whiskers: 1.5 times the interquartile range) and outliers. Dotted lines indicate the upper (90%) and lower (65%) limits of S_{CTO_2} for healthy children.

Figure 3. Correlation between peripheral hemoglobin saturation (S_{pO_2}) and cerebral tissue hemoglobin saturation (S_{CTO_2})
 (Correlations between S_{pO_2} and S_{CTO_2} in the right (Panel A) and left (Panel B) hemispheres, respectively, for patients with sickle cell anemia and sickle- β^0 -thalassaemia (HbSS/ $S\beta^0$). Spearman ρ correlation coefficients are shown, and the lines depict the linear relationships between S_{pO_2} and S_{CTO_2}).

Figure 4. Effect of transfusion on cerebral tissue hemoglobin saturation (S_{CTO_2})
 S_{CTO_2} in the right (Panel A) and left (Panel B) hemispheres, respectively, before and after transfusion. S_{CTO_2} increased significantly after transfusion on the left. Median values are shown for each group before and after transfusion. Dotted lines indicate the upper (90%) and lower (65%) limits of S_{CTO_2} for healthy children.

Figure 5. Effects of vasculopathy and transfusion on cerebral tissue hemoglobin saturation (S_{CTO_2})

Cerebral tissue is relatively desaturated on the side of occlusive sickle cerebral vasculopathy, but transfusion minimizes the difference between the sides. The graph shows the changes in S_{CTO_2} on the right (red) and left (blue) during the course of transfusion. Magnetic resonance angiography is shown for both patients. Patient 1 has severe stenosis of the left internal carotid artery (arrows), and patient 2 has a completely occluded right internal carotid artery (arrows). The reasons for the differences in the shapes of the curves between patients is not known, but the response to transfusion in patient 2 suggests a threshold effect for perfusion of the anterior and middle cerebral artery watershed territories. That is, perhaps a small increase in total Hb or blood volume to some minimum critical value that occurred early in transfusion was sufficient to improve blood flow to certain blood vessels by overcoming steal or other abnormalities of cerebral autoregulation).

Table I

Characteristics of participants by genotype group.

Characteristic	HbSS/S β^0 N=112	HbSC/S β^+ N=37
	Mean (S.D.)	Mean (S.D.)
Age (years)	8.0 (4.9)	7.2 (5.0)
Sex (M:F)	57:55 ^I	17:20 ^I
Hb (g/dL)	8.1 (1.4)	10.4 (0.7)
Retic (%)	11.4 (6.6)	2.5 (1.0)
HbF (%)	16.6 (16.0)	15.8 (26.2)
S _P O ₂ (%)	98.8 (1.6)	99.8 (0.8)
Right S _{CT} O ₂ (%)	53.3 (14.2)	66.1 (9.2)
Left S _{CT} O ₂ (%)	51.0 (14.4)	61.2 (11.3)

^I Presented as the ratio of the number of males to females.

Table II
Spearman rank correlations between S_{CT}O₂ and clinical and laboratory variables by genotype group.

Variable	HbSS/S β^0 (N=102)				HbSC/S β^+ (N=37)			
	S _{CT} O ₂ right		S _{CT} O ₂ left		S _{CT} O ₂ right		S _{CT} O ₂ left	
	π	<i>p</i>	π	<i>p</i>	π	<i>p</i>	π	<i>p</i>
Age	-0.54	<0.001	-0.55	<0.001	-0.45	0.006	-0.29	0.08
Sex ¹	0.38	<0.001	0.30	0.002	-0.06	0.72	0.04	0.82
Hb	0.38	<0.001	0.37	<0.001	-0.07	0.67	0.03	0.85
Retc	-0.30	0.002	-0.23	0.023	-0.38	0.02	-0.34	0.04
HbF	0.37	0.001	0.38	0.001	0.17	0.51	0.27	0.28
SpO ₂	0.40	<0.001	0.32	0.001	-0.34	0.05	-0.19	0.27

¹ Male coded as 0, female coded as 1.

Table III

Multivariable linear regression models of S_{CT}O₂ in HbSS/S β ⁰ participants.

Independent Variables	S _{CT} O ₂ right		S _{CT} O ₂ left	
	β	Partial r ²	β	Partial r ²
Intercept	-125.4	—	-122.4	—
S _P O ₂	2.07	0.09	1.59	0.05
Hb	2.87	0.09	3.35	0.11
Age	-1.24	0.25	-1.30	0.27
Female ¹	7.67	0.10	—	—
Adjusted model r ² = 0.46		Adjusted model r ² = 0.40		

¹ Sex encoded as a binary indicator variable.