Middle Cerebral Artery Velocity Changes During Transfusion in Sickle Cell Anemia

N. Venketasubramanian, MD; Isak Prohovnik, PhD; Ann Hurlet, MD; J.P. Mohr, MD; S. Piomelli, MD

Background and Purpose  Sickle cell disease is associated with cerebral hyperemia, which is therapeutically reduced by transfusion; however, the process of transfusion-induced cerebral arterial velocity changes has heretofore not been observed.

Methods We document the acute changes of intracranial arterial velocity in 10 patients (7 with strokes, 3 without) undergoing transfusion therapy using transcranial Doppler ultrasonography. Middle cerebral artery velocities were bilaterally measured every 30 minutes for the duration of transfusion (4 to 5 hours). Regional cerebral blood flow was quantified in 5 of these patients before the transfusion and 24 hours later by the 133Xe technique.

Results  Velocities in stroke-associated vessels (64.3±18.65 cm/s; n=6) were significantly lower than in uninfarcted territories (99.5±27.39 cm/s; n=13), and both types of vessels showed a robust reduction of blood flow velocities during transfusion. The rates of reduction were not significantly different as a function of prior stroke but did correlate with pretransfusion velocities and with the rise in hematocrit (multiple r=.887, P<.001). These reductions occurred rapidly within the first 3 hours of transfusion. Velocities attained at the end of transfusion were maintained in the hour after transfusion and the next day.

Conclusions We conclude that transfusion induces rapid changes in cerebral hemodynamics that are related to pretransfusion velocities and a rise in hematocrit. Transcranial Doppler provides a safe, simple, and noninvasive technique of monitoring these changes and may provide a means of making therapeutic decisions regarding transfusion therapy in patients with sickle cell anemia. (Stroke. 1994;25:2153-2158.)

Key Words  • anemia, sickle cell • blood flow velocity • blood transfusion • cerebral blood flow • Doppler

Long-term transfusion therapy is the standard treatment for stroke in patients with sickle cell anemia.1 It has been shown to reduce the recurrence of stroke2-3 and may reverse cerebral angiographic abnormalities in patients with sickle cell anemia.6 It is not without risk, and thus there is still debate as to some aspects of its use, including levels at which hemoglobin S (%HbS) may be safely maintained,10 the length of time a patient needs to remain on transfusion therapy,11 and the role of alternative, less intensive transfusion regimens.12-14 Cerebral blood flow (CBF) abnormalities have been observed in patients with sickle cell anemia.15-19 Most commonly hyperemia has been described, with its severity strongly correlated with the degree of anemia. This cerebral hyperemia is reduced by transfusion, possibly providing a putative mechanism for the reduction of stroke risk.

The acute time course of cerebral perfusion changes during transfusion has never been observed, primarily because of lack of appropriate technology. Transcranial Doppler ultrasonography (TCD) techniques, now widely used in the evaluation of cerebrovascular disease,20-22 are safe, noninvasive, inexpensive, repeatable, and exceedingly portable. Previous studies have established the range of CBF velocities in normal subjects23,24 and in anemic patients,25 confirming the relation of higher velocities with lower hematocrit values.26 Further studies have indicated that TCD may be used to detect concomitant intracranial vessel stenosis in the setting of anemia in sickle cell disease27 and even to predict stroke in patients with sickle cell anemia.28,29 Although initial studies demonstrated poor agreement between regional CBF (rCBF) and TCD velocities,30-34 more recent data suggest that the correlation is better at higher flow values.35 Thus, TCD may be used to provide an indication of CBF and has previously shown velocity changes after transfusion.36,37 In this study we used TCD and 133Xe rCBF techniques to describe the acute changes of cerebral perfusion during and immediately after transfusion in patients with sickle cell disease and to relate them to stroke, baseline velocities, and hematologic changes.

Subjects and Methods

We studied 11 consecutive patients (6 male and 5 female) attending the Comprehensive Sickle Cell Center at the Columbia-Presbyterian Medical Center for routine transfusion. All patients were on a long-term transfusion program, and none of them were suffering from an acute illness at the time of the study. Neither middle cerebral artery (MCA) could be insolated in 1 patient who had clinical and radiological evidence of bilateral hemispheric infarct and bilateral MCA occlusion by magnetic resonance angiography. The final study sample therefore includes 10 patients.

Blood was drawn for hematocrit, total hemoglobin, and %HbS estimations shortly before and at the end of transfusion and on the next day. Hematocrit was determined by means of the Coulter Counter Plus-4, and %HbS was determined after elution by optical density techniques by means of the Gilford Spectrophotometer-260. Six of the patients were undergoing transfusion after known strokes, 3 others for acute chest
syndrome, and 1 prophylactically after a transient ischemic attack. Cranial computed tomograms and magnetic resonance images were recalled in those patients with stroke, and the side of hemispheric infarct was recorded. The transfusion program at the center is designed to maintain HbS concentrations below 20% by keeping hematocrit levels above 30 mL/100 mL. The patients undergo transfusion on an outpatient basis, and from 5 to 15 mL/kg of blood is given (for the current sample, 498 ± 66 mL), usually every 3 to 4 weeks. Blood is delivered via an infusion pump at 100 to 150 mL/h (for the current sample, 498 ± 66 mL), usually every 3 to 4 weeks. Blood is delivered via a peripheral vein or a central catheter.

We did not obtain blood samples during the transfusions. To predict hemodynamics, we calculated the changes expected in hematocrit. Initial (pretransfusion) hematocrit was known. Initial whole-body blood volume (in liters) was assumed to be 8% of body weight (in kilograms). The rate of infusion (milliliters per hour) was also known, and the hematocrit of infused blood was assumed to be 80 mL/100 mL. From these values and assumptions, it follows that hematocrit can be computed for any time during transfusion. Following the baseline hematocrit of 28.76 ± 2.65, these calculated values were 30.45 ± 2.76, 32.03 ± 2.93, 33.3 ± 3.14, and 34.88 ± 3.36 after 1, 2, 3, and 4 hours, respectively.

TCD measurements were conducted with the EME TC 2-64B (Eden Medical Electronics), which used pulsed ultrasound beams at 2 MHz delivered by a small hand-held transducer. This transducer was placed over the temporal window, the MCA covering the cortex. By means of the 133 Xe inhalation method, gray matter flow was derived with the six-unknown model and expressed in milliliters per 100 mg per minute, using a standard correction for hemoglobin. Blood pressures and pulse rates were recorded at frequent intervals during both TCD and rCBF procedures.

**Results**

**Patient and Transfusion Variables**

Patient and transfusion characteristics are provided in Table 1; pretransfusion and posttransfusion hematocrit and %HbS values are listed in Table 2. Posttransfusion hematology was performed immediately after

<p>| TABLE 1. Treatment Characteristics In 10 Patients With Sickle Cell Disease |
|-------------------------|-------------------|--------------|----------------------|</p>
<table>
<thead>
<tr>
<th>Pt</th>
<th>Age, y</th>
<th>Weight, kg</th>
<th>Sex</th>
<th>Baseline Hct</th>
<th>Baseline MCA Vm (L, R)</th>
<th>Transfusion Volume, mL/kg</th>
<th>Reason for Transfusion and CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.2</td>
<td>28.5</td>
<td>M</td>
<td>26.1</td>
<td>94, 90</td>
<td>14.5</td>
<td>Recurrent acute chest syndrome</td>
</tr>
<tr>
<td>2</td>
<td>23.8</td>
<td>75</td>
<td>M</td>
<td>28.3</td>
<td>76, 72</td>
<td>6.8</td>
<td>Recurrent acute chest syndrome</td>
</tr>
<tr>
<td>3</td>
<td>12.2</td>
<td>32</td>
<td>F</td>
<td>29.0</td>
<td>134, 140</td>
<td>15.2</td>
<td>Recurrent acute chest syndrome</td>
</tr>
<tr>
<td>4</td>
<td>13.7</td>
<td>53.7</td>
<td>M</td>
<td>30.6</td>
<td>72, 64</td>
<td>8.5</td>
<td>TIA</td>
</tr>
<tr>
<td>5</td>
<td>12.7</td>
<td>57.5</td>
<td>F</td>
<td>31.1</td>
<td>86, 90</td>
<td>10.1</td>
<td>Stroke: small pontine infarct</td>
</tr>
<tr>
<td>6</td>
<td>20.8</td>
<td>60</td>
<td>M</td>
<td>25.4</td>
<td>56, 134</td>
<td>8.4</td>
<td>Stroke: L caudate infarct</td>
</tr>
<tr>
<td>7</td>
<td>16.2</td>
<td>39</td>
<td>F</td>
<td>28.6</td>
<td>108</td>
<td>13.1</td>
<td>Stroke: L frontal and frontoparietal infarct</td>
</tr>
<tr>
<td>8</td>
<td>22.5</td>
<td>46</td>
<td>M</td>
<td>31.1</td>
<td>70, 66</td>
<td>13.2</td>
<td>Stroke: extensive R frontal, L frontal, and parieto-occipital infarct</td>
</tr>
<tr>
<td>9</td>
<td>10.4</td>
<td>32</td>
<td>F</td>
<td>32.6</td>
<td>134, 96</td>
<td>12.2</td>
<td>Stroke: R frontoparietal infarct</td>
</tr>
<tr>
<td>10</td>
<td>24.8</td>
<td>73.8</td>
<td>F</td>
<td>24.8</td>
<td>58, 40</td>
<td>7</td>
<td>Stroke: R and L frontal infarct</td>
</tr>
</tbody>
</table>

Mean ± SD: 16.8 ± 5.6, 49.8 ± 16.6, 28.8 ± 2.6, 86.7 ± 29.4, 90.0 ± 31.4.

Pt indicates patient; Hct, hematocrit; MCA, middle cerebral artery; Vm, mean velocity; L, left; R, right; CT, computed tomography; MRI, magnetic resonance imaging; and TIA, transient ischemic attack.

**TABLE 2. Systemic Hemodynamic Variables Immediately Before and After Treatment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Transfusion</th>
<th>After Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit, mL/100 mL</td>
<td>28.8 ± 2.7 (24.8-32.6)</td>
<td>34.9 ± 3.4 (30-38.9)</td>
</tr>
<tr>
<td>HbS, %</td>
<td>15.8 ± 8 (0-26)</td>
<td>12.2 ± 5.8 (0-18)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>107 ± 6.3 (100-120)</td>
<td>106.5 ± 7.9 (100-120)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>66.5 ± 8.9 (50-80)</td>
<td>70 ± 6.7 (60-80)</td>
</tr>
<tr>
<td>Pulse rate, bpm</td>
<td>79.6 ± 11.8 (66-102)</td>
<td>78 ± 13.1 (62-106)</td>
</tr>
</tbody>
</table>

HbS indicates hemoglobin S; BP, blood pressure; and bpm, beats per minute. Values are mean±SD (range).
transfusion in 5 patients and in 3 the next day; in 2 patients posttransfusion hematocrit was not available. In the 2 patients in whom it was available on both occasions, hematocrit and %HbS immediately posttransfusion and the next day were identical.

Furthermore, when the hematocrit values during the transfusion were theoretically calculated, we found that the change was exponentially decelerating. Throughout, hematocrit values rose by 6.1 units (from 28.8 pretransfusion to 34.9 posttransfusion); the change during the first hour was calculated as 1.7 units, followed by 1.6 and 1.5 during the second and third hours, respectively. Thus, 79% of the ultimate hematocrit change occurred in the first 3 hours.

The mean rise in hematocrit was positively correlated with weight-adjusted transfusion volume in milliliters per kilogram ($r=0.823$, $P=0.01$; $n=8$) but not with unadjusted volume. A negative correlation was found between adjusted transfusion volume and weight ($r=-0.934$, $P<0.001$). These findings indicate that heavier children were given less blood per kilogram due to constraints on clinic time and that the acute increase of hematocrit was highly predictable by the volume of blood transfused per kilogram.

TCD Findings

Of the 20 MCAs investigated, one could not be insonated, presumably due to complete occlusion (left MCA, patient 7). For all vessels insonated ($n=19$), MCA mean velocity was reduced within the first 30 minutes of transfusion and continued to fall linearly during the first 3 hours at the rate of 6%/h (Fig 1). After the first 3 hours, changes were minimal and nonsignificant (on average, a further drop of 2% between 3 and 5 hours). The ratios of velocities attained at 3 and 5 hours to the pretransfusion mean velocity were 0.78 and 0.76, respectively, in the non-stroke-related vessels and 0.82 and 0.80, respectively, in the stroke-related vessels.

Further analyses were performed to compare vessels in infarcted territories with noninfarcted vessels. Six MCAs were ipsilateral to historical and radiological evidence of hemispheric cerebral infarct in the MCA-supplied territory (both MCAs in patients 8 and 10 with bilateral strokes, the left MCA in patient 6, and the right MCA in patient 9). The effect of prior infarction is shown in Fig 2, which depicts mean velocities measured during the course of transfusion in the vessels without ($n=13$) and with ($n=6$) ipsilateral hemispheric infarct in the 10 patients. A repeated-measures ANOVA on mean velocities (with stroke as grouping factor and 10 time points as repeated observations) yielded a significant effect of stroke ($F=11.83$, $P<0.005$) and time ($F=23.80$, $P<0.0001$). This analysis suggested that velocities were reduced with time and were lower ipsilateral to stroke. Unpaired $t$ tests between the two groups were significant at all time points.

In particular, velocities before transfusion were lower ($t_{17}=2.84$, $P=0.01$) in vessels in infarcted territories (64.33 ± 18.65 cm/s) than in vessels in noninfarcted territories (99.54 ± 27.39 cm/s). This difference was also observed after 5 hours (51.00 ± 7.56 versus 75.23 ± 14.04 cm/s; $t_{17}=3.93$, $P=0.001$). The lack of significant interaction between stroke occurrence and time during transfusion in the ANOVA, as well as the all-significant $t$ tests, suggests that the slope of velocity reduction over time was equivalent in the two groups. To verify this similarity of slopes, velocities were normalized to baseline (ie, expressed as percentage of baseline velocity of each patient) for all time points, and the repeated-measures ANOVA was again performed. Only the effect of time was significant ($F_{11,58}=24.61$, $P<0.0001$), confirming the lack of difference in velocity changes between the two groups of vessels.

Overall, therefore, vessels in infarcted territories had lower mean velocities at baseline than vessels in noninfarcted territories, but the rate of reduction of velocity during transfusion was the same.

Regression Analyses

Several determinants of baseline velocity in these patients (in addition to stroke) were suggested by significant correlations. These included the patients' age ($r=-0.58$, $P<0.01$), weight ($r=-0.62$, $P=0.005$), and dia-
stroke blood pressure \((r = -0.49, P < 0.05)\). Of note, hematocrit and HbS fraction did not significantly predict baseline velocity within their ranges of 24.8 to 32.6 and 0% to 26%, respectively. Furthermore, when interrelations were addressed by stepwise multiple regression analysis, only the patients' weight remained significant. This relation (mean velocity = 143 ± 1.09 kg), which appeared similar in both infarcted and noninfarcted territories, is shown in Fig 3.

The final velocity obtained after 5 hours of transfusion was strongly predictable by baseline velocity \((r = 0.91, P < 0.0001)\). The reduction of flow after transfusion (velocity at 5 hours normalized to baseline velocity) was negatively related to baseline velocity (Fig 4). The only other baseline variable accepted into a stepwise multiple regression was the patients' weight, which brought the multiple \(r\) to 0.79. In addition, the drop of velocities during transfusion was significantly correlated with the rise of hematocrit \((r = 0.55, P < 0.05)\). When all predictive variables were combined into a stepwise multiple regression (baseline velocity, weight, and increase of hematocrit), weight was rejected, and initial velocity and hematocrit change yielded a multiple \(r\) of .86. Furthermore, there was a very strong relation at all time points between the measured MCA velocity and the calculated hematocrit (Fig 5).

Velocities attained at the end of transfusion were maintained into the next hour in all 10 patients and into the next day in all 5 who were seen the next morning. The pulsatility index was variable before and during transfusion without any clear pattern of change. Blood pressure and heart rate did not change significantly during transfusion.

Regional CBF

\(rCBF\) was elevated in all 5 children in whom the procedure was performed (2 with stroke, 3 without). It fell by the next day in 4 of the 5, parallel to the falls in mean velocity in these patients. No change was seen in the \(rCBF\) of 1 child who had shown a fall in mean velocity but no detectable levels of HbS pretransfusion or posttransfusion. A patient with bilateral extensive infarction (patient 8) had the lowest \(rCBF\) values (64 and 66 mL/100 g per minute) and the lowest velocities (70 and 66 cm/s).

Discussion

This is the first demonstration of the immediate hemodynamic effect of transfusion in patients with sickle cell disease, although this effect was indirectly inferred and predicted by us\(^{16}\) and observed in other circumstances by others.\(^{36,37}\) Additional novel aspects of this experiment include the precise rate and time course of this reduction, its predictors, and the differences between infarcted and noninfarcted vascular territories. MCA mean velocity was found to fall immediately (within 30 minutes) on initiation of transfusion and to maintain a constant rapid rate of decline (6%/h) during the first 3 hours. It did not continue to decline appreciably for the remaining duration of transfusion (up to 5 hours) and remained stable for the next 24 hours in both patients in whom it was monitored. Furthermore, despite marked effects of stroke on initial velocity, the relative rate of decline was uniform across both noninfarcted and infarcted territories.
Because these patients were all transfused on a long-term basis, the small change in HbS fraction during a single transfusion is improbable as the hemodynamic effector. The most likely explanation of the rapid drop of velocities is the rise of hematocrit. Previous studies have reported cross-sectional correlations between hematocrit and TCD velocities. It follows that as hematocrit rises, velocities should fall, which is in agreement with our findings. Our theoretical calculations suggest that the rise of hematocrit during the first hour was similar in magnitude to the fall of velocity (6% in both cases). Furthermore, there was a near-perfect correlation between hematocrit and velocity values at all time points (Fig 5), and velocities did not change appreciably toward the end, when hematocrit was stable. From these observations we conclude that CBF velocity was rapidly and precisely being adjusted by the rising hematocrit.

The high velocities seen in sickle cell anemia may be due to a combination of factors, including the lowered viscosity of anemic blood, local stenoses, and cerebral vasodilation of cortical blood vessels caused by the requirement to maintain oxygen delivery. The present data cannot discriminate between the hemodynamic effects of viscosity and oxygen content, but it is extremely improbable that obstructive stenoses were being removed during transfusion. Rather, we propose that the high pretransfusion velocities merely reflect the hyperemia we previously reported by other techniques, and its reduction indicates normalized CBF. Mean MCA velocity in this study was approximately 64 cm/s in infarcted territories and 100 cm/s in noninfarcted hemispheres, dropping to approximately 75 cm/s after treatment. Previous studies of TCD did not specifically investigate this difference. Adams et al reported an expected velocity of approximately 70 cm/s in healthy children aged 14 to 16 years and approximately 100 cm/s for hematocrit values equivalent to our sample in patients with sickle cell disease. Thus, our noninfarcted values are in extremely good agreement with theirs but are here shown to exist in disparate territories within the same brain. That the velocity in infarcted territories is similar to that observed in normal, nonanemic subjects is probably coincidental. Lower velocity in infarct areas is consistent with the well-documented tendency of stroke to lower parenchymal metabolic demand, and therefore tissue perfusion, in patients with sickle cell disease as well as in other populations. In this case, the flow elevation due to anemia and flow reduction due to infarct approximately balanced each other to result in velocity values that were close to normal.

In contrast to previous reports, however, our study failed to show a clear correlation between pretransfusion velocities and hematocrit. That is not surprising for the vessels in infarcted hemispheres, because the effects of disease, both stenosis-induced acceleration and infarct-induced metabolic reduction, can easily mask the influence of anemia. The lack of correlation does, however, appear unexpected for the vessels in noninfarcted territories. One likely explanation is the fairly limited range of hematocrit values in this study (between 25 and 31) compared with the study by Adams et al, which included patients with hematocrit of 17 to 38; the very large variation shown in that study makes it unlikely that restricted ranges will have the power to demonstrate significant correlations. Similarly, our own previous study, which did report significant correlations, had a hematocrit range of 10 to 38. The restricted range hypothesis is also supported by the findings in another study, which reported nonsignificant correlations between CBF and hematocrit in patients with sickle cell disease.

The decline of MCA velocity during transfusion was strongly predicted by initial velocity and hematocrit change (multiple r = 0.86). Patients with higher levels of pretransfusion mean velocity (mostly noninfarcted territories) registered greater falls than those with lower levels (mostly infarcted territories). It is unclear why vessels with lower pretransfusion mean velocity show a less marked change. Also, despite marked differences of initial velocity between stroke-related vessels and noninfarcted territories and the relation between initial velocity and velocity decrease, there was no significant difference in the rates of decline between the two groups of vessels. Thus, although stroke tends to lower MCA velocity as well as rCBF (eg, Reference 16), an additional mechanism, as yet undefined, is present. Tissue perfusion and MCA velocity are probably affected by the presence and severity of anatomic abnormalities, such as stenoses, as well as oxygen delivery and viscosity. Because angiograms were not available for these patients, we can only speculate regarding the relevance of such factors. Of interest are patients 6 and 9, who had unilateral hemispheric infarct. Both had remarkably higher pretransfusion velocities in the noninfarcted hemisphere, presumably due to the metabolic suppression of the stroke side. The relative decline of velocity, however, was bilaterally similar for patient 9, reaching approximately 70% of baseline at 90 minutes and approximately 60% after 5 hours. In contrast, the symptomatic hemisphere of patient 6 showed no decline whatsoever due to transfusion, while the noninfarcted side showed the usual drop. Thus, within the same patient, a radically different response to transfusion can be seen in the left and right MCAs. The reason for the lack of response in the left MCA of patient 6 is currently unknown, partly because we are not sure about the nature and anatomic origin of the vascular regulatory mechanisms.

In conclusion, our data further validate the TCD technique as uniquely appropriate for evaluation of the cerebrovascular system. They suggest that TCD may be useful to aid the physician in deciding the timing and adequacy of transfusion and the efficacy of different transfusion regimens in the determination of optimal treatment in patients with sickle cell anemia. It is conceivable that patients with high TCD velocities would benefit from transfusion in the prevention of stroke and that decreases in the velocities into the
normal range after transfusion may indicate that the patient has been adequately transfused. This hypothesis requires further study. Another study of particular interest would attempt to isolate the precise correlations between velocity and tissue perfusion, unconfounded by anatomic vascular abnormalities.

Acknowledgments

This study was supported in part by grant HL-28381 from the National Institutes of Health. We thank Wendy Winer, RN, Amy Wu, MD, and Dorothy Patterson, AA, for their help with this project.

References


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Stroke. 1994;25:2153-2158
doi: 10.1161/01.STR.25.11.2153

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