Neglect Is More Common and Severe at Extreme Hemoglobin Levels in Right Hemispheric Stroke

Rebecca F. Gottesman, MD, PhD; Zainab Bahrainwala, BS; Robert J. Wityk, MD; Argye E. Hillis, MD

Background and Purpose—Anemia is 1 potential mechanism by which the brain receives inadequate oxygenation. The purpose of this study was to determine in acute stroke patients whether lower hemoglobin values were associated with worse hemispatial neglect.

Methods—In 203 subjects, neglect testing batteries were administered within 24 hours of admission for acute right hemispheric stroke. We analyzed the error rate on each test as well as “any neglect” (z score ≥2 on any of 3 selected tests compared with normal controls), as predicted by hemoglobin level, with adjustment for infarct size, National Institutes of Health Stroke Scale score, age, and sex.

Results—The association between hemoglobin and neglect varied on the basis of hemoglobin level. At lower hemoglobin levels (<12 g/dL), each 1-point higher hemoglobin value was protective (adjusted odds ratio=0.56; 95% CI, 0.35 to 0.89) from having “any neglect.” However, for a hemoglobin value >14 g/dL, each 1-point higher hemoglobin value was associated with higher odds of having neglect (adjusted odds ratio=1.67; 95% CI, 1.09 to 2.57). Similar relations were found for predicted error rate on the horizontal line bisection, line cancellation, and copy Ogden scene neglect tests. These relations seemed to be more pronounced in individuals who had a diffusion/perfusion mismatch.

Conclusions—Lower and higher hemoglobin levels were each associated with increased odds of neglect and with worse severity of neglect, independent of stroke size and severity. Higher hemoglobin values may represent dehydration or hyperviscosity. The importance of the extremes of hemoglobin in identifying individuals at risk for worse functional consequences of stroke warrants further study. (Stroke. 2010;41:1641-1645.)

Key Words: neglect ■ anemia ■ stroke ■ cognition

Many patients with acute ischemic stroke have low hematocrit levels, likely reflecting the level of comorbid chronic illness in many hospitalized stroke patients. Although anemia at the time of stroke has been associated with higher mortality and worse long-term outcomes, the importance of low hemoglobin values in the clinical presentation of stroke symptoms is less clearly established.

The response of the brain to anemia is 1 of vasodilation as well as upregulation of mediators in an attempt to compensate for this decrease in hemoglobin, but eventually, as hemoglobin falls, this compensation fails and cerebral blood flow is inadequate. Lower hemoglobin levels are associated with a higher risk of stroke after cardiac surgery and with higher mortality among stroke patients. In addition, in the Women’s Health and Aging Study II, the presence of anemia was associated with worse cognitive performance in multiple domains.

If a lower hemoglobin value is associated with inadequate cerebral perfusion and oxygenation, then clinical symptoms of stroke might be even worse in individuals with lower hemoglobin values. This might be even more pronounced in situations where the blood-brain barrier is compromised. In this study, we investigated this question by evaluating the relation between neglect test performance, as an example of cognitive function after stroke, and the level of hemoglobin in individuals with right hemispheric stroke. We hypothesized that lower hemoglobin levels would be associated with more severe neglect and that neglect would be more frequent in individuals with lower than with higher hemoglobin levels. Furthermore, we hypothesized that these associations would be independent of infarct size and stroke severity.

Methods

Subjects were a consecutive series of right-handed patients with acute right hemispheric stroke admitted at 2 academic hospitals (Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center). Participants were excluded if they were unable to have brain magnetic resonance imaging (MRI) performed, had a cerebral hemorrhage, did not speak English, or had preexisting dementia or other neurologic disease. All participants had some area of restricted diffusion, consistent with acute infarction on diffusion-weighted imaging (DWI) with a corresponding area of hypointensity on apparent diffusion coefficient imaging. All participants were evaluated by neglect testing and MRI within 24 hours of admission and within 5 days of symptom onset. The 1 participant with a missing hemoglobin value was excluded.
Testing

All patients were administered a part of or the entire neglect battery including 8 tests: (1) oral reading (reading 30 words and 5 sentences); (2) copy scene (copying the "Ogden scene"; a house, a fence, and 2 trees; there are 16 total components to the picture, so each missing component yields a percent error); (3) clock copying (copying an analog clock); (4) vertical line bisection (drawing a short horizontal line at the middle of a vertical line); (5) horizontal line bisection (drawing a short vertical line at the middle of a horizontal line); (6) line cancellation (crossing out all 28 vertical lines on a piece of paper); (7) visual extinction; and (8) tactile extinction. Scores were recorded as percent error.

We defined “any neglect” as positive when the subject had a z score \( z \geq 2 \) on at least 1 of the following tests: horizontal line bisection, line cancellation, or copying the Ogden scene (the tests with the most complete data). z Scores were created on the basis of a separate group of comparison individuals of similar age who were undergoing preoperative testing before coronary artery bypass graft surgery or who had transient ischemic attacks. A stricter definition of “severe neglect” was created, requiring a z score of \( z \geq 2 \) on at least 2 of these 3 tests. These methods have been reported previously.

The National Institutes of Health Stroke Scale (NIHSS) score was calculated for each patient by chart review. For some patients, the NIHSS score was directly recorded in the chart at the time of admission. For others, the previously validated retrospective technique in calculating the NIHSS score was used. Hemoglobin levels (in g/dL) were recorded from the electronic record from the date of MRl testing or, if unavailable, from the date of admission.

Volumetric Analysis

Volumetric analysis was performed by a technician or investigator with the assistance of Imaged software from the DWI images. Lesions were traced on individual slices, and volumes of infarct were calculated on the basis of slice thickness and were recorded in cubic centimeters. Patients with left hemispheric or infratentorial acute infarcts were excluded. For 10% of scans, volumetric analysis was repeated by the lead investigator. The intraclass correlation coefficient was high, at 0.978 (95% CI, 0.958 to 0.997).

Statistical Analysis

STATA version 8.0 for Macintosh was used for all analyses. We used descriptive statistics to characterize the study population. For analysis of the association between hemoglobin level (in g/dL) and neglect, specific scores on neglect tests were used as the outcome in linear-regression models, with hemoglobin measured continuously as an independent variable. These models also included age, sex, NIHSS score, and infarct size on DWI images. The same models were repeated as logistic regressions, with "any neglect" (defined earlier) and "severe neglect" each as the dependent variables.

Analyses were repeated by examining hemoglobin as a nonlinear predictor. Hemoglobin level was used to create a cubic spline with 3 knots (at the tertiles of hemoglobin levels). Graphs were created to show the adjusted (for age, sex, NIHSS score, and DWI volume) predicted results (for presence/absence of neglect as well as for individual test results) versus the hemoglobin level by using these cubic splines.

In a secondary analysis, we analyzed the effect of diffusion/perfusion mismatch (DWI/perfusion-weighted imaging [PWI]) on the association between hemoglobin concentration and neglect score/frequency. A DWI/PWI mismatch was present when the mismatch, [(PWI−DWI)/DWI]×100], was >20%. Analyses were stratified according to the presence/absence of this mismatch.

Results

In 203 individuals meeting our inclusion criteria, the mean hemoglobin level was 12.9 g/dL (13.4 g/dL in men and 12.3 g/dL in women; Table 1). According to standard clinical definitions of anemia (<12 g/dL in women and <13 g/dL in men), 37% of individuals were anemic. NIHSS score ranged from 0 to 28, and DWI volume ranged from 0.03 to 258.3 cm³.

Hemoglobin as a Linear Predictor

Associations between hemoglobin level and score on neglect tests were consistent with worse performance in association with lower hemoglobin levels (Table 2). When "any neglect" was the outcome, a 1-point higher hemoglobin level (g/dL) was nonsignificantly associated with 9% lower odds of having any neglect in a fully adjusted model (crude odds ratio [OR]=0.94; 95% CI, 0.73 to 1.21; adjusted OR=0.91; 95% CI, 0.76 to 1.09) when hemoglobin was analyzed as a linear predictor. Similar results were found for “severe neglect.”

Hemoglobin as a Nonlinear Predictor

The associations between hemoglobin, modeled with a cubic spline (adjusted for age, sex, DWI volume, and NIHSS score), and error rate on each of the 3 most frequently completed neglect tests (line cancellation, copying the Ogden scene, and horizontal line bisection) showed a U-shaped relation. For line cancellation, at lower hemoglobin levels, each 1-point higher hemoglobin value (g/dL) was associated with a 3.6-point lower error rate (a better score, \( P=0.06 \)), but at higher levels, each 1-point higher hemoglobin value was associated with a 3.6-point higher error rate (\( P=0.06, \) Figure 1). For the copy scene task, a 1-point increase in hemoglobin

Table 1. Characteristics of 203 Individuals With Acute Right Hemispheric Stroke

<table>
<thead>
<tr>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
</tr>
<tr>
<td>Male, No. (%)</td>
</tr>
<tr>
<td>Race, No. black (%)</td>
</tr>
<tr>
<td>Hemoglobin level, mean±SD, g/dL</td>
</tr>
<tr>
<td>Hematocrit, mean±SD, %</td>
</tr>
<tr>
<td>Presence of any neglect, No. (%)*</td>
</tr>
<tr>
<td>Presence of severe neglect, No. (%)*</td>
</tr>
<tr>
<td>NIHSS score, mean±SD</td>
</tr>
<tr>
<td>DWI volume, mean±SD, cm³</td>
</tr>
</tbody>
</table>

*Total No. = 174 or 166 to calculate presence/absence of any neglect or of severe neglect, respectively.

Table 2. Coefficient (No. of Points Higher [Positive] or Lower [Negative]) on a Sample of Neglect Tests, Associated With a 1-Point Higher Hemoglobin Value (in g/dL)

<table>
<thead>
<tr>
<th>Neglect Test</th>
<th>Unadjusted β</th>
<th>Unadjusted P Value</th>
<th>Adjusted β</th>
<th>P Value for Adjusted Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line cancellation</td>
<td>-1.9</td>
<td>0.09</td>
<td>-0.53</td>
<td>0.60</td>
</tr>
<tr>
<td>Copy Ogden scene</td>
<td>-2.8</td>
<td>0.02</td>
<td>-0.64</td>
<td>0.51</td>
</tr>
<tr>
<td>Horizontal line bisection</td>
<td>-1.13</td>
<td>0.003</td>
<td>-0.39</td>
<td>0.24</td>
</tr>
<tr>
<td>Clock copy</td>
<td>-1.37</td>
<td>0.25</td>
<td>0.08</td>
<td>0.94</td>
</tr>
<tr>
<td>Oral reading</td>
<td>-2.4</td>
<td>0.04</td>
<td>-0.34</td>
<td>0.77</td>
</tr>
<tr>
<td>Vertical line bisection</td>
<td>-3.17</td>
<td>&lt;0.001</td>
<td>-2.35</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Points are error rates, with higher numbers indicating worse scores. *Adjusted for DWI volume, NIHSS score, age, and sex.
was associated with a 4-point decrease in error rate at lower levels ($P=0.03$) but with a 3.9-point increase (worse performance) at higher levels ($P=0.04$; Figure 2). For horizontal line bisection, the error rate was 2.3 points lower per 1-point hemoglobin higher at lower levels ($P=0.001$) but 2.1 points higher at higher hemoglobin levels ($P=0.002$).

For logistic models (Figure 3), at lower hemoglobin levels, each 1-point higher hemoglobin level was associated with 44% lower odds (adjusted OR $=0.56; 95\%$ CI, 0.35 to 0.89), whereas at higher levels, each additional point higher hemoglobin level was associated with higher odds (adjusted OR $=1.67; 95\%$ CI, 1.09 to 2.57) of neglect. For severe neglect, the adjusted OR was 0.64 per 1 point higher hemoglobin at lower hemoglobin levels only (95% CI 0.43 to 0.96), but the adjusted OR was 1.60 (95% CI, 1.10 to 2.35) per 1 point higher hemoglobin level at elevated hemoglobin levels.

Secondary Analysis: Role of DWI/PWI Mismatch

In the subset of individuals ($n=125$) with both DWI and PWI imaging, the U-shaped relation between hemoglobin and neglect performance was even more extreme among individuals with a DWI/PWI mismatch (mismatch was present in 27% of individuals; Table 3), although this stratification did not impact prediction of the horizontal line bisection test. The adjusted OR for having any neglect, per 1-point higher hemoglobin value at lower hemoglobin levels, was 0.54 (95% CI, 0.28 to 1.03) when there was no mismatch, but the adjusted OR was 0.03 (95% CI, 0.0003 to 4.26) when a mismatch was present. Similarly, at higher hemoglobin levels, each 1-point increase in hemoglobin was associated with increased odds of any neglect, with an adjusted OR of 1.90 (95% CI, 1.00 to 3.64) for individuals without mismatch, but the OR was 132.3 (95% CI, 0.13 to 135 686.2) for individuals with a mismatch.

**Discussion**

We found that hemoglobin levels have a U-shaped relation with the presence of neglect and with extent of neglect. These associations are independent of stroke severity, measured by NIHSS score and DWI infarct size. This finding that both low and high hemoglobin levels might be indicative of worse

### Table 3. Regression Coefficients for Cubic Spline Analysis of Hemoglobin Values (in g/dL)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted $\beta$ Coefficient at Lower Hemoglobin Values</th>
<th>Adjusted $\beta$ Coefficient at Higher Hemoglobin Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P$ Value</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Individuals with a DWI/PWI mismatch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copy scene test</td>
<td>$-11.5$</td>
<td>$0.001$</td>
</tr>
<tr>
<td>Line cancellation test</td>
<td>$-10.8$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Horizontal line bisection test</td>
<td>$-2.5$</td>
<td>$0.02$</td>
</tr>
<tr>
<td>Individuals without a DWI/PWI mismatch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copy scene test</td>
<td>$-1.7$</td>
<td>$0.60$</td>
</tr>
<tr>
<td>Line cancellation test</td>
<td>$-0.5$</td>
<td>$0.89$</td>
</tr>
<tr>
<td>Horizontal line bisection test</td>
<td>$-2.7$</td>
<td>$0.16$</td>
</tr>
</tbody>
</table>

Table shows worse performance at both lower and higher hemoglobin values for individuals who have a DWI/PWI mismatch of at least 20%. All values are equal to the change in error rate associated with a 1-point higher value of hemoglobin, adjusted for DWI volume, age, sex, and NIHSS score.
performance after stroke is consistent with previous physiologic and clinical data supporting optimal outcomes with a hematocrit between 42% and 45%. This U-shaped curve seems to be most pronounced in individuals with hemodynamic compromise in the form of a DWI/PWI mismatch.

Other authors have reported a J-shaped relation between hemoglobin level and cognitive decline and dementia, although not in the poststroke setting, and these results have been inconsistent. In a systematic review of 3 observational studies, anemia was associated with an increased risk for dementia (relative risk = 1.94; 95% CI, 1.32 to 2.87), but risk was not similarly increased at higher hemoglobin levels. The importance in analyzing predictors in a nonlinear fashion is emphasized here: blood pressure in acute ischemic stroke also appears to have a nonlinear relation with outcome (a U-shaped relation was found in the International Stroke Trial).

High hemoglobin levels (such as from polycythemia vera) have been associated with a higher risk of stroke. Higher hemoglobin levels may be associated with worse stroke symptoms because of hemoconcentration and dehydration, and high hemoglobin may be a marker of this poor volume status. Lower blood pressure has been associated with worse cognitive performance and cerebral perfusion among individuals with acute stroke, which may also be an indication of lower volume status. In addition, stroke patients have been noted to have higher plasma osmolality, consistent with volume depletion, which has been associated with higher poststroke mortality. Higher hemoglobin values may also represent hyperviscosity.

In the absence of sickle-cell disease, in which the role of hyperviscosity is clearer, maximum oxygen transport occurs at a hematocrit of 40%, with an inverse U-shaped curve around this value. Values above or below this are associated with worse oxygen transport, which is due to the reduction in cardiac output that occurs with hematocrit in the polycythemic range, probably because of hyperviscosity. Other authors have found a similar relation (with optimal performance at an intermediate level of hematocrit) between hematocrit and exercise performance in a mouse model. Interestingly, the value of maximal oxygen transport, as hypothesized by Richardson and Guyton, was at a hematocrit of 40%, which is equivalent to a hemoglobin value in the same range (~13 g/dL), as observed in our study to be associated with optimal neglect performance. A similar ideal intermediate hematocrit range (between 36% and 40%) has been reported in the setting of cerebral ischemia, with reduced tissue perfusion at higher levels due to hyperviscosity. This theoretical finding was 1 of the underlying principles behind the (ultimately negative) hemodilution trials for acute ischemic stroke in the 1980s.

Among individuals at the lower end of the spectrum, we hypothesize that lower hemoglobin levels might lead to decreased cerebral oxygenation and ultimately, decreased cerebral metabolism and thus, worse neglect. If lower hemoglobin levels directly impact cerebral perfusion and cerebral function, then it could be hypothesized that transfusion might improve both of these. In 1 study of red blood cell transfusion in individuals with subarachnoid hemorrhage, cerebral oxygen delivery did appear to improve, with minimal decreases in cerebral blood flow. In adults with ischemic stroke, however, most decisions about transfusion are made on the basis of concerns about myocardial ischemia, not about the direct consequences of anemia on cerebral function. If further research emphasizes worse performance associated with anemia, transfusion might need to be considered as a potential means by which cerebral performance could improve.

Cerebral blood flow increases in response to anemia (in animal models and in positron emission tomography studies of individuals with renal failure most likely in an attempt to compensate for this reduction in hemoglobin concentration. In healthy brains, cerebral oxygen metabolism has a fairly linear association with hemoglobin concentration, although hemoglobin’s association with oxygen delivery is more parabolic. These relations may not apply to individuals with acute stroke, however; a more acute reduction in hemoglobin concentration, if present, may lead to alterations in this relation, and the presence of major arterial stenosis may further impact oxygen extraction. Specifically, the combination of decreased localized perfusion and reduced systemic hemoglobin concentration may act together to further influence oxygen metabolism. Our secondary analysis findings support this hypothesis: the U-shaped pattern that we observed seemed to be most pronounced in individuals with a DWI/PWI mismatch. These estimates are imprecise, however, given small numbers for this secondary analysis. Future research is also needed to determine whether deterioration in cerebral oxygen metabolism is associated with cognitive impairment, in both stroke and nonstroke cohorts.

The primary limitation of this study is the lack of standardized assessment of neglect. We have previously described the technique used in this article by comparing performance on a subset of the cognitive tests with performance by a set of controls. In addition, we found similar results across multiple definitions of neglect (any neglect and severe neglect) and found the same pattern when we looked at severity of neglect by test score. Another limitation is the lack of detailed medical information about these participants, with the potential for unmeasured confounders in these associations. Although we adjusted for infarct size (on DWI) and NIHSS score, it is possible that individuals with high and low hemoglobin levels have other comorbidities, and hemoglobin level may just be a surrogate for other illness. With this study design, we cannot make conclusions about causality. Another possible limitation is the timing of the hemoglobin measurement: we used levels from the date of MRI, when possible, but otherwise took values from admission. It is possible that individuals would have received either a blood transfusion or, more likely, intravenous fluids, which would lead to a respective higher or lower hemoglobin level from the one at the time of admission. Thus, the hemoglobin values used could have been influenced by some unmeasured confounder. The consistency of our findings, however, in addition to the remarkable similarity between our curves and the earlier hypothetical curves demonstrating optimal oxygen transport suggest that the U-shaped association is real and warrants further investigation. Finally, we do not know whether similar findings exist between hemoglobin level and long-term functional outcome after stroke because our study only assessed neglect in the short-term period after stroke. We also cannot be sure that findings in our study population would be
generalizable to other stroke populations, wherein distribution of stroke mechanisms might differ.

Our study is strengthened by the detailed information on infarct size and severity (with DWI and NIHHSS) and detailed neglect testing in the acute poststroke period. This study emphasizes not only the potential importance of extremes of hemoglobin levels in the care of patients with acute ischemic stroke but also the importance of the methods chosen with which to study predictors of outcome. Although a slight linear association was found between hemoglobin and neglect, the strongest associations were found when hemoglobin was analyzed as a nonlinear variable. Blood pressure has shown similar U-shaped associations with cognitive performance, further emphasizing the importance of the methods chosen in clinical research in cognitive aging.

**Summary**

In our study of 203 individuals with acute right hemispheric stroke, both high and low hemoglobin levels were associated with worse performance on tests of hemispatial neglect, independent of infarct size and stroke severity. Our results emphasize the importance of monitoring hemoglobin levels to identify individuals who might be at higher risk for worse functional consequences after stroke. Further studies are needed to determine whether a similar U-shaped relation exists for other symptoms after stroke and to determine whether the higher risk at higher hemoglobin values is due to dehydration and hemoconcentration, or perhaps hyperviscosity, even across a range of relatively normal hemoglobin and hematocrit values. Finally, studies are needed to determine whether normalization of the hemoglobin levels is sufficient to improve cognitive performance or whether these levels are markers of strokes that are more likely to lead to worse functional outcomes.

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**Disclosures**

None.

**References**

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