Red Blood Cell Transfusion Increases Cerebral Oxygen Delivery in Anemic Patients With Subarachnoid Hemorrhage

Rajat Dhar, MD; Allyson R. Zazulia, MD; Tom O. Videen, PhD; Gregory J. Zipfel, MD; Colin P. Derdeyn, MD; Michael N. Diringer, MD

Background and Purpose—Anemia is common after subarachnoid hemorrhage and may exacerbate the reduction in oxygen delivery (DO2) underlying delayed cerebral ischemia. The association between lower hemoglobin and worse outcome, including more cerebral infarcts, supports a role for red blood cell transfusion to correct anemia. However, the cerebral response to transfusion remains uncertain, because higher hemoglobin may increase viscosity and further impair cerebral blood flow (CBF) in the setting of vasospasm.

Methods—Eight patients with aneurysmal subarachnoid hemorrhage and hemoglobin <10 g/dL were studied with 15O-positron emission tomography before and after transfusion of 1 U red blood cells. Paired t tests were used to analyze the change in global and regional CBF, oxygen extraction fraction, and oxygen metabolism after transfusion. DO2 was calculated from CBF and arterial oxygen content. CBF, oxygen metabolism, and DO2 are reported in mL/100 g/min.

Results—Transfusion resulted in a 15% rise in hemoglobin (8.7±0.8 to 10.0±1.0 g/dL) and arterial oxygen content (11.8±1.0 to 13.6±1.1 mL/dL; both P<0.001). Global CBF remained stable (40.5±8.1 to 41.6±9.9), resulting in an 18% rise in DO2 from 4.8±1.1 to 5.7±1.4 (P=0.017). This was associated with a fall in oxygen extraction fraction from 0.49±0.11 to 0.41±0.11 (P=0.11) and stable oxygen metabolism. Rise in DO2 was greater (28%) in regions with oligemia (low DO2 and oxygen extraction fraction 0.5) at baseline but was attenuated (10%) within territories exhibiting angiographic vasospasm, where CBF fell 7%.

Conclusions—Transfusion of red blood cells to anemic patients with subarachnoid hemorrhage resulted in a significant rise in cerebral DO2 without lowering global CBF. This was associated with reduced oxygen extraction fraction, which may improve tolerance of vulnerable brain regions to further impairments of CBF. Further studies are needed to confirm the benefit of transfusion on delayed cerebral ischemia and balance this against potential systemic and cerebral risks.

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Key Words: anemia ■ blood transfusion ■ positron emission tomography ■ subarachnoid hemorrhage ■ vasospasm

Delayed cerebral ischemia (DCI) is the principal cause of secondary brain injury after aneurysmal subarachnoid hemorrhage (SAH). Several factors converge to impair cerebral blood flow (CBF) and oxygen delivery (DO2), including vasospasm, hypovolemia, and failure of cerebral autoregulation. The cerebral circulation compensates for this reduction in DO2 by increasing oxygen extraction fraction (OEF) so that the total amount of oxygen available for cellular metabolism (DO2×OEF) is maintained and ischemia, with a fall in cerebral metabolic rate of oxygen (CMRO2), is averted. Tissue in this precarious state of raised OEF, termed oligemia, may be threatened by further reductions in DO2 (eg, worsening vasospasm) beyond the ability of increased extraction to compensate. Beyond this threshold, CMRO2 becomes compromised, neurological deficits may develop, and such ischemic tissue will progress to infarction if DO2 is not promptly restored. Avoiding critical reductions in DO2, therefore, is central to any therapy that aims to minimize morbidity from DCI.

Cerebral DO2 is determined by both CBF and arterial oxygen content (CaO2), with the latter primarily determined by hemoglobin levels. Therefore, anemia may further impair DO2 to brain regions with reduced CBF and could promote ischemia. Not only is anemia extremely common after SAH, but it has been consistently associated with worse outcome, including an increased rate of cerebral infarction. However, higher hemoglobin may increase blood viscosity and, combined with autoregulatory vasoconstriction in response to increased CaO2, further reduce CBF, counteracting any benefit on DO2. The traditional management of DCI has favored...
a paradigm of hemodilution, lowering hemoglobin in an attempt to augment CBF. Because the fundamental objective in managing DCI is maximizing DO₂, not CBF, hemodilution, by reducing CaO₂, may actually be detrimental to this goal. This has generated interest in the ability of red blood cell (RBC) transfusion, by increasing hemoglobin and CaO₂, to improve DO₂ and protect against DCI. However, transfusion of stored RBCs may confer additional risks beyond increased viscosity, including an increased risk of vasospasm in one retrospective study. Therefore, the management of anemia after SAH requires a balancing of risks and benefits with the optimal hemoglobin level and role of transfusion in these patients remaining unclear.

We studied the cerebral vascular and metabolic response to raising hemoglobin with RBC transfusion using positron emission tomography (PET) in a series of anemic patients after SAH who were at risk for DCI. We tested the hypothesis that transfusion would increase cerebral DO₂ to determine whether the metabolic state of brain regions exhibiting oligemia and supplied by vessels with vasospasm would improve after transfusion.

**Methods**

**Patient Selection**

Patients were eligible for this study if they: (1) had a spontaneous SAH; (2) had a ruptured cerebral aneurysm secured by endovascular or surgical means; (3) had hemoglobin <10 g/dL; and (4) were at risk for DCI based on ischemic neurological deficits, angiographic vasospasm, or admission CT grade. Exclusion criteria included active congestive heart failure, pregnancy, or inability to obtain matched blood. Informed consent was obtained from patients or their surrogates. The Human Research Protection Office and Radioactive Drug Research Committee of Washington University approved the study protocol.

**Intensive Care Unit Care and Data Collection**

All patients with SAH were cared for in the Neurology/Neurosurgery Intensive Care Unit. Patients received nimodipine and a 3-day course of anticonvulsants. Ruptured aneurysms were treated within 24 hours of admission. Patients were maintained in a euvolemic state by adjustment of intravenous fluids. New or worsening neurological deficits were promptly evaluated, and if no alternative cause was identified, patients underwent cerebral angiography and hemodynamic augmentation with fluids and induced hypertension. Many received endovascular interventions for vasospasm, including angioplasty and/or intra-arterial vasodilators. Anemia was generally not treated until hemoglobin fell <7 g/dL, although some patients were transfused if hemoglobin was <10 g/dL in the presence of angiographic or symptomatic vasospasm.

Data collected on each patient included demographics, medical and social history, and neurological status at the time of admission. Admission CT was rated using the Fisher scale, and the amount of intraventricular hemorrhage was measured. Daily hemoglobin levels and all RBC transfusions were recorded. Cerebral angiograms were reviewed for the presence of arterial vasospasm, graded as mild, moderate, or severe in each vascular territory.

**Experimental Protocol for PET Studies**

All patients were studied on the Siemens/CTI ECAT EXACT HR+ PET Scanner located in the Neurology/Neurosurgery Intensive Care Unit. Image acquisition was performed as detailed previously to measure CBF, cerebral blood volume, OEF, and CMRO₂. After the first series of scans, a single unit of RBCs (volume 350 mL) was transfused over 1 hour in the PET facility. Once the transfusion was complete, scans were repeated to obtain posttransfusion images. A Neurology/Neurosurgery Intensive Care Unit physician was present throughout the study and all ongoing therapies for DCI, including fluids and vasopressors, were continued. At the time of each image acquisition, physiological data were recorded including central venous pressure if available. Subsequent management of anemia and vasospasm was at the discretion of the clinical team.

**PET Processing**

All PET scans for each patient were coregistered and aligned to the initial baseline CBF study using Automated Image Registration software (AIR, Roger Woods, University of California, Los Angeles, Calif). These images were then coregistered to a reference brain image and resliced so that data could be localized in Talairach atlas space. The patient’s CT scan in closest temporal proximity to the PET study was also realigned with the PET images. Using the individual CT images and brain atlas coordinates as guides, an image mask was created that included the brain below the superior sagittal sinus down to the level of the pineal gland. This was used to measure global values for each parameter before and after transfusion.

Spherical regions of 10-mm diameter were placed in 36 predetermined locations covering the major vascular territories bilaterally as previously outlined. CT images were reviewed and regions corresponding to hematoma, infarcted tissue, or ventricular system were excluded. Regional values were then calculated within each of the remaining spheres.

**Data Analysis**

Cerebral DO₂, the product of CBF and CaO₂, was considered low <4.5 mL/100 g/min (equivalent to CBF of 25 mL/100 g/min at low-normal CaO₂ of 18 mL/dL). Total oxygen extracted was calculated as the product of CaO₂ and OEF (net amount of oxygen extracted). Regions with oligemia were defined by low DO₂ associated with OEF ≥0.5. These thresholds are conservative estimates guided by data from normal controls and previous PET studies of patients with SAH.

Global values before and after transfusion were compared using Wilcoxon signed ranks tests, whereas regional values were compared using paired t tests. Response in regions supplied by vessels with and without moderate to severe angiographic vasospasm was compared using one-way analysis of variance. A differential response in regions with oligemia was also similarly examined. We searched for any regions where delivery fell (≥10%) after transfusion to evaluate the potential for increased hemoglobin to significantly impair DO₂.

**Results**

Eight patients with SAH were studied an average of 8 days after aneurysm rupture (Table 1). All were at high risk for DCI based on the presence of angiographic vasospasm, thick cisternal clot, and/or intraventricular blood. Three patients were being actively treated for ischemic neurological deficits (decreased or altered mental status in all 3, focal deficits in one), all associated with severe bilateral arterial vasospasm. Four had received a RBC transfusion before, but none within 24 hours of the PET study. No patients were on sedative medications at the time of study. O-labeled oxygen studies in 2 patients were unusable due to technical problems, limiting OEF and CMRO₂ data to only 6 patients. However, measurements of CBF and DO₂ were available for all patients.

RBC transfusion resulted in a 15% rise in both hemoglobin and CaO₂ (Table 2). There was also a small rise in mean arterial pressure and trend to higher central venous pressure after transfusion. No transfusion reactions, changes in temperature, or alterations in neurological status were observed.
after transfusion. Mean storage duration of transfused RBCs was 26±12 days.

Mean global CBF was unchanged after transfusion (Figure 1), resulting in DO₂ rising by almost 20% on average. This increase in DO₂ was associated with a fall in OEF and a stable CMRO₂. Mean global cerebral blood volume was unchanged (3.8±0.3 to 3.7±0.3 mL/100 g) as was net amount of oxygen extracted (5.9±1.9 to 5.7±1.7 mL/DL).

Regional Analyses

Of 288 regions in 8 patients, 25 were excluded. The range of the regional DO₂ values for each patient before and after transfusion is plotted in Figure 2. There was an inverse correlation between baseline DO₂ and OEF (r=−0.46). The cutoff for the lowest quartile of DO₂ was 4.2 mL/100 g/min. This group had the highest mean regional OEF at 0.57 compared with 0.39 in those in the highest quartile (P<0.001). Eighty-eight percent of regions with low DO₂ had an improvement after transfusion with number of regions still having low DO₂ decreasing by 50% after transfusion.

There were 56 regions with oligemia (mean baseline DO₂ 3.7±0.6, OEF 0.62±0.1). Improvement in DO₂ in regions was greater compared with nonoligemic regions (28% versus 15%, P<0.001) and fall in OEF was larger (−0.14 versus −0.08, P<0.001; Figure 3A). Almost all such regions (95%) demonstrated improved DO₂ after transfusion, and although CBF was unchanged in nonoligemic regions, it actually rose by 11% in oligemic regions (P<0.001). Only 15 of these 56 regions still met criteria for oligemia and no previously normal regions became oligemic after transfusion. Despite the significant improvement in DO₂ to oligemic regions, we did not identify any rise in CMRO₂.

Territories With Arterial Vasospasm

Four patients had vasospasm demonstrated on angiography (a median of 1.5 days before PET), resulting in 86 regions falling within affected territories. These regions had significantly lower baseline CBF (38.4±11.3 versus 47.8±11.7, P<0.001), lower baseline DO₂ (4.7±1.3 versus 5.5±1.5, P<0.001), and higher OEF (0.51±0.18 versus 0.47±0.13, P=0.04) than other regions. Low DO₂ was present in 47% of regions with vasospasm compared with 28% of those without (P=0.002). Oligemia was present in 28% of affected regions compared with 22% of those without vasospasm (P=0.32).

There was a smaller increase in DO₂ after transfusion in these regions (10% versus 24%, P<0.001), although reduction in OEF was similar (Figure 3B). This corresponded to a significant (7%) drop in CBF within these regions. Even restricting this analysis to only the patients with vasospasm, affected regions had lower CBF and DO₂ and an attenuated response to transfusion compared with those regions located outside affected territories. Only 57% of oligemic regions within territories of vasospasm resolved after transfusion compared with 85% of similar at-risk regions not affected by angiographic vasospasm (P=0.02).

Discussion

In this series of anemic patients at risk for cerebral ischemia after SAH, we have shown that RBC transfusion significantly increased cerebral oxygen delivery throughout the brain. This improvement was greatest in oligemic regions at highest risk for ischemia. The number of brain regions with low delivery was reduced by half after transfusion. This novel finding is clinically relevant, because maximizing oxygen delivery is the cornerstone of preventing neurological injury from DCI. Although this goal is typically achieved by maneuvers intended to augment CBF, our results show that raising hemoglobin can provide similar benefits. Not only did transfusion improve CaO₂, but this was not at the expense of reduced CBF as some have feared. This suggests that any increase in

### Table 1. Description of Patients Studied

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (%)</th>
</tr>
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<tbody>
<tr>
<td>Age, mean±SD</td>
<td>60.4±13.0</td>
</tr>
<tr>
<td>Gender, female</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Race, white</td>
<td>5 (63)</td>
</tr>
<tr>
<td>World Federation of Neurological Surgeons grade, N−V</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Fisher Grade 3</td>
<td>6 (75)</td>
</tr>
<tr>
<td>IVH present</td>
<td>6 (75)</td>
</tr>
<tr>
<td>IVH score, mean±SD</td>
<td>4.6±3.9</td>
</tr>
<tr>
<td>Study on SAH day, mean±SD</td>
<td>8.0±4.1</td>
</tr>
<tr>
<td>Admission hemoglobin, mean±SD</td>
<td>12.1±1.8</td>
</tr>
<tr>
<td>Clip versus coil</td>
<td>4/4</td>
</tr>
<tr>
<td>Angiographic vasospasm</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Ischemic deficits</td>
<td>3 (38%)</td>
</tr>
<tr>
<td>Intubated at time of study</td>
<td>4 (50%)</td>
</tr>
</tbody>
</table>

IVH indicates intraventricular hemorrhage.

### Table 2. Physiological Variables Before and After Transfusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Transfusion</th>
<th>After Transfusion</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>8.7±0.8</td>
<td>10.0±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial oxygen content, mL/dL</td>
<td>11.8±1.0</td>
<td>13.6±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>106.3±21.5</td>
<td>109.5±24.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Heart rate, beats/min⁻¹</td>
<td>90.6±22</td>
<td>86.3±21</td>
<td>0.13</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg (n=4)</td>
<td>7.7±1.5</td>
<td>11.0±2.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>37.5±1.0</td>
<td>37.3±0.9</td>
<td>0.60</td>
</tr>
<tr>
<td>Paco₂, mm Hg</td>
<td>38.1±4.7</td>
<td>39.1±4.7</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Low delivery (<4.5 mL/100 g/min) at baseline was present in 89 regions (34%). These had higher baseline OEF (0.56 versus 0.45) and lower CMRO₂ (2.0 versus 2.6, both P<0.001) compared with other regions. DO₂ increased by 25% in these at-risk regions and OEF fell by 0.12 (compared with 0.09 in regions with normal DO₂ at baseline, P=0.05). Eighty-eight percent of regions with low DO₂ had an improvement after transfusion with number of regions still having low DO₂ decreasing by 50% after transfusion.
viscosity resulting from raising hemoglobin (at least to these levels) does not adversely affect CBF. In addition, it appears that after SAH, cerebral vessels do not vasoconstrict to lower CBF in compensation for higher \( \text{CaO}_2 \). An analogous impairment of pressure autoregulatory capacity underlies the ability of hypertensive therapy to augment CBF after SAH in areas of reduced perfusion.

Transfusion did result in a small drop in CBF in territories affected by arterial vasospasm. Although net \( \text{DO}_2 \) still improved, the benefit was attenuated. It is possible that the rise in viscosity at higher hemoglobin levels might be more significant within abnormal vessels, where flow is already reduced and compensatory vasodilatation is not possible. Transfusion may not be as effective in reversing hypoperfusion-induced reductions in \( \text{DO}_2 \) related to vasospasm as it is in correcting oligemia related to anemia in regions with preserved vascular tone. This hypothesis is preliminary, based on a few patients, but deserves further study.

The brain compensates for reductions in CBF and \( \text{DO}_2 \) through vasodilatation and by increasing the OEF as seen in the setting of unilateral carotid occlusion as well as cerebral vasospasm. This response maintains oxidative metabolism at levels adequate to prevent ischemia, but can be exhausted if \( \text{DO}_2 \) falls further. Abnormal vessels may not be able to vasodilate to preserve flow in the setting of vasospasm or anemia, and so increasing OEF is of central importance to averting cerebral ischemia. We demonstrated that transfusion reversed the elevated OEF seen in these patients. Interventions that reduce tissue OEF should restore critical compensatory reserve and improve tolerance to further ischemic insults. The ability to prevent progression of hemodynamic compromise to frank ischemia is the central goal of managing DCI.

Our findings, coupled with the strong association between anemia and poor outcome in patients with SAH, suggest that RBC transfusion may be a rational approach to minimizing the burden of DCI. However, enthusiasm for the use of RBC transfusion has been tempered by a number of increasingly recognized risks in critically ill patients, including increased rates of nosocomial infections and organ dysfunction. Much of this has been attributed to the deleterious effects of storage of RBCs, which leads to morphological and biochemical alterations that may also limit their ability to supply oxygen to tissues. The \( P_{50} \) of transfused blood is reduced, because 2,3-diphosphoglycerate is depleted over time, impairing oxygen unloading. Stored RBCs change shape and become less deformable, which may impair their passage through the microcirculation.

The clinical implications of these changes are uncertain; transfused RBCs are diluted within a much larger pool of endogenous erythrocytes and 2,3-diphosphoglycerate is rapidly regenerated in vivo. We did not detect any drop in CBF in our patients after transfusion to corroborate concerns over reduced flow, except in areas of vasospasm. It is also unlikely that the observed reduction in OEF was explained by impaired oxygen unloading (ie, a left shift in the oxyhemoglobin dissociation curve), because the net amount of oxygen extracted remained stable. This issue could be further explored by comparing the efficacy of fresh versus stored blood on cerebral oxygen transport and metabolism.
There is also specific concern about the use of RBC transfusion in SAH, because one retrospective study found an association between postoperative transfusion and a higher rate of angiographic vasospasm. Although a more recent study could not confirm this finding, it did show that transfusion was more strongly associated with death, disability, and delayed infarction than anemia itself. Whether transfusion directly contributes to poor outcomes, or is simply a marker for more severe SAH, remains unclear from these studies but bears further evaluation.

The optimal hemoglobin level for patients with SAH at risk for cerebral ischemia remains uncertain. We have shown a beneficial effect on oxygen delivery when transfusing patients with severe anemia (hemoglobin <10 g/dL). Yet after transfusion, all still remained anemic and many had brain regions with persistently low DO₂. However, at higher hemoglobin levels, increased blood viscosity might impair CBF sufficiently to counter any benefits of higher CaO₂ on net DO₂. This might be especially the case in patients and regions affected by vasospasm. Further study is needed to ascertain whether such a hemoglobin ceiling exists above which delivery cannot be further optimized.

Our study has a number of limitations. These findings elucidate the acute response to transfusion, whereas the sustained effects of raising hemoglobin remain unclear. There may have been a small volume-mediated effect of transfusing blood rapidly to these patients; however, it is unlikely that the small increase in mean arterial pressure (3 mm Hg) and the trend to higher central venous pressure sufficiently accounts for the large improvement in DO₂ that was observed after transfusion. All our subjects were female, largely related to the natural history of SAH and their lower baseline hemoglobin placing them at higher risk for anemia; we are planning on studying male patients with SAH in future studies at varying hemoglobin levels. We cannot conclude that 10 g/dL is the optimal hemoglobin threshold for transfusion in these patients or whether transfusing to higher levels would further improve DO₂. Finally, how this improvement translates into the ability to minimize ischemia, infarction, and neurological morbidity remains to be determined.

Until further physiological and clinical studies outline the benefits and exact role of transfusion in these patients, a liberal transfusion strategy for all patients with SAH cannot be recommended based on our findings. However, we have shown that transfusing patients with anemia can reverse the impairments in oxygen delivery and compensatory increases in OEF that are seen after SAH and that this strategy shows promise in minimizing cerebral ischemia in high-risk patients. Large randomized studies are needed to test the benefits of RBC transfusion on clinical outcomes and determine the balance between the systemic and cerebral risks of transfusion and the benefits we have begun to elucidate here.

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Disclosures
None.

References
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