Comparison of induced hypertension, fluid bolus, and blood transfusion to augment cerebral oxygen delivery after subarachnoid hemorrhage

Clinical article

RAJAT DHAR, M.D.,1 MICHAEL T. SCALFANI, M.S.C.I.,1 ALLYSON R. ZAZULIA, M.D.,1,3 TOM O. VIDEEN, PH.D.,1,3 COLIN P. DERDEYN, M.D.,1,3 AND MICHAEL N. DIRINGER, M.D.1,2

Departments of 1Neurology, 2Neurological Surgery, and 3Radiology, Washington University School of Medicine, St. Louis, Missouri

Object. Critical reductions in oxygen delivery (DO₂) underlie the development of delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH). If DO₂ is not promptly restored, then irreversible injury (that is, cerebral infarction) may result. Hemodynamic therapies for DCI (that is, induced hypertension [IH] and hypervolemia) aim to improve DO₂ by raising cerebral blood flow (CBF). Red blood cell (RBC) transfusion may be an alternate strategy that augments DO₂ by improving arterial O₂ content. The authors compared the relative ability of these 3 interventions to improve cerebral DO₂, specifically their ability to restore DO₂ to regions where it is impaired.

Methods. The authors compared 3 prospective physiological studies in which PET imaging was used to measure global and regional CBF and DO₂ before and after the following treatments: 1) fluid bolus of 15 ml/kg normal saline (9 patients); 2) raising mean arterial pressure 25% (12 patients); and 3) transfusing 1 U of RBCs (17 patients) in 38 individuals with aneurysmal SAH at risk for DCI. Response between groups in regions with low DO₂ (< 4.5 ml/100 g/min) was compared using repeated-measures ANOVA.

Results. Groups were similar except that the fluid bolus cohort had more patients with symptoms of DCI and lower baseline CBF. Global CBF or DO₂ did not rise significantly after any of the interventions, except after transfusion in patients with hemoglobin levels < 9 g/dl. All 3 treatments improved CBF and DO₂ to regions with impaired baseline DO₂, with a greater improvement after transfusion (23%) than hypertension (14%) or volume loading (10%); p < 0.001. Transfusion also resulted in a nonsignificantly greater (47%) reduction in the number of brain regions with low DO₂ when compared with fluid bolus (7%) and hypertension (12%) (p = 0.33).

Conclusions. The IH, fluid bolus, and blood transfusion interventions all improve DO₂ to vulnerable brain regions at risk for ischemia after SAH. Transfusion appeared to provide a physiological benefit at least comparable to IH, especially among patients with anemia, but transfusion is associated with risks. The clinical significance of these findings remains to be established in controlled clinical trials. (DOI: 10.3171/2011.9.JNS11691)

Key Words • subarachnoid hemorrhage • vasospasm • intracranial pressure • cerebral ischemia • blood transfusion • cerebrovascular circulation • triple-H therapy • vascular disorders

The major threat to neurological recovery for survivors of aneurysmal SAH is the development of DCI. In association with arterial vasospasm, CBF falls below critical ischemic thresholds such that brain regions receive inadequate DO₂ relative to metabolic demands.13,29 This may induce the development of ischemic neurological deficits, and if the impairment in DO₂ is not promptly reversed, cerebral infarction with permanent disability may ensue.28 For this reason, the principal focus of managing DCI centers on improving CBF and DO₂, especially to vulnerable regions where DO₂ is already impaired.

The primary medical strategy to manage DCI has involved triple-H (or hemodynamic) therapy, incorporating elements of hypervolemia, hypertension, and hemodilution.1 The goal of these interventions is to increase CBF and thereby restore DO₂ to regions at risk for ischemia.27 Although significant anecdotal evidence exists to support the ability of hemodynamic augmentation to reverse ischemic deficits,18,23 the way in which each component has an impact on CBF and DO₂ has not been as well established.10,24 Induced hypertension appeared to raise CBF most consistently in previous studies,3 but giving a fluid

Abbreviations used in this paper: CaO₂ = arterial oxygen content; CBF = cerebral blood flow; CMRO₂ = cerebral metabolic rate for O₂; CVP = central venous pressure; DCI = delayed cerebral ischemia; DO₂ = O₂ delivery; IH = induced hypertension; MAP = mean arterial pressure; NNICU = Neurology/Neurosurgery ICU; OEF = O₂ extraction fraction; RBC = red blood cell; SAH = subarachnoid hemorrhage; triple-H therapy = hypervolemia, hypertension, and hemodilution.
Augmenting cerebral oxygen delivery in subarachnoid hemorrhage

Informed consent was obtained from each patient or a legally authorized surrogate. Results for a subset of patients who received either the fluid bolus (7) or transfusion (8) have been previously published separately, but additional patients (23 in total, including the entire IH cohort) and completely new analyses have been included in this comparison.

**Care and Data Collection in the ICU**

All patients with SAH were cared for in the NNICU at Barnes-Jewish Hospital. Ruptured aneurysms were treated within 24 hours of admission in all cases. Patients were intubated for respiratory failure or if they were unable to maintain an adequate airway. All received enteral nimodipine. They were maintained in a euvolemic state by daily adjustments of intravenous fluids to keep ins and outs balanced, but prophylactic hypervolemia or hypertensive therapy was not used. Anemia was generally tolerated (and transfusion generally reserved) until hemoglobin fell below 7 g/dl in the absence of significant angiographic or symptomatic vasospasm. New or worsening neurological deficits were promptly evaluated, and if no alternative cause was identified, patients underwent cerebral angiography and hemodynamic augmentation (primarily involving IH). They could also receive endovascular interventions for proximal angiographic vasospasm. In the absence of intervening symptoms, patients underwent cerebral angiography screening on or around Day 7 after SAH.

Data collected on each patient included demographic characteristics and neurological status at the time of admission and at the start of the study. The admission CT scan was graded for amount of subarachnoid and intraventricular blood. The cerebral angiogram performed closest to each PET study was reviewed for the presence of arterial vasospasm, which was graded as mild, moderate, or severe in each vascular territory, based on interpretation of the attending neuroradiologist. If a given patient had at least one vessel with moderate-to-severe vasospasm, he or she was classified as having significant angiographic vasospasm. Delayed cerebral ischemia was defined as the presence of new or worsened neurological deficits presumed to be ischemic after exclusion of other confounding causes, generally confirmed by the presence of vasospasm on cerebral angiography.

**Experimental Protocol**

All PET studies were performed on either the Siemens/CTI ECAT EXACT HR 47 or HR+ scanner located in the NNICU. The NNICU PET Research Facility is equipped with the same life support and monitoring equipment available at each patient bed in the NNICU (that is, continuous electrocardiography, MAP, and O₂ saturation monitoring, as well as intracranial pressure monitoring if required). An attending neurointensive care physician was present throughout each study. If a patient was already receiving hemodynamic augmentation (that is, vasopressors or fluids) for vasospasm and/or ischemic deficits, this was continued throughout the study, both before and after the added intervention, with care taken to

**Methods**

**Patient and Study Selection**

We collectively analyzed and compared patients enrolled in 3 separate but technically similar prospective clinical studies. Each used ¹⁵O-PET imaging to measure CBF (in the IH and transfusion studies, OEF and CMRO₂ were also assessed) before and after the specified intervention. The trials are compared in Table 1. All studies enrolled patients with aneurysmal SAH from among the approximately 120 patients admitted to the neurosurgery service at our institution each year. Participants were studied during the period of highest risk for vasospasm and DCI, between 4 and 14 days after SAH, and were enrolled once they met inclusion criteria for a specific study; allocation was not randomized.

Studies shared much of the same patient selection criteria, but varied in specific ways, as outlined in Table 1. In the first study, participants were given a 0.5-ml/kg bolus of isotonic crystalloid to induce hypervolemia. In the second study, hypertension was induced by raising the MAP 20%–30% above baseline (measured at the time of initial PET) with phenylephrine. The third transfused 1 U of RBCs to raise hemoglobin and CaO₂. Patients were excluded if CBF data could not be obtained from the PET studies for technical reasons (4 of 42 total patients enrolled). The Human Research Protection Office and the Radioactive Drug Research Committee of Washington University approved each of these studies individually.

Hemodilution is no longer widely used for DCI because, although it may improve CBF to a small extent, related to reduced blood viscosity at lower hematocrit, the associated fall in CaO₂ actually threatens to impair instead of improve DO₂. This paradox of improved CBF but lower net DO₂ exemplifies why DO₂ and not CBF must be the outcome of interest in physiological studies evaluating the benefits of interventions for DCI (especially those that manipulate hemoglobin levels). Interest has recently been raised in RBC transfusion as a therapeutic modality that may increase cerebral DO₂ in the presence of anemia; reductions in hemoglobin are common after SAH and have been consistently associated with worse outcome and more cerebral infarction.

No studies have assessed the relative ability of transfusion to improve DO₂ compared with the more traditional methods of hemodynamic augmentation (that is, hypertension and hypervolemia). We have used a standardized brain imaging protocol to measure CBF and DO₂ before and after therapeutic interventions (including IH, volume loading, and RBC transfusion) in patients with SAH. We sought to compare the effect of each of these interventions on DO₂ as a physiological surrogate for their ability to reduce the risk of cerebral ischemia. Specifically, we wanted to determine whether transfusion could augment DO₂ to a degree comparable with IH (the clinical gold standard) and greater than a fluid bolus alone, particularly to vulnerable brain regions where DO₂ was impaired at baseline.

bolus has also been shown to improve CBF (and thereby DO₂) to regions with low baseline flow. Hemodilution is no longer widely used for DCI because, although it may improve CBF to a small extent, related to reduced blood viscosity at lower hematocrit, the associated fall in CaO₂ actually threatens to impair instead of improve DO₂. This paradox of improved CBF but lower net DO₂ exemplifies why DO₂ and not CBF must be the outcome of interest in physiological studies evaluating the benefits of interventions for DCI (especially those that manipulate hemoglobin levels). Interest has recently been raised in RBC transfusion as a therapeutic modality that may increase cerebral DO₂ in the presence of anemia; reductions in hemoglobin are common after SAH and have been consistently associated with worse outcome and more cerebral infarction.

No studies have assessed the relative ability of transfusion to improve DO₂ compared with the more traditional methods of hemodynamic augmentation (that is, hypertension and hypervolemia). We have used a standardized brain imaging protocol to measure CBF and DO₂ before and after therapeutic interventions (including IH, volume loading, and RBC transfusion) in patients with SAH. We sought to compare the effect of each of these interventions on DO₂ as a physiological surrogate for their ability to reduce the risk of cerebral ischemia. Specifically, we wanted to determine whether transfusion could augment DO₂ to a degree comparable with IH (the clinical gold standard) and greater than a fluid bolus alone, particularly to vulnerable brain regions where DO₂ was impaired at baseline.

**Experimental Protocol**

All PET studies were performed on either the Siemens/CTI ECAT EXACT HR 47 or HR+ scanner located in the NNICU. The NNICU PET Research Facility is equipped with the same life support and monitoring equipment available at each patient bed in the NNICU (that is, continuous electrocardiography, MAP, and O₂ saturation monitoring, as well as intracranial pressure monitoring if required). An attending neurointensive care physician was present throughout each study. If a patient was already receiving hemodynamic augmentation (that is, vasopressors or fluids) for vasospasm and/or ischemic deficits, this was continued throughout the study, both before and after the added intervention, with care taken to
maintain a stable physiological milieu. However, in the fluid bolus study, patients were taken to the PET scanner at the onset of suspected ischemic deficits (prior to angiography and initiation of therapy). That is, the fluid bolus was given prior to induction of hypertensive therapy. No sedative infusions were used in any patient, and only opioids (not benzodiazepines or propofol) were given to maintain patient comfort during the duration of the study, on an as-needed basis. The RBCs administered in the transfusion group were provided by the hospital blood bank.

Image acquisition was performed as detailed previously to measure CBF, OEF, and CMRO₂ (only CBF was measured in the fluid bolus study). A transmission scan was also obtained and used for subsequent attenuation correction of emission scan data. After the first series of scans, the particular intervention (fluid bolus, hypertension, or transfusion) was administered (over 1 hour for transfusion and fluid bolus; phenylephrine was titrated over 15–30 minutes for IH), and scans were repeated immediately thereafter. At the time of each scan, physiological data were recorded, including CVP, when available (not measured in the IH study). Arterial blood was analyzed for hemoglobin level and CaO₂ with each study.

**Processing of PET Scans**

All PET scans for each patient were coregistered and aligned to the initial baseline CBF study by using Automated Image Registration software (AIR; developed by Roger Woods, University of California, Los Angeles). They were calibrated for conversion of PET counts to quantitative radiotracer concentrations, as previously described. Radioactivity in arterial blood was measured using an automated blood sampler. The arterial time–radioactivity curve recorded by the sampler was corrected for delay and dispersion by using previously determined parameters.

All images were then coregistered to a reference brain image and resliced so that data could be localized in Talairach atlas space. Global values for CBF, OEF, and CMRO₂ were obtained using a standard image mask covering the brain from below the superior sagittal sinus down to the level of the pineal gland. Spherical regions of 10-mm diameter were placed in 36 predefined locations distributed across the major vascular territories bilaterally, as previously outlined. All images were reviewed and any regions corresponding to hematoma, visibly infarcted tissue, or ventricular system were excluded. Regional values were then calculated within each of the remaining spheres.

**Data Analysis**

The change in cerebral DO₂ (the product of CBF and CaO₂) was our primary outcome measure both globally and regionally. We defined vulnerable regions as those with baseline DO₂ < 4.5 ml/100 g/min (equivalent to a CBF of 25 ml/100 g/min at a low-normal CaO₂ of 18 ml/dl). We evaluated the response to each intervention (that is, change in DO₂) within all such regions. For patients in whom OEF was measured, we also determined which regions had OEFs ≥ 0.5 (as evidence of increased extraction compensating for insufficient DO₂). Regions were then classified as oligemic if both of the following occurred: DO₂ was low and OEF was elevated. The thresholds used are conservative estimates guided by data from normal control volunteers and previous PET studies of patients with SAH both with and without vasospasm.

We performed paired t-tests to evaluate the response to each intervention (effect on CBF, DO₂, OEF, and CMRO₂) within each individual study group, both globally and in vulnerable regions (that is, low DO₂ or oligemia). We then used a repeated-measures ANOVA model to compare the effect of each intervention on global and regional DO₂. A differential effect of the interventions on change in DO₂ was considered present if the interaction statistic had a p value < 0.05. If a significant effect was found, we then performed post hoc testing to evaluate which intervention had greater impact on DO₂. We controlled for potential imbalances between (nonrandomized) groups by adjusting for covariates in the generalized linear model, including hemoglobin level and presence of angiographic vasospasm and/or DCI.

We specifically analyzed the response in the subgroup of patients with hemoglobin < 9 g/dl prior to transfusion.

---

### Table 1: Comparison of the 3 included studies performed in 38 patients with SAH*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Fluid Bolus</th>
<th>IH</th>
<th>Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>intervention</td>
<td>hypervolemia; normal saline 15 ml/kg over 1 hr</td>
<td>phenylephrine to raise MAP by 20–30%</td>
<td>1 U packed RBCs over 1 hr</td>
</tr>
<tr>
<td>physiological goal</td>
<td>increase plasma volume by 10% increase MAP at least 20%</td>
<td>increase Hb by at least 1 g/dl (approx 10%)</td>
<td></td>
</tr>
<tr>
<td>specific inclusion criteria</td>
<td>new ischemic neuro deficits randomized to statin or placebo for 21 days</td>
<td>low risk for DCI</td>
<td></td>
</tr>
<tr>
<td>specific exclusion criteria</td>
<td>already receiving hemodynamic therapy for DCI other untreated aneurysms; premorbid statin therapy</td>
<td>PET planned on Day 7, around time of routine angiogram</td>
<td></td>
</tr>
<tr>
<td>angiography</td>
<td>performed w/in 12 hrs of PET</td>
<td>optional (on Day 7 &amp;/or if symptoms)</td>
<td></td>
</tr>
</tbody>
</table>

* Shared inclusion criteria were as follows: spontaneous SAH with ruptured cerebral aneurysm secured. Abbreviations: approx = approximately; Hb = hemoglobin; neuro = neurological.
Augmenting cerebral oxygen delivery in subarachnoid hemorrhage

(a threshold derived from a prior analysis of this cohort). This allowed us to evaluate the efficacy of transfusion in the subgroup with the most severe anemia, in which this treatment might most often be used in clinical practice, without diluting any physiological effect by including those with higher hemoglobin levels, whose benefit may be more marginal. We also analyzed and compared the subgroups of patients with angiographic vasospasm, DCI, and low global DO$_2$ (< 4.5 ml/100 g/min) in each arm to provide an equivalent fair comparison, minimizing the imbalances that might have existed between groups as a whole.

Finally, we calculated the number of regions with low DO$_2$ and oligemia in each patient, before and after the intervention (to estimate any reduction in the volume or “burden” of underoxygenated and oligemic brain tissue at highest risk for ischemia). We compared the proportion of these vulnerable regions before and after intervention by using the Wilcoxon signed-rank test and compared this response between the 3 groups by using repeated-measures ANOVA.

**Results**

A total of 38 patients with aneurysmal SAH were studied; 9 received fluid bolus, 12 underwent IH, and 17 had blood transfusion. The demographic and clinical characteristics of the patients are outlined in Table 2. Participants were similar between groups, except that all patients (by selection) in the fluid bolus study had neurological deficits presumed to be ischemic (of whom only 2 did not have moderate-to-severe vasospasm on subsequent angiography). Patients in this group were younger and on average were studied 2 days earlier in their course. A minority of patients in the IH and transfusion studies were already receiving hemodynamic therapy with vasopressors at the time of the study, compared with none (by design) in the fluid bolus cohort. However, a significant proportion in all 3 groups (33%–78%) had significant vasospasm on angiography. The transfused blood had a median storage duration of 31 days.

Physiological data are compared between groups in Table 3. There was a small rise in MAP after fluid bolus and blood transfusion, but a much larger intentional 25% rise in the IH group related to titration of vasopressors. The CVP was not available in the IH group, but only a small rise was seen after both fluid bolus and transfusion; neither the baseline CVP nor rise in CVP after each intervention was significantly different between groups. Hemoglobin was stable pre- and postintervention in the fluid bolus and IH groups, but rose 15% after transfusion, and CaO$_2$ rose 14%. Temperature, heart rate, and PaCO$_2$ all remained stable. No patient had a rise in intracranial pressure during the study. Only one transient febrile response to transfusion was seen, but no other transfusion reactions or complications associated with fluid bolus or IH (that is, no cases of pulmonary edema or arrhythmia) were encountered.

**Global PET Measurements**

Global CBF and DO$_2$ were not significantly changed with any of the interventions (Table 4). There was a trend toward lower CBF after transfusion (p = 0.10) and a lower OEF after IH (p = 0.11). Cerebral metabolism (measured by the CMRO$_2$) was unchanged. Evaluating only patients with angiographic vasospasm (7 in the fluid bolus, 4 in the IH, 7 in the transfusion group), there was still no change in global CBF or DO$_2$ with any of the interventions, and no differential response between treatments. Among patients with ischemic deficits (9, 2, and 6, respectively), only IH led to a small but significant rise in CBF (from 37.1 ± 11 to 41.2 ± 11; p = 0.01) and DO$_2$ (from 4.7 ± 0.4 to 5.2 ± 0.4; p = 0.06), but ANOVA did not confirm the superiority of this response over the other two interventions (probably due to small numbers). There were too few patients (5 overall) with low global CBF (< 25 ml/100 g/min) to permit analysis of this subgroup. There were 12 patients with low global DO$_2$ at baseline divided between the 3 cohorts. In this subgroup, transfusion resulted in a significantly larger rise in global DO$_2$ than either IH or fluid bolus (21% vs 7% increase for IH and 7% decrease for fluid bolus; p = 0.02, ANOVA).

Among the 9 anemic patients with hemoglobin < 9 g/dl in the transfusion study, blood transfusion resulted in a significant rise in global DO$_2$ (from 4.7 ± 0.9 to 5.4 ± 0.8; p = 0.002) with no fall in CBF. Comparing the response to transfusion in these anemic patients to the response to fluid bolus and IH in all patients receiving those interventions, the 17% rise in global DO$_2$ after transfusion was
significantly better than the lack of improvement seen in the other two groups (p = 0.015).

**Regional PET Data**

A total of 111 regions were excluded (62 were in the ventricular system, 35 were within infarcts or edema, and 14 were in regions of hematoma), leaving 1257 regions across 36 patients available for regional analysis (300 in the fluid bolus, 396 in the IH, and 561 in the transfusion group). Low DO2 was present in 351 (28%), including 123 in the fluid bolus group (41% of regions), 99 in the IH (25%), and 129 in the transfusion cohort (23%). Low CBF was present in 117 regions (9%), including 62 in the fluid bolus, 44 in the IH, and 11 in the transfusion group. Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bolus, 44 in the IH, and 11 in the transfusion group). Oligemia was present in 74 (11% of 673 regions in the fluid bul

**Discussion**

**Effect of Triple-H Therapy on CBF**

For this exploratory analysis, we combined data from 3 distinct but similarly designed prospective physiologi-

---

**Table 3: Physiological data before and after intervention**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fluid Bolus</th>
<th>IH</th>
<th>Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>Pre-Tx: 111.6 ± 17</td>
<td>Post-Tx: 119.7 ± 23</td>
<td>Pre-Tx: 109.1 ± 11</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>7.9 ± 5</td>
<td>8.9 ± 5</td>
<td>NA</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>10.9 ± 2</td>
<td>10.7 ± 2</td>
<td>9.9 ± 2</td>
</tr>
<tr>
<td>CaO2 (ml/dl)</td>
<td>14.4 ± 3</td>
<td>14.3 ± 3</td>
<td>13.1 ± 3</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>36.3 ± 3</td>
<td>36.0 ± 4</td>
<td>34.9 ± 5</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± SD. Abbreviation: NA = not available.
† p < 0.001.
‡ p < 0.05.

---

**Table 4: Global PET measurements before and after intervention**

<table>
<thead>
<tr>
<th>Parameter†</th>
<th>Fluid Bolus</th>
<th>IH</th>
<th>Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF</td>
<td>34.4 ± 10.6</td>
<td>34.8 ± 12.6</td>
<td>43.7 ± 16.4</td>
</tr>
<tr>
<td>DO2</td>
<td>4.9 ± 1.5</td>
<td>4.9 ± 1.8</td>
<td>5.5 ± 1.8</td>
</tr>
<tr>
<td>OEF</td>
<td>NA</td>
<td>NA</td>
<td>0.34 ± 0.11</td>
</tr>
<tr>
<td>CMRO2</td>
<td>NA</td>
<td>NA</td>
<td>1.94 ± 0.47</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± SD (values for CBF, DO2, and CMRO2 are expressed in ml/100 g/min).
† The OEF and CMRO2 values were available for only 6 of the patients in the IH cohort and for 12 in the transfusion cohort.
Augmenting cerebral oxygen delivery in subarachnoid hemorrhage

...cal studies in which PET imaging was used to evaluate the effects of important hemodynamic interventions on cerebral oxygen delivery and utilization in patients with SAH. This allowed us to broadly compare the efficacy of IH (raising MAP by 25%) and volume loading (with an isotonic crystalloid bolus of 15 ml/kg) to transfusion of 1 U of RBCs. The first 2 interventions form the core of triple-H therapy, which is used as the central medical management strategy to treat ischemic deficits related to vasospasm. It is presumed that they act to reverse or prevent progression of ischemia primarily through their ability to raise CBF, reversing critical reductions in DO2 to brain regions at risk for metabolic failure. Despite their widespread clinical use, only a limited number of studies have investigated their effect on CBF to confirm this fundamental assumption. A recent systematic review of this evidence found that their effect on global or focal CBF was inconsistent. Few controlled studies have compared them with each other or evaluated their benefits relative to placebo. One small study used a regional CBF monitor to evaluate the response to hypertension and hypervolemia, as well as triple-H in combination. This found a 10%–20% rise in focal CBF with IH (in response to a 50% increase in MAP), compared with no significant rise after hypervolemia (induced by fluid boluses of 1–3 L). The hemodilution resulting from fluid boluses actually may have reduced DO2, as estimated by a fall in brain tissue O2 tension. Triple-H therapy in combination did not lead to a greater rise in CBF than IH alone. None of these studies examined multiple regions, evaluating the effect of treatment in those brain areas at highest risk, as we have performed here.

Oxygen Delivery as a Physiological Surrogate

We selected DO2 and not CBF as our primary outcome for two important reasons. First, it would be impossible to achieve a fair comparison of the physiological benefits of hypertension and fluid bolus to those expected from transfusion by using CBF alone. Blood transfusion increases hemoglobin and CaO2, and primarily in this manner augments tissue DO2 (the product of flow and CaO2). Transfusion is not expected to improve CBF (except perhaps through an increase in blood volume and/or blood pressure), and may even reduce flow at higher hemoglobin levels, a trend we observed in this study that may relate to the effects of increased blood viscosity.

More importantly, it is DO2 and not CBF that is directly relevant to the development of tissue ischemia. Flow is only important insofar as it provides blood rich in substrates such as O2 (carried on hemoglobin). Ischemia occurs not when CBF falls below a set threshold, but when CBF is insufficient to provide adequate DO2 to brain tissues, such that oxidative metabolism becomes impaired. We set our DO2 threshold at a level that corresponds to a CBF of 25 ml/100 g/min (the ischemic threshold has variably been measured between 17 and 25 ml/100 g/min), at a low-normal CaO2. Although this may not represent the threshold for cell death, it serves as a practical cutoff to define regions at risk for imminent ischemia. The use of elevated OEF as an additional marker of hemodynamic compromise (that is, oligemia) may further refine our ability to define vulnerable regions, but these data were not available in the fluid bolus study, and so were not the primary focus of this analysis. Although we believe that DO2 is the primary physiological surrogate for tissue viability in ischemia, we recognize that improvement in DO2 (as measured here) has not been validated as a marker of response to hemodynamic manipulation correlated with clinical outcomes.

Effect of Interventions on DO2

We found that none of the interventions had a significant impact on global DO2 in this small cohort of patients (apart from IH in patients with ischemic deficits, which increased global CBF and DO2 by 10%, and transfusion in those with hemoglobin < 9 g/dl, which increased global DO2 by 17%). This does not, however, negate their utility in treating DCI, because we would not require or expect interventions to increase flow or delivery averaged across all regions of the brain. It is most likely their ability to
reverse regional reductions in DO\textsubscript{2} (that is, to vulnerable regions with low DO\textsubscript{2} and oligemia), not their global impact, that contributes to their clinical efficacy in reversing neurological deficits and preventing tissue progressing to infarction. It was reassuring, therefore, that we found a significant rise in both CBF and DO\textsubscript{2} within such vulnerable regions with all 3 interventions (as shown in Fig. 2). We also demonstrated that these interventions can reverse the state of low delivery and oligemia found at baseline. This may most meaningfully translate into protection against regional ischemia. One explanation for the variable and often negative results of previous trials examining CBF after IH and hypervolemia is that those studies often only measured CBF globally (or in a single region), ignoring the possibility demonstrated here that interventions may be neutral globally but still have a positive impact in vulnerable regions.

Furthermore, we found that transfusion was more effective in improving regional DO\textsubscript{2} than a fluid bolus, and even more than raising blood pressure, with a trend to a greater reduction in vulnerable brain regions. A major contributing factor is that CBF did not fall within regions with low DO\textsubscript{2} even as transfusion increased hematocrit; the long-standing concern has been that as viscosity rises at higher hematocrit levels, transfusion may impair flow. If this was the case, any benefit from raising CaO\textsubscript{2} may be negated by the concomitant fall in CBF. If CBF remains stable (as seen here), transfusion will consistently raise DO\textsubscript{2} 10\%–20\% per unit of blood (that is, the amount that CaO\textsubscript{2} rises). Conversely, IH (raising MAP by an average of 25\%) did not result in an equivalent rise in CBF, either globally or even in vulnerable regions (where CBF and/or DO\textsubscript{2} rose only 14\% in response to a larger rise in cerebral perfusion pressure). This suggests that there is neither global nor even complete regional failure of autoregulatory responses, a vascular phenomenon on which the physiological benefit of IH rests (that is, that a rise in cerebral perfusion pressure will improve CBF). Although IH undoubtedly displays clinical efficacy in reversing deficits associated with cerebral vasospasm, our ability to explain this effect through an improvement in DO\textsubscript{2} appears marginal. The IH intervention was able to lower OEF and reverse oligemia, and it may be that these highest-risk regions benefit preferentially due to focal loss of autoregulation, and that this improvement results in resolution of clinical deficits.

**Utility of Fluid Bolus Versus Transfusion in DCI**

We have previously demonstrated the efficacy of a fluid bolus in reversing regional reductions in CBF despite no change in global CBF.\textsuperscript{17} This study extends those results with a larger cohort and now compares the observed response to that seen with other interventions for DCI. It may be reasonable to use a fluid bolus of 15 ml/kg (that is, volume loading/transient hypervolemia) in patients with suspected ischemic deficits while other more durable interventions are being planned, including angiography (with angioplasty if possible for proximal vasospasm) and IH. Given the rapid redistribution of crystalloids out of the plasma compartment, it is unlikely that most of the immediate benefit we observed with a fluid bolus would last more than a few hours. We cannot comment on the delayed efficacy of fluid versus IH versus transfusion because our protocol did not include a PET scan at a later time point. The argument against repeated fluid boluses might be that, although we saw an immediate rise in regional CBF, the improvement in DO\textsubscript{2} was smaller. This is probably explained by the progressive hemodilution (with lowering of CaO\textsubscript{2}) that occurs with volume loading.\textsuperscript{24} Hemodilution attenuates the benefit of increased fluid administration for patients with SAH and ischemia. Blood transfusion provides both volume replacement that remains in the vascular compartment and improves CaO\textsubscript{2}, resulting in a larger and more durable effect on DO\textsubscript{2}. However, especially given the significant risks known to be associated with transfusion,\textsuperscript{25} we cannot suggest giving blood to patients with hemoglobin > 9–10 g/dl until further studies are performed to evaluate the optimal threshold and safety of transfusion in this population.

**Limitations of the Study**

There are a few significant limitations to this type of exploratory analysis. Our comparison of the 3 interventions was not based on randomization of a single cohort of patients with SAH, but on an uncontrolled retrospective review of distinct studies, each with only a limited number of patients. This means that the patients studied in each trial were not entirely equivalent. However, we feel that the broad population from which each study was drawn (that is, aneurysmal SAH at risk of DCI) was fundamentally similar and that management in the NNICU was standardized across all groups. Differences in inclusion criteria meant that the fluid bolus study included only symptomatic patients and that the patients receiving transfusion were all anemic, introducing some heterogeneity. However, even after controlling for these variables or examining patients of a certain type (for example, only those with ischemic deficits or vasospasm), our results remained largely unchanged. Furthermore, by selecting regions with low DO\textsubscript{2} across all patients and cohorts, we formed our primary analysis around a similar at-risk population (of brain regions) in each study. Nonetheless, without a properly controlled study comparing IH, fluid bolus, and RBC transfusion, firm comments on relative efficacy cannot be made.

Another potential confounder in comparing these interventions is that the “dose” of each might not be similar, and so the exact response might similarly be different and hard to compare. It is impossible to meaningfully equalize the amount of fluid or blood that is equivalent to a given rise in blood pressure. However, we believe that the size of the intervention in each study was clinically meaningful (that is, similar to what would be used in clinical practice to manage DCI) and of comparable potency. In fact, we would argue that raising MAP by 25\% should have at least equivalent potency to a single unit of RBCs (which only raise CaO\textsubscript{2} by 15\%) or a single fluid bolus (which might raise plasma volume by 10\%). The finding that IH was no better than the other two modalities, even despite this uncertainty, provides some pause when considering which intervention best minimizes the risk of ischemia.
and infarction. Even if quantitative comparisons are inexact, the qualitative differences we have highlighted are hard to discount entirely.

Finally, our study lacks clinical outcome measures, and so we cannot comment on the clinical efficacy of any of the interventions used. Regional DO$_2$ is only a surrogate for the risk of ischemia, albeit one we think is valid and important. Although it seems intuitive that reversing critical reductions in DO$_2$ would serve to minimize DCI and eventual infarction, this has not been clearly demonstrated. Nonetheless, we believe that one must first understand the physiological effects of these interventions before testing them in clinical trials. We also only measured response (change in DO$_2$) immediately after the intervention. Our findings therefore reflect only the immediate effects of each intervention. We cannot comment on how sustained or transient any benefit from a fluid bolus compared with IH or blood transfusion would be. It may be that raising MAP can be best sustained over the time period required to treat DCI, whereas the acute CBF-raising effects of a fluid bolus are rapidly dissipated. Whether the benefits of transfusion on DO$_2$ are sustained is also unknown and forms the basis of an ongoing study.

Conclusions

We were able to broadly compare the efficacy of transfusion to that of a fluid bolus and IH for augmenting cerebral DO$_2$ to vulnerable brain regions in patients with SAH. We demonstrated that the transfusion of RBCs may be an equally or even more potent intervention than the traditional measures of treating DCI, such as raising blood pressure or increasing volume, especially in more anemic patients or to vulnerable brain regions at highest risk for ischemia. Any potential benefits must be weighed against the known risks of excessive or unnecessary blood transfusion. Direct comparative studies, including those with clinical outcomes, are required to define this relative efficacy and risk-benefit ratio. However, for the first time we have provided data that suggest that transfusion may be a meaningful alternative or adjunct to hemodynamic augmentation.

Disclosure

This work was supported by grants from the National Institutes of Health/National Institute of Neurological Disorders and Stroke (5P50NS35966-10 to Dr. Diringer and P50NS55977 to Dr. Derdeyn); the American Heart Association (10SDG3440008 to Dr. Dhar); and the Barnes-Jewish Hospital Foundation (00956-0807-01 to Drs. Diringer and Dhar). Mr. Scaflani received support from Grant No. UL1 RR024992 from the National Institutes of Health–National Center for Research Resources. Dr. Derdeyn is a consultant for W. L. Gore and Associates. The authors have no other relevant financial disclosures.

Author contributions to the study and manuscript preparation include the following: Conception and design: Dhar, Scaflani, Diringer. Acquisition of data: Dhar, Scaflani. Analysis and interpretation of data: all authors. Drafting the article: Dhar. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dhar. Statistical analysis: Dhar, Scaflani. Study supervision: Videen, Derdeyn, Diringer.

Acknowledgments

The authors thank Lennis Lich, Angola Shackelford, John Hood, and the cyclotron and ICU staff for their invaluable assistance in performing this research and caring for these complex patients.

References


Augmenting cerebral oxygen delivery in subarachnoid hemorrhage


---


Please include this information when citing this paper: published online November 18, 2011; DOI: 10.3171/2011.9.JNS11691. Portions of this work were presented in poster form at the Society of Critical Care Medicine’s 40th Critical Care Congress on January 16, 2011.

Address correspondence to: Rajat Dhar, M.D., Department of Neurology, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8111, St. Louis, Missouri 63110. email: dharr@neuro.wustl.edu.