Effect of Hypertonic Saline on Cerebral Blood Flow in Poor-Grade Patients With Subarachnoid Hemorrhage

Ming-Yuan Tseng, MD, MPhil; Pippa G. Al-Rawi, BSc; John D. Pickard, FRCS, MChir; Frank A. Rasulo, MD; Peter J. Kirkpatrick, FRCS (SN)

Background and Purpose—The goal of this study was to examine the effects of hypertonic saline on cerebral blood flow (CBF) in poor-grade patients with subarachnoid hemorrhage.

Methods—We administered 23.5% hypertonic saline (2 mL/kg IV) 1 time to 10 patients, 2 times to 7 patients, and 3 times to 1 patient. All patients had transcranial Doppler (TCD), intracranial pressure (ICP) monitoring, and analysis of serum sodium and osmolality; 6 had xenon CT (XeCT). Data were used to characterize the changes in CBF, cerebral vascular resistance (CVR), ICP, cerebral perfusion pressure (CPP), and potential rheological mechanisms of action.

Results—In the first treatment episode, CPP increased 26.8% \((P=0.0003, \text{at} 28.3 \text{~minutes})\) from a rise in mean arterial blood pressure (ABP) of 10.5% \((P=0.02, \text{at} 22.2 \text{~minutes})\) and a fall in ICP \((P=0.002, \text{at} 60.0 \text{~minutes})\). Flow velocity (FV) of the middle cerebral artery increased 70.8% \((P=0.00005, \text{at} 20.0 \text{~minutes})\), resulting in a corresponding fall in estimated CVR \((P=0.01, \text{at} 16.3 \text{~minutes})\). The half-lives of effects on ABP, CPP, ICP, FV, and estimated CVR were 20.0, 53.6, 139.1, 42.7, and 27.1 minutes, respectively. In the second treatment episode, all these parameters had the same response except estimated CVR, which did not reach statistical significance. XeCT confirmed the increase in CBF (22.9%, \(P=0.02\)) without regional differences. A fall in CBF after hypertonic saline was identified in only a single region of interest in a patient in whom baseline flow was low but not infarcted. Serum sodium rose by 11.4 and 8.8 mmol/L, and osmolality rose by 26.7 and 16.3 mosm/L in the first and second treatment episodes, respectively. Hemoglobin decreased by 0.7 and 0.6 g/L and hematocrit decreased by 1.9% and 2.4% in the first and second treatment episodes, respectively.

Conclusions—We found that 23.5% hypertonic saline increases CBF in poor-grade patients with subarachnoid hemorrhage. These effects are associated with improved indexes of blood rheology. Potential therapeutic benefits are discussed. (Stroke. 2003;34:1389-1397.)

Key Words: cerebral blood flow ■ computed tomography ■ saline solution, hypertonic ■ subarachnoid hemorrhage ■ xenon

Cerebral blood flow (CBF) decreases globally after spontaneous subarachnoid hemorrhoid (SAH). The worse the neurological grade is at presentation, the lower the CBF is. In poor-grade patients, CBF may remain depressed for several weeks. Regional perfusion defects correlate with areas of severe vasospasm, intracerebral hematomas, and ventricular dilatation. Such defects may be a source of cerebral ischemia, infarction, and subsequent poor outcome.

In experimental studies, potential beneficial effects of hypertonic saline on CBF have been seen. Although hypertonic saline can improve intracranial pressure (ICP) and cerebral perfusion pressure (CPP) in patients with brain injury, the effects on CBF in the clinical arena have yet to be explored. This study tests the hypothesis that a bolus infusion of hypertonic saline can improve CBF to areas of poor cerebral perfusion in patients with poor-grade SAH without compromising flow to other areas.

Materials and Methods

Patients
This study was approved by the Local Research Ethics Committee (LREC No. 01/354). From January 20 to May 20, 2002, patients 19 to 80 years of age with poor-grade SAH (World Federation of Neurological Surgeons grade 4 or 5) admitted to the Neurosciences Critical Care Unit (NCCU) of Addenbrooke’s Hospital (Cambridge, UK) were considered for the study. Consent was obtained from next of kin. Exclusion criteria were (1) traumatic SAH, (2) initial serum sodium level <155 mmol/L, (3) initial serum osmolality >320 mmol/L, and (4) impaired renal or cardiovascular function. Female patients who had a positive pregnancy test were also excluded. For xenon CT (XeCT), the individual’s oxygen require-
ment had to be <55%. When it was clinically indicated to improve CPP and CBF, patients would receive ≥1 treatment episodes with hypertonic saline.

Monitoring
Patients were managed according to the SAH protocol of the NCCU with routine monitoring of mean arterial blood pressure (ABP), heart rate, central venous pressure (CVP), hourly urine output, fluid balance, and temperature (tympanic temperature). ABP was measured continuously by an arterial line. An ICP probe (Codman MicroSensor, Johnson & Johnson Medical Ltd) or an external ventricular drainage was inserted into the nondominant frontal region for ICP monitoring. Full blood cell counts, including hemoglobin and hematocrit estimations, serum biochemistry, and arterial blood gas (ABG) analysis at the time of admission, were recorded as baseline data.

Transcranial Doppler
A transcranial Doppler (TCD; DWL Multi-Dop X4, DWL-Electronics) was used to record the flow velocity (FV) of the middle cerebral artery (MCA) bilaterally. Signal capture (with ABP, ICP, and CPP) was maintained for 20 minutes before baseline XeCT. To measure the maximal effect of hypertonic saline, only the side with larger changes was chosen for later analysis.

Xenon CT
XeCT (XeCT System, Diversified Diagnostic Products Inc, DDP) was carried out with 28% xenon gas (Air Product plc). Immediately after the baseline scan, 2 mL/kg of 23.5% hypertonic saline was infused via a central venous catheter for 20 minutes. Ten minutes after the completion of this infusion, a second XeCT was acquired. Each patient had 1 paired XeCT study only. When the patient’s oxygen requirement was >55%, the infusion was monitored by TCD only.

Blood Analysis
Full blood cell counts, serum biochemistry, and ABG were checked in the first hour and then every 6 hours for a total of 24 hours after the infusion. We aimed to keep serum sodium concentration within an acceptable range (145 to 155 mmol/L) to avoid azotemia. Likewise, the maximum rate of decrease in serum sodium considered acceptable was 10 mmol · L⁻¹ · d⁻¹.13,14,19

Data Acquisition and Analysis
In the whole investigation, the duration of collecting laboratory data was 24 hours, but the duration of online monitoring, including ABP, ICP, CPP, and TCD, and treatment records, including infusion therapy, vasopressor drugs, and ventilation settings, was between 2 and 6 hours, during which the frequency of changing position was
Figure 2. Changes in ABP (A1, A2), ICP (B1, B2), CPP (C1, C2), FV (D1, D2), eCVR (E1, E2), serum sodium level (F1, F2), and hematocrit (G1, G2) after infusion of 23.5% saline. Left, first infusion; right, second infusion. The 2 infusions were given 2.7 ± 1.5 days apart.
kept as minimal as possible. When the data quality was not satisfactory because of essential nursing care or clinical management such as operations or cerebral angiography, bedside recording was terminated.

The online monitoring signals were averaged at 5-minute intervals. The maximum response and the time to reach this response in each treatment episode were analyzed separately. The mean half-life (T1/2) was obtained by averaging the time when the maximum effect had diminished to 50%. The Kolmogorov-Smirnov test was used to verify the normal distribution of the maximum response. Because of the relatively small sample size, the maximum response was compared with baseline by use of the paired \( t \) test, and adjustment for multiple comparisons was not undertaken. To explore potential mechanisms of the action of hypertonic saline, cerebral vascular resistance (CVR=CPP/CBF) and the estimated CVR (eCVR=CPP/ FV) were calculated.

Analysis and comparison of CBF were performed by use of the DDP XeCT software (XeCT System, DDP Inc). Each CBF map was divided into 10 regions of interest (ROI) according to the major arterial areas and subcortical nuclei. CBF in each ROI (rCBF) was calculated by averaging the pixels in all levels. Global CBF was obtained by summarizing all rCBFs. Linear regression analysis determined the correlation between FV and rCBF from relevant ROI.

Hematological, biochemical, and ABG indexes were obtained at 1, 6, 12, and 24 hours. Hourly urine output and fluid balance were monitored over the initial 6 hours, and the maximal changes were compared with baseline by use of Statistica 5.1 (StatSoft Inc) and expressed as mean±SE. Statistical significance was defined for \( P<0.05 \).

**Results**

**Patients**

Ten patients (2 male, 8 female; average age, 50.2±14.8 years) were examined. Seven had 2 and 1 had 3 treatment
episodes. In addition, 6 had XeCT scans. The times between the SAH ictus and the first and second infusion episodes were 4.8±3.4 and 8.6±4.1 days, respectively. The 2 treatment episodes were 2.7±1.5 days apart (range, 1 to 5 days). A total of 18 infusions were given. Only 1 patient had the third treatment episode; therefore, this episode was excluded from analysis. No side effects were observed during the whole investigation.

**Monitored Online Variables**

Significant effects after infusion were seen in each treatment episode. Figure 1 shows an example of the first treatment episode of a patient. After the maximum effects, the changes in these parameters, including serum sodium level and hematocrit, decreased exponentially (Figure 2). The maximum effects with a T1/2 of all patients are shown in Table 1. The time to reach the maximum effects had reduced to 50%. Although there was a trend of delayed responses in the second treatment episode, the differences in maximal responses and the time to reach them between the 2 treatment episodes were not statistically significant.

The time for the ICP, CPP, and FV to return to their baseline values varied widely in each patient, ranging from 100 to >510 minutes. In 6 infusions, the effects on ICP, CPP, and FV lasted beyond the time of observation. In 4 patients whose initial ICP was >20 mm Hg during the first treatment episode, the average time for the ICP to return to this level was 243.8±51.9 minutes.

**XeCT CBF**

XeCT showed an augmentation of global CBF after infusion, and a good correlation was found between FV and rCBF (r=0.67, P=0.034). The average increase was 8.9±6.4 mL/100 g brain tissue per 1 minute (22.9±12.8%, P=0.02). Figure 3A shows an example. Table 2 shows the changes in rCBF and global CBF after infusion. In each ROI, the changes in rCBF varied widely, but most of the rCBF remained >20 mL/100 g brain tissue per 1 minute. In patient A, whose baseline XeCT showed ischemia in the bilateral anterior cerebral artery (ACA) ROI, rCBF increased after infusion. In patients C and E with signs of infarction on CT scans and corresponding rCBF <18 mL · 100 g⁻¹ · min⁻¹ (patient C, left ACA ROI; patient E, right MCA and putamen)

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### TABLE 1. Maximum Effects, Time to Reach Maximum Effects, and T₁/₂ of These Effects After Infusion of 23.5% Saline, 2 mL/kg, in 10 Poor-grade SAH Patients in 2 Treatment Episodes

<table>
<thead>
<tr>
<th>Treatment Episode</th>
<th>Parameter</th>
<th>Maximum Effects</th>
<th>Time to Maximum Effects, min</th>
<th>T₁/₂, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>First (n=10)</td>
<td>ABP</td>
<td>10.5±10.7%</td>
<td>0.02</td>
<td>22.2±17.2</td>
</tr>
<tr>
<td></td>
<td>CPP</td>
<td>26.8±19.5%</td>
<td>0.0003</td>
<td>28.3±24.4</td>
</tr>
<tr>
<td></td>
<td>ICP</td>
<td>-74.7±15.6%</td>
<td>0.002</td>
<td>60.0±33.6</td>
</tr>
<tr>
<td></td>
<td>FV</td>
<td>70.8±44.8%</td>
<td>0.00005</td>
<td>20.0±16.0</td>
</tr>
<tr>
<td></td>
<td>eCVR</td>
<td>-26.6±18.8%</td>
<td>0.01</td>
<td>16.3±20.5</td>
</tr>
<tr>
<td>Second (n=7)</td>
<td>ABP</td>
<td>13.9±7.4%</td>
<td>0.007</td>
<td>42.9±43.3</td>
</tr>
<tr>
<td></td>
<td>CPP</td>
<td>36.0±20.9%</td>
<td>0.01</td>
<td>60.0±40.0</td>
</tr>
<tr>
<td></td>
<td>ICP</td>
<td>-71.9±11.8%</td>
<td>0.03</td>
<td>94.0±27.2</td>
</tr>
<tr>
<td></td>
<td>FV</td>
<td>53.8±33.2%</td>
<td>0.004</td>
<td>29.0±36.8</td>
</tr>
<tr>
<td></td>
<td>eCVR</td>
<td>-29.6±14.4%</td>
<td>0.3</td>
<td>25.0±36.7</td>
</tr>
</tbody>
</table>

Values are mean±SE when appropriate.

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### TABLE 2. Changes in rCBF and Global CBF From Baseline to After Infusion of 23.5% Saline, 2 mL/kg, in 6 Poor-Grade SAH Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>rCBF Before Infusion in Each Patient</th>
<th>CBF After Infusion in Each Patient (Difference, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>R ACA</td>
<td>24.3</td>
<td>57.5</td>
</tr>
<tr>
<td>R MCA</td>
<td>45.5</td>
<td>60.7</td>
</tr>
<tr>
<td>R PCA</td>
<td>44.3</td>
<td>59.1</td>
</tr>
<tr>
<td>R PUT</td>
<td>52.8</td>
<td>73.2</td>
</tr>
<tr>
<td>R THA</td>
<td>43.0</td>
<td>65.8</td>
</tr>
<tr>
<td>L ACA</td>
<td>19.4</td>
<td>59.8</td>
</tr>
<tr>
<td>L MCA</td>
<td>34.3</td>
<td>59.2</td>
</tr>
<tr>
<td>L PCA</td>
<td>45.9</td>
<td>58.8</td>
</tr>
<tr>
<td>L PUT</td>
<td>37.5</td>
<td>63.4</td>
</tr>
<tr>
<td>L THA</td>
<td>44.8</td>
<td>71.1</td>
</tr>
</tbody>
</table>

Global 38.2 60.3 24.3 56.4 23.0 45.2 53.1 (38.8) 78.9 (30.9) 29.5 (21.4) 59.3 (5.1) 27.3 (18.3) 53.1 (17.3)

PCA indicates posterior cerebral artery; PUT, putamen; and THA, thalamus. Values for rCBF and global CBF are given in mL · g⁻¹ · min⁻¹.
ROI), rCBF fell or remained unchanged. Only a single ROI in 1 patient (patient C, right ACA ROI) showed a significant fall in rCBF after infusion, indicating potential steal of blood from ischemic (noninfarcted) tissue. This ROI represented a penumbra surrounding infarcted tissues and a hematoma.

There was no correlation between baseline CBF and the quantified CBF change after infusion, and the extent of increase did not vary according to different brain structures (such as cerebral cortex and subcortical nuclei) (Figure 3B). Global CVR decreased in 5 of the 6 patients, but the changes failed to reach statistical significance.

**Blood Osmolality and Hematology**

After the infusion, serum sodium levels increased by 11.4 (P=0.00002) and 8.8 (P=0.003) mmol/L and serum osmolality by 26.7 (P=0.02) and 16.3 (P=0.046) mmol/L within the first hour after the first and second treatment episodes, respectively. The T_{1/2} of serum sodium is ~12 hours in each treatment episode. Serum levels of potassium and creatinine did not change in all treatment episodes. Hemoglobin levels decreased by 0.7 (P=0.005) and 0.6 (P=0.04) g/L within 2 hours, and hematocrit decreased by 1.9% (P=0.03) and 2.4% (P=0.048) within 6 hours after the first and second treatment episodes, respectively.

ABG analysis showed that all blood gas parameters (pH, PaO₂, PaCO₂, bicarbonate) were unchanged in both the first and second treatment episodes.

Hourly urine output increased during the second hour only (from 110.8±64.4 to 260.0±203.0 mL/h, P=0.03) in the first treatment episode and during the first 4 hours (reaching a peak during the first hour, from 94.3±55.3 to 274.3±123.5 mL/h, P=0.01) in the second treatment episode. The hourly fluid balance did not change in the first treatment episode, but it became negative during the first 4 hours (reaching a peak during the third hour, from 117.9±169.5 to −143.1±159.1 mL/h, P=0.02). The initial central venous pressures were 11.8±3.8 and 11.2±1.9 mm Hg in the first and the second treatment episodes, respectively. Six patients in the first treatment episode and 3 patients in the second treatment episode had vasopressor drugs. During clinical observation for 2 to 6 hours, CVP,
Discussion
This study has characterized the augmenting effects of hypertonic saline on CBF after SAH and confirmed previous reports on ICP reduction. Because the potential for developing infarction is high when rCBF is <18 mL · 100 g⁻¹ · min⁻¹, the clinical aim for hypertonic saline is to protect ischemic areas while awaiting spontaneous recovery of CBF.

Augmentation of CBF was confirmed by both qualitative (TCD) and quantitative (XeCT) methods. Factors altering CBF include PaCO₂, PaO₂, and temperature, all of which were unchanged during our examinations. Xenon gas (especially when administered in high concentrations of ≥30%) can cause cerebral vasodilation and increase CBF. However, because 28% xenon was used and comparisons were made between baseline and post–hypertonic saline under strict physiological control, we do not believe that the comparative CBF estimations were altered significantly by xenon administration.

The early increase in CBF without regional differences was consistent with some but not all animal studies, a possible reflection of different mechanisms of cerebral injury in different experimental models. Although CBF increases were seen for the vast majority of regions examined, differences in CBF augmentation were identified. Infarcted tissues with rCBF <18 mL · 100 g⁻¹ · min⁻¹ showed unchanged or even decreased values. One penumbra area with compromised rCBF showed a significant fall (~21.6%) in rCBF, suggesting steal of flow from critically perfused tissues. Although an isolated finding, this raises special concern because the hypotheses stated were not completely satisfied. Further investigations are needed to increase sample size and variety of the baseline CBF and for different pathological entities.

Because changes in FV correlated well with XeCT, FV may be used to monitor CBF response. The increase in FV lasted 175 to 450 minutes, indicating that the effect of CBF augmentation is considerable. The time for maximum response for FV was shorter than that for CPP. CBF augmentation therefore appeared more quickly, and the mechanisms involved are partly independent of CPP. Hyperosmolality can have a rapid effect on swollen ischemic capillary endothelia, and hemodilution induced by an influx of fluid from the interstitium into the intravascular space will further reduce CVR. Likewise, reduction in erythrocyte volume and hematocrit and improved red cell deformability may be rapid. These mechanisms combine to lower CVR and improve perfusion before an increase in CPP is fully realized.

The increase in CPP results from both a lowering of ICP and an increase in ABP, an effect reported previously. The ICP-lowering effect occurred immediately during infusion and continued for >200 minutes. The mechanism of the ICP-lowering effect includes dehydration of the intracranial compartments and cerebral vasoconstriction during hemodilution brought about by hypertonic saline infusions. The dehydration effect is reflected by an increase in urine output and negative fluid balance. In contrast, when a smaller dose of sodium chloride (~160 mosm) is used, the increase in urine output and the negative fluid balance are not observed. Although CVP was unchanged in this study, the increase in ABP probably reflects an expansion of plasma volume and a positive inotropic effect. Again, when lower doses of hypertonic saline are used, the ABP remains unchanged.

In conclusion, we are satisfied that hypertonic saline does cause a significant increase in CBF to most regions of the brain in patients with poor-grade SAH, an action that is durable and hence of potential clinical utility. The effect appears to depend on a reduction in CVR, an increase in CPP, and improved hemorheology from a multitude of mechanisms. However, repeated treatment is restricted by hypernatremia, and repeated infusions may be directed by the T₁/₂ for serum sodium levels (T₁/₂, 12 hours). Before these findings are extrapolated to the clinical arena, the beneficial effect of CBF augmentation needs further exploration, particularly in light of the isolated finding of intracranial steal in 1 ROI. Any increase in CBF may result in preferential flow through intraparenchymal or extraparenchymal microvascular (nonexchange) shunts not involved in substrate delivery, and the observed mechanical increase in CBF may not translate into metabolic improvement. Monitoring the effects of hypertonic saline solutions on cerebral tissue metabolite concentrations seems a sensible approach, with particular attention given to cerebral tissue oxygen concentration and lactate-to-pyruvate ratios, parameters that are predictive of cerebral infarction and poor clinical outcome, and cerebral metabolism of oxygen and substrates. The former can be elucidated by the use of tissue oxygen probes and microdialysis in particular ROI; the latter can be revealed through PET and related radiopharmaceuticals.

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References
Hypertonic saline solutions (HSs) have been used in various concentrations in patients with intracranial pathologies to treat cerebral edema and elevated intracranial pressure (ICP). Since the first animal experiments by Weed and McKibben in 1919, many data have been published on the use of HSs in both animal models and human patients with hemorrhagic shock with and without elevated ICP and with isolated intracranial processes. All these studies have shown that HSs effectively reduce ICP and cerebral edema with subsequent enhancement of cerebral perfusion pressure. Another beneficial effect of HS is an increase in intravascular volume and therefore maintenance of adequate cardiac output and blood pressure. Several possible mechanisms of action of HS have been reported: reduction in brain water by creation of an hypertonic/hyperoncotic saline/dextran and hypertonic mannitol experimental study. Neurosurgery. 1995;37:98–108.


osmotic effect to draw water from the brain to the intravascular space; improvement of cerebral blood flow (CBF), presumably by exertion of a dehydrating effect of cerebrovascular endothelium and erythrocytes; restoration of normal membrane resting potential; and reduction in adhesion of polymorphonuclear cells to cerebral microvasculature with attenuation of pial vessel dilatation. Taken together, all these effects may reduce cerebral ischemia and improve cerebral oxygen delivery.

Subarachnoid hemorrhage (SAH) is a devastating condition that carries high morbidity and mortality. A major cause of poor outcome after SAH is the development of cerebral vasospasm with subsequent infarction. Because of the CBF-enhancing properties noted in animal models and its maintenance of adequate intravascular volume, HS may be a good candidate for fluid resuscitation in SAH patients. Despite this evidence, there is a scarcity of studies in this area. In a case series of patients with cerebral vasospasm after SAH, administration of an HS achieved a positive fluid balance and short-term clinical improvement without adverse effects. However, CBF was not measured. In this issue of Stroke, Tseng et al present an interesting report on the effect of HS on CBF in poor-grade patients with SAH. Although its sample size is small, this attempt represents the first human study investigating this topic. The authors have convincingly found that HS exerts an early CBF-augmenting effect in this patient population. Such a phenomenon was independent of ICP or cerebral perfusion pressure and was present up to 7.5 hours after HS administration. These findings are certainly preliminary but raise the possibility that HS may be useful in situations in which CBF is diminished after SAH. A likely scenario would be in the presence of cerebral vasospasm. Patients can be resuscitated aggressively with HS to achieve hypervolemia and hyperdynamia with the possible added advantage of improved CBF for several hours. This may allow clinicians extra time until a more definitive treatment, ie, cerebral angioplasty, is carried out. Alternatively, HS administration may lead to sustained clinical improvement, thus avoiding further invasive treatments. Until such evidence becomes available, I agree with the authors that further studies are needed to elucidate the effects of HS on cerebral metabolism and long-term clinical outcome in these patients. This is even more pressing and important when we consider that cerebral vasospasm after SAH is associated with a 30% mortality rate.

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References
Editorial Comment: Salting the Brain to Improve CBF in SAH Patients
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