Hypertonic Saline In Patients With Poor-Grade Subarachnoid Hemorrhage Improves Cerebral Blood Flow, Brain Tissue Oxygen, and pH

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Background and Purpose—Delayed cerebral ischemia and infarction due to reduced CBF remains the leading cause of poor outcome after aneurysmal subarachnoid hemorrhage. Hypertonic saline (HS) is associated with an increase in CBF. This study explores whether CBF enhancement with HS in patients with poor-grade subarachnoid hemorrhage is associated with improved cerebral tissue oxygenation.

Methods—Continuous monitoring of arterial blood pressure, intracranial pressure, cerebral perfusion pressure, brain tissue oxygen, carbon dioxide, pH, and middle cerebral artery flow velocity was performed in 44 patients. Patients were given an infusion (2 mL/kg) of 23.5% HS. In 16 patients, xenon CT scanning was also performed. CBF in a region surrounding the tissue oxygen sensor was calculated. Data are mean±SD.

Results—Thirty minutes postinfusion, a significant increase in arterial blood pressure, cerebral perfusion pressure, flow velocity, brain tissue pH, and brain tissue oxygen was seen together with a decrease in intracranial pressure (P<0.05). Intracranial pressure remained reduced for >300 minutes and flow velocity elevated for >240 minutes. A significant increase in brain tissue oxygen persisted for 240 minutes. Average baseline regional CBF was 33.9±13.5 mL/100 g/min, rising by 20.3%±37.4% (P<0.05) after HS. Patients with favorable outcome responded better to HS in terms of increased CBF, brain tissue oxygen, and pH and reduced intracranial pressure compared with those with an unfavorable outcome. A sustained increase in brain tissue oxygen (beyond 210 minutes) was associated with favorable outcome (P<0.023).

Conclusion—HS augments CBF in patients with poor-grade subarachnoid hemorrhage and significantly improves cerebral oxygenation for 4 hours postinfusion. Favorable outcome is associated with an improvement in brain tissue oxygen beyond 210 minutes. (Stroke. 2010;41:122-128.)

Key Words: brain tissue oxygen ■ cerebral blood flow ■ hypertonic saline ■ subarachnoid hemorrhage ■ xenon computed tomography

Poor outcome after aneurysmal subarachnoid hemorrhage (SAH) is associated with low cerebral blood flow (CBF), ischemia, and stroke.1 The diffuse nature of SAH and action of red cell breakdown products has widespread effects on the cerebral vasculature. In patients with poor-grade SAH, global CBF may be significantly reduced2 and regional perfusion deficits can develop, correlating with areas of severe vasospasm, intracerebral hematomas, and/or ventricular dilatation.3 Loss of autoregulation, vasospasm, and reduced CBF combine to cause cerebral hypoxia, metabolic abnormalities, raised intracranial pressure (ICP), and subsequent cerebral ischemic infarction.

Reduction in CBF below a critical threshold results in a loss of neuronal function, which may be reversible or permanent depending on the depth and duration of the episode.4 Patients who present with a poor clinical grade and remain comatose after initial resuscitation have a particularly bleak outlook.5 In traumatic brain injury, episodes of low cerebral oxygenation are also associated with poor outcome.6,7 Brain tissue oxygen tension (P\textsubscript{b}O\textsubscript{2}) reflects the availability of oxygen for oxidative energy production and represents the balance between oxygen supply and demand. Ischemic thresholds for P\textsubscript{b}O\textsubscript{2} have been described, ranging from 1.1 kPa to 3.3 kPa.8 A threshold of 1.1 kPa has been identified after temporary clipping during aneurysmal surgery as an indicator of postoperative deficits.9 CBF augmentation using hypertensive agents and agents that dilute and expand the plasma volume are already used to

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reverse ischemic neurological deficits.10 In head-injured patients, mannitol has long been favored for lowering ICP while increasing cerebral perfusion pressure (CPP) and CBF.11,12 Other agents include rheological fluids such as hypertonic saline (HS), which has been shown to have similar effects to mannitol in various intracranial pathologies, but the duration of its action is longer.13,14 It has been suggested that mannitol may have a detrimental effect on mortality in patients with brain injury when compared with HS.15

We have previously demonstrated that intravenous infusion of 23.5% HS exerts an early CBF-augmenting effect in patients with poor-grade SAH.16,17 A 20% to 50% increase in CBF in ischemic regions was seen without compromising blood flow to other areas. Despite the small sample size, these preliminary results showed promise. Additionally, a correlation between HS administration and outcome has been demonstrated.18 Although a metabolic benefit to cerebral tissues has not been proven outside animal studies, preliminary data from a small subset of patients (n=14) showed short-term improvement in P_O2.17 Our hypothesis is that low CBF after SAH can be reversed with HS resulting in an improved cerebral oxygenation profile. These effects may be greater in patients with poor-grade SAH and who have the lowest CBF.

In this study, we used bedside multimodality monitoring and quantified xenon CT scanning (XeCT) to determine the effect of 23.5% HS on CBF augmentation and cerebral oxygenation.

Materials and Methods

Patients
After Local Research Ethics Committee (LREC 02/392) approval and with informed assent from the next of kin, 44 patients (23 male and 21 female) with poor-grade aneurysmal SAH (World Federation of Neurological Surgeons IV or V) were studied between March 2003 and March 2006 (data from the same patient group has been included for analysis in 2 previous publications17,18).

The mean age was 52 years (range, 34 to 74 years). All patients had a Glasgow Coma Scale score of <8 and required ventilation. Patients were excluded if they had a traumatic SAH, baseline serum sodium level was >155 mmol/L, baseline serum osmolarity was >320 mOsm/kg, or they had impaired renal or cardiovascular function.

Monitoring
All patients underwent continuous monitoring at the bedside, including arterial blood pressure (ABP), ICP, CPP, and transcranial Doppler flow velocity of the middle cerebral artery (FV). P_O2, carbon dioxide (P_CO2), and pH (pHb) were monitored using a multiparameter sensor (Neurotrend; Codman) inserted through the same access device. Sensors were placed ipsilateral to the ruptured aneurysm in either middle cerebral artery or anterior cerebral artery territories at a depth of 5 cm. At the time of the study, treatment of the aneurysm was clipped (n=24), coiled (n=7), wrapped (n=1), or conservative (n=12).

Procedure
After a 60-minute baseline (and >3 hours after sensor insertion), patients were given an infusion of 23.5% HS at a dose of 2 mL/kg through a central venous catheter over 10 to 30 minutes. The mean interval between ictus and administration of HS was 3.2±2.3 days. Patients were maintained in stable condition and undisturbed for the duration of the monitoring. Where possible, XeCT (XeCTscanning, Duration 320 mOsm/kg, or they had impaired renal or cardiovascular function.

Data Analysis
XeCT data were analyzed using customized software (XeCTscanning). CBF in a region of interest (mean area=223.8±19.1 pixels) around the Neurotrend sensor (regional CBF) was calculated before and after HS infusion (Figure 1).

Bedside monitoring data were digitized and collected using specialized software. Mean values were averaged at baseline and at 30-minute intervals postinfusion for up to 5 hours. Absolute values and percentage difference from baseline (Δ) were calculated.

Data were tested for normality with the Kolmogorov–Smirnov test, and one-way repeated-measures analysis of variance was used to identify a significant difference over time. Significance against baseline was demonstrated with Dunnett t test. Statistical significance was considered at P<0.05. Values are mean±SD.

Twelve-month outcome was assessed using the modified Rankin Scale (mRS). An mRS score ≥4 was regarded as an unfavorable outcome. Independent group t test and Pearson χ2 test were used to determine any differences between parameters and outcome.

Results
There were no adverse events after HS. In particular, no episodes of rebound intracranial hypertension or hypokalemia were seen.

Baseline serum sodium and osmolarity were 145.63 (±4.92) mmol/L and 302.14 (±10.42) mOsm/L, respectively, and increased after infusion to 156.75 mmol/L (±5.91 mmol/L) and 325.03 mOsm/L (±14.59 mOsm/L). Hemoglobin and hematocrit levels decreased from a baseline of 9.98 g/dL (±0.91 g/dL) and 29.59% (±2.54%), respectively, to 9.46 g/dL (±0.91 g/dL) and 27.69% (±2.60%) at 1 hour postinfusion.

Parameter Responses to HS Infusion
Arterial Blood Pressure and Intracranial Pressure
Baseline ABP was 97.6 mm Hg (±12.6 mm Hg) and increased to 105.4 mm Hg (±14.8 mm Hg) at 30 minutes postinfusion (P<0.05; Figure 2A). Baseline ICP was 17.5 mm Hg (±9.1 mm Hg) and baseline CPP was 80.3 mm Hg (±13.1 mm Hg). ICP decreased to 5.4 mm Hg (±4.2 mm Hg) at 30 minutes. Maximal change in ABP, ICP, and CPP occurred 30 minutes after HS with maximum Δ of 8.6 (±13.2), −67.4 (±21.7), and 26.2 (±19.8), respectively. ABP returned to baseline at 60 minutes postinfusion but showed small fluctuations over the whole monitoring period (Figure 2A). The duration of changes in ICP and CPP were longer with ICP remaining significantly reduced for 240 minutes (%Δ= −29.1±34.2) and CPP showing a significant increase for up to 60 minutes (P<0.05; Figure 2B–C). ICP showed a slow but steady increase over time after HS and had not returned to baseline levels at 5 hours. CPP approached baseline by 270 minutes.

Cerebral Blood Flow
Baseline FV was 90.1 cm/s (±41.5 cm/s) and increased to 116.1±45.2 cm/s (Δ=40.6±44.7) by 30 minutes, remaining elevated for 90 minutes postinfusion (P<0.05). FV had not returned to baseline by the end of the transcranial Doppler monitoring period at 240 minutes (Figure 2D). Sixteen patients underwent XeCT scanning.
Baseline regional CBF was $33.9 \pm 13.5$ mL/100 g/min. A significant change in regional CBF ($\Delta$CBF) was observed after HS ($\Delta$CBF = 20.3 ± 37.4; $P < 0.05$).

**Brain Tissue Oxygen**

Baseline $P_{\text{bO}_2}$ was 2.19 kPa ($\pm 1.58$ kPa) and increased significantly from 30 minutes postinfusion to a maximum of 3.17 kPa ($\pm 2.16$ kPa) at 150 minutes ($\Delta$ = 172.1 ± 558.56). This increase was maintained for up to 240 minutes ($P < 0.05$) and returned to near baseline levels by 300 minutes (Figure 3A).

**Brain Tissue Carbon Dioxide and pH**

Baseline $pH_b$ and $P_{\text{bCO}_2}$ were 7.04 ($\pm 0.21$) and 6.34 kPa ($\pm 0.89$), respectively. $pH_b$ showed a significant increase at 30 and 60 minutes ($P < 0.05$) but had returned to baseline levels by 120 minutes (Figure 3B). Maximum rise in $pH_b$ to 7.08 ($\pm 0.21$) occurred at 60 minutes ($\Delta$ = 0.35 ± 0.65). The mean $pH_b$ for the whole group of patients did not drop below 7.00.

No significant change was seen in $P_{\text{bCO}_2}$ (Figure 3C).

**Parameter Responses in Relation to Outcome**

Sixty-four percent of patients had an unfavorable outcome (mRS 4 to 6). The mortality rate was 33%. Patients with a favorable outcome (mRS 1 to 3) had a higher baseline $P_{\text{bO}_2}$ (2.78 ± 1.6 kPa; range, 0.92 to 5.2 kPa) compared with those with an unfavorable outcome (1.86 ± 1.51 kPa; range, 0.06 to 6.25 kPa; Figure 4). Similarly, patients with a favorable outcome had a higher baseline FV (101.5 ± 42.6 cm/s; range, 51 to 195 cm/s) compared with patients with an unfavorable outcome (83.8 ± 40.3 cm/s; range, 30.4 to 210 cm/s). Baseline $pH_b$ was lower in those with an unfavorable outcome (7.01 ± 0.23; range, 6.64 to 7.26; compared with 7.10 ± 0.19; range, 6.64 to 7.29). However, there was no statistically significant difference between groups, and no baseline parameter was an independent predictor of outcome.

The increase in FV and decrease in ICP after HS was more pronounced and sustained in patients with a favorable outcome. Patients with a favorable outcome showed a significantly greater response in terms of ICP reduction ($\Delta$ = −71.4 ± 15) and FV improvement ($\Delta$ = 48.4 ± 61.7) at 30 minutes after HS compared with patients who had an unfavorable outcome ($\Delta$ ICP = −63.6 ± 24.2; $\Delta$ FV = 35.9 ± 31.5).

The increase in $P_{\text{bO}_2}$ after HS was greater in magnitude and duration in patients with a favorable outcome reaching significance at 210 to 300 minutes (3.64 ± 1.68 kPa compared with 1.99 ± 1.35 kPa at 240 minutes; $P = 0.008$; Figure 4).

All patients in whom the $P_{\text{bO}_2}$ remained below 1.8 kPa eventually died.
Brain pH was higher throughout the monitoring period in patients with a favorable outcome, although this failed to reach statistical significance.

Discussion

This study shows that administering HS to patients with poor-grade SAH improves CBF, PbO2, and pHb. The effect on PbO2 is significant and durable. The rise in ABP at 30 minutes postinfusion probably reflects volume expansion from fluid shifts (secondary to an increase in plasma osmolarity) and a positive inotropic effect. The transient decrease in ABP seen in 19 patients may be due to a rapid decrease in vascular resistance, which may be related to the infusion rate and total osmotic load, a phenomenon observed experimentally. The effect of HS infusion on ICP was significant and long-lasting and may result from dehydration of the intracranial compartments due to hyperosmolarity and cerebral vasocostriction due to hemodilution. The dehydration effect was reflected by polyuria and a negative fluid balance observed during the first 2 hours after HS.

FV is an accurate tool for assessment of CBF and can provide a noninvasive evaluation of CBF trends. Changes in FV are known to correlate well with changes in regional CBF assessed with XeCT. In this study, augmentation of CBF after HS infusion was confirmed by both transcranial Doppler and XeCT. The effect of HS on CBF augmentation is lengthy as illustrated by the sustained increase in FV postinfusion.

Changes in CBF are independent of ABP and long-lasting. The increase in FV was associated with an increase in CPP driven by a fall in ICP rather than solely by increasing ABP. However, previous work showed that a concomitant fall in cerebrovascular resistance occurs, suggesting that CPP alone cannot explain the effect of CBF augmentation.

A significant and sustained improvement was seen in PbO2, with maximal effect at 150 minutes after HS, maintained for up to 4 hours. The changes in PbO2 were independent of ABP and paralleled the increase in FV. After severe SAH, there may be insufficient cerebral oxygen delivery to meet the demand despite maintaining an adequate CPP. By increasing CBF and decreasing cerebrovascular resistance, 23.5% HS improved extracellular PbO2.

Unfavorable outcome has been associated with a decrease in PbO2 and aPbO2 associated with cerebral infarction. In this study, baseline PbO2 was 1.1 kPa in 10 individuals. In all but 2 patients, PbO2 increased >1.1 kPa after HS and may have reduced the risk of regional cerebral infarction. One patient with a PbO2 of 0.92 kPa showed a substantial increase with HS (2.60 kPa at 30 minutes) and made a very good recovery. The low baseline pHb (7.04) may be common in patients with poor-grade SAH. The mechanism for this may be a combination of deranged metabolism and impaired homeostatic mechanisms, both related to a low CBF state. pHb has been shown to be a useful marker for assessing the severity of focal cerebral injury and outcome in patients with traumatic brain injury. Where pHb fell <7.0, patients had a significantly higher hospital mortality, and it has been suggested that derangement of
pHb may provide a more robust indicator of local metabolic compromise than PbO2.27

In this study, 23.5% HS resulted in a significant improvement in pHb at 30 and 60 minutes postinfusion, and pHb remained elevated for up to 120 minutes. In 27 patients (61%), pHb remained >7.00 for the duration of the study. However, in those patients who had a baseline pHb of ≤7.00 (n=10), HS did not increase the pH above this threshold value, suggesting anaerobic metabolism and potential ischemia. Of these, only 2 made a favorable recovery. The remainder died (n=6) or had a poor outcome (mRS 5), a poor response to HS possibly being a reflection of poor vascular and tissue viability.

Despite poor outcome being related to lower baseline PbO2, FV, and pH, no baseline parameter was an independent predictor of outcome. Similarly, change in PbO2 was not an independent predictor of outcome.

There are a number of study limitations, in particular, the small sample size and the fact that this study was designed to look at the effect of one treatment episode taken from a very

**Figure 3.** Absolute values at baseline (Time 0) and at 30-minute intervals after HS infusion for PbO2 (A), pHb (B), and PbCO2 (C). Values are mean (±95% CI). The asterisk denotes P<0.05.

**Figure 4.** PbO2 at baseline (Time 0) and at 30-minute intervals after HS infusion for patients with a favorable outcome (mRS 1 to 3) and those with an unfavorable outcome (mRS 4 to 6). Error bars show 95% CI. The asterisk denotes a significant difference between groups (P<0.05).
small time window during the patients’ overall stay in intensive care. This is also a highly heterogeneous group of patients who, although all had severe aneurysmal SAH, have varying ischemic and nonischemic pathologies. Secondary ischemic events associated with vasospasm, hydrocephalus, sepsis, or rebleeds may still occur, which will not be targeted by early HS therapy. Additionally, many variables are difficult to control in the clinical setting.

Although this study is unable to determine an absolute independent association between clinical outcome and PbO2, over such a small time window, the data suggest that those patients who have a favorable outcome respond very well to HS administration in terms of an increase in CBF, reduction in ICP, and an increase in PbO2 and pH. We believe that the enhanced increase in PbO2, which is sustained beyond 210 minutes and is associated with a favorable outcome, is of considerable interest. A larger randomized study would be needed to definitively determine the relationship between HS, increase in PbO2, and outcome.

The mechanisms by which HS leads to improved tissue perfusion are complex and have been discussed in previous publications.16,18 In addition to hemodilution and hyperosmolarity, there is also an improvement in hemodynamics and a positive inotropic effect. The hypertensive, hypervolemic, and hemodilution effect is similar to triple-H therapy.

Because compromised CBF and cerebral oxygenation is a precursor for ischemic infarction regardless of underlying pathology, the findings in this study may have implications for other conditions. Improving cerebral physiological parameters with HS may increase the window of opportunity for other therapeutic strategies, including thrombolysis and new pharmacological approaches as well as reduce infarct size by protecting penumbral regions. Reduced CBF states after SAH may last for 48 to 72 hours before spontaneous reversal. Given the relatively long-lasting effect of HS, the clinical aim, therefore, would be to protect ischemic areas in the early vulnerable period until spontaneous recovery of CBF occurs.

Theoretical problems with HS include central pontine myelinolysis, seizures, subdural hematoma, and rebound malignant cerebral edema. Other possible complications include congestive heart failure, hypotension, metabolic acidosis, and hypokalemia. We saw no short- or long-term adverse events after administration of 23.5% HS, which is in agreement with several other reports. However, repeated administration is restricted by hypernatremia. Further repeated administrations may be possible at a lower dose and should be investigated to determine its efficacy on CBF and metabolic oxygenation.

Summary

HS safely and effectively augments CBF in patients with poor-grade SAH, improves pHb, and significantly improves P1O2 for up to 4 hours after administration. A sustained improvement in P1O2 after HS administration is associated with a favorable outcome. Most importantly, this study demonstrates that the increase in CBF seen after HS therapy is not a simple washthrough effect, but improves oxygen delivery to poorly perfused areas. The responsiveness of CBF and PbO2 also seems to hold prognostic value.

To determine whether the observed mechanical increase in CBF and associated oxygen delivery is also related to improved metabolic and tissue integrity, further data analysis is in progress to investigate brain tissue chemistry, ischemic stroke, and long-term outcome.

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Disclosures

P.J.H. is a director of Technicam.

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