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# Cerebral blood flow augmentation in patients with severe subarachnoid haemorrhage

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## Summary

Following aneurysmal subarachnoid haemorrhage (SAH), cerebral blood flow (CBF) may be reduced, resulting in poor outcome due to cerebral ischaemia and subsequent stroke. Hypertonic saline (HS) is known to be effective in reducing intracranial pressure (ICP) [16]. We have previously shown a 20–50% increase in CBF in ischaemic regions after intravenous infusion of HS [17]. This study aims to determine the effect of HS on CBF augmentation, substrate delivery and metabolism.

Continuous monitoring of arterial blood pressure (ABP), ICP, cerebral perfusion pressure (CPP), brain tissue oxygen ($P_bO_2$), middle cerebral artery flow velocity (FV), and microdialysis was performed in 14 poor grade SAH patients. Patients were given an infusion of 23.5% HS, and quantified xenon computerised tomography scanning (XeCT) was carried out before and after the infusion in 9 patients.

The results showed a significant increase in ABP, CPP, FV and $P_bO_2$, and a significant decrease in ICP ($p < 0.05$). Nine patients showed a decrease in lactate-pyruvate ratio at 60 minutes following HS infusion.

These results show that HS safely and effectively augments CBF in patients with poor grade SAH and significantly improves cerebral oxygenation. An improvement in cerebral metabolic status in terms of lactate-pyruvate ratio is also associated with HS infusion.

*Keywords:* Subarachnoid haemorrhage; hypertonic saline; brain tissue oxygen; microdialysis; xenon computerised tomography; cerebral blood flow.

## Introduction

Death and disability following SAH is associated with cerebral ischaemia and subsequent stroke, which are often delayed by several days [9]. Combined mortality and morbidity approaches 50%, and long-term morbidity is substantial [1]. Processes are complex, combining to impair blood flow to several territories. Episodes of low CBF are common, particularly in patients who have a poor clinical grade or who deteriorate, and regional perfusion deficits are known to occur. Reduction in CBF below a critical threshold has been shown to result in a loss of function, which may be reversible or remains permanent depending upon the depth and duration of the ischaemic episode [18]. Episodes of low cerebral oxygenation and abnormal profiles of metabolic parameters, in particular a high lactate-pyruvate (L-P) ratio, are also associated with a poor outcome [13]. A threshold for low cerebral tissue oxygen has been identified, below which cerebral infarction occurs [4, 5].

It has been shown that in head injured patients, mannitol can effectively lower ICP whilst increasing CPP [6]. Hypertonic saline (HS) has been shown to have similar effects to mannitol but the duration of action is longer [14, 16]. Experimental studies have shown potential beneficial effects of HS on CBF [8]. However, studies on the use of osmotic agents, including HS, in patients with SAH are limited.

We have previously shown a 20–50% increase in CBF in ischaemic regions after intravenous infusion of hypertonic saline in patients with poor grade SAH, without compromising flow to other areas [17]. While the effects of augmenting CBF with HS appear impressive, a metabolic benefit to cerebral tissues has not been proven outside animal studies. Our hypothesis therefore is that low CBF following SAH can be reversed with HS, resulting in an improved oxygenation and metabolic profile. These effects may be greater in patients with poor grade SAH and who have poorer cerebral blood flow. By using bedside multimodal monitoring and XeCT, our aim was to determine the effect of HS on CBF augmentation, substrate delivery and metabolism.

Table 1. *Table of absolute values and % difference from baseline (% Diff.), at 30 and 60 minutes post infusion for mean arterial blood pressure (MAP), intracranial pressure (ICP), cerebral perfusion pressure (CPP) and MCA flow velocity (FV)*

| | MAP | | ICP | | CPP | | FV | |
|---|---|---|---|---|---|---|---|---|
| | mmHg | % Diff. | mmHg | % Diff. | mmHg | % Diff. | cm/sec | % Diff. |
| Baseline | 102.2 (±10.2) | – | 20.8 (±8.2) | – | 81.5 (±11.0) | – | 86.4 (±19.7) | – |
| 30 Mins | 114.0* (±9.5) | 12.9* (±9.6) | 5.9* (±2.6) | −66.0* (±15.5) | 108.1* (±8.9) | 36.6* (±15.6) | 103.4* (±22.0) | 50.5* (±24.6) |
| 60 Mins | 103.6 (±8.9) | 2.4 (±7.9) | 5.9* (±2.8) | −61.0* (±20.2) | 88.5 (±17.1) | 12.6 (±22.9) | 97.6* (±14.9) | 28.6* (±20.8) |

Values are mean (±95% CI), * denotes $p < 0.05$.

Table 2. *Table of absolute values and % difference from baseline (% Diff.), at 30 and 60 minutes post infusion for brain tissue oxygen ($P_bO_2$), carbon dioxide ($P_bCO_2$) and pH ($pH_b$)*

| | $pH_b$ | | $P_bCO_2$ | | $P_bO_2$ | |
|---|---|---|---|---|---|---|
| | pH | % Diff. | kPa | % Diff. | kPa | % Diff. |
| Baseline | 6.8 (±0.2) | – | 6.5 (±0.65) | – | 1.7 (±0.65) | – |
| 30 Mins | 6.9 (±0.2) | 0.4 (±0.5) | 6.4 (±0.65) | −1.2 (±3.3) | 2.3* (±0.86) | 45.9* (±29.4) |
| 60 Mins | 6.9 (±0.2) | 0.4 (±0.6) | 6.4 (±0.65) | −1.2 (±4.8) | 2.1* (±0.86) | 26.8* (±25.1) |

Values are mean (±95% CI), * denotes $p < 0.05$.

## Materials and methods

After Local Research Ethics Committee approval and following informed assent, 14 patients (7 male and 7 female) suffering from poor grade SAH underwent continuous multimodal monitoring at the bedside, including ABP, ICP, CPP and transcranial Doppler FV. Brain tissue oxygen, carbon dioxide and pH were monitored using a multiparameter sensor (Neurotrend™, Codman, Bracknell, UK) and brain tissue chemistry via a microdialysis catheter (CMA-70, CMA, Sweden), inserted through a triple lumen access device (Technicam, Newton Abbot, UK). This has been described in detail previously [4]. The mean age was 57 years (range 44–74). All patients had a Glasgow Coma Score (GCS) of 8 or less and required ventilation on the Neuro Critical Care Unit (NCCU).

The microdialysis catheter was perfused with CMA perfusion fluid (CMA, Sweden) at a rate of 0.3 µl/min. Vials were changed every 20 minutes. Microdialysis samples were analysed at the bedside for glucose, lactate, pyruvate and glutamate using a CMA 600 analyser (CMA, Sweden). Patients were given an infusion of 23.5% HS via a central venous catheter at a dose of 2 ml/kg. XeCT (Diversified Diagnostic Products, DDP$^{inc}$, Houston, Texas, USA) [18] was performed before and after HS administration in 9 of the 14 patients.

### *Data processing and analysis*

CBF in a region of interest around the microdialysis and Neurotrend™ probes was calculated (ROI CBF). Data from all the monitored parameters was averaged at baseline and at 30 and 60 minutes post infusion. Absolute values and percentage difference from baseline (%Δ) was calculated. Comparison was made using Student's t-test. Values are given as mean ± 95% confidence intervals. Statistical significance was considered at $p < 0.05$.

## Results

Pooling the data for all patients, baseline ICP was 20.8 mmHg (±3.8), with a baseline CPP of 81.5 mmHg (±5.1) (Table 1). At 30 minutes post HS infusion there is a significant increase in ABP and CPP, a significant drop in ICP and a significant increase in FV ($p < 0.05$) (Table 1). At 60 minutes, ICP & FV still showed significant changes, whilst the other parameters tended toward baseline levels. Average baseline ROI CBF was 30.4 ± 7 ml/100 g/min. In 2 patients, ROI CBF decreased after HS. In the remaining 7, a significant increase in ROI CBF following HS infusion was observed ($p < 0.05$).

Looking at the results from the Neurotrend™ sensor (Table 2), baseline brain tissue oxygen ($P_bO_2$) was low at 1.7 kPa (±0.3) and increased significantly at 30 and 60 minutes post infusion ($p < 0.05$) (Fig. 1). Very little change was seen in either brain tissue carbon dioxide ($P_bCO_2$) or pH ($pH_b$).

Turning to the microdialysis data, there was no significant change seen in any parameter when looking at the pooled data for all patients (Table 3). However, Fig. 2 demonstrates a graphical example of the bedside monitoring of L-P ratio seen in one patient. There is a

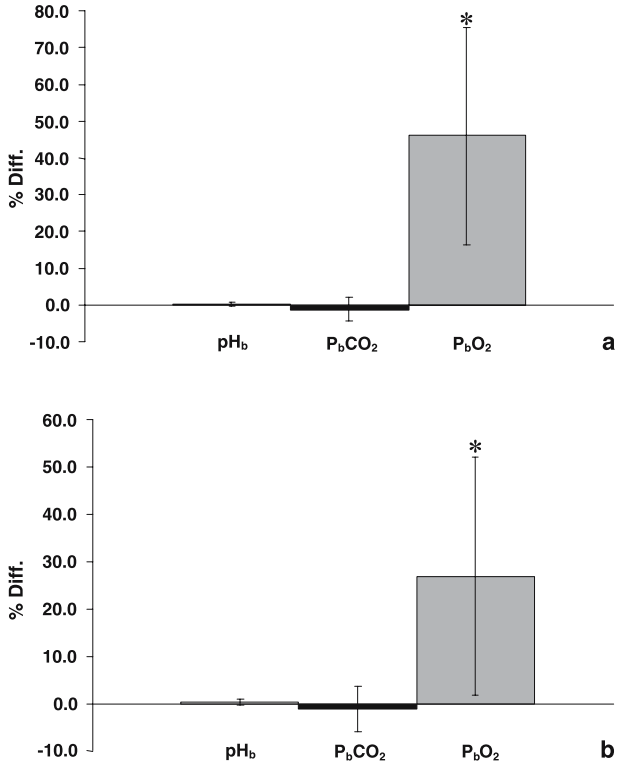


Fig. 1. Graphs of % difference from baseline (*%Δ*) for brain tissue oxygen ($P_bO_2$), carbon dioxide ($P_bCO_2$) and pH ($pHb$) at 30 (a) and 60 (b) minutes post hypertonic saline administration. Error bars represent 95% CI, * denotes $p < 0.05$

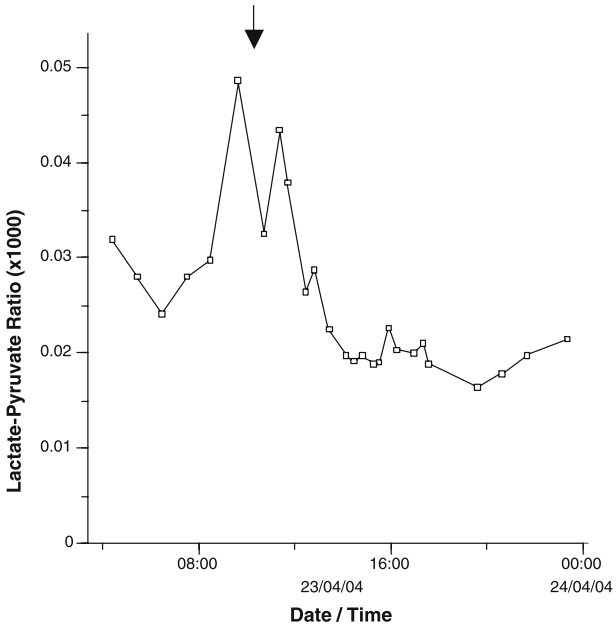


Fig. 2. Graph of lactate-pyruvate ratio monitored at the bedside for an individual patient. Time of administration of HS is marked (arrow)

distinct improvement (i.e. a decrease) in L-P ratio seen after administration of hypertonic saline. Figure 3 shows individual patients L-P ratio at baseline and at 30 and 60 minutes post infusion. At 60 minutes the L-P ratio can be seen to decrease in 9 of the 14 patients. However, one patient demonstrated a very high baseline L-P ratio (>40), which increased further after HS infusion. There were no complications throughout the duration of the study.

## Discussion

In accordance with our previous study, this data has shown that 23.5% HS significantly decreases ICP whilst increasing CPP and FV. In addition, a significant improvement was seen in $P_bO_2$ with maximal effect at 30 minutes post infusion. A decrease in L-P ratio was seen in 9 patients although this did not reach significance for the group as a whole. Baseline glucose and glutamate are lower than previously reported, whilst baseline lactate and L-P ratio are higher. However, all the patients in this cohort were poor grade SAH patients. Previous studies have looked either exclusively at better grade SAH patients, or the data has been derived from a more heterogeneous group, in-

Table 3. *Table of absolute values and % difference from baseline (% Diff.), at 30 and 60 minutes post infusion for brain chemistry data*

| | Glucose | | Lactate | | Pyruvate | | Glutamate | | L-P ratio | |
|---|---|---|---|---|---|---|---|---|---|---|
| | mg/ml | % Diff. | mM | % Diff. | μM | % Diff. | μM | % Diff. | Ratio | % Diff. |
| Baseline | 0.16 (±0.06) | – | 1.57 (±0.4) | – | 65.2 (±18.6) | – | 4.15 (±4.9) | – | 25.2 (±8.0) | – |
| 30 Mins | 0.16 (±0.06) | −9.1 (±17.2) | 1.67 (±0.6) | −0.7 (±13.5) | 68.1 (±27) | −3.3 (±17.6) | 4.01 (±3.7) | 32.0 (±68.0) | 35.1 (±27.4) | 22.6 (±59.9) |
| 60 Mins | 0.19 (±0.09) | 11.4 (±26.1) | 1.89 (±0.9) | 6.9 (±24.8) | 78.9 (±32.4) | 10.7 (±23.3) | 3.93 (±2.6) | 97.7 (±135.6) | 29.5 (±19.9) | 5.52 (±43.26) |

Values are mean (±95% CI).

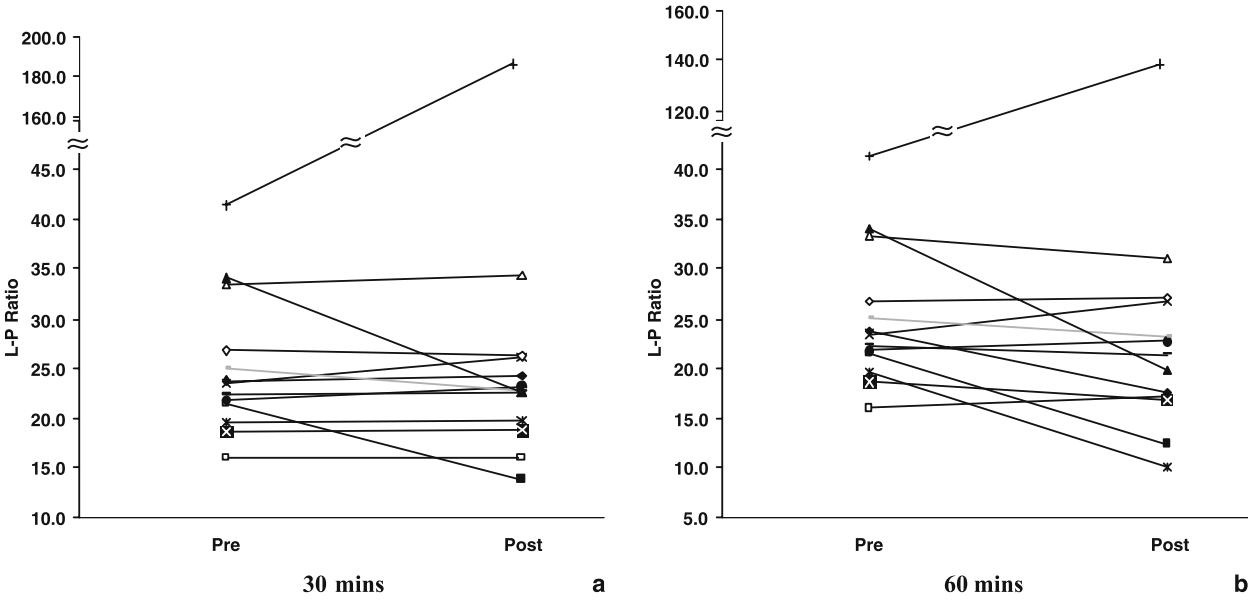


Fig. 3. Graphs showing the lactate-pyruvate (*L-P*) ratio for individual patients, pre and at 30 (a) and 60 (b) minutes post hypertonic saline infusion

cluding good grade SAH or unruptured aneurysms [2, 12]. Glutamate has been suggested to be a sensitive and early marker of cerebral hypoxia [10]. This is not our experience in this study, where considerable variation in glutamate was seen, as indicated by the large 95% CI (Table 3). Significant changes in L-P ratio have been seen in patients with SAH associated with cerebral infarction [11] and L-P ratio has been proposed as a more robust marker of acute ischaemia with a high sensitivity and specificity [4, 7].

Baseline $pH_b$ was low, which may suggest metabolic disturbance as a result of injury severity or secondary insults. However these values may be typical of poor grade SAH patients. The fact that neither $pH_b$ nor $P_bCO_2$ showed significant changes after HS compared to $P_bO_2$ may indicate that they are perhaps not such sensitive markers of improved metabolism. It has been suggested that $pH_b$ and $P_bCO_2$ have a lower predictive value than $P_bO_2$ [3]. The mechanism of action of HS is probably threefold. It has a strong osmotic and haemodilution effect and improves haemorheology [15, 16]. Comparisons between HS and mannitol have suggested that HS is the more effective osmotic agent [14, 16]. Most importantly HS does not deplete intravascular volume. Whilst there are potential complications associated with administration of 23.5% HS, we did not find any short or long term side effects. Since compromised CBF is a precursor for stroke regardless of the underlying pathology, the findings in this study may have implications for other conditions. Prolonging neuroprotection may increase the window of opportunity for other therapeutic strategies, including thrombolysis, as well as reduce infarct size by protecting penumbral regions.

In conclusion, this initial data is encouraging and shows that HS safely and effectively augments CBF in patients with poor grade SAH and significantly improves cerebral oxygen. An improvement in cerebral metabolic status in terms of lactate-pyruvate ratio is also associated with HS infusion. The study is ongoing, and further numbers are needed to assess outcome and radiological stroke.

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