Effect of hypothermia on brain tissue oxygenation in patients with severe head injury

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Background. There is renewed interest in the use of induced hypothermia as a method of neuroprotection both intraoperatively and in the intensive care management of severe brain injury. In this study we have investigated the effects of hypothermia on brain tissue oxygenation in patients with severe head injury.

Methods. Thirty patients with severe head injury (Glasgow coma score <8) were monitored with a multimodal sensor inserted into the brain which measures tissue $P_{O2}$, $P_{CO2}$, pH and temperature in addition to routine monitoring. Patients were cooled to a minimum of 33°C when clinically indicated.

Results. For all 30 patients brain and systemic temperature correlated well ($r=0.96$). Brain temperature was consistently higher than systemic temperature by $0.41 \pm 0.26$°C (confidence limits). Brain tissue $P_{O2}$ decreased with hypothermia, with a significant reduction below 35°C ($P<0.05$).

Conclusions. These results emphasize the advantage of measuring brain temperature directly, and suggest that decreasing brain temperature below 35°C may impair brain tissue oxygenation.

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Important advances have been made in understanding the mechanisms of secondary brain damage in patients with severe head injury. Attempts to interfere pharmacologically with these mechanisms have so far been unsuccessful.

Hypothermia has been used as a method of brain protection in a clinical setting in patients with traumatic brain injury for many years. Moderate hypothermia (temperature 32–34°C) in animal models of focal and global ischaemia and traumatic brain injury has been shown to reduce secondary brain injury and improve behavioural outcome.2–5 There are also clinical reports of patients with traumatic brain injury treated with moderate hypothermia (32–33°C for 24 h) suggesting hastened neurological recovery and an improved outcome in a subgroup of patients.6 In addition to cerebral metabolic suppression, hypothermia has also been found to modify a number of molecular responses such as the release of excitatory amino acids,7 cytokines,6,8 free radicals9 and inflammatory mediators.10 However, in an animal model of transient global ischaemia, Bacher et al. demonstrated that brain tissue oxygen was no better preserved during hypothermic ischaemia compared with normothermic ischaemia.11 In this study we have investigated the effects of decreasing brain temperature on indices of brain parenchymal oxygenation and metabolism in patients with severe head injury.

Methods

Patients

As part of a prospective study of continuous multimodal monitoring in head-injured patients, data from 30 patients with severe head injury (Glasgow coma score [GCS] <8) who were admitted to our neuro intensive care unit were analysed. All patients were managed according to the protocol for severe head injury followed on our neuro intensive care unit.12 This included sedation with propofol (3–5 mg kg⁻¹ h⁻¹), fentanyl (1–2 μg kg⁻¹ h⁻¹) and paralysis with atracurium 0.5 mg kg⁻¹ h⁻¹. Before induction of hypothermia, propofol was changed to midazolam (0.1–0.2 mg kg⁻¹ h⁻¹). Mean arterial pressure was also manipulated to achieve a cerebral perfusion pressure (CPP) greater than 70 mm Hg, with the use of fluid loading and...
Monitoring

All patients had routine invasive monitoring applied, which included mean arterial pressure, central venous pressure, intracranial pressure (ICP) (Codman, Raynham, USA) and continuous jugular bulb oximetry (S_jO_2; Baxter, Northampton, UK). Pulmonary artery catheters were inserted into those patients requiring inotropic support, those with pre-existing cardiac disease and those with significant myocardial contusion. In addition, and after Institutional Ethics Committee approval and written consent from the next of kin, multimodal sensors were inserted to measure brain and arterial O_2, CO_2, pH and temperature. After calibration with three precision gases, two sensors (Paratrend 7, Diametrics Medical, High Wycombe, UK) were inserted into each patient. One was inserted through an 18-gauge cannula into a femoral artery for continuous blood-gas analysis. The second was inserted into brain tissue through a specially designed bolt which was placed in the non-dominant frontal region of the skull.

Hypothermia was induced when ICP was sustained above 25 mm Hg after standard medical treatment. The patient’s core temperature was reduced to a target temperature of 33°C using an air cooling system (Bair Hugger™, Augustine Medical, Eden Prairie, MN, USA) and cold fluids. Brain and arterial blood temperatures were measured by the respective Paratrend sensors. Haemodynamic variables, ICP, temperature and Paratrend data were downloaded onto a computer and time averaged over 2 min. Hypothermia therapy was continued until control of ICP <25 mm Hg was achieved.

Statistical analysis

Data were analysed using a Tukey-HSD one-way analysis of variance (SPSS package) with a significance level of 0.05. Multivariate linear regression was used to calculate the correlation coefficient between arterial and brain temperature. Analysis of oxygen and S_jO_2 was performed for data with the criteria of CPP >50 mm Hg, and arterial CO_2 4–5 kPa. Analysis of CO_2 and pH was performed for data within the criteria of CPP >50 mm Hg. Data are expressed as mean (±95% confidence limits).

Results

Patients

Thirty patients (22 male, 8 female), all with GCS <8, were monitored for up to 14 days (mean 5 days). The mean age was 39 yr (range 17–78). Seventeen patients had their brain temperature reduced below 35°C. Data from all 30 patients were pooled for analysis.

Temperature measurement

Analysis of all 30 patients revealed a close correlation between arterial and brain temperature (r=0.96, P<0.001). In individual patients, brain temperature was found to be higher than arterial temperature. The mean (±SD) difference between the sites was 0.41 (0.26)°C.

Brain and arterial Po_2, P_CO_2 and pH

Figure 1 shows the changes in mean brain tissue oxygen (PbO_2) and arterial oxygen concentration (PaO_2) with brain temperature reduction. There is a significant decrease in dopamine (up to 15 μg kg^{-1} min^{-1}). If required, norepinephrine was also started at a rate of 0.5 μg kg^{-1} min^{-1}.
PbO2 below 35°C (P<0.05) with a highly significant reduction below 34°C (P<0.001) compared with 37°C, whereas PbO2 increased below 37°C. Brain tissue and arterial CO2 (PbCO2, PaCO2 respectively) both decreased with reduced brain temperature to a temperature of 34°C, below which CO2 increased (Figure 2). Very little change occurred in brain tissue or arterial pH with temperature, as shown in Figure 3. SjO2 increased with reduction in temperature (Figure 4).

Discussion

Brain temperature is generally estimated using indirect methods from easily accessible sites such as the rectum, oesophagus or tympanic membrane. In order to avoid the detrimental effects of hyperthermia and maximize the potential beneficial effects of induced hypothermia, it is essential to know the temperature gradients between these sites and the brain. The results of this study show that brain temperature is greater than arterial temperature, with a mean difference of 0.41°C. Gradients of between 0.5 and 2°C have been demonstrated in other studies. The importance of direct brain temperature measurement is emphasized by the variability between systemic and brain temperature and the inability to identify the most appropriate site for measuring core temperature.

The data show that as brain temperature is reduced to 35°C, there is no significant change in brain tissue O2, CO2 and pH. The increase in SjO2 observed below 37°C is most likely the result of cerebral metabolic suppression resulting in a reduction in oxygen extraction from cerebral tissue. Below 35°C, however, there is a significant reduction in PbO2, which occurs despite an increase in PaO2. Arterial PCO2 and SjO2 also increase, although there is little change in
tissue or arterial pH. Although the target temperature for induced hypothermia was 33°C, there was some overshoot in a number of patients, with brain tissue temperatures decreasing below 33°C but not below 32°C. Data were collected in these patients but were not significantly different from those at 33°C for all measured variables.

The increase in $S_jO_2$ with decreasing brain temperature is a predictable response to the global reduction in brain metabolism. However, the reduction in $P_bO_2$ (in association with maintenance of $P_aO_2$) below 35°C suggests that although reduction in brain metabolism is undoubtedly a factor contributing to these changes, other mechanisms may be involved. While well oxygenated blood is arriving at the capillaries, oxygen is not being transferred efficiently to the extracellular compartment. One factor contributing to this may be the leftward shift of the oxygen dissociation curve associated with hypothermia. This enhances the affinity of oxygen to haemoglobin, causing reduced oxygen release and thereby reducing the availability of oxygen to diffuse into cells.

An oxygen delivery/metabolism mismatch may develop after head injury, and may result from a combination of diffusion abnormalities (microvascular failure), arteriovenous shunts directing flow away from capillaries, increased diffusion distances because of cytotoxic oedema, or mitochondrial abnormalities resulting from membrane alterations. These factors combined with the reduced availability of oxygen at the capillary level as described above would contribute to impaired diffusion of oxygen into the mitochondria and relative tissue hypoxia.

Differences in methods of measurement may also be a factor in these observations. Jugular bulb oximetry is an established method of measuring global cerebral oxygenation. The major limitation of this technique is that regional changes in cerebral oxygenation may not be detected unless the changes are large enough to affect the global measurements. It is accepted that regional variations in brain temperature occur as a result of the heterogeneous nature of cerebral blood flow and metabolism. Changes in brain temperature will therefore affect both global and regional brain oxygenation. Thus, the regional variations of brain oxygenation arising from changes in brain temperature may not be detected by jugular venous oximetry. Tissue sensors, however, have been shown to be a more sensitive measure of regional oxygenation compared with $S_jO_2$, and will therefore be more likely to detect these regional changes.

The small changes in tissue pH with hypothermia reflected changes in arterial pH, indicating that ischaemic acidosis was probably not occurring. There are two possible explanations. First, the development of tissue acidosis during cerebral ischaemia in human brain has been shown to be slower with deep hypothermia (18°C) compared with mild hypothermia. Secondly, the Paratrend sensor measures pH and CO$_2$ by the pH-stat method, which corrects for the actual temperature of the patient. This produces relative hypercarbia because of the increased solubility of CO$_2$ during hypothermia. If the alternative $\alpha$-stat method were used (pH and CO$_2$ measurement corrected to 37°C), changes in pH may have become more apparent. Evidence from in vitro preparations has suggested that the $\alpha$-stat method applies during hypothermia and that there are similarities in the effect of hypercarbia and moderate hypothermia on postischaemic recovery in tissue pH, with additive detrimental effects.

Our results demonstrate that brain parenchymal oxygenation is maintained with induced hypothermia to 35°C. Below this temperature $P_bO_2$ is not preserved, which supports the findings in an animal model of transient global ischaemia. Although the effect of induced moderate
hypothermia on outcome has not been addressed in this study, a recent multicentre trial has demonstrated no beneficial effect of hypothermia to 33°C in traumatic brain injury.22 Our results imply that the neuroprotective effects of induced hypothermia may be most beneficial at a temperature of 35°C. Hypothermia below this level results in impairment of cerebral oxygenation. The precise mechanisms of these changes require further investigation.

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