Randomized controlled trial of effects of the airflow through the upper respiratory tract of intubated brain-injured patients on brain temperature and selective brain cooling

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Background. Pyrexia is common after brain injury; it is generally believed to affect outcome adversely and the usual clinical methods of reducing temperature are not effective. The normal physiological mechanisms of brain cooling are heat loss from the upper airways and through the skull, and these can produce selective brain cooling.

Methods. Air at room temperature and humidity was continuously administered to 15 brain-injured, intubated and mechanically ventilated patients via a sponge-tipped oxygen catheter in each nostril at a combined rate of 115 ml kg⁻¹ min⁻¹. Brain temperature was measured using a pressure-temperature Camino catheter which is designed to site the thermistor 1 cm into the parenchyma in the frontal lobe. Oesophageal temperature was measured using an oesophageal stethoscope with a thermistor. After establishing baseline for 30 min, patients were randomized to receive airflow or no airflow for 6 h and then crossed over for a further 6 h.

Results. Airflow replicating normal resting minute volume did not produce clinically relevant or statistically significant reductions in brain temperature [0.13 (SD 0.55) °C; 95% CI, 0.43–0.17 °C]. However, we serendipitously found some evidence of selective brain cooling via the skull, but this needs further substantiation.

Conclusions. A flow of humidified air at room temperature through the upper respiratory tracts of intubated brain-injured patients did not produce clinically relevant or statistically significant reductions in brain temperature measured in the frontal lobe.


Keywords: brain, direct brain cooling; brain, injury; brain, selective brain cooling; complications, head injury; complications, subarachnoid haemorrhage

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Pyrexia is common after brain injury and is generally believed to affect outcome adversely. The usual clinical methods of reducing temperature are not particularly successful.1 2 Systemic hypothermia is considered potentially beneficial after witnessed cardiac arrest,3–5 but recent evidence suggests it is not of benefit after traumatic brain injury.6 Selective head cooling in adults has had limited effect on brain temperature, possibly because the methods used did not exploit normal physiological cooling mechanisms sufficiently well.7 8

The human brain is believed to have three cooling mechanisms: cooling of venous blood through the entire skin surface, which in turn cools the arterial blood supply to the brain, cooling by heat loss through the skull via the venous sinuses and the diploic and emissary veins, and cooling by heat loss from the upper airways (which is abolished by endotracheal intubation).9–11 The last two are thought to be mechanisms of selective brain cooling, i.e. ways of reducing brain temperature below that of core trunk temperature.

Mariak and colleagues12 measured the intracranial temperature between the frontal lobes and the cribriform plate in four conscious intubated patients under conditions of mild hyperthermia (oesophageal temperatures ranging from 36.9 to 37.5 °C). When airflow through the upper respiratory tract was reinstated by extubation, the brain temperature fell
by 0.4–0.85°C, and in three patients it decreased below the oesophageal temperature.

Methods of cooling the brain that utilize normal physiological mechanisms have not been fully explored clinically. Since intubated brain-injured patients are denied heat loss from the upper airways, our aim was to find out whether restoring airflow, at normal minute volumes, room temperature and humidity, through these patients’ noses would produce a decrease in brain temperature and/or selective brain cooling. In this pilot exploratory trial, we were not seeking to determine whether there was a therapeutic effect but to find out whether the method worked.

Methods

Permission for the trial was obtained from Lothian Regional Ethics Committee and the Lothian University Hospitals NHS Trust management.

The power calculation was based on the data of Mariak and colleagues as there are no other data on direct brain temperature measurement with heat loss from the upper airways in humans. With the cross-over design a sample size of 15 patients would give 80% power to detect a treatment effect of 78% of the within-patient standard deviation at the 5% significance level.

From September 2002 to June 2003 we enrolled 15 brain-injured patients admitted to the intensive care unit (ICU) at the Western General Hospital, Edinburgh. All patients were intubated, mechanically ventilated and had intracranial pressure (ICP) monitoring. The level of ICP was considered high and treatments were given when ICP was >25 mm Hg. The cardiovascular parameters monitored were ECG, invasive blood pressure, mean arterial blood pressure (MAP) from arterial line monitor, central venous pressure (CVP) and cardiac output (CO) when indicated. Adequate hydration and nutritional support were provided. Propofol, thiopental or midazolam were used as sedatives. Appropriate analgesia with alfentanil and atracurium as a muscle relaxant were administered if required. Patients with subarachnoid haemorrhage were given nimodipine. Inotropic support (norepinephrine and/or dobutamine) was administered to maintain cerebral perfusion pressure (CPP) above 70 mm Hg and MAP >90 mm Hg.

All intubated ventilated patients with head injury due to trauma or haemorrhage and intracranial pressure–temperature monitoring were screened for inclusion. Thirty-three patients were screened, and 15 of these were recruited. The other 18 could not be studied for the following reasons: not expected to survive (five); fractured base of skull (five); lack of assent (five); other (three). The age of the patients ranged from 17 to 70 yr; six were male, nine were female, nine had traumatic brain injury and six had subarachnoid haemorrhage (Table 1).

To replicate normal resting air intake through the nose, air at room temperature and humidity (Airlife Humidifiers, RMS Healthcare, Stirling, UK) was continuously administered via a sponge-tipped oxygen catheter in each nostril (Unoplast, Maersk Medical Ltd, Redditch, Worcs, UK) at a combined rate of 115 ml kg⁻¹ min⁻¹ approximating normal minute volume. After establishing a baseline for 30 min, patients were randomized to receive airflow or no airflow for 6 h and then crossed over for a further 6 h.

Brain temperature was measured using a pressure–temperature Camino catheter (Integra NeuroCare, Newbury Road, Andover, Hants, UK) designed to site the thermistor 1 cm into the parenchyma in the frontal lobe. The oesophageal temperature was measured with an oesophageal stethoscope (Sims Graseby Ltd, Watford, Herts, UK) with the thermistor sited behind the heart, determined by the position of maximum heart sounds.

Data for most of the physiological parameters were collected electronically at intervals of 1 min. Temperature, interventions and drugs were recorded manually. Microsoft Excel and the Statistical Package for the Social Sciences (SPSS 12.0, SPSS Inc., Chicago, IL, USA) were used for organizing and analysing the data.

The Camino catheter in one patient (patient 13) was replaced during the first (no-airflow) period because the

Table 1 Patient details and Glasgow Outcome Score. *Five-point GOS categories: dead; VS, vegetative state; SD, severe disability; MD, moderate disability; GR, good recovery; GCS, Glasgow Coma Score; GOS, Glasgow Outcome Score; SAH, subarachnoid haemorrhage

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<th>Gender</th>
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ICP measurements were considered unreliable. Therefore the data from the first Camino catheter was not used in the analysis and hence this patient has no brain temperature and ICP data for the baseline and part of the first (no-airflow) period.

Cleaning of the temperature data was limited to removal of known anomalies in oesophageal temperature. These occurred when boluses of drugs diluted with cold water were administered through the orogastric tube and caused a temporary decrease in oesophageal temperature as the fluid passed the thermistor. No changes in oesophageal temperature occurred when starting and stopping infusions of orogastric feed, because of the rate of administration and because the feed was at room temperature. Objective data validation was possible for the cerebral perfusion pressure (CPP) and the blood pressure.

The median was chosen a priori as a summary descriptor of the minute-by-minute temperature measurements for each individual patient. These medians were then analysed descriptively using parametric methods to derive 95% confidence intervals for mean differences in temperature.

Results
Airflow commensurate with normal breathing in terms of volume and humidity did not produce consistent reductions in brain temperature, measured at a distance from the nasopharynx (frontal lobe). Figure 1 shows the median brain temperatures for each patient for the 6-h airflow and 6-h no-airflow periods. Although some patients showed reductions in median brain temperature, the difference (airflow minus no airflow) was small [0.13 (SD 0.55) °C; 95% CI, 0.43–0.17°C]. The change in brain temperature after 30 min of nasal airflow, the difference between the mean brain temperatures over the last 5 min before airflow started and the last 5 min of the first 30 min with airflow showed a small difference

![Fig 1](image1.png)

**Fig 1** Median brain temperatures for the airflow and no-airflow periods. Note that the data for patients 9 and 15 are identical and hence only 14 lines appear on the graph.

![Fig 2](image2.png)

**Fig 2** Difference between median brain temperatures in no-airflow and airflow periods with median ICP in the airflow period.
(airflow minus no airflow) but, with the exception of patient 10, was not clinically relevant [0.04 (0.16) °C; 95% CI, 0.13–0.04°C].

Figure 2 shows the difference in median brain temperature between the airflow and no-airflow periods with median ICP in the airflow period. It suggests that a high median ICP made no difference to our results.

None of the six patients whose brain temperatures were above their oesophageal temperatures before starting nasal airflow decreased their brain temperatures below their oesophageal temperatures with airflow. Figure 3 shows the differences between mean brain and oesophageal temperatures for the last 5 min before airflow and for the last 5 min at the end of 30 min of airflow. Positive differences mean that the brain temperature was higher than the oesophageal temperature (patients 1, 5, 6, 7, 11 and 15). Negative differences mean that the brain temperature was lower than oesophageal temperature, i.e. patients were exhibiting selective brain cooling. Of the patients who had a negative difference between their brain and oesophageal temperatures, five (patients 2, 4, 9, 10 and 14) increased this difference with airflow. This increased difference could be due to a reduction in brain temperature and/or a rise in oesophageal temperature. Only increased differences due to a reduction in brain temperature relative to oesophageal temperature are indicative of an increase in selective brain cooling with airflow, and only patients 9, 10 and 14 satisfy this criterion.

Fig 3 Mean brain-oesophageal temperature over the last 5 min before airflow and over the last 5 min of the first 30 min of airflow.

Fig 4 Patient 10: brain and oesophageal temperatures with air conditioning. When patient 10 was exposed to the air conditioning her brain temperature decreased, and when her head was insulated from the draught by a towel her brain temperature increased. The Camino catheter pressure and temperature probe were insulated from the draught by a polythene sheath.
During the trial, evidence of convective cooling due to heat loss through the skull was demonstrated in patients 6 and 10 as a result of a draught from the air-conditioning system. The finding that air conditioning could affect brain temperature was unexpected. Figure 4 shows that when patient 10 was exposed to air conditioning her brain temperature decreased, and when her head was insulated from the draught by a towel her brain temperature increased. The Camino catheter pressure–temperature probe was insulated from the draught by a polythene sheath during these observations.

Discussion

Although the results of this trial are negative, it is evident from Figures 1 and 2 that the median brain temperatures of some patients were clinically significantly lower with airflow. One of the difficulties with research on intensive care patients is that their underlying conditions can change suddenly and unpredictably, for reasons unconnected with the research intervention. These patients illustrate this point.

Figure 1 shows that the median brain temperatures of patients 6, 9, 11, 12 and 15 were variously 0.5–1.3°C lower in the 6 h with airflow than with no airflow. Patient 15’s temperature was on a downward trend during the no-airflow period and this continued through the subsequent airflow period. The other four all had purulent sputum. For example, patient 12 was known to have a Haemophilus influenzae chest infection. Halfway through the airflow period his chest became increasingly productive and he had a rigor; his temperature rose from 38 to 39.4°C and remained above 39°C for almost the entire no-airflow period. Therefore the differences in median brain temperature in these patients are likely to be attributable to an increase in temperature in the no-airflow periods caused by a worsening of their clinical conditions, rather than a reduction in temperature in the airflow periods caused by the airflow.

A change in brain temperature would be expected to occur within 30 min of starting airflow. Only patient 10 showed a clinically relevant reduction in brain temperature (~0.5°C) after 30 min of airflow. A change due to airflow would be more likely to affect brain temperature alone, or at least affect it to a greater extent than body temperature. However, this patient’s oesophageal temperature reduced by the same amount as her brain temperature and therefore the change was more likely to be caused by factors other than the airflow.

The narrow confidence intervals indicate that the negative results of this study were not caused by too small a sample size. Indeed, the study had 80% power to detect a change of 0.44°C in the median brain temperature over the 6 h with airflow (Fig. 1) and a change of 0.12°C after 30 min of airflow. However, there are a number of alternative possible explanations for our inability to demonstrate a reduction in brain temperature.

It is possible that brain cooling by heat loss through the upper airways does not occur in humans, although this seems unlikely since various investigators, notably Mariak and colleagues, have demonstrated that it does. There is a view that selective brain cooling only occurs during hyperthermia and not during normothermia or fever. It is supposed that selective brain cooling is not necessary in normothermia because the brain can be sufficiently cooled by arterial blood from the trunk. However, although they do not point this out, Mariak and colleagues demonstrate selective brain cooling in normothermia in humans. Towards the end of their study, the oesophageal temperature in one patient was 36.8°C and in another 37°C; in both cases the brain temperature was about 0.2°C lower. This shows that selective brain cooling can occur in normothermia in humans but that the differential may be smaller. Nevertheless, passively blowing air continuously through the nose may not have the same physiological effect as actively breathing air.

Heat loss from the upper airways may be impaired by severe brain injury because of increased sympathetic tone. Heat loss from the upper airways is reduced, if not abolished, by increased sympathetic tone, which causes nasal mucosal vasoconstriction and hence reduced nasal resistance and reduced heat loss to inspired air. Sympathetic tone is greatly increased for some days after brain injury, and furthermore all but two of our patients were on norepinephrine infusions. It is possible that this affected heat loss from the upper airways with nasal airflow.

The higher the flow rate and the lower the temperature and humidity of inspired air, the more heat it takes up from the body. The patients studied by Mariak and colleagues breathed ambient air but were not severely brain injured, having had a minor subarachnoid haemorrhage 7–10 days previously. When they breathed more intensively this produced a greater decrease in brain temperature than normal breathing. Einer-Jensen and Khorooshi flowed oxygen, with no added heat or humidity, through the noses of non-brain-injured intubated rats and showed greater decreases in brain temperature with higher flows. We used air at flow rates commensurate with normal minute volume and at room temperature and humidity, and perhaps this does not result in significant heat loss in the severely brain injured.

If brain cooling by heat loss from the upper airways and heat loss through the skull via emissary veins are complementary mechanisms, it is perhaps more likely that temperature changes due to the first mechanism would be detected nearer to the nasopharynx and changes due to the second nearer to the skull. Tentatively, this may be the case, since Mariak and colleagues used two thermocouples, and those sited between the frontal lobes above the cribriform plate recorded a decrease in temperature with extubation whereas those cited subdurally did not. Therefore the position of our brain thermistors may have been too far from the
nasopharynx to detect changes due to nasal airflow. However, we did detect temperature changes attributable to heat loss through the skull in one of our patients, although this requires further substantiation.

The thermistor in a Camino catheter is sited approximately 1 cm from the tip and the pressure sensor is at the tip. Towards the end of this study, the manufacturer introduced a red mark to allow the insertion depth of the catheters to be checked externally. Because a good ICP trace was obtained in all the patients studied we are confident that the thermistors were all intracranial. The data from trial patients with catheters that had the insertion depth markers were no different from those of the earlier patients, who had no depth marker. In addition, review of repeat CT scans of some of the patients monitored in the study without the depth marker revealed intraparenchymal placement.

Selective brain cooling is defined as natural cooling of parts of the brain, or the whole brain, below aortic (arterial blood) temperature (Commission for Thermal Physiology of the International Union of Physiological Sciences, 1987). It is probably a moot point what ‘brain’ means in this context. i.e. is it parenchyma, cerebrospinal fluid, blood or any intracranial temperature. In animal research a reduction in hypothalamic temperature below incoming carotid temperature is generally sought. However, the point about selective brain cooling mechanisms is that they involve heat transfer from inside to outside the cranium (whether through skull or upper airways). Therefore we believe that, in humans, demonstrating reductions in an intracranial temperature potentially due to these heat loss mechanisms is the first step. There is very little human research on heat loss through the upper airways using direct brain temperature measurement. However, the study by Mariak and colleagues showed that cooling due to heat loss through the upper airways appears to be local in humans, and the fact that our study did not show a change in frontal lobe temperature with nasal airflow may support this.

It is thought that raised ICP may prevent selective brain cooling because emissary veins are involved in both mechanisms and reversal of emissary flow may not be possible in the presence of raised ICP. Figure 2 shows the difference in median brain temperature between the airflow and no-airflow periods with median ICP in the airflow period. It suggests that a high median ICP made no difference to our results. In fact the two patients who showed the greatest median decrease in brain temperature with airflow compared with no airflow also had the highest median ICPS in the airflow period. This is not, of course, the same as saying that ICP does not affect brain cooling.

In conclusion, flowing air through the upper respiratory tracts of intubated brain-injured patients, at rates commensurate with normal minute volume and at room temperature and humidity, did not produce clinically relevant or statistically significant reductions in brain temperature measured at a distance from the nasopharynx.

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References