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Enhanced upper respiratory tract airflow and head fanning reduce brain temperature in brain-injured, mechanically ventilated patients: a randomized, crossover, factorial trial

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Background. Heat loss from the upper airways and through the skull are physiological mechanisms of brain cooling which have not been fully explored clinically.

Methods. This randomized, crossover, factorial trial in 12 brain-injured, orally intubated patients investigated the effect of enhanced nasal airflow (high flow unhumidified air with 20 p.p.m. nitric oxide gas) and bilateral head fanning on frontal lobe brain temperature and selective brain cooling. After a 30 min baseline, each patient received the four possible combinations of the interventions—airflow, fanning, both together, no intervention—in randomized order. Each combination was delivered for 30 min and followed by a 30 min washout, the last 5 min of which provided the baseline for the next intervention.

Results. The difference in mean brain temperature over the last 5 min of the preceding washout minus the mean over the last 5 min of intervention, was 0.15°C with nasal airflow (P=0.001, 95% CI 0.06–0.23°C) and 0.26°C with head fanning (P<0.001, 95% CI 0.17–0.34°C). The estimate of the combined effect of airflow and fanning on brain temperature was 0.41°C. Selective brain cooling did not occur.

Conclusion. Physiologically, this study demonstrates that heat loss through the upper airways and through the skull can reduce parenchymal brain temperature in brain-injured humans and the onset of temperature reduction is rapid. Clinically, in ischaemic stroke, a temperature decrease of 0.27°C may reduce the relative risk of poor outcome by 10–20%. Head fanning may have the potential to achieve a temperature decrease of this order.

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Pyrexia has a detrimental effect on the compromised brain,¹² is common and associated with poor outcome after brain injury and stroke.³⁴ As brain rather than body temperature is important in cerebral protection from further injury, there is logic in targeting cooling at the brain.⁵ The human brain is considered to have three cooling mechanisms: cooling by arterial blood supply from the body (which is cooled by venous blood from the skin), cooling by heat loss through the skull via the venous sinuses and diploic and emissary veins, and cooling by heat loss from the upper airways.⁶⁻⁸ The latter two can produce selective brain cooling, that is natural cooling of parts of the brain, or the whole brain, below aortic temperature.⁹ Methods of cooling the brain which utilize these physiological mechanisms of convective heat loss from the upper airways and through the skull have not been fully explored clinically and are the subject of this trial.

In a previous trial we investigated the effect of heat loss from the upper airways on brain temperature, using continuous nasal airflow replicating normal minute volume, in brain-injured, intubated patients and found it did not produce significant reductions (mean −0.04°C, sd 0.16°C, 95% CI −0.13–0.04°C over 30 min; mean −0.13°C, sd 0.55°C, 95% CI −0.43–0.17°C over 6 h).¹⁰ We did, however,
serendipitously find some evidence of heat loss through the skull caused by air conditioning fans. In this trial it was therefore hypothesized that heat loss from the upper airways using nasal airflow, with enhancements to overcome some of the possible reasons for the negative results in the previous trial, and heat loss through the skull using head fanning could reduce brain temperature and might produce selective brain cooling. This trial was not designed to show whether the interventions affected clinical outcome.

Methods

Permissions and consent

Permission for the trial was obtained from the Multi-Centre Research Ethics Committee for Scotland and Lothian University Hospitals NHS Trust management. None of the patients were able to give consent because of the nature of their injuries and assent was obtained from their next of kin.

Participants

The trial participants were patients on a neurological intensive care unit. The inclusion criteria were brain injury, resulting from trauma or haemorrhage, requiring intubation, mechanical ventilation and intracranial pressure (ICP)/temperature monitoring.

The exclusion criteria were lack of assent, patient not expected to survive long enough for recruitment and participation in the trial (in the opinion of the Intensive Care Consultant or Consultant Neurologist), fractured base of skull, facial fractures in the region of the nasal airway, age <18 yr, disorder of temperature regulation, seizures, cerebral neoplasm or abscess, meningitis, encephalitis, penetrating brain injury and contraindications to both oesophageal and rectal temperature monitoring.

Trial design and interventions

This was a randomized, crossover, factorial trial in brain-injured, orally intubated, mechanically ventilated patients, to investigate the effect on frontal lobe brain temperature and selective brain cooling of two interventions:

i. Heat loss from the upper airways with continuous ‘enhanced’ nasal airflow. The enhancements comprised unhumidified air (water content approximately 3 mg litre\(^{-1}\)) from the compressed air supply at twice the patients’ minute ventilation volumes, with the addition of 20 p.p.m. nitric oxide (NO) gas (mucosal vasodilation to facilitate heat loss), and an 85 g lead weight over the facial vein on each side of the nose (to facilitate intracranial venous drainage, considered important in heat loss from the upper airway\(^{11}\)). The maximum airflow any patient received was 24 litre min\(^{-1}\) (mean 17.7 litre min\(^{-1}\)). Nitrogen dioxide was continuously monitored for safety according to standard practice on our unit when administering NO. In the first four patients the nasal airflow was delivered from the compressed air port via a Whispaflow valve (Vital Signs Inc., Totowa, NJ, USA) through a paediatric tracheal tube [Portex Ltd (Smiths), Hythe, UK] in each nostril. In the remaining patients it was delivered via a double air flow meter (Therapy Equipment Ltd, Cranbourne Industrial Estate, Potters Bar, UK) through oxygen tubing (Universal Hospital Supplies, Enfield, UK) in each nostril. Bilateral nasopharyngeal suction was performed immediately before delivering nasal airflow.

ii. Heat loss through the skull with bilateral head fanning using two electric fans (CED Ltd, Dagenham, UK), total airspeed approximately 8 m s\(^{-1}\). Bilateral fanning was used to maximize the effect and to minimize lateral temperature gradients within the brain.\(^{12}\) Ambient air temperature was 23.2–26.8°C and relative humidity 21.6–38.2%. Patients’ bodies were covered with bedclothes, they had no head bandages or dressings and their heads were not shaved, except for small areas in the vicinity of the pressure/temperature probe and around surgical wounds.

After a 30 min baseline, each patient received the four possible combinations of the interventions (factors) in a randomized order. Each combination, that is:

i. enhanced nasal airflow;
ii. head fanning;
iii. enhanced nasal airflow plus head fanning;
iv. no intervention,

was delivered for 30 min and followed by a 30 min washout, the last 5 min of which provided the baseline for the next intervention. The purpose of the trial was to find out if the interventions could reduce temperature; therefore it was kept as short as possible in order to reduce the likelihood of temperature changes occurring for other reasons, such as infection. Data from Mariak and colleagues\(^{13}\) and observational data from our previous trial indicated that 30 min for interventions and washouts would be long enough for temperature to change and for the last 5 min of each washout to be used as the baseline for the following intervention.

Beginning prior to baseline and continuing throughout the whole trial, patients were peripherally warmed by an electric heating pad (Winterwarm, Aston, Birmingham, UK) placed over one foot. The purpose was to trigger heat loss responses at lower temperatures\(^{14}\) and also to decrease sympathetic activity in the nose.\(^{15,16}\) No patients had paracetamol during the trial or in the preceding 6 h.

Temperature monitoring

Brain temperature was measured with a pressure/temperature Camino catheter [Integra NeuroCare, Andover, Hants, UK; accuracy (0.3°C) over 30–40°C] sited in the right or left prefrontal area, 2–3 cm anterior to the coronal
suture in the mid-pupillary line, with the tip 2 cm ventral to the skull bone and the thermistor about 1 cm into parenchyma. Core trunk temperature was measured with an oesophageal stethoscope [Sims Graseby Ltd, Watford, Herts, UK; accuracy (0.3°C) over 5–45°C] with the thermistor sited behind the heart, determined by the position of maximum heart sounds.17 One patient in whom an oesophageal stethoscope was contraindicated had rectal temperature measurement.

**Standard intensive care**

Patients’ standard intensive care continued throughout the 4.5 h trial. This included treatment of ICP ≥25 mm of mercury (mm Hg), norepinephrine to maintain cerebral perfusion pressure (CPP) ≥70 mm Hg and mean arterial pressure ≥90 mm Hg. Adequate hydration and nutrition were provided (enteral tubes were orogastric), sedation with propofol or midazolam, analgesia with alfentanil, and atracurium for neuromuscular block if required. Patients with subarachnoid haemorrhage were given nimodipine (60 mg, 4 h orogastrically). All patients were maintained in a 45° head-up position as part of their standard care, which by increasing the venous pressure gradient across the skull by gravity can increase emissary flow and may enhance brain cooling.18

**Power calculation**

There were no adequately controlled data available on heat loss through the skull in humans on which to base a power calculation and no data on the effect of enhanced airflow on brain temperature. Therefore, we based our power calculation on data from Mariak and colleagues,13 as for our previous trial. This indicated that with the crossover design a sample size of 15 patients would give 80% power to detect a treatment effect of 0.78 of the within patient so at the 5% significance level. On the basis of data from our previous trial we expected to be able to detect a temperature change of at least 0.12°C (i.e. 78% of 0.16°C).

**Randomization**

The randomization was undertaken by the statistician using random number tables. The results were placed in sealed, opaque envelopes and opened by the researcher during the baseline period of each patient’s trial.

**Statistical design**

We did not anticipate that there would be an interaction between heat loss through the upper airways as a result of nasal airflow and heat loss through the skull as a result of head fanning, but we did expect that, together, the interventions would have an additive effect on brain temperature.1 This meant that a factorial design would be an efficient way to investigate the effects of the two interventions, and, moreover, it gave the opportunity to test whether the effects were additive.

**Data collection and analysis**

Data collection was electronic, at minute intervals, for temperatures, heart rate, arterial pressure, central venous pressure, ICP and CPP. Microsoft Office Excel (Excel 2003, Microsoft Corporation, Redmond, WA, USA) 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 primary single summary outcome variable used in the analysis, which was specified a priori, was a within patient comparison of each patient’s mean brain temperature for the last 5 min of each intervention with the last 5 min of the preceding washout. The results of the differences between these temperatures for each intervention combination were compared within each patient with the differences for every other intervention combination, using three-way univariate analysis of variance, with nasal airflow and fanning as controlled (fixed) effects and the sampled patients as an uncontrolled (random) effect, representative of the variation in the population.

**Results**

Every patient admitted to the intensive care unit with a head injury was screened for inclusion (95 patients). Forty-one met the inclusion criteria and of these 29 were excluded, 16 for exclusion criteria, three for lack of assent and 10 for other reasons (the majority because their brain temperature monitoring was removed soon after admission, before assent could be obtained and the trial conducted). Twelve patients were enrolled, received the interventions in random order and were included in the analysis. They were aged 20–67 yr, six were male, six female, eight had traumatic brain injury and four subarachnoid haemorrhage.

The primary aim of this trial was to find out if the interventions affected brain temperature but the longer term aim of our research programme is to find a simple, low-cost means of reducing brain temperature. During the trial the cost of using NO increased considerably from a negligible amount to around £50 per hour which meant that enhanced nasal airflow was no longer a low-cost intervention. It also became clear that it was not simple to administer high airflows. For these reasons we did not think we could justify continuing the trial to obtain 15 patients.

**Brain cooling**

Figure 1 shows brain temperature differences (the mean brain temperature over the last 5 min of each intervention minus the mean over the last 5 min of the previous washout) with each intervention for each patient. The interventions are shown in non-randomized order for comparative purposes. Temperature differences above zero are increases in brain temperature with interventions, those below are reductions. The greatest reductions occurred with enhanced nasal airflow and head fanning together.
The formal univariate analysis of variance (Table 1) shows that nasal airflow and head fanning produced a statistically significant reduction in both brain and oesophageal temperatures. The observed reduction in mean brain temperature with nasal airflow plus head fanning was 0.31°C and the observed reduction in oesophageal temperature with airflow plus fanning was 0.24°C. Univariate analysis of variance with nasal airflow, head fanning and subject as main effects showed no evidence of an interaction between nasal airflow and head fanning for brain (P=0.60) or oesophageal temperature (P=0.64) in the last 5 min of washouts and interventions; interaction between them was therefore omitted from the models. The lack of a statistically significant interaction between them means that the data support the effects of the two interventions being additive, as is shown with the estimate of combined effect in Table 1.

Selective brain cooling
Mean brain temperature overall (38°C, SD 0.60) was higher than mean core body temperature (37.7°C, SD 0.56). In three individuals, including the patient with rectal temperature monitoring, the relationship was not constant and brain temperature was sometimes lower but there was no evidence of selective brain cooling in response to the cooling interventions, although systemically there was less reduction in core body temperature than in brain temperature. The mean brain minus mean oesophageal temperature difference, for all patients, over the last 5 min with nasal airflow and head fanning respectively was very slightly lower than over the last 5 min before these interventions (0.02 and 0.07°C), but only the difference with head fanning was statistically significant (P=0.02, 95% CI 0.01–0.12°C). Univariate analysis of variance with nasal airflow, head fanning and subject as main effects showed that there was no evidence of an interaction between nasal airflow and head fanning (P=1.00) and interaction between them was omitted from the model.

Temperature at the start of interventions
The lowest mean temperatures at the start of an intervention were brain 37.92°C and oesophageal 37.55°C. The range was from a brain temperature of 36.9°C and oesophageal temperature of 36.5°C in one patient to a brain temperature of 39.1°C and oesophageal temperature of 38.4°C in another. Five patients had brain temperatures ≥38°C at the start of the interventions and in three oesophageal temperature was also ≥38°C.

ICP
Nine patients had an ICP above normal (>10 mm Hg) during the trial. Although ICPs of ≥25 mm Hg were treated, the treatment effects are not instantaneous and six patients had ICPs transiently above this. The maximum (n=1) was 33 mm Hg.
Nasal air and head fanning reduce brain temperature

Discussion

This is the first human trial to show a reduction in brain temperature as a result of heat loss from the upper airways with continuous nasal airflow and heat loss through the skull with head fanning, and to demonstrate that these mechanisms have an additive effect on brain temperature reduction. Selective brain cooling did not occur.

It is possible that the estimated absolute difference between brain and oesophageal temperature lacked precision, given the accuracy of the devices, but the relationship between them changed and only if there was drift during each patient’s trial would this have affected the change in relationship. There was no evidence of drift on the individual patient’s graphs but, in any event, while systematic drift could mask a real effect it could not generate a spurious effect. Drift could not be ascertained definitively without checking the calibration of each probe before and after use. Checking beforehand was not possible because the probes are supplied sterilized, and afterwards it could be misleading as brain temperature probes are very susceptible to damage on removal and were also required to be sent for microbiological culture. This is just one of the problems of conducting a trial in the clinical situation and without knowing what temperature change, if any, to expect.

Patients who did not respond to the interventions

Patients consistently cooled in response to every cooling intervention, with the exception of four who did not respond to nasal airflow [brain temperature unchanged (n=2) or increased (n=2)] and one who did not respond to head fanning (brain temperature increased) (Fig. 1). There is debate about whether mechanisms of heat loss from the upper airways and through the skull work in fever (a regulated increase in temperature) and normothermia, as opposed to hyperthermia (an unregulated increase in temperature).7 Fever, resulting from infection or inflammation, was the most likely cause of temperature increase in this patient group, although neurogenic fever can also occur after brain injury. However, failure to respond to cooling showed no evidence of being related to temperature level. Cooling started at brain temperatures in the range 36.9–39.1°C but non-responders had brain temperatures over a similar range, between 37.2 and 39.1°C at the start of the airflow (n=4) and fanning (n=1). Non-responders could have had increased thermoregulatory response thresholds because of fever but the foot warming was intended to counter this. Two patients had microbiologically confirmed infections, one responded and one did not.

It has been suggested that above normal ICP interferes with reversal of emissary flow and therefore heat loss through the skull.518 The patient who did not respond to head fanning (Fig. 1) did have an increased ICP during fanning (mean 20, range 17–26 mm Hg). However, three patients who cooled with head fanning had mean ICPs at least as high.

In one patient brain temperature increased by 0.42°C during nasal airflow (Fig. 1). This patient’s airflow had to be aborted and started again because of problems with the airflow equipment. Therefore there was nearly an hour between the temperature measurements at the end of the preceding washout and the end of the restarted airflow, instead of 30 min, and during this time the patient’s temperature was rising as a result of a confirmed chest infection. However, leaving this patient out of the analysis makes little difference to the brain temperature results with airflow (Table 1) (0.17°C, P<0.001, 95% CI 0.09–0.25°C).

Heat loss from the upper airways and through the skull in humans

There are few studies of the mechanisms of heat loss from the upper airways and through the skull in humans with intracranial temperature monitoring. Mariak and colleagues13 studied heat loss from the upper airways in patients who had had a good grade subarachnoid haemorrhage 1–2 weeks previously. When airflow through the upper respiratory tract was reinstated by extubation brain temperature decreased by 0.4–0.85°C and in three patients reduced below oesophageal temperature. The reduction in brain temperature began immediately and reached its lowest point within about 5–18 min. In our study it took a mean of 10 (SD 7) min for nasal airflow to begin to reduce brain temperature. Mariak and colleagues13 also demonstrated larger reductions in temperature with restoration of nasal breathing than we did with continuous nasal airflow. Both these differences could be because the temperature probes were nearer to the nasopharynx than ours, ‘on the midline between the cribriform plate and frontal lobes’,13 and temperature reductions will be apparent sooner, and also larger, nearest to the point of cooling. However, the larger reduction in brain temperature could be an indication that normal breathing, in which air is actively entrained in boluses, is physiologically different from continuous passive airflow with regard to brain cooling and does not produce equivalent heat loss.

Shiraki and colleagues19 investigated the effect of face fanning with ambient air on brain temperature in a 12-yr-old boy 8 days after insertion of a ventricular drain. Thermocouples were sited in the lateral ventricle and in parenchyma 1 cm above the ventricle. Brain temperature did not reduce with fanning but the thermocouples appear to have been sited within the ventricular drain, which is likely to have insulated them to some extent. Possibly also the 20 min fanning periods were not long enough to affect these deeper sites of temperature measurement with face fanning alone.

Manipulation of the heat loss mechanisms

In our previous trial, nasal airflow at normal minute volume, room temperature and humidity did not reduce brain temperature.10 therefore in this trial the airflow was
enhanced to try and overcome some of the possible physiological reasons for that negative result. To increase heat loss by evaporation, nasal airflow was delivered straight from the compressed air outlet with no added humidification and at twice patients’ minute ventilation volumes. NO gas was added to the airflow to help overcome vasoconstriction in the nasal mucosa resulting from norepinephrine administration and increased sympathetic tone after brain injury, which reduces heat loss to inspired air by reducing nasal resistance.

Increased sympathetic tone also dilates the facial veins and constricts the angularis oculi veins; therefore blood cooled in the nose flows to the jugular veins rather than to the brain and selective brain cooling does not occur. Conversely, compression of the facial veins increases blood flow to the brain through the angularis oculi veins and the weights were used for this purpose.

Temperature increase is common after brain injury; if this is because of fever patients have an elevated hypothalamic set point which they will defend. Foot warming was used to shift the set point in the preoptic region of the brain to a lower temperature. As all heat loss mechanisms may be activated at a lower central temperature with peripheral warming this was applied throughout the trial so that the conditions were the same for all the interventions. Peripheral warming causes local vasodilatation in the nasal mucosa by loss of sympathetic vasoconstriction and therefore may also help to overcome the effects of increased sympathetic tone on the nasal mucosa.

Given the physiological manipulations used, it is perhaps debatable whether the cooling shown with nasal airflow can be considered entirely natural, in terms of the definition of selective brain cooling. Normal physiology was not reproduced because air was flowed continuously into the upper airways, rather than inhaled, and the facial veins were physically compressed. On the other hand the concentration of NO was possibly no greater than patients could have had in their nasal cavities had they had no airflow, and the airflow was no higher than patients could have achieved themselves with exercise.

**Difficulties with nasal airflow**

Changing the nasal airflow system after four patients was undesirable but resulted from unforeseen problems. The delivery system had to accommodate the volume of air and allow the NO to be added safely. An adaptation of our usual clinical method of delivering NO worked well in pre-trial testing but proved to be unsatisfactory in the trial itself, with sedated patients with decreased tone in their nasopharynxes and therefore increased resistance to the airflow. Although the second delivery system worked better, it became apparent that giving high nasal air flows in this patient group was not simple. Continuous monitoring and frequent adjustment by the researcher was necessary to ensure the air flowed through the upper airways and out of the mouth.

The trial was stopped after 12 patients because it became evident that enhanced nasal airflow was not going to provide a simple or low-cost (with the increase in the price of NO) method of reducing brain temperature. The results are consistent and the CIs are tight, which shows the study was not underpowered. The results confirm that the changes in brain temperature with nasal airflow are too small to justify the cost and difficulties in administration.

**Clinical relevance**

Our results are potentially clinically relevant despite the small reductions in brain temperature. After ischaemic stroke, Dippel and colleagues have argued that a tympanic temperature decrease of 0.27°C may reduce the relative risk of poor outcome by 10–20% because this has been found to increase by a factor of 2.2 for each degree centigrade increase in body temperature (95% CI 1.4–3.5). Head fanning, with peripheral warming to trigger heat loss responses at lower temperatures, produced a mean brain temperature reduction of 0.26°C within 30 min. Head fanning is quick to instigate, simple, inexpensive and low risk and could be used for longer periods or continuously in patients with temperature increase after brain injury and stroke. For optimum effect it may be necessary to combine it with peripheral warming and perhaps paracetamol.

**Conclusions**

We have shown in brain-injured patients that parenchymal brain temperature reductions occurred with nasal airflow and head fanning and were larger with the two interventions together, although selective brain cooling did not occur. This is of physiological relevance because it adds to the knowledge and understanding of the mechanisms of heat loss from the upper airways and the skull. It is also potentially clinically important because factors which enhance or inhibit these mechanisms may have an effect on brain temperature, and because head fanning could provide a simple, inexpensive, low-risk intervention for reducing increased brain temperature after brain injury and stroke.

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Nasal air and head fanning reduce brain temperature

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