Hot or cold? Warm heart, cool brain

Peter JD Andrews

There is considerable interest in cooling as a therapy after acute brain injury. This is fuelled by laboratory evidence showing that a reduction in systemic temperature reduces neuronal loss and improves global functional recovery in models of acute brain injury of all aetiologies and in all species, and the strong association between pyrexia and poor neurological outcome in head injury (Jones et al, 1994) and stroke. Reproducing these positive results in clinical trials has been problematic and it can be argued that a more sophisticated approach might be necessary.

INTRODUCTION

It is thought that the best source of reliable evidence about the effects of health care are well-conducted systematic reviews and meta-analyses. It is important to have confidence in the effect of cooling as a therapeutic intervention before it is offered to patients. In the area of traumatic brain injury, there have been four systematic reviews in the last 2 years, and with the exception of McIntyre et al (2003), these reviews have found little evidence for the use of therapeutic hypothermia at present.

There are problems associated with performing meta-analyses in this area, including extreme heterogeneity in inclusion criteria, the relatively small number of patients enrolled, the time from the injury until the target temperature is reached, the degree of hypothermia, the duration of hypothermia, the management of rewarming, the management of the control groups in the trial and the additional medical interventions. Henderson et al (2003) concluded that, although

Dr Peter JD Andrews is Reader in Anaesthesia, Intensive Care and Pain Medicine at the University of Edinburgh, and Lead Clinician for Critical Care Services, Western General Hospital, Edinburgh EH4 2XU

there was a marginal decrease in poor outcome (odds ratio 0.75, 95% confidence interval (CI) = 0.56–1.01, *P*=0.06), there was no mortality benefit and increased risk of pneumonia with hypothermia.

Only two of the trials were adequately powered to show a treatment effect. One trial (Zhi et al, 2003) had a control group that did not reflect current standard of care and the other (Clifton et al, 2001) has been criticized because the control group was managed at normothermia and electrolyte abnormalities were sub-optimally managed.

UNWANTED EFFECTS OF COOLING

Infection

Pneumonia and other infections are associated with hypothermia. This is unsurprising given that elevation of core temperature is an innate response to infection and improves leucocyte function and body's eradication of infection.

Shivering

Shivering is caused when there is an increased temperature gradient between the core setpoint and periphery. Shivering can increase body metabolism up to 500% and increases myocardial oxygen demand but can be reduced by the use of buspirone, pethidine and other pharmacological interventions and by reducing the core–periphery temperature gradient by warming of the feet and hands.

Electrolyte imbalance

During the induction of hypothermia in traumatic brain injury (TBI) patients there is a significant decrease in plasma levels of magnesium, phosphate, potassium and calcium. When the target temperature is reached (32°C) the diuresis subsides and electrolyte requirements return to normal (Polderman et al, 2001). Management of hypothermia-induced diuresis is very important as is management of potassium during rewarming with risk of sudden hyperkalaemia and cardiac arrest.

OUT-OF-HOSPITAL CARDIAC ARREST

The Hypothermia After Cardiac Arrest (HACA) study (2002) was a European, nine-centre, five-country study. Patients were enrolled if they had a witnessed collapse and cardiopulmonary resuscitation was commenced within 15 minutes with a return of spontaneous circulation in <60 minutes. The study showed a 40% improvement in favourable neurological outcome in the hypothermia group and a reduction in the probability of death by 20% in the hypothermia group. There was an increase in systemic complications in the hypothermia group including pulmonary complications of all causes, cardiac arrhythmias, bleeding and sepsis of all causes. These data showed that 3246 were screened but only 275 patients were enrolled, suggesting that this intervention is not generalizable to cardiac arrest as a whole. There was a significant difference in the number of deaths between the cooling and standard care group (*n*=20). This difference in outcome is maintained when good outcomes within the cooling group and standard care group are compared and suggests that the majority of the effect is on mortality.

Bernard et al (2002) enrolled 43 patients to hypothermia and 34 to normothermia after out-of-hospital cardiac arrest, but interestingly there was no difference in the death rate. The treatment effect in this trial was improvement in global functional recovery. Thus there are two trials that were successful after cardiac arrest, one showing an improvement in functional neurological recovery, the other showing a reduction in mortality. It may be that hypothermia after cardiac arrest benefits the myocardium rather than the brain; however, larger trials are needed.

STROKE

To date there have been no large randomized trials reporting on cooling after stroke. Hajat et al (2000) performed a meta-analysis of the observational studies in stroke and showed a 90% increase in mortality in pyrexial *vs* apyrexial patients. The authors concluded that hypothermia after the onset of stroke had a detrimental effect on stroke outcome and that as little as a 0.3°C reduction in temperature might have a significant impact on recovery after stroke on a population basis.

SYSTEMIC HYPOTHERMIA *VS* DIRECT BRAIN COOLING

Direct brain cooling may have fewer side effects than systemic hypothermia and it is logical to target the brain because brain rather than trunk temperature is important in cerebral protection (Cabanac, 1998). Selective brain cooling, by contrast, 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).

There are a number of ways of inducing brain cooling. These can be either:

1. Non-invasive methods including heat loss from the upper airway or heat loss through the skull

2. Invasive methods which include anterograde cerebral perfusion, intercarotid flush, open and semi-closed irrigation, and contact cooling of surface areas of the brain.

Non-invasive methods have obvious advantages and are thought to provide complementary mechanisms to provide cooling to the entire surface area of the brain; notably heat loss from the upper airways is abolished by endotracheal intubation. In human thermoregulatory physiology (TRP) research data support selective brain cooling mechanisms. In hyperthermic humans it has been shown that blood flow in the emissary veins is from the scalp to the brain. Under conditions of normothermia the flow is either undetectable or reversed (Desruelle and Candas, 2000).

Evidence for direct brain cooling comes from piglet cooling cap work performed using magnetic resonance spectroscopy. Brain temperature was assessed and shown to decrease by as much as 3.5°C with a cooling cap at 10°C placed on the cranium. Experimental work in rat has shown that insufflating dry gas at increasing flow rates into the nostrils of intubated, ventilated rats reduces brain cortical temperature. These experimental data show direct brain cooling mechanisms work in animals that do not have a carotid rete and similar TRP to humans (Einer-Jensen et al, 2001).

In Edinburgh two direct brain cooling trials have been conducted. Initially, airflow trials were performed instituting dry airflow continuously through both nostrils at equivalent to normal minute ventilation. These were unable to demonstrate direct brain cooling effects using a Camino pressure/temperature device placed in the right frontal cortex (Andrews et al, 2004). A subsequent trial where nasal air flow and head fanning were performed either in combination or alone showed evidence of direct brain cooling (*Figure 1*). The magnitude of the cooling is such that it would be considered clinically relevant and deserves further investigation.

Therefore there are interventions that can directly cool the brain but there are a number of unresolved issues including the effect of brain temperature gradients, the effect of direct brain cooling on cerebral blood flow, whether brain cooling is neuroprotective and whether it causes systemic complications.

In a fetal model of brain asphyxia, direct brain cooling showed a reduction in neuronal loss throughout deep brain structures (Gelman et al, 1996). It is likely that brain temperature gradients do occur with thermal conduction. The magnitude of any gradient is likely to be a complex function dependent on multiple variables, including tissue heat production, local blood flow, perfusion blood temperature, insulating tissue, ambient air temperature, naso-mucosal temperature and non-CNS cranial blood flow.

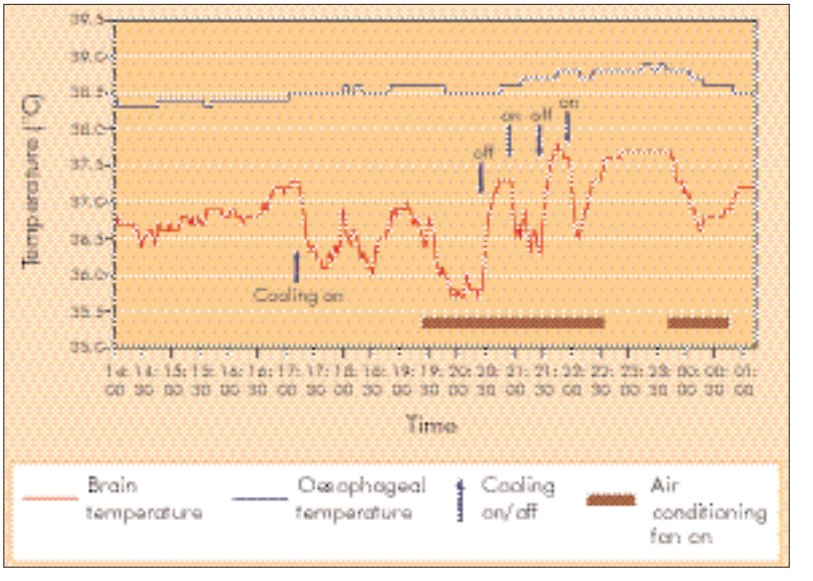
CONCLUSIONS

Brain cooling induced by whole-body cooling results in homogeneous cooling of the cerebral cortex. Direct brain cooling exaggerates temperature gradients between the deeper brain and the surface brain and, given the extent of head surface cooling necessary to cool the deep brain structures, a mild reduction in body temperature would facilitate some cooling of the deeper brain structure. These observations provide a firm rationale for clinical trials that combine less intense head cooling with some decrease in core body temperature. HM

Conflict of interest: none

Andrews PJD, Harris B, Murray GD (2004) 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. *Br J Anaesth.* http://bja.oupjournals.org/cgi/content/abstract/

Figure 1. Brain and oesophageal temperatures with direct brain cooling.



KEY POINTS

- There is no class 1 evidence of benefit from systemic cooling after traumatic brain injury or stroke.
- There is class 1 evidence for clinical benefit from systemic cooling after witnessed cardiac arrest but the mechanism of action is unclear.
- Brain cooling induced by whole-body cooling results in homogeneous cooling of the cerebral cortex.
- Direct brain cooling in humans is possible.
- There is justification for clinical trials that combine less intense head cooling with some decrease in core body temperature.

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POINTS OF AGREEMENT

- Systemic cooling is beneficial after witnessed cardiac arrest in a selected sub-group of patients.
- Brain cooling induced by whole-body cooling results in homogeneous cooling of the brain.
- Feasibility to selectively cool the human brain to levels of hypothermia needed to improve outcome from cerebral insults such as trauma and haemorrhage is yet to be determined.

POINTS OF DISAGREEMENT

- Selective brain cooling has little role after systemic insults such as hemorrhagic shock.
- Selective cooling of the human brain to levels needed to improve outcome from stroke is possible.