

## Direct brain cooling versus systemic hypothermia following acute brain injury

After brain injury pyrexia is common and generally believed to adversely affect outcome. Systemic hypothermia is considered potentially beneficial after witnessed cardiac arrest, but recent evidence suggests it is not of benefit after other brain injuries. Attempts at direct head cooling in adults has had limited effect on brain temperature, because the methods used have not exploited normal physiological cooling mechanisms sufficiently well. We present a case for the use of two simple and widely applicable interventions that may modify this risk factor (post-brain injury fever) for poor outcome.



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### Introduction

Acute brain injury is a common cause of disability and death worldwide. Common forms of brain injury include traumatic brain injury (TBI) and stroke affecting the young and the old, respectively. Recently, systemic hypothermia has been shown to improve outcome after cardiac arrest and, in a subgroup with moderate injury, after neonatal birth asphyxia. The mechanism of the therapeutic effect is likely to include a reduction in brain temperature accompanying the systemic reduction of body temperature. As both TBI and acute stroke patient populations present to healthcare services rapidly and without posing a diagnostic dilemma, the intervention of therapeutic systemic hypothermia may be implemented within a short time window. These two scenarios come close to replicating the laboratory models in which systemic therapeutic hypothermia has previously shown so much promise. However, it is important to note that the bulk of evidence in the experimental setting relates to the intervention of systemic hypothermia prior to, or shortly after the experimental insult.

In contrast, in TBI and acute stroke the need for resuscitation or delay to hospital presentation respectively, in addition to the need for computed tomography (CT) imaging to confirm the diagnosis, are all factors that delay intervention with temperature reduction strategies. This time delay may adversely affect both the potential therapeutic benefit of systemic hypothermia and the attendant risks of therapy. More modest temperature reductions may be achieved by non-invasive methods of direct brain cooling coupled with drug therapy. In this article we propose to introduce these concepts and suggest the hypothesis that in some forms of brain injury where there is a delay in initiation of temperature reduction, that these more modest methods of temperature reduction warrant further investigation.

### Traumatic brain injury

The best source of reliable evidence about the effects of healthcare are well conducted systemic reviews and meta-analyses. In the area of traumatic brain injury there have been four [1-3] systematic reviews in the last three

years. With the exception of McIntyre's review in 2003 [4], they have suggested that there is little evidence for the use of therapeutic hypothermia at present.

A major issue is that only two trials that were included in the meta-analyses were adequately powered to show a treatment effect. Zhi *et al.* included a control group that did not reflect current standard of care, and the other trial (Clifton *et al.*, 2001) has been criticised because the control group subjects were managed at normothermia and electrolyte abnormalities were sub-optimally managed. There are additional problems associated with performing meta-analyses in this area and these include heterogeneity in inclusion criteria, the small number of patients enrolled, the time to target temperature, the degree and duration of hypothermia, the management of re-warming and the management of the control groups. Hence at present, it is felt that the therapeutic effect of systemic hypothermia on patient outcome after TBI is unclear.

### Stroke

To date, there have been no adequately powered randomised controlled trials reporting on patient outcome following the intervention of cooling after stroke.

### Out-of-hospital cardiac arrest

The Hypothermia after Cardiac Arrest (HACA) Study was a European, nine-centre, five-country study. Patients were enrolled if they had a witnessed collapse and CPR was commenced within 15 minutes with a return of spontaneous circulation in less than 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, cardiac arrhythmias, bleeding and sepsis of all causes. Of 3246 patients screened, only 275 patients were enrolled, suggesting that this intervention is not generalisable 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. It may be that hypothermia after cardiac arrest benefits the myocardium rather than the brain, however, larger trials are needed.

Bernard *et al.* 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. However, randomisation was unbalanced. The treatment effect in this trial was improvement in global functional recovery. There are thus two trials that were successful after cardiac arrest, one showing an improvement in functional neurological recovery, the other showing a reduction in mortality.

### Systemic hypothermia

The therapeutic benefit (neuroprotection) of systemic hypothermia is likely to reduce with time from neuronal injury and adverse effects are likely to become more prominent.

### Unwanted effects of systemic cooling

**Infection.** Pneumonia and other infections are associated with hypothermia. This is not surprising considering 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 hypothalamic "setpoint" and periphery. Shivering can increase body metabolism up to 500% and increases myocardial oxygen demand, but can be reduced by the use of pharmacological interventions and by reducing the core-periphery temperature gradient by warming of feet and hands.

**Electrolyte imbalance.** During the induction of hypothermia in TBI patients, there is a significant decrease in plasma levels of magnesium, phosphate, potassium and calcium. Management of hypothermia-induced diuresis is important as is management of potassium during re-warming with risk of sudden hyperkalaemia and cardiac arrest.



Figure 1. Complementary cooling mechanisms.

Three cooling mechanisms:  
1. Cooling of venous blood by the skin which cools the arterial (carotid) blood supply to the brain.  
2. Cooling by heat loss through the skull.  
3. Cooling by heat loss from the upper airways (which is abolished by endotracheal intubation).

### Direct brain cooling

Direct brain cooling (DBC) may have fewer side effects than systemic hypothermia and targeting the brain is logical since it is brain rather than trunk temperature that is important in cerebral protection (Cabanac, 1998). 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 antero-grade 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 induce cooling to the entire surface area of the brain (Figure 1). It is important to note that physiological heat

loss from the upper airways is abolished by endotracheal intubation in many critical care patients. In human thermoregulatory physiology (TRP) research there are data to support selective brain cooling mechanisms. In hyperthermic humans it has been shown that blood flow in the emissary veins is reversed. Normally, there is flow from the scalp to the brain, but under conditions of hyperthermia, flow is from the brain to the scalp and this may facilitate cooling of neuronal tissue. [5]

Further evidence to support direct brain cooling comes from several animal studies. Piglet cooling cap work performed using magnetic resonance spectroscopy to assess brain temperature demonstrated that a temperature reduction of 3.5°C was achieved with a cooling cap at 10°C placed on the cranium. Experimental work in rats has shown that insufflating dry gas at increasing flow rates into the nostrils of intubated, ventilated rats reduced brain cortical temperature. In a fetal model of brain asphyxia, direct brain cooling showed a reduction in neuronal loss throughout deep brain structures. [6] These experimental data show direct brain cooling mechanisms work in animals that have similar TRP to humans. [7]

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. [8] A subsequent trial where nasal air flow and head fanning were performed, either in combination or alone, showed evidence of direct brain cooling (0.26°C within 30 minutes).

Therefore, there are non-invasive interventions that can augment normal physiological mechanisms and effect direct brain cooling. There are a number of unresolved issues, however, and these include the effect of induced brain temperature gradients, the effect on cerebral blood flow and neuroprotection, and whether DBC causes systemic complications.

#### Combined direct brain cooling and pharmacological modification of systemic temperature

In prospective case series, a raised body temperature after acute ischaemic stroke (AIS) was shown to be associated with adverse patient outcome. A meta-analysis of these data concluded that a difference of 1°C is

associated with a doubling in mortality after AIS. Subsequent studies have demonstrated that paracetamol can reduce body temperature by 0.3-0.4°C after AIS. A large multicentre RCT is currently exploring the question of whether 1G of paracetamol given every 4 hours over 3 days improves patient outcome (<http://www.strokecenter.org/trials/TrialDetail.aspx?tid=623>). In addition, drug therapy and DBC have independent mechanisms of action and hence may have additive effects. These two methods of temperature reduction are likely to be more widely applicable and less intensive to implement compared to systemic methods of achieving hypothermia and hence warrant further investigation.

Drug therapy could include the administration of paracetamol, acetaminophen, non-steroidal anti-inflammatory drugs and selective cyclo-oxygenase inhibitors, although concerns about the anti-platelet effect of the latter two classes of drugs may limit their use in brain injury.

#### Clinical Relevance.

Dippel *et al.* have argued that a tympanic temperature decrease of 0.27°C may reduce the relative risk of poor outcome after ischaemic stroke by 10-20%. DBC produced a mean brain temperature reduction of 0.26°C within 30 minutes and would be easy to use in stroke patients, even if awake. This is likely to be augmented by additional drug therapy (0.3-0.4°C). However, the rapid 3-4°C temperature reductions mandated after cardiac arrest and neonatal birth asphyxia may not be necessary in TBI and stroke and more modest modification of the risk factor, pyrexia, may improve outcome.

#### Conclusion

Brain cooling induced by whole body cooling results in homogeneous cooling of the cerebral cortex. Direct brain cooling exaggerates temperature gradients between 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. Intervening with more modest temperature reductions may explore the hypothesis that *early fever after brain injury is a secondary modifiable risk factor.*

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