Core temperature and brown adipose tissue activity during therapeutic whole body cooling in human neonates

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THESIS SUMMARY

Brain injury caused by the combination of inadequate blood flow and oxygen delivery to the brain before and during birth is called neonatal hypoxic ischaemic encephalopathy (HIE). Whole body hypothermia has been shown by randomised controlled trials to reduce brain injury due to hypoxic-ischaemic insults, and is an accepted treatment for HIE. However, HIE still results in considerable morbidity with 40% or more of cooled neonates nevertheless dying or suffering moderate or severe long-term impairment.

The aim of whole body hypothermia is to lower brain temperature to 33-34°C within 6 hours of birth and continue this for 72 hours before rewarming to normothermia. However, direct measurement of brain temperature is not generally possible in the human neonate during whole body hypothermia and there is a reliance on proxy measures of systemic core temperature, the most common of which is rectal temperature (T_{rec}).

The inability of hypothermia to prevent all brain injury following HIE is likely to relate to a complex interplay of many factors, including the timing of injury and application of cooling, and inadequate knowledge of the ideal depth and duration of cooling. However, hypothermia is also energetically costly where thermoregulation is activated to defend a core temperature set-point, and induces a hormonal stress response which may be harmful. An important concept is that induced hypothermia is quite different to anapyrexia, which is the adaptive response to hypoxia highly conserved in evolution where the core set point is lowered thus reducing oxygen consumption and stress responses.

Brown adipose tissue (BAT) thermogenesis is the metabolic mechanism used by neonates to defend core temperature during exposure to cold, and has an essential role in warming the brain in animal models. The activity of BAT during hypothermia treatment for HIE has not been examined in the human neonate.

Furthermore, the premise that T_{rec} reflects brain temperature is weakly supported with a paucity of human neonatal data. Extrapolation from animal data and adult human data may be invalid due to thermoregulatory differences, in particular BAT thermogenesis. T_{rec} as a monitoring site has not been adequately validated by comparison with temperature at other core sites during whole body hypothermia.

In this thesis, temperature control during whole body hypothermia in human neonates is studied, with an emphasis on BAT activity and temperature gradients between core body sites.

The following hypotheses are tested: (i) thermogenesis in BAT is active during therapeutic hypothermia for HIE; (ii) BAT activity influences temperature in the lower oesophagus (T_{oes}) more than T_{rec}; (iii) T_{rec} does not accurately reflect T_{oes}; (iv) BAT activity is associated with severity of brain injury.

Manually controlled hypothermia using T_{rec} as the target temperature site was studied because this is the standard practice in South Australian tertiary neonatal intensive care units. Furthermore, servo-controlled cooling blankets (by cooling the skin of the back) preclude the assessment of changes in inter-scapular skin temperature (T_{scap}) that may be associated with BAT thermogenesis. A series of experiments measured core temperature (T_{rec} and T_{oes}) and T_{scap} using standard temperature probes, and exposed surface temperatures using infrared imaging, both in healthy neonates, and in critically ill normothermic and hypothermic neonates nursed supine with the back in contact with an insulating mattress of an open radiant warmer.

These studies conclude that rectum is an inappropriate site to monitor and regulate core temperature during manually controlled hypothermia. T_{rec} underestimates T_{oes}, appears to be influenced by leg skin temperature, and demonstrates a long lag time to change after a change in environmental temperature that promotes temperature fluctuations in more rapidly responding sites such as T_{oes}. Evidence is presented that supports the presence of BAT thermogenesis in many neonates during whole body hypothermia, and that thermogenesis is more closely aligned to T_{oes} than T_{rec}. If T_{oes} is considered more reflective of central venous and aortic blood temperature, then T_{rec} monitoring will result in warmer than expected blood perfusing deep brain. T_{oes} is therefore more likely to provide a stable and relevant measure of brain temperature and should be used in clinical practice.

The data presented in this thesis also suggest that neonates with HIE can be divided into those that demonstrate anapyrexia and those that defend core temperature via activation of BAT. Those neonates with anapyrexia have a greater likelihood of MRI visible brain injury. The data do not suggest that activation of BAT results in harm to the brain. However conclusions are limited by small study numbers and a lack of clinical follow-up. The influence of BAT thermogenesis on the recovery of the brain during hypothermia requires further study and consideration should also be given to the study of therapeutic interventions that turn off BAT as a means of inducing therapeutic hypothermia.

DECLARATION OF ORIGINALITY OF THIS REPORT

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Anthony Carlisle Date:

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