Therapeutic hypothermia is the only treatment shown to improve outcome among comatose adult survivors of cardiac arrest,1,2 and thus forms part of the standard care of these patients.3 It may improve outcome by attenuating the pathophysiological consequences of cerebral ischaemia and reperfusion, which may themselves result in secondary injuries.4 Intensive efforts are underway to determine the molecular and cellular mechanisms underlying the therapeutic benefit of hypothermia, and to determine clinical issues such as its optimal depth, timing and duration.2

Optimisation of cerebral blood flow and oxygenation after ischaemic injury is a logical goal. Cerebral blood flow is determined by the cerebral haemodynamic resistance and by cerebral perfusion pressure, which is the difference between mean arterial pressure and central venous pressure or intracranial pressure (if greater). When intact, autoregulation maintains adequate cerebral blood flow across a wide range of cerebral perfusion pressures by modulating cerebrovascular resistance. There is however a paucity of data on the influence of hypothermia on autoregulation after an ischaemic episode, and moreover, cerebrovascular resistance is modulated by a variety of other factors, such as drugs, brain metabolism, and arterial oxygen and carbon dioxide tensions.

Hypothermia reduces metabolism, and thus oxygen requirements and carbon dioxide production, in all tissues. This, combined with the influence of temperature on gas solubility, complicates ventilatory management of hypothermic patients. Normal minute volumes will cause hypocarbia, which when significant will cause cerebral vasoconstriction and ischaemia. Frequent blood gas analysis is required, but this raises the thorny issue of which strategy should be chosen for ventilatory management – the “alpha stat” or “pH-stat”? Blood gas machines measure blood gas tensions after warming the sample to 37 °C. For a given CO2 content, measurement at 37 °C will yield a higher PaCO2 value than that measured at a cooler temperature. With the pH-stat strategy, the results from the blood gas machine are corrected back to the actual patient temperature, and ventilation is adjusted to maintain normal CO2 and pH at the patient’s actual temperature. This results in a higher CO2 content (addition of deadspace or even CO2 to the breathing circuit may be necessary to achieve this), which results in cerebral vasoconstriction and increased cerebral blood flow. The popularity of this strategy is based on the beneficial effect this can have on cerebral oxygenation. However, it does result in disconnection of flow-metabolism coupling,5 which is disadvantageous in patients with cerebral injury, in whom hyperaemia will increase cerebral blood volume and increase intracranial pressure.

With alpha stat strategies minute volume of ventilation is adjusted to achieve normal PaCO2 measured at 37 °C. While this strategy may be associated with better myocardial function, it results in a lower CO2 content in hypothermic patients, and can result in cerebral vasoconstriction sufficient to impair cerebral blood flow.

During therapeutic hypothermia close attention is paid to monitoring of respiratory and cardiovascular function. Yet, the brain, the very organ upon which good outcome depends, often receives scant attention. Ideally, cerebral blood flow and oxygenation should be optimised using accurate measurements of these variables. For a long time yet, there were no routinely available bedside methods for doing so. For flow, transcranial Doppler ultrasonography is available, but this method only measures flow velocity, not flow. For regional oxygenation and metabolism, cerebral microdialysis and measurements of tissue oxygenation are possible, but these require invasive placement of measurement filaments, which introduces logistical constraints and additional risks. Other methods, such as use of positron-emission tomography (PET) may be less invasive, but are expensive, and require the administration of radioactive tracers and transfer to a PET scanner.

In recent years there has been increasing interest in the use of near-infrared cerebral spectroscopy (NIRS) for non-invasive bedside assessment of cerebral tissue haemoglobin oxygen saturation (SctO2).6 While this method does not directly measure cerebral blood flow or tissue oxygenation, it does give an indication of the adequacy of blood flow and oxygen delivery in relation to oxygen consumption. When oxygen supply falls relative to oxygen uptake and requirements, then SctO2 will decrease, and vice versa.

In this issue of Resuscitation, Meex and colleagues report on the results of an interesting observational study where they took the logical step of monitoring SctO2 in a cohort of patients in whom therapeutic hypothermia was administered for treatment of coma following successful ROSC after out-of-hospital cardiac arrest.7 They found that in the first 3 h of hypothermia, SctO2 values fell significantly, indicating an adverse change in the balance between oxygen delivery and consumption. In 3 patients there was EEG evidence of seizures, suggesting increased oxygen requirements, but even after excluding these patients, the findings were similar. This was unexpected, given the known effects of hypothermia and sedation on cerebral oxygen requirements, and of hypothermia on haemoglobin oxygen affinity. In all patients systemic oxygenation levels were normal, so we can assume that oxygen content was also normal. Essentially, it is reasonable to conclude that cerebral blood flow decreased, and that this was the result of increased cerebrovascular resistance, since mean arterial pressures were well maintained.
There are several reasons why cerebral vasocostriction may have occurred. Although a pH-stat ventilatory strategy was used, moderate hypocarbia (PaCO\textsubscript{2} 32–38 mmHg) was applied. However, as only moderate hypocarbia and hypothermia were used, it is unlikely that CO\textsubscript{2} content was sufficiently reduced to cause cerebral vasocostriction. Another possibility is that this resulted from blood pressure augmentation with phenylephrine. Recently it has been shown that use of pure alpha-adrenoceptor agonists can be associated with reductions in SctO\textsubscript{2}.\textsuperscript{8,9} Particularly in the setting of hypothermia.\textsuperscript{10} It is uncertain why pure alpha agonists should cause reductions in SctO\textsubscript{2}. Some authors have suggested it is the result of contamination of the NIRS signal by signals arising from the scalp, where vasopressors can cause marked vasocostriction and ischaemia.\textsuperscript{11} Others have suggested that despite current theories of cerebral autoregulation, CBF and thus SctO\textsubscript{2} might be influenced by cardiac output.\textsuperscript{12} The cerebral vasculature receives sympathetic innervation, and so others have suggested that alpha agonists may cause direct vasoconstriction.\textsuperscript{13} A final possibility is that the patients were developing cerebral oedema, or another cause of intracranial hypertension, and that this impaired cerebral perfusion pressure and flow.

Another interesting finding of the study by Meex and colleagues is that SctO\textsubscript{2} values at 3 h were significantly worse among non-survivors.\textsuperscript{7} Given the observational nature and small sample size of the study, statements about cause and effect, and about prognostic value remain speculative. There was a clear difference in outcome among patients in whom the SctO\textsubscript{2} was above and below 60. It is possible that this difference is simply a biomarker of more severe primary or secondary neuronal injury, since these might cause inadequate or adverse responses to the physiological perturbances associated with hypothermia. Another possibility is that these lower values were the consequence of more severe cardiac injury and dysfunction. Although baseline SctO\textsubscript{2} levels were similar in both groups, baseline cardiac output was significantly worse among non-survivors, and tended to decrease during the early phase of hypothermia, suggesting that hearts of non-survivors were less able to compensate for increases in systemic resistance associated with hypothermia. Even if these lower SctO\textsubscript{2} values are more effect than cause, they may at least have prognostic value.

In common with all therapeutic interventions, hypothermia has both advantages and disadvantages for a variety of organs.\textsuperscript{2,4} It is thus worth considering whether the lower SctO\textsubscript{2} values in non-survivors were an indication that the combination of therapies was causing harm, or was at least less beneficial than in survivors.

Finally, it is noteworthy that after the first few hours of ongoing hypothermia, the SctO\textsubscript{2} values gradually returned to baseline. This suggests an adaptive or compensatory mechanism, which should be elucidated in further studies. Furthermore, during rewarming an increase in SctO\textsubscript{2} above baseline values was found. This indicates “rebound” or “luxury” perfusion during rewarming, probably caused by a derangement of vasoactive reactivity, which has been demonstrated at similar rewarming rates (0.3°C/h).\textsuperscript{13} Impaired autoregulation after rewarming can be harmful since, when occurring after hypothermic cardiopulmonary bypass, it is associated with a high stroke incidence.\textsuperscript{14} Other clinical consequences of altered cerebral perfusion and oxygenation have been reviewed recently.\textsuperscript{15}

The work of Meex and colleagues is a good start, but clearly more work is required. If their findings are confirmed by subsequent studies, then studies with more invasive techniques (ideally pre-clinical) are warranted to glean more information about the consequences of these therapies on cerebral blood flow and metabolism. These could also be performed in parallel with studies of the effect of interventions to prevent desaturation (e.g. algorithm-based approaches to ventilatory and blood pressure management) on outcome. Whether or not cerebral NIRS monitoring is shown to indicate adverse effects of hypothermia, to be a useful guide to ventilatory and cardiovascular management, or to provide prognostic information, it is likely to be a useful monitoring modality in these patients.

1. Conflict of interest statement

No conflicts of interest to declare.

References


A.R. Absalom *\textsuperscript{Q1} T.W.L. Scheeren

Department of Anesthesiology, University Medical Center Groningen, University of Groningen, The Netherlands

* Corresponding author: Department of Anesthesiology, University Medical Center Groningen, Post Box 30.001, 9700 RB Groningen, The Netherlands.

E-mail address: a.r.absalom@umcg.nl (A.R. Absalom)

13 March 2013

Available online xxx

Please cite this article in press as: Absalom AR, Scheeren TWL. NIRS during therapeutic hypothermia: Cool or hot? Resuscitation (2013), http://dx.doi.org/10.1016/j.resuscitation.2013.03.024