Review Article

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Temperature and the Injured Brain

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Abstract: Traumatic brain injury initiates several metabolic processes that can exacerbate the injury. Role of temperature in modulating and managing the injured brainis well known. There is evidence that cerebral ischaemia occurs after severe traumatic brain injury and therapy is directed towards the adequate supply of oxygen to meet cerebral metabolic demand, in order to avoid a secondary injury. It is seen that moderate hypothermia not only decreases metabolic rate, but also decreases intracranial pressure. Moderate hypothermia may be induced for more prolonged periods and is relatively safe and feasible therapeutic option in the treatment of selected patients with severe traumatic brain injury.

Keywords: brain injury, cerebral ischaemia, head injury, hypothermia

Introduction

Monitoring and regulating temperature in neurosurgical patients plays a dominant role in its outcome. As it is for other organ systems, cerebral metabolism decreases with decreasing temperature. It is seen that for each 1°C decrease in body temperature, $CMRO_2$ decreases by approximately 7%.

Hypothermia

It as a strategy for intraoperative neuroprotection has been recognized by neuro-anaesthesiologists for decades. In large part it was abandoned early because it was thought that the principal mechanism by which hypothermia protects is by reduction in CMR. This implied that deep levels of hypothermia are necessary to provide meaningful benefits. Accordingly, cardiopulmonary bypass would be essential to avoid complications of arrhythmia and coagulopathy. Besides logistical issues, bypass also requires administration of heparin, which considerably increases the complexity of performing surgery on the brain.

Largely by accident it has become evident that mild levels of hypothermia can provide substantial and lasting protection in laboratory animals. Active investigation is now defining the relevance of these findings to the human conditions. Further, advances in animal modeling have allowed clearer definition of mechanisms of hypothermic brain protection as well as limitations regarding efficacy. The discussion below outlines these developments.

Laboratory Evidence of Hypothermia Protection

Dramatic reduction in neural injury was observed when brain temperature was reduced by only 3° to 5°C in models of focal ischemia[1-3] global ischemia[4,5], brain trauma[6,7] or status epilepticus[8]. This is well studied in rodent models.

Anesthesiologists promptly recognized the logical extension that mild hypothermia might also be beneficial in the care of patients at risk for preoperative ischemic insults. Mild hypothermia is easy to induce in the anaesthetized patient and presumably the risk associated with this practice is small, particularly if the patient is rewarmed before emergence from anaesthesia. Second, anaesthesiologists were beginning to recognize the improbable benefit from anaesthetic agents that purportedly offer ischemia protection simply by reduction of CMR. Thus, alternative therapies were actively being sought. This was most clearly demonstrated by Sano and colleagues who observed that histologic outcome from global ischemic were poor and similar for halothane and isoflurane anaesthetized rats (despite large difference in CMR). In contrast, virtually all damage was inhibited by reducing brain temperature by only 3 °C (small effect on CMR)[5]. Work such as this has caused those caring for patients with acute cerebral insults to seriously consider application of mild hypothermia as a tool for improving outcome.

Evidence also suggests that postischemic hypothermia is protective. Original work indicated that the therapeutic window might persist for only 30 min after reperfusion of the brain[9]. Later work indicates that the window for onset of hypothermia may extend up to 12 hrs. after reperfusion. This is true, however, only if the duration of hypothermia lasts at least several hours[10].

There also has been some discussion as to whether hypothermia truly offers protection or instead causes only a delay in the cascade of pathophysiologic events that ultimately results in a similar outcome as observed for nomothermic comparators. Indeed, the majority of

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laboratory studies that examined hypothermic protections have only evaluated animals as far out as several days after the ischemic event. Others who have examined animals at weeks to months after ischemia have observed that long-term hypothermic protective effects against histologic changes become small if the duration of hypothermia is 12 hours or less[11,12]. Perhaps the definitive study has recently been performed, wherein gerbils with appropriate monitoring of brain temperature were exposed to mild hypothermia for 24 hours after global ischemia. Examination of histologic and neurologic changes at 6 months revealed a persistent benefit from hypothermia[13]. The clinical relevance of this is unknown. The data suggest, however, that should postischemic hypothermia be used, prolonged intervals (up to 24 hours) may be required to obtain lasting benefit.

Mechanisms of Hypothermia Protection

For several decades it was thought that the predominant mechanism by which hypothermia caused protection was by virtue of its effects on CMR. This has been called into question because mild hypothermia offers potent neuroprotection although CMR is only minimally reduced. Other cellular and biochemical effects better explain how hypothermia protects. For example, during an ischemic insult, extra cellular concentrations of glutamate become massively increased. Such increases in glutamate are believed to initiate an excitotoxic cascade ultimately resulting in cell death. Mild hypothermia effectively blocks this increase in glutamate[14–16]. The mechanism for this is unknown. What is becoming clear is that the postsynaptic consequences may be important. One postsynaptic glutamate receptor type (NMDA) is coupled with a calcium channel. Because there is an approximate 10,000 : 1 gradient between extra cellular and intracellular calcium, intracellular calcium is tightly regulated. Energy failure is associated with a large influx of calcium. In vitro studies have shown that mild hypothermia reduces calcium influx[17]. Presumably, such an effect causes decreased opportunity for intracellular calcium to accumulate to concentrations sufficient to exert toxic effects.

Undoubtedly there are also numerous generalized effects of hypothermia on intracellular enzymatic activity. Mild reductions in brain temperature, while having no effect during the early recirculation interval[18], hasten recovery of protein synthesis several hours after reperfusion[19]. However, specific effects are also being defined. Protein *kinas* C (PKC) an enzyme involved in regulating neuronal excitability and neurotransmitter release, is activated in response to an increase in cytosolic calcium. Hypothermia diminishes membrane-bound PKC activity in selectively vulnerable regions of the postischemic brain[20].

Nitric oxide syntheses activity in the ischemic brain is also suppressed by hypothermia[21]. It is not clear, however, whether this is beneficial or detrimental because of the variability in results obtained when nitric oxide syntheses inhibitors are examined in outcome models of ischemia[22]. If nitric oxide or other free radical mechanisms are germane to the pathogenesis of neuronal death, then the effects of hypothermia are again relevant. Hypothermia has been demonstrated to reduce accumulation of lipid peroxidation products and the consumption of free radical scavengers in ischemic brain[23,24].

Other information is available regarding free radical effects of hypothermia. Using two different models of brain injury (global ischemia or traumatic brain injury), Globus and colleagues have demonstrated that free radical production persists for at least several hours after reperfusion[25,26]. The quantity of free radical generated is reduced to almost normal values by moderate hypothermia.

Perhaps of greatest interest are the electrophysiologic effects of hypothermia during focal ischemia. It monitored for direct current potential, tissue in the ischemic penumbra shows recurrent episodes of depolarization that have been associated with transient intervals of tissue hypoxia and depression of electrical activity[17,49]. If such events can be considered as insults secondary to the primary etiology of ischemia, then the observation that hypothermia greatly diminishes the frequency of such depolarization provides an additional mechanistic basis for its protective effects.

Human Evidence of Hypothermia Protection

Evidence that profound reduction of brain temperature can reduce injury resulting from prolonged intervals of ischemia seems strong. Perhaps the most convincing example was provided by Silverberg and coworkers[28], who reported that adults undergoing cardiopulmonary bypass for cerebral aneurysm clipping were capable of sustaining up to 1 hr of circulatory arrest when core temperature was reduced to approximately 20^{o}C.

Although an extension from laboratory models to human efficacy for mild or moderate hypothermia may seem intuitive, it is not that simple. For example, there is not uniform agreement that even deep hypothermia is of value in cardiac surgery where considerable experience already has been had. The incidence of frank stroke was not different in population of 1732 patients randomized to either "warm" (core temperature, 33^{o} to 37^{o}C) or "cold" (25^{o} to 30^{o}) groups during coronary artery bypass grafting[29]. Even if hypothermia is efficacious, other factors involved with the surgical technique may have overshadowing

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importance such as the use of cardiac standstill versus low-flow bypass in pediatric heart surgery[30]. No data exist with respect to neurosurgical procedures, but it seems obvious that hypothermia will not protect against a variety of estrogenic events including excision of an eloquent area of the brain. However, of greatest relevance to the use of mild hypothermia in the neurosurgical patients were three reports made almost simultaneously in 1993. All three studies were only preliminary trials because of small sample size. Nevertheless, either a clear benefit or a trend toward benefit was observed inpatients being rendered mildly hypothermic in the acute phase after head injury[31 – 33].

Until studies are performed that examine outcome in neurosurgical patients that clinician must decide to use mild intraoperative hypothermia in the presence of sound animal evidence for efficacy but in the absence of direct human data to support that practice. Fortunately, as far as it is known, the risk associated with use of mild hypothermia is small. In a recent poll taken from members of the society of Neurosugical Anesthesia and critical care, 40 % of clinicians practiced induced hypothermia in patients undergoing cerebral aneurysm surgery[34].

Practical Considerations for Hypothermia Protection

If one accepts that mild hypothermia is indicated in either the intraoperative period or intensive care environment, then several questions regarding the method of cooling and monitoring of temperature arise. For example, during craniotomy, the brain is differentially exposed to ambient temperature. Despite core normothermia, some regions of the brain may undergo substantial cooling while other regions will not. Because it is difficult to define exactly which regions are at greater risk (i.e., tissues under a retractor versus tissue distal to a cerebral artery potentially undergoing occlusion), it is virtually impossible to use core temperature to accurately define ideal conditions for specific tissue at risk. Some work has been done to relate temperature to core temperature, but most data are derived from the cardiopulmonary bypass literature. For example, Stone and colleagues directly measured cortical surface temperature during cooling and rewarming for circulatory arrest in cerebral aneurysm surgery[35]. Temperature from other measurement sites (e.g, nasopharynx, tympanic membrane, etc.) often varied by 2 to 3°C from brain temperature during various stages of cooling and rewarming. Although such differences might be negligible during profound hypothermia, when mild hypothermia is in question, such errors constitute the full therapeutic range. Others have examined the effects of various methods of cooling on brain temperatures of patients in intensive care units. Intraventricular thermistors were used to compare brain temperature against rectal temperature[36]. During normothermia, rectal temperature underestimated brain temperature by as much as 2° to 3°C although most often values were within 0.5°C. When attempts were made to specifically reduce brain temperature to 34°C, rectal temperature values (while tracking brain temperature) were often at variance from the brain by 1° to 2°C[36]. The same study also showed that brain temperature in the comatose patient was surprisingly resistant to efforts of cooling combined with pharmacologic therapy was effective in achieving that result. These data would suggest a role for either intracranial pressure monitors or ventriculostomy drains with incorporated thermistors to be made commercially available if induced hypothermia is to become routine practice and if maximal efficacy is desired.

With respect to craniotomy, it therefore remains to be decided what end point is ideal for induced hypothermia. An additional concern in the patient undergoing craniotomy is the practicality of cooling and rewarming in an interval of only several hours. One investigation has examined this practice and found that indeed it is feasible to achieve core temperatures of about 34°C but that full rewarming to normothermia before emergence from anaesthesia is unlikely[37]. As expected, rewarming was most easily accomplished in adult patients with a low body surface area. Overall, a rewarming rate of 0.7 + - 0.6°C / hour was obtained using standard surface rewarming techniques.

Mild hypothermia is not known to be associated with the life-threatening complications found with deep hypothermia (e.g coagulopathy, arrhythmia). Nevertheless, several factors have potential relevance to patient outcome and may influence the decision whether to use this technique. During emergence from anaesthesia, myocardial ischemia may occur in patients who develop shivering in response to incomplete recovery to normothermia. To date, this has not been associated with an increased incident of myocardial infarction. However, the incidence of electrocardiographic ischemic changes is nearly tripled when peripherals vascular patients are allowed to begin recovery from anaesthesia with core temperatures less than 34.5°C[38]. Follow-up work in similar patients population has shown that hypothermic patients exhibits greater peripheral vasoconstrictions, increased nor epinephrine concentrations and higher blood pressures in the early postoperative period[39].

Mild hypothermia may also alter the dose of anaesthetic required. Volatile anaesthetic MAC is known to decrease with decrease in temperature[40]. The fall in MAC with temperature has been shown to be rectilinear over the range of 39° to 20°C in the goat. At 20°C, hypothermia provides a

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sufficient state of anaesthesia in and of itself[41]. However, it is unlikely that the effect on MAC is clinically relevant at temperatures of 33°C to 35°C. In contrast, the MAC for nitrous oxide appears largely resistant to the effects of body temperature[42].

The duration of action of muscle relaxants is likely to be increased by mild hypothermia. For example a twofold increase in the duration of action of vecuronium has been documented when body temperature is reduced from 36.8°C to 34.4°C[43]. The cause for this is unknown although it is clear that it is not attributable to changes in a plasma concentration effect relationship[44]. At the same time, neostigmine – induced reversal of neuromuscular blockade may be enhanced at lower temperatures[45].

Three concerns remain for complications from induced mild hypothermia. First it is well known that significant coagulopathies become manifest at temperature less than 30°C. However, within the range of mild hypothermia clinical evidence of coagulopathies in neurosurgical patients has been absent. Second, there is some concern that mild hypothermia may suppress the immune system[46], allowing a greater chance of infection. Although animal evdence supports the contention that hypothermia during anaesthesia may increase risk of dermal wound infection[31-33,46] an increase in infections was not noted in any of the three trials of mild hypothermia in head injured patients[31–33]. Finally, there is concern that rapid intraoperative rewarming may increase the risk of thermal injury to the patient. Indeed, burns from warming devices used during anaesthesia constitute about 1% of anaesthesia malpractice claims in the U.S.A[48]. these cases were not those that used induced hypothermia and active rewarming but instead were simply those where an attempt was being made to maintain normothermia. Most of these injuries were attributable to placing heated saline bottles adjacent to the skin.

The short intervals between completion of the high-risk phase of neurosurgical procedure (e.g temporary vascular occlusion during aneurysm clipping) and emergence from anaesthesia requires that aggressive rewarming techniques to be used. The most appropriate approach to rewarming from induced hypothermia has not yet been defined. However, it seems reasonable that the simultaneous use of heating devices including warmed intravenous fluid, forced air heating blankets, circulating warmed water blankets and heated humidified inspiratory gases should be efficacious, but requires the temperature of no single device to increase to the level where the risk of thermal injury is present.

Hyperthermia

Another series of laboratory-based observations have been made in recent years, which have relevance to intraoperative neuroprotection. Hyperthermia causes adverse effects on both pathophysiologic processes as well as histologic / neurologic outcome from brain ischemia or trauma. The first observation was made by Busto and colleagues who showed in the rat that the increasing brain temperature from 36°C to 39°C during global ischemia caused an approximate 50% increase in neuronal injury[3]. Others have repeated this observation. Perhaps the most convincing data regarding global ischemia come from a canine study conducted by Wass and coworkers. Dogs were subjected to transient global ischemia with brain temperature held 37.0°C, 38.0°C or 39.0°C. Normothermic animals (37°C) were left essentially neurologically normal by the ischemic insult. In contrast, hyperthermic animals (39ºC) were either comatose or died.

The mechanistic basis for this potent adverse effect of hyperthermia is not entirely worked out, but some clues have been provided. Glutamate release in the penumbra of a rat focal ischemic lesion is increased by about tenfold when brain temperature is increased from 37°C to 39°C. The frequency of spontaneous depolarization occurring in the ischemic penumbra is also markedly increased during mild hyperthermia. In both head injury and ischemic models, mild hyperthermia increases the rate of free radical formation.

While debate continues regarding the efficacy and role for mild hypothermia as a strategy for intraoperative neuroprotection, there is little disagreement that mild hyperthermia presents an adverse challenge to the injured brain. It is imperative that hyperthermia be guarded against in the anaesthetized patient at risk for ischemic complications.

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