Points of View

Clinical Use of Mild Hypothermia for Brain Protection: A Dream Revisited

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The capacity of hypothermia to protect the brain and other vital organs during periods of ischemia is well known and used daily during cardiac surgery. It is common for total circulatory arrest to be induced in patients for 60–90 min at 15–18°C without subsequent neurologic injury (1,2). In the 1960s profound hypothermia with circulatory arrest was used to protect the brain from temporary ischemia during the clipping of intracranial aneurysms (3,4). It provided excellent surgical exposure, but an increase in postoperative bleeding with subsequent neurologic deficits. Because of the complexity of the technique and the unacceptable risk/benefit ratio, the technique was largely abandoned (5). However, the dream of brain protection from ischemia remained. The theory of hypothermic brain protection was based on the fact that hypothermia empirically delayed those processes leading to irreversible loss of cell function and cell death. Therefore, the classic mechanism proposed for protection by hypothermia was a decrease in oxygen and glucose metabolism sufficient to permit tolerance of the brain to increased periods of ischemia. It was reported that hypothermia decreased the energy requirements of the brain by decreasing both the activation metabolism required for neuronal function as indicated by electroencephalogram (EEG) activity and the residual metabolism necessary for the maintenance of cellular integrity. The relation between temperature and cerebral metabolism has been expressed by the temperature coefficient Q10, which is the ratio of two rates of oxygen consumption separated by 10°C (6). However, this relationship between temperature and cerebral oxygen consumption is not a constant single exponential, nor is it linear, because hypothermia affects both components of neuronal oxygen consumption: activation metabolism and residual metabolism. A Q10 of approximately 2.2 to 2.4 between the temperatures of 37°C and 27°C is consistent with the Q10 for most biologic reactions and is due to a decrease in residual metabolism with little effect on activation metabolism (6–8). However, between 27°C and 14°C the Q10 is significantly increased, to approximately 4.5 (6,8). The large increase in Q10 that occurs in this temperature range is due both to a continuing decrease in residual metabolism and to a significant decrease in activation metabolism as the EEG is progressively suppressed and eventually becomes isoelectric. Below 14°C, after the total cessation of neuronal function (activation metabolism), the Q10 is approximately 2.2–2.4 again (6). Thus, if a decrease in cerebral metabolism were the only mechanism by which hypothermia protected the brain from ischemia, knowledge of the Q10 should permit calculation of the duration of protection from ischemia that could be anticipated at any given temperature; the lower the temperature, the greater the duration of brain protection.

However, recent studies have indicated that a decrease in cerebral oxygen consumption may not be the only mechanism by which hypothermia provides protection from ischemia. Several animal studies have demonstrated that small differences in
brain temperature can critically affect the extent of neuronal injury. It has been reported in rats (9) that decreases of 2–6°C in brain temperature markedly attenuated or abolished histopathologic damage in areas of the brain selectively vulnerable to ischemia. These dramatic changes in histopathology occurred despite the fact that the small differences in brain temperature had no significant influence on cerebral metabolism as measured by concentrations of cerebral metabolites. This study was confirmed by another in rats (10) in which spontaneous cooling of the brain to approximately 32°C or deliberate cooling of the brain to 35 or 33°C significantly attenuated the ischemic damage in the brain regions vulnerable to ischemia. A subsequent study by the same investigators (11) was designed to determine what temperature decrease could provide protection from graded levels of ischemia in rats. They reported that only a 2°C decrease in body temperature was necessary to produce a significant decrease in the histopathologic damage in selectively vulnerable areas. Another study in the gerbil (12) confirmed a temperature-dependent decrease in neuronal injury following ischemia in one of the vulnerable areas of the brain, the CA1 region of the hippocampus. Neuronal injury was decreased at head temperatures of 35.5 and 33.5°C but was abolished at 32.5°C. A more recent study in rats (13) also reported that a decrease in brain temperature of 3°C during incomplete global ischemia significantly reduced the histologic damage in the brain regions selectively vulnerable to ischemia. In addition to these specific studies of hypothermia, several studies on the effects of pharmacologic agents in preventing or ameliorating neurologic damage following cerebral ischemia have demonstrated that the observed brain protection may not be a direct effect of the agent per se, but an indirect effect of mild hypothermia caused by the pharmacologic agent. Part of the protective effect of barbiturates has been ascribed to their interference with temperature regulation (14–16). In some studies the protective effect of dizocilpine maleate has been attributed to significantly lower body temperature if it is not rigorously maintained.

While these studies are quite convincing that mild hypothermia does indeed decrease the amount of neuronal injury in those areas of the brain that are selectively vulnerable to ischemia, to date few studies have been done to determine the effect of mild hypothermia on neurologic outcome following ischemia. It is well known that histopathologic damage does not necessarily correlate with neurologic outcome. The brain regions selectively vulnerable to ischemia control cognition, coordination, recent memory, emotion, and drive, which are difficult to quantitate in animal studies of neurologic outcome. Significant numbers of neurons may be damaged in these areas in rodents without overt changes in neurologic outcome. In a model of fluid percussion brain injury, a decrease in brain temperature of 6°C significantly reduced mortality and neurologic deficit in rats (17). In a dog model of cardiac arrest produced by ventricular fibrillation, hypothermia to 34°C produced by head cooling during the period of cardiac arrest followed by systemic cooling during reperfusion significantly improved neurologic outcome (18). Mild hypothermia is the only therapy that has significantly improved neurologic outcome in this model. However, when hypothermia was induced only after the period of ischemia, during the reperfusion period, it not only failed to significantly improve neurologic outcome but worsened myocardial damage (19). Lastly, in a rabbit model of complete global ischemia, hypothermia to 29°C induced prior to the ischemic event significantly improved neurologic outcome when compared to normothermic controls (20).

These studies would indicate that mechanisms other than a reduction in cerebral metabolism are operative in protection from ischemic damage by hypothermia. However, an earlier study (21) did report that small (1–3°C) differences in body temperature during incomplete global ischemia significantly reduced the amount of anaerobic metabolism that occurred, as measured by concentrations of cerebral metabolites. This study was accompanied by an editorial (22) which elaborated complex equations of energy flux in order to explain how the observed small but significant changes in energy production and metabolism accompanying the minimal decrease in temperature could explain the observed protection from neuronal or neurologic damage. When this editorial was written, change in metabolism was the only known and measurable subcellular mechanism to explain the observed phenomenon. Subsequent studies using more sophisticated techniques have failed to demonstrate that a
small decrease in temperature produces a significant change in adenylate intensities, although it does produce a significant decrease in intracellular acidosis (9,23).

Because this is the only evidence that small changes in brain temperature significantly alter cerebral metabolism, other mechanisms for the observed protective effect have been proposed as we have learned more about the cellular changes occurring during ischemia and following reperfusion. These mechanisms include effects on ion homeostasis, acid-base balance, excitatory neurotransmission, calcium flux, arachidonic acid cascade, membrane lipid peroxidation, free radical reactions, and permeability of the blood-brain barrier. It has been reported that mild hypothermia has an effect on the arachidonic acid cascade during ischemia in the gerbil (24). Mild hypothermia to 30–31°C has no effect on the cyclo-oxygenase system in that the production of prostaglandins (measured as 6-keto-prostaglandin F₂α) was not decreased by hypothermia. However, the lipoxygenase pathway was affected by mild hypothermia in that the production of leukotriene B₄ was significantly decreased. This was accompanied by a concomitant decrease in edema formation following ischemia. Several studies have demonstrated that mild hypothermia significantly attenuates or abolishes the increase in excitatory neurotransmitters that occurs during and following cerebral ischemia (20,25–27). These excitatory neurotransmitters are glutamate and aspartate which act on the N-methyl-D-aspartate (NMDA) receptor-controlled ion channel to allow the influx of sodium and calcium into cells and on the quisqualate (or AMPA) receptor-controlled ion channel to allow the influx of sodium, and may gate the sodium/calcium exchange mechanism. It has been hypothesized that increased concentrations of these excitatory neurotransmitters produced during ischemia perform a pivotal role in the production of irreversible cell injury. In addition, two studies have demonstrated that mild hypothermia attenuates or abolishes the increase in glycine which occurs during and following ischemia (20,26). Glycine acts as an allosteric upregulator of the NMDA receptor-controlled channel in that much lower concentrations of glutamate are necessary to activate the NMDA-receptor in the presence of glycine. Lastly, one study (28) has reported that mild hypothermia attenuates the depletion of ubiquitin (a protein that maintains cellular integrity by binding to short-lived or abnormal intracellular proteins, allowing for their digestion by protease) which occurs during ischemia. This indicates that less abnormal proteins are produced during ischemia in the presence of mild hypothermia. Obviously, as we learn more about the intracellular events that occur during and following ischemia, we may discover other mechanisms by which mild hypothermia protects the brain from ischemia.

From the studies cited above, it can be estimated that a brain temperature of 35°C is the critical temperature for exhibiting a significant protective effect (26,28), whereas an almost completely protective effect can be obtained at 32°C in those models of ischemia (12). Mild hypothermia to a core temperature of 33°C can be easily attained in humans by active surface cooling with a cooling blanket or ice and cooling intravenous fluids or simply by passive cooling with an operating room at 21°C and eliminating measures to prevent cooling. These include avoiding the use of heated humidifiers, air exchangers, or warming blankets.

The significant side effects occurring with profound hypothermia are attenuated or avoided with mild hypothermia. Profound hypothermia of less than 27°C requires cardiopulmonary bypass with surgery, general anesthesia, and support of the circulation, because the heart commonly fibrillates at temperatures below 26–28°C. Complications of deep hypothermia include myocardial depression, arrhythmias, hypotension, and tissue injury due to inadequate tissue perfusion. Metabolic acidosis may result from decreased perfusion due to inadequate blood flow and temperature gradients between core and periphery. Profound hypothermia may also produce bleeding disorders such as thrombocytopenia (29), fibrinolysis (30), and platelet dysfunction (31) with increased blood loss. Profound hypothermia increases protein catabolism (32) and produces hypokalemia (33) following surgery. Postoperative complications of profound hypothermia include shivering with increased oxygen consumption and carbon dioxide production, hemodynamic instability, arterial oxygen desaturation because of changes in the oxyhemoglobin desaturation curve, increased oxygen solubility at low temperatures, and inhibition of hypoxic pulmonary vasoconstric-
tion. These complications do not occur during transient temporary mild hypothermia induced for the duration of temporary ischemia. Patients who have undergone induced mild hypothermia can be easily warmed to normal body temperature by the time they leave the operating room with the use of warming blankets, heated humidifiers, air exchangers, the Bair Hugger, or simply by warming the room. The pharmacologic induction of poikilothermia to block shivering via a sympathetic discharge and thermogenesis can be easily achieved by small doses of narcotic (e.g., meperidine 12.5–25 mg) and/or phenothiazines (e.g., chlorpromazine 25 mg). However, even mild hypothermia will slow drug metabolism and prolong neuromuscular blockade to some extent, and this should be remembered whenever inducing mild hypothermia (34,35).

The above studies are uniformly convincing that mild hypothermia significantly reduces the amount of neuronal injury in several animal models of ischemia. If these protective effects of small decreases in brain temperature can be substantiated with other animal studies of neurologic function or outcome following focal ischemia, mild hypothermia may become a very useful clinical technique for patients undergoing transient cerebral ischemia during such procedures as the temporary clipping of a major cerebral artery. Given the consistency of the results of the recent studies on the protective effect of mild hypothermia and given the relatively minor side effects of mild hypothermia, I would advocate its use for cerebral protection during temporary ischemia. For major cerebrovascular procedures, it is now my clinical practice to allow the body temperature to drift down to 33°C simply by the use of a normally cold operating room and by not taking any active measures to maintain normal body temperature. The patient’s body temperature is thus usually 33–34°C when temporary occlusion of a cerebral vessel is necessary. Following vascular anastomosis, I warm the room and use an air exchanger or heated humidifier. This increases the patient’s body temperature to 35–36°C by the end of the surgery. In the recovery room, I use a Bair Hugger to rapidly warm the patient to normal body temperature and prevent shivering, although shivering is usually not a problem with a narcotic-based anesthetic technique. Despite this clinical practice, I would advocate that a large multicenter clinical study be performed to determine whether mild hypothermia does improve neurologic outcome following temporary focal ischemia.

REFERENCES


