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## Early induction of hypothermia: Will sooner be better?\*

[Editorials]

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In recent years, there has been an increasing awareness of potential medical applications of induced hypothermia. Interest increased significantly when the results of three randomized, controlled trials suggested that mild-to-moderate hypothermia could improve neurologic outcome and survival in selected patients after cardiac arrest (1–3). A meta-analysis of these studies published recently in *Critical Care Medicine* concluded that in the category of patients studied (witnessed cardiac arrest, short ambulance response times, ventricular fibrillation or tachycardia on arrival of the ambulance), the number needed to treat to achieve favorable neurologic outcome in one additional patient was 6, with a range of 4–13 (4). The odds ratio for survival and good neurologic outcome at 6 months was 1.44 (95% confidence interval, 1.11–1.76). It should be noted that cooling rates in these clinical studies were relatively low, with target temperatures being reached only after an average of 8 hrs in the largest study (1). Animal studies and some clinical data strongly suggest that protective effects of hypothermia may increase significantly when the treatment is initiated in the very early stages after the occurrence of injury (5).

Many animal studies assessing protective effects of induced hypothermia have focused on one specific underlying mechanism for cellular injury after ischemia and reperfusion, which can be modified by hypothermia. This mechanism, known as the neuroexcitotoxic cascade, involves a severe disturbance of intracellular ion homeostasis induced by accumulation of excitatory neurotransmitters such as glutamate around the cell after an ischemic event. This excess of neurotransmitters causes prolonged and excessive influx of  $Ca^{2+}$  into the cell, inducing a permanent state of hyperexcitability and hyperactivity that can lead to additional cell injury and death (5–7).

In this issue of *Critical Care Medicine*, Dr. Takata and colleagues (8) report the results of an animal study assessing the effects of very short-term (20 mins) moderate hypothermia (31°C) on extracellular glutamate release and the degree of histologic injury in a rat cardiac arrest model. The authors also measured direct-current potentials, which is a sensitive measure for the functional status of neurons. Cold saline nasopharyngeal cooling was used for selective brain cooling, which was initiated either before initiation of cardiac arrest, at the onset of resuscitation, immediately after the completion of direct-current recovery, or 10 or 20 mins after the onset of resuscitation. The authors observed that histologic injuries were significantly decreased by hypothermia if this was initiated before injury (94% reduction), at the onset of resuscitation (65% reduction), or immediately after direct-current recovery ( $\pm 5$  mins after start

of resuscitation, 29% reduction). Excessive glutamate release was prevented or mitigated if hypothermia was initiated before cardiac arrest or at the onset of resuscitation but not in later stages (8).

These observations would seem to suggest that the therapeutic time window for the application of therapeutic hypothermia, at least for very brief periods, is very short: about 10 mins after the onset of ischemia in this study. However, hypothermia has been shown to improve neurologic outcome in numerous animal and clinical studies even when its application was delayed for prolonged periods of time, up to 8 hrs in one clinical study (1). How can this apparent discrepancy be explained?

First, hypothermia influences not just one but many destructive mechanisms that can develop after ischemic or traumatic injury. Some of these mechanisms are listed in Table 1; all are stimulated by fever and blocked or inhibited by hypothermia (5). Affecting the glutamate concentration and the neuroexcitotoxic cascade is just one of these mechanisms. The relative importance of these different mechanisms is very difficult to determine and may vary both in time and between different types of injury (traumatic, focal ischemic, global ischemic, and a "second-hit" ischemic episode in already injured neurons). In addition, the relative importance of destructive mechanisms may vary between different species. The rodent brain is comparatively small and lissencephalic; its rheologic and metabolic properties are different from those of the larger mammalian brain, which is much more complex, comparatively enormous, and gyrencephalic. Although the neuroexcitotoxic cascade appears to be a crucial mechanism in the development of brain injury in rodents, its relative importance may be less in mammals (including humans).

**Table 1.** Destructive mechanisms after ischemia/reperfusion that are all favorably influenced by hypothermia.

Mechanism	Explanation	Time Frame After injury
Ion homeostasis/neuroexcitotoxic cascade*	Ischemia induces accumulation of excitatory neurotransmitters such as glutamate and prolonged excessive influx of $Ca^{2+}$ into the cell. This induces a state of permanent excitability (excitotoxic cascade) that can be attenuated by hypothermia.	First minutes to 72 hrs
Free radical production and reperfusion injury	Production of free radicals such as superoxide, peroxynitrite, hydrogen peroxide and hydroxyl radicals occurs during ischemia and (especially) reperfusion. Hypothermia blocks or mitigates free-radical production.	Hours to days
Coagulation activation and formation of microthrombi	Coagulation and blockage of small vessels may occur in the brain after trauma or ischemia. Hypothermia has a mild anticoagulatory effect.	Hours to days
Apoptosis	Ischemia can induce apoptosis (i.e., programmed cell death). Hypothermia can prevent this.	Hours to many days or even weeks
Permeability of the blood—brain barrier and the vascular wall; reduced edema formation	Both the blood—brain barrier and the walls of blood vessels become more permeable after trauma or ischemia. These effects are moderated by hypothermia.	Hours to days
Cellular membrane permeability	Hypothermia can decrease the leakage of cellular membranes, thereby improving cell function and cellular homeostasis and decreasing intracellular acidosis.	Hours to days
Mitochondrial injury and dysfunction	Intracellular energy stores are quickly depleted after ischemia; mitochondrial dysfunction prevents rapid repletion and prevents recovery. The recovery process can be favorably affected by hypothermia.	Minutes to hours (days?)
Metabolic rates	Hypothermia reduces oxygen and glucose requirements by $\approx 7\%$ per degree of temperature decrease.	Hours to days
Inflammatory response	After ischemia, there is a sustained destructive inflammatory reaction with secretion of large amounts of proinflammatory cytokines. This can be blocked or mitigated by hypothermia.	First hour to 5 days
Cerebral thermopooling	There are areas in the brain with higher temperatures than the surrounding brain areas and measured core temperature. These differences increase dramatically (up to 2-3°C) in injured brains, with higher temperatures in injured areas. Hyperthermia can increase damage to injured brain cells, whereas hypothermia can mitigate such damage.	Minutes to many days

\*Subject of the study by Takata et al (8).

**Table 1.** Destructive mechanisms after ischemia/reperfusion that are all favorably influenced by hypothermia

Second, the time during which hypothermia is applied is important. The effects of excessive glutamate begin almost immediately after injury but may persist for several hours, especially in energy-deprived cells; even after glutamate levels return to normal shortly after reperfusion, glutamate receptor activation may persist. Some of the other injurious mechanisms, such as inflammatory responses and apoptosis, begin much later (hours after injury) and continue for many hours to several days. Thus, prolonged hypothermia may be required to improve outcome in these situations. However, in the study by Dr. Takata and colleagues (8), positive effects *were* seen in some animals when hypothermia was initiated before or immediately after injury, despite its extremely brief application. This suggests that perhaps the initiation of some of these other harmful processes could be largely or wholly prevented by very early initiation of hypothermia. If this observation holds true for large mammalian brains (including the human brain), this may imply that the beneficial effects of hypothermia on neurologic and overall outcome after restoration of spontaneous circulation in cardiac arrest patients could be further enhanced by (much) earlier application of hypothermia. Techniques such as rapid infusion of refrigerated saline and ice-pack cooling at the scene or in the ambulance may allow us to achieve such rapid induction of hypothermia.

Based on their observations, Dr. Takata and colleagues (8) suggest that moderate induced hypothermia of brief duration may be helpful for neurosurgical procedures. However, a recently published large clinical study assessing the effects of mild intraoperative hypothermia on neurologic outcome after intracranial aneurysm surgery found no or, at best, only marginal benefits on neurologic outcome compared with normothermia (9). One reason for the apparent discrepancy may be the use of more profound hypothermia in the animal study (31.0°C) compared with the clinical study (33.0°C). However, the risk of side effects may increase at lower temperatures. In humans, at temperatures  $\leq 35^{\circ}\text{C}$ , there is a significant impairment of neutrophil and macrophage functions and suppression of proinflammatory mediator release. When temperatures drop to  $< 33^{\circ}\text{C}$ , white blood cell count also decreases, which leads to a further increase in infection risks, especially for airway and wound infections (10). Clinically significant arrhythmias may develop if core temperatures decrease below  $28^{\circ}\text{C}$ – $30^{\circ}\text{C}$ . This risk may be increased further if electrolyte disorders develop, a complication that can also be induced by hypothermia (10–12). Apart from arrhythmias, electrolyte disorders (particularly loss of magnesium) can have many other serious consequences, especially in patients with neurologic injuries (13). Although many of these problems and side effects can be prevented or well managed with proper intensive care treatment (10, 11, 14), the potential risks should be outweighed by clear and proven benefits. All this underscores that translating the results of the study by Dr. Takata and colleagues (8) into clinical practice will not be easy and that further studies will be required to address issues such as the required depth and duration of hypothermia in various types of neurologic injury. At this moment, the overall evidence suggests that temperatures of  $32$ – $33^{\circ}\text{C}$  should be regarded as the lower limit for use in the clinical setting. We recommend that lower temperatures should not be used outside the context of clinical trials, and then, only in centers with a great deal of experience in applying induced hypothermia and in managing its potential side effects and risks.

Regarding interruption of the neuroexcitotoxic cascade that was the aim of the study by Dr. Takata and colleagues (8), some additional strategies may shortly become available to achieve this goal. Various studies have shown that glutamate transporters play an important role in preventing glutamate neurotoxicity; the most important glutamate transporter is GLT1, the physiologically dominant astroglial protein. Recently, Rothstein et al. (15) reported that

[beta]-lactam antibiotics (in contrast to several other classes of antibiotics) reduce extracellular glutamate levels and stimulate GLT1 expression. Thus, in theory, combining hypothermia with [beta]-lactam antibiotics could have synergistic effects, and using [beta]-lactam antibiotics to treat infections in patients with neurologic injuries may be a good choice.

In conclusion, hypothermia (even if initiated several hours after injury) has been shown to improve outcome in patients who remain comatose after cardiac arrest. The study by Dr. Takata and colleagues (8) suggests that perhaps even greater benefits could be achieved, or required cooling periods reduced, if cooling could be initiated in the very early stages after cardiac arrest. The next step should be the confirmation of these findings in other animal models, specifically in larger mammalian brains, which can be more easily translated to the human brain. In the end, clinical studies will be required to determine both optimum temperature levels and optimum duration of hypothermia therapy.

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**\*See also p. 1340.** [\[Context Link\]](#)

Key Words: hypothermia; cardiac arrest; neurologic injury; glutamate; side effects; timing

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