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New Research in the Field of Stroke: Therapeutic Hypothermia after Cardiac Arrest

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Therapeutic hypothermia as a potential treatment for stroke, cerebral ischemia, and other neurological diseases has gained momentum since the initial discovery that relatively small differences in intraischemic brain temperature critically determine ischemic neuronal vulnerability.[1] Since that time, laboratories throughout the world have investigated the potential use of mild-to-moderate hypothermia in many ischemia models.[2,3] Various studies have also investigated potential mechanisms contributing to hypothermic protection. Pathomechanisms sensitive to intra- and postischemic temperature reductions and elevations include glutamate release, stabilization of the blood-brain barrier, oxygen radical production, intracellular signal conduction, protein synthesis, ischemic depolarization, reduced cerebral metabolism, membrane stabilization, inflammation, activation of protein kinases, cytoskeletal breakdown, and early gene expression.[2,4] Because the pathophysiology of ischemic brain injury is complex, the fact that many injury mechanisms have been reported to be temperature sensitive may account for the dramatic effects of temperature on ischemic outcome. Thus, therapeutic hypothermia has the necessary support from preclinical data to initiate well-designed clinical studies targeting various patient populations.

In a recent issue of *The New England Journal of Medicine*, the results of 2 randomized clinical trials showed clearly that mild hypothermia improves neurologic outcome and reduces overall mortality in survivors of out-of-hospital–witnessed cardiac arrest.[5,6] In the study from Australia, a total of 77 patients who remained comatose after the return of spontaneous circulation (ROSC) were randomized to receive 12 hours of hypothermia or standard normothermic temperature management.[5] In that study, surface cooling was begun in the field and the target temperature of 32°C to 34°C was reached within 2 hours of ROSC. Forty-nine percent of those treated with hypothermia were discharged home or to a rehabilitation facility, as compared with 26% of those not treated with hypothermia ($P=0.046$). In the second study from Europe, 9 centers in 5 countries participated, with a total enrollment of 136 patients.[6] Cooling was initiated at a median of 105 minutes after ROSC, and the target temperature of 32°C to 34°C was not reached until 8 hours after ROSC. After 24 hours of hypothermia, passive rewarming was allowed to occur over the next 8 hours. These investigators found that a favorable neurologic outcome occurred in 55% of hypothermic patients compared with 39% of normothermic patients ($P=0.009$). Hypothermic patients also had a lower 6-month mortality rate (41% versus 55%, $P=0.02$). Importantly, in neither study was hypothermia associated with deleterious side effects such as sepsis, bleeding, severe electrolyte disturbances, or myocardial dysfunction, although in the Australian study systemic vascular resistance was significantly higher during hypothermia. The fact that 2 independent studies resulted in the same findings and conclusions is extremely encouraging.

From the clinical perspective, these are landmark studies in the field of cerebral resuscitation because to date no resuscitative therapy has ever been proven to be effective in improving neurologic outcome from any type of global cerebral ischemic insult.[7] While these results are very encouraging, one cannot assume that similar beneficial effects of mild therapeutic hypothermia can be achieved in victims of cardiac arrest from other causes. In both investigations, the study population was very carefully selected and included only adults with primary cardiac arrest, most of which were witnessed arrests, and had either ventricular fibrillation or pulseless ventricular tachycardia. Patients with terminal illnesses and prolonged hypoxemia or hypotension after ROSC were not included. The mean interval between collapse and ROSC was 21 and 26.5 minutes in the 2 studies, and the arterial pH on admission in the Australian study was only 7.29, both of which are relatively good prognostic factors for favorable neurologic outcome. In fact, 39% and 26% of normothermic patients in the European and Australian studies, respectively, had a good neurologic outcome. Therefore,

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one can only be cautiously optimistic about the potential for therapeutic hypothermia in the setting of prolonged resuscitations, near-drownings, sudden infant death syndrome, cardiac arrests from noncardiac etiologies and arrest victims who present with apnea and pulselessness.

If, however, a relatively brief duration of mild systemic hypothermia can be shown to be effective and without adverse effects in patients with more severe brain and systemic insults, then the entire clinical approach to these patients, who until now have had abysmal neurologic outcomes, will need to be carefully redefined, both in the emergency department and intensive care unit. Many challenging questions will arise if these arrest victims can be treated effectively with therapeutic hypothermia, such as: (1) Are previously recognized poor prognostic factors still reliable? (2) Will these patients benefit from intracranial pressure monitoring and control and other cerebral resuscitative maneuvers? (3) How can the effectiveness of hypothermia be measured to determine if it should be continued (SPECT, PET, fMRI, biomarkers, etc)? (4) Will other previously ineffective cerebroprotective agents, in combination with hypothermia, have synergistic effects on neurologic outcome? and (5) Will hypothermia prevent brain death in some patients only to result in survival in the persistent vegetative state?

Since the 1950s, moderate and deep hypothermia have been utilized for various surgical procedures as well as to reverse neurological insults of cardiac arrest.[8] During that time, numerous experimental studies provided some evidence of profound hypothermia improving outcome in animal models.[9] However, because of the numerous complications of moderate-to-profound hypothermia and the difficulty in inducing these temperature reductions, enthusiasm for the use of therapeutic hypothermia waned. Also, the introduction of new neuroprotective agents in some ways directed the field away from therapeutic hypothermia. In the 1980s, experimental observations were made that changed the way that many investigators felt about therapeutic hypothermia. Several laboratories reported the importance of relatively small variations in intraischemic and postischemic brain temperature in determining neuronal vulnerability and behavioral outcome,[1,2,10,11] thus emphasizing that profound reductions in brain temperature were not necessary to provide neuroprotection. Studies by Safar and colleagues[3,7] demonstrated the beneficial effects of mild-to-moderate hypothermia induced very early after cardiac arrest in dogs lasting 10 to 12 minutes. These observations were important from a treatment perspective and studies were initiated to determine the therapeutic window for postischemic hypothermia.[12] Also, temperature became a useful experimental tool by which to manipulate ischemic neuropathology and to clarify which pathomechanisms were sensitive to temperature manipulations. In this regard, relatively small elevations in temperature leading to mild hyperthermia were shown to worsen ischemic outcome and aggravate some ischemic pathomechanisms.[11,13,14]

Various experimental studies have also reported that both intraischemic and postischemic hypothermia are neuroprotective in models of focal brain ischemia produced by occlusion of the middle cerebral artery (MCA).[15–20] Cooling initiated during the occlusive period as well as during early reperfusion has been shown to reduce overall infarct volume and to improve functional outcome. Most studies have demonstrated that neuroprotection with mild hypothermia is more potent in models of transient versus permanent MCA occlusion and may target penumbral regions surrounding the ischemic core.[16,19,20]

The feasibility and safety of inducing modest hypothermia in patients with acute stroke has recently been reported.[21–24] Schwab and colleagues[21] induced moderate hypothermia in 25 patients with severe ischemic stroke of the MCA territory. Patients were kept at a core temperature of 33°C for 48 to 72 hours by surface cooling. Reduced intracerebral pressure (ICP) with hypothermia was demonstrated, with brain herniation and death caused by a secondary rise in ICP after passive rewarming. Recently Steiner and colleagues[23] studied the feasibility of slow controlled rewarming and found that this approach helped control ICP and cerebral perfusion pressure (CPP) during the critical posthypothermic period. In another study, reduced levels of extracellular excitatory amino acids were observed in stroke patients who were cooled compared with normothermic subjects.[25] Taken together, these initial studies provide important information that support multicenter trials targeting acute stroke.

Alternative methods of cooling patients is an active area of investigation. Georgiadis and colleagues[26] have used an endovascular cooling procedure produced by circulating temperature-adjusted normal saline in a closed-loop system in patients with acute ischemic stroke. In that study, induction and maintenance of hypothermia with intravenous cooling was feasible and allowed for more control during the critical rewarming phase. It should be also mentioned that in many of these trials, unwanted effects of whole-body hypothermia including thrombocytopenia, bradycardia, and pneumonia have been reported[27] and remain a concern with extended periods of hypothermic treatment. Thus, there is a continued interest in developing strategies that may deliver hypothermic treatment locally to specific brain or spinal cord regions.

A limitation of many therapeutic interventions targeting cerebral ischemia and other brain injuries relates to the therapeutic window for treatment. A common explanation for failed trials, for example, is that the drug was not administered in time to treat the pathophysiological event it was targeting. Early treatment is emphasized in the organization of new clinical trials. In the 2 randomized clinical trials of mild hypothermia, a benefit was reported in spite of relatively late and slow surface cooling as well as brief periods of hypothermia. Although in the Australian study cooling was initiated in the field and the target temperature was reached within 2 hours, in the European study cooling was not begun until 105 minutes and the target temperature was not reached until an average of 8 hours after ROSC.[6] The neuronal hippocampal pathology observed in cardiac arrest patients occurs in a delayed fashion.[28] Neuronal damage in selectively vulnerable brain regions after cardiac arrest may therefore be sensitive to hypothermic therapy even when the treatment is begun hours after the insult.

Experimental and clinical data have emphasized the importance of the duration of cooling and the rewarming phase

after hypothermic therapy.[2,23] For example, relatively short hypothermic periods and uncontrolled rapid rewarming can significantly minimize the beneficial effects of hypothermia.[17,29] In the recent cardiac arrest clinical studies, mild hypothermia was induced in patients for 12 or 24 hours and passive rewarming to a temperature above 36°C lasted for a minimum of 8 hours. In the study by Bernard and colleagues,[5] patients were actively rewarmed over 6 hours by external warming with a heated air blanket. Because the rewarming phase may have significant consequences on outcome, better methods of manipulating temperature and preventing periods of hyperthermia, which can occur during active rewarming, should be developed. Also, the potential for prolonged periods of hypothermic therapy to suppress endogenous reparative processes that may promote circuit plasticity and functional recovery remains a concern.

Nevertheless, these clinical trials of therapeutic hypothermia after cardiac arrest are extremely exciting. They are the outgrowth of a large number of preclinical data emphasizing the importance of temperature on ischemic outcome and the benefits of therapeutic hypothermia. In a decade in which large numbers of clinical trials targeting neurological disorders have failed,[30] it appears that a significant positive step has been made in changing the way we treat patients following cardiac arrest. We hope that more continued investigations yielding clinically important data may also allow us to successfully apply therapeutic hypothermia to other patient populations in the near future.[31,32]

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