Editorial

Therapeutic Hypothermia after Cardiac Arrest

In this issue of the *Journal*, the reported results of two randomized clinical trials, one in Australia[1] and the other in Europe,[2] showed a neurologic benefit of mild therapeutic hypothermia (33°C in the first study and 32°C to 34°C in the second) in survivors of out-of-hospital cardiac arrest.[3] In the Australian study, which involved a total of 77 patients who remained comatose after the restoration of spontaneous circulation, 49 percent of those treated with hypothermia were discharged home or to a rehabilitation facility, as compared with 26 percent of those not treated with hypothermia ($P=0.046$).[1] There were no significant differences between the two groups with respect to the frequency of adverse events. The results of the European study, which involved nine centers in five countries and had a larger number of enrolled patients, were similar.[2] Taken together, the findings in these trials are important, because in the United States so far, permanent brain damage after cardiopulmonary–cerebral resuscitation[3] causes many delayed deaths and is seen in about 10 to 30 percent of survivors of out-of-hospital cardiac arrest.[4] The fact that the two studies yielded similar results makes the important conclusions even more compelling.

The rationale for the use of therapeutic hypothermia,[4-6] which was pioneered in the 1950s and 1960s, is complex. Spontaneous, uncontrolled hypothermia starts with potentially deleterious shivering, thermogenesis, catecholamine release, and vasoconstriction,[6,7] whereas therapeutic, controlled hypothermia is potentially beneficial.[1,2,4,8] Therapeutic hypothermia after cardiac arrest, as used in the two studies reported in this issue,[1,2] is directed at mitigating neurologic injury. Temperature levels are important; mild hypothermia (33°C to 36°C) may be most effective, and it is simple and safe. Moderate hypothermia (28°C to 32°C) can cause arrhythmias or even ventricular fibrillation and, if prolonged, can lead to coagulopathy and infection.[6,7] The timing and duration are important; mild hypothermia should be initiated as soon as possible after resuscitation,[4,8-11] but even when delayed for a few hours, mild hypothermia has been shown to have some benefit in animal models of global ischemia or cardiac arrest.[4,12] Mild hypothermia induced in patients for 12 hours, as in the Australian study,[1] or 24 hours, as in the European study,[2] does not appear to have the putative complications of moderate hypothermia (i.e., ventricular fibrillation, coagulopathy, and infection).[4-7]

Since the 1950s, moderate and deep hypothermia have been used for special surgical procedures,[6] but research on hypothermia to help reverse the neurologic insult after normothermic cardiac arrest lay dormant for over 20 years. In the early 1980s, our group rekindled research on therapeutic hypothermia after cardiac arrest, using clinically relevant models in dogs.[4,8,13] In 1987, mild hypothermia, accidentally present during prolonged cardiac arrest in dogs, was discovered to be beneficial.[13] This observation was followed by five studies in dogs showing positive outcomes with the use of mild hypothermia after cardiac arrest lasting 10 to 12 minutes without blood flow.[4,8] After resuscitation from ventricular fibrillation of 11 minutes' duration,[8] the use of mild hypothermia for 12 hours, combined with strategies to promote blood flow,[14] resulted in normal brain function and histologic findings.[8] At the same time, neuroscientists reported that mild changes in brain temperature can alter the degree of histologic damage to the hippocampus after incomplete forebrain ischemia in rats.[15]

In the 1950s, it was believed that the benefit of hypothermia was due to a reduction in oxygen requirements.[16] However, since even mild hypothermia, which does not lower oxygen uptake after cardiac arrest,[4] may be beneficial, it seems more likely that hypothermia provides protection against numerous deleterious biochemical mechanisms. Over a period of days after the restoration of spontaneous circulation, these mechanisms, which include calcium shifts, excitotoxicity, lipid peroxidation and other free-radical reactions, DNA damage, and inflammation, lead to the death of some neurons in vulnerable regions of the brain, such as the hippocampus and cerebellum.[4]

Surprisingly, the current trials[1,2] showed a benefit in spite of late and slow surface cooling. In the hypothermia group in the Australian study,[1] the core temperature decreased from 34.9°C at 30 minutes after the restoration of spontaneous circulation by 0.9°C per hour. In the hypothermia group in the European study,[2] cooling was initiated at a median of 105 minutes, and the target temperature of 32°C to 34°C was reached an average of eight hours after the restoration of spontaneous circulation. The majority of patients in the hypothermia and normothermia groups had mild hypothermia on arrival at the hospital. This suggests that early rewarming, as occurred in the control group, may be detrimental. Mild cerebral hyperthermia worsens brain injury.[9] The proportion of patients in whom cardiopulmonary resuscitation had been performed by a bystander was higher in the normothermia group than in the hypothermia group in the study by Bernard et al.[1] Had the proportions been equal and had the hypothermia group undergone immediate cooling and hypertensive reperfusion,[8,14] the beneficial effect of hypothermia

might have been even greater. The positive outcomes observed in the Australian and European studies had not been achieved with pharmacologic interventions in past clinical trials.[4] The fact that in the study by Bernard et al., the platelet count did not differ significantly between the hypothermia and normothermia groups suggests that mild hypothermia may also be safe in patients with trauma.[7]

Although brain and core temperatures equilibrate rapidly when the circulation is normal, brain temperature should be monitored during resuscitation. Monitoring can be performed noninvasively with the use of tympanic or nasopharyngeal temperature as a proxy measurement. Currently available cooling methods are not ideal for the induction of hypothermia. Immersion in ice water causes rapid cooling but is impractical. The removal of clothing and the application of ice packs to the head and torso, as in the study by Bernard et al.,[1] result in very slow cooling. The selective induction of cerebral hypothermia by surface cooling of the head and neck seems feasible only in infants. The method used in the European study[2] involves the circulation of cool air over the patient's body. Peritoneal cooling is rapid but is not generally used. Extracorporeal blood cooling is the most rapid method of reducing temperature, but it involves logistical difficulties. Although the use of cardiopulmonary bypass and a heat exchanger causes a rapid reduction in temperature, cooling is delayed because of the time required to obtain vascular access and to prepare the apparatus. In large animals, venovenous shunt cooling is rapid. Blood cooling through the lungs is currently under investigation.

The dismal outcomes after cardiac arrest call for novel therapeutic approaches. The investigators in the Australian and European studies[1,2] have successfully applied an old therapy — hypothermia — to a new clinical problem. We cannot rule out the possibility that despite the overall benefit, hypothermia has deleterious effects on regenerative or reparative mechanisms; such effects would warrant the use of titrated hypothermia in combination with other therapies. The need for additional laboratory studies, however, should not prevent clinical trials from proceeding. Clinical trials of mild hypothermia are also indicated for stroke,[17] traumatic brain injury, spinal cord injury, and hemorrhagic shock[7]; clinical trials of profound hypothermia (5°C to 15°C) induced at the start of cardiac arrest due to refractory, traumatic exsanguination are also indicated.[18] Additional experimental work is needed to determine whether hypothermia is beneficial for the treatment of septic shock and myocardial infarction. Although we await further studies with great interest, we recommend the use of mild hypothermia in survivors of cardiac arrest — as early as possible and for at least 12 hours.

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REFERENCES

1. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
2. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549-56.
3. Safar P, Bircher NG. Cardiopulmonary cerebral resuscitation: an introduction to resuscitation medicine. 3rd ed. London: W.B. Saunders, 1988: 267.
4. Safar P. Resuscitation of the ischemic brain. In: Albin MS, ed. Textbook of neuroanesthesia: with neurosurgical and neuroscience perspectives. New York: McGraw-Hill, 1997:557-93.
5. Negovsky VA, Gurvitch AM, Zolotokrylina ES. Postresuscitation disease. Amsterdam: Elsevier, 1983.
6. Dripps RD, ed. The physiology of induced hypothermia: proceedings of a symposium, 28–29 October 1955. Washington, D.C.: National Academy of Sciences, 1956.
7. Tisherman SA, Rodriguez A, Safar P. Therapeutic hypothermia in traumatology. Surg Clin North Am 1999;79:1269-89.
8. Safar P, Xiao F, Radovsky A, et al. Improved cerebral resuscitation from cardiac arrest in dogs with mild hypothermia plus blood flow promotion. Stroke 1996;27:105-13.
9. Dietrich WD, Busto R, Valdes I, Loor Y. Effects of normothermic versus mild hyperthermic forebrain ischemia in rats. Stroke 1990;21:1318-25.
10. Xiao F, Safar P, Radovsky A. Mild protective and resuscitative hypothermia for asphyxial cardiac arrest in rats. Am J Emerg Med 1998;16:17-25.
11. Eisenburger P, Safar P. Life supporting first aid training of the public — review and recommendations. Resuscitation 1999;41:3-18.
12. Hickey RW, Ferimer H, Alexander HL, et al. Delayed, spontaneous hypothermia reduces neuronal damage after asphyxial cardiac arrest in rats. Crit Care Med 2000;28:3511-6.
13. Safar P. Resuscitation from clinical death: pathophysiologic limits and therapeutic potentials. Crit Care Med 1988;16:923-41.
14. Safar P, Kochanek P. Cerebral blood flow promotion after prolonged cardiac arrest. Crit Care Med 2000;28:3104-6.
15. Busto R, Dietrich WD, Globus MY, Ginsberg MD. Postischemic moderate hypothermia inhibits CA1 hippocampal ischemic neuronal injury. Neurosci Lett 1989;101:299-304.
16. Rosomoff HL, Holaday DA. Cerebral blood flow and cerebral oxygen consumption during hypothermia. Am J Physiol 1954;179:85-8.
17. Krieger DW, De Georgia MA, Abou-Chebl A, et al. Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke. Stroke 2001;32:1847-54.
18. Safar P, Tisherman SA, Behringer W, et al. Suspended animation for delayed resuscitation from prolonged cardiac arrest that is unresuscitable by standard cardiopulmonary-cerebral resuscitation. Crit Care Med 2000;28: Suppl 11:N214-N218.