

## CLINICAL THERAPEUTICS

# Targeted Temperature Management for Comatose Survivors of Cardiac Arrest

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*This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

**A 62-year-old man collapses on the street, and emergency medical personnel who are called to the scene find that he is not breathing and that he has no pulse. The first recorded cardiac rhythm is ventricular fibrillation. Advanced cardiac life-support measures, including intubation, a total dose of 2 mg of epinephrine, and six defibrillation attempts, restore spontaneous circulation 22 minutes after the onset of the event. On admission to the emergency department, his condition is hemodynamically stable and he has adequate oxygenation and ventilation, but he is still comatose. A neurologic examination reveals reactive pupils and a positive cough reflex. The core body temperature is 35.5°C. A diagnosis of the post-cardiac arrest syndrome with coma is made. An intensive care specialist evaluates the patient and recommends the immediate initiation of targeted temperature management.**

## THE CLINICAL PROBLEM

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N Engl J Med 2010;363:1256-64.  
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The annual incidence of out-of-hospital cardiac arrest in industrialized countries has been estimated to be 92 to 189 cases per 100,000 inhabitants.<sup>1-3</sup> According to one estimate, 350,000 to 450,000 out-of-hospital cardiac arrests occur in the United States annually; resuscitation is attempted in the case of 100,000 of these arrests, and 40,000 patients survive to hospital admission.<sup>4</sup>

Unfortunately, even among patients who survive to hospital admission, the prognosis is uncertain. These patients may have multiple consequences of cardiac arrest, including brain injury, myocardial dysfunction, systemic ischemia, and reperfusion responses, as well as consequences of the disorder that caused the cardiac arrest. This constellation of pathophysiological processes has been termed the “post-cardiac arrest syndrome.”<sup>5</sup> The effects of this syndrome are sufficiently severe and pervasive that only about one third of patients who are admitted to the hospital after cardiac arrest survive to hospital discharge.<sup>5</sup>

Perhaps the most important manifestations of the post-cardiac arrest syndrome are neurologic. Approximately 80% of patients remain comatose for more than 1 hour after resuscitation, and fewer than half of admitted patients have a good neurologic recovery, as defined by a score on the Cerebral Performance Category (CPC) scale (which ranges from 1 to 5, with higher scores indicating increased disability) of 1 (good recovery) or 2 (moderate disability) on neurologic examination (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org); such patients have sufficient cerebral function to live independently and work at least part-time.<sup>6</sup> Patients who are more severely affected may remain comatose or in a persistent vegetative state or may suffer from varying degrees of cognitive dysfunction and other neurologic deficits. In one study, it was estimated that the cost of care during the first 6 months after a cardiac arrest was approxi-

mately \$200,000 for a patient with a CPC score of 1 or 2, \$300,000 for a patient with a CPC score of 3 or 4, and less than \$10,000 for a patient with a CPC score of 5 (indicating brain death).<sup>7</sup>

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#### PATHOPHYSIOLOGY AND EFFECT OF THERAPY

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In animal models of cardiac arrest, stores of oxygen in the brain are lost in seconds, and stores of glucose and ATP are lost within 5 minutes.<sup>8</sup> Tissue hypoxia and substrate depletion quickly lead to the loss of transmembrane electrochemical gradients and sequential failure of synaptic transmission, axonal conduction, and action-potential firing.<sup>9</sup> The neurotransmitter glutamate is released and intracellular calcium accumulates, leading to a phenomenon known as excitotoxic cell death.<sup>10,11</sup> Some regions of the brain are especially vulnerable to global ischemia, including the hippocampus, neocortex, cerebellum, corpus striatum, and thalamus.<sup>12</sup> Both neuronal necrosis and apoptosis have been reported after cardiac arrest, although the contribution of each mechanism of cell death to the resulting brain injury remains unclear.<sup>5</sup>

After restoration of circulation, reperfusion and reoxygenation can cause further neuronal damage over a period of hours to days, owing to the phenomenon of reperfusion injury. Cerebral microcirculation fails with an initial transient global hyperemia due to vasomotor paralysis, followed by delayed, prolonged global and multifocal hypoperfusion.<sup>13</sup> Reoxygenation initiates chemical cascades producing reactive oxygen species that cause lipid peroxidation and other oxidative damage.<sup>14</sup> Alterations in the inflammatory response can cause endothelial activation, leukocyte infiltration, and further tissue injury.<sup>15</sup> Other contributing factors, including hypotension, hypoxemia, impaired cerebrovascular autoregulation, and brain edema, can further impede the delivery of oxygen to the brain.

Targeted temperature management, also known as therapeutic hypothermia, is a therapeutic intervention that is intended to limit neurologic injury after a patient's resuscitation from cardiac arrest. Hypothermia causes a reduction in brain metabolism, including a reduction in oxygen utilization and ATP consumption.<sup>16,17</sup> However, it does not appear that these metabolic effects correlate well with the protective effects of hypothermia,<sup>18</sup> and numerous other effects of hypothermia have also been observed. Hypothermia inhibits the release

of glutamate and dopamine and induces brain-derived neurotrophic factor, which further reduces the release of glutamate.<sup>19,20</sup> Oxidative stress is attenuated and lipid peroxidation is reduced.<sup>21,22</sup> Apoptosis is inhibited as a result of a reduction in calcium overload and glutamate release, as well as the induction of antiapoptotic Bcl-2 and the suppression of the proapoptotic factor BAX.<sup>23</sup> Hypothermia has also been shown to suppress the inflammation that occurs after global cerebral ischemia<sup>24</sup> and to reduce both early hyperemia and delayed hypoperfusion.<sup>25</sup>

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#### CLINICAL EVIDENCE

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The first major clinical trials that provided direct evidence of a benefit of targeted temperature management were published in 2002.<sup>26,27</sup> These two trials, one conducted in Australia and the other in Europe, have become the basis for clinical guidelines regarding the use of therapeutic hypothermia in patients who have had a cardiac arrest.

In the Australian trial, 77 comatose survivors of a cardiac arrest were enrolled.<sup>26</sup> Participants were required to have had an initial rhythm of ventricular fibrillation or pulseless ventricular tachycardia, and the arrest had to be of presumed cardiac origin. Patients who were enrolled on odd-numbered days of the months were assigned to hypothermia (target temperature, 33°C; cooling duration, 12 hours; cooling performed with the use of ice packs), and patients who were enrolled on even-numbered days were assigned to standard treatment with normothermia. A total of 21 of the 43 patients (49%) who were treated with hypothermia survived and had a favorable neurologic recovery at hospital discharge, as compared with 9 of the 34 patients (26%) treated with normothermia ( $P=0.05$ ). The odds ratio for a favorable neurologic recovery with hypothermia therapy was 5.25 (95% confidence interval [CI], 1.47 to 18.76;  $P=0.01$ ), after adjustment for age and duration of the arrest.

In the European multicenter trial, 275 comatose survivors of a cardiac arrest of cardiac cause (ventricular fibrillation or pulseless ventricular tachycardia) were enrolled.<sup>27</sup> Patients were randomly assigned to targeted temperature management (target temperature, 32 to 34°C; cooling duration, 24 hours; cooling with the use of cold air) or to standard treatment with normothermia. A total of 75 of the 136 patients (55%) in the hypothermia group had a favorable neurologic

recovery (CPC score of 1 or 2) after 6 months, as compared with 54 of 137 patients (39%) in the normothermia group (risk ratio for a favorable outcome with hypothermia, 1.40; 95% CI, 1.08 to 1.81). In addition, as compared with standard treatment with normothermia, there was a significant reduction with hypothermia in the rate of death at 6 months (risk ratio for death, 0.74; 95% CI, 0.58 to 0.95).

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#### CLINICAL USE

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Targeted temperature management should be implemented in the context of a broader strategy of critical care for a comatose patient with the post-cardiac arrest syndrome.<sup>5</sup> All patients require protection of their airway and mechanical ventilation. Hemodynamic support should be given with the use of intravenous fluids, inotropic agents or pressors, or even mechanical cardiac assistance, if necessary. If the patient had an acute myocardial infarction, prompt revascularization should be considered. Hemofiltration or hemodialysis may be necessary for patients with substantial renal injury. Monitoring and management of blood glucose levels, antibiotic therapy for infection, and other disease-specific interventions should be implemented as appropriate. Targeted temperature management is focused mainly on mitigating brain injury associated with the post-cardiac arrest syndrome but may have a beneficial effect on other elements of the syndrome as well.

A list of indications for targeted temperature management is given in Table 1. The criteria are based on the enrollment criteria of the two major trials and additional retrospective data. In general, therapeutic hypothermia should be considered in the case of patients who have had a cardiac arrest with an initial rhythm of ventricular fibrillation or pulseless ventricular tachycardia, who have been successfully resuscitated, and whose condition is hemodynamically stable, but who are comatose (as indicated by a score on the Glasgow Coma Scale of less than 8 [see Table 2 in the Supplementary Appendix] and a lack of verbal response).

Animal models suggest that any delay in the initiation of targeted temperature management may diminish or even abrogate the beneficial effects of this form of therapy.<sup>31,32</sup> Unfortunately, no data are available from large-scale clinical trials to confirm the time dependence of treatment in humans. Nevertheless, it seems reasonable that

hypothermia should be initiated as early as possible and not later than 10 hours after the cardiac arrest.

Before hypothermia is induced, sedation, analgesia, and paralysis should be initiated to prevent shivering (which can lead to increased oxygen consumption, excessively laborious breathing, an increase in the heart rate, and a general stresslike response, and can also impede the cooling process) and to minimize the patient's discomfort.<sup>33</sup> My colleagues and I use midazolam at a dose of 0.15 mg per kilogram of body weight per hour and fentanyl at a dose of 2.5  $\mu$ g per kilogram per hour initially, with adjustment of the doses to facilitate mechanical ventilation. To prevent shivering, paralysis is induced by means of the intravenous administration of rocuronium at a dose of 0.5 mg per kilogram as a bolus and a dose of 0.5 mg per kilogram per hour thereafter. Physiological monitoring during sedation and paralysis should be undertaken only by personnel who have the appropriate experience and expertise in the use of these agents.

Several different cooling methods are available for use in therapeutic hypothermia (Fig. 1).<sup>34,35</sup> In the pivotal clinical trials, cooling was achieved by the application of numerous ice packs around the head, neck, torso, and limbs (in the Australian trial) or with the use of a cold-air mattress covering the entire body (in the European trial). Other methods of surface cooling include the use of water-circulating cooling pads and precooled (refrigerated) cooling pads. Core cooling can be achieved with the use of intravascular cooling catheters (made of metal or containing balloons filled with cold saline) or by means of intravenous infusion of cold fluids. Many of these techniques make use of commercially developed equipment that is specifically designed for the purpose of targeted temperature management.

We generally use a combination of core-cooling and surface-cooling methods. In a patient who does not have pulmonary edema, we administer 30 ml of cold (4°C) lactated Ringer's solution per kilogram (about 2 liters for a patient who weighs 70 kg), administered intravenously over the course of 30 minutes. At the same time, we apply refrigerated cooling pads to cover most of the body surface. Our objective is to reach a target temperature of 32 to 34°C and to maintain that temperature for 24 hours, if feasible.

Measurement of the core body temperature is essential in targeted temperature management.

For accurate assessment, core body temperature should be measured at central monitoring sites, such as the esophagus (in which temperature is monitored with the use of a multipurpose temperature probe) or the central venous system (in which temperature is monitored with the use of a Swan–Ganz catheter), since the temperature in the bladder and rectum may be slow to reflect a change in core body temperature.<sup>36</sup> Blood gases should be measured at least every 4 hours to allow for the adjustment of respiratory therapy to meet the patient's needs (with the goal of achieving normal partial pressure of carbon dioxide [PaCO<sub>2</sub>] and sufficient oxygenation).<sup>37</sup>

Hypothermia can induce metabolic disturbances, including hypokalemia, hypomagnesemia, hypophosphatemia, and hyperglycemia.<sup>38–40</sup> Therefore, regular measurement of electrolyte and glucose levels is necessary to guide the appropriate amount of electrolyte substitution and insulin therapy. Leukopenia and thrombocytopenia may occur but typically do not require intervention. Rarely, severe thrombocytopenia, coagulation disorders, or pancreatitis may develop. In such circumstances, it is reasonable to raise the temperature level until these side effects resolve.

Since there are reports that indicate that non-convulsive seizures can occur during hypothermia, it is reasonable to perform continuous electroencephalographic monitoring to detect these seizures and to treat them if they occur, but whether this approach improves the long-term outcome has not yet been established.<sup>41</sup> Standard intensive care measures should be applied to monitor and manage the patient's condition: invasive blood-pressure measurement, continuous monitoring of electrocardiographic findings and oxygen saturation levels, establishment of central venous line access, and assessment and replacement of fluid balance. If the patient's condition becomes hemodynamically unstable during hypothermia, rewarming may not be helpful, since vasodilatation can occur during rewarming.<sup>27</sup> Fluid replacement and inotropic and pressor therapy should instead be used to support blood pressure.

After maintenance of hypothermia for 24 hours, the patient should be rewarmed slowly (0.3 to 0.5°C per hour) to normal core body temperature (36.5 to 37.5°C). The rewarming can be performed with the use of the same device that was used for cooling, by blowing warm air over the patient, or by covering the patient with blankets. Above-normal body temperatures should be avoided, and

**Table 1. Indications and Contraindications for Targeted Temperature Management in Comatose Patients after Cardiac Arrest.**

**Patients for whom therapeutic hypothermia should be considered**

- Adult patients successfully resuscitated from a witnessed out-of-hospital cardiac arrest of presumed cardiac cause (patients after in-hospital cardiac arrest may also benefit)<sup>28</sup>
- Patients who are comatose (i.e., patients with a score on the Glasgow Coma Scale of less than 8 or patients who do not obey any verbal command at any time after restoration of spontaneous circulation and before initiation of cooling)
- Patients with an initial rhythm of ventricular fibrillation or nonperfusing ventricular tachycardia (patients presenting with other initial rhythms such as asystole or pulseless electrical activity may also benefit)<sup>28</sup>
- Patients whose condition is hemodynamically stable (retrospective data suggest that patients in cardiogenic shock may also safely undergo hypothermia treatment)<sup>29,30</sup>

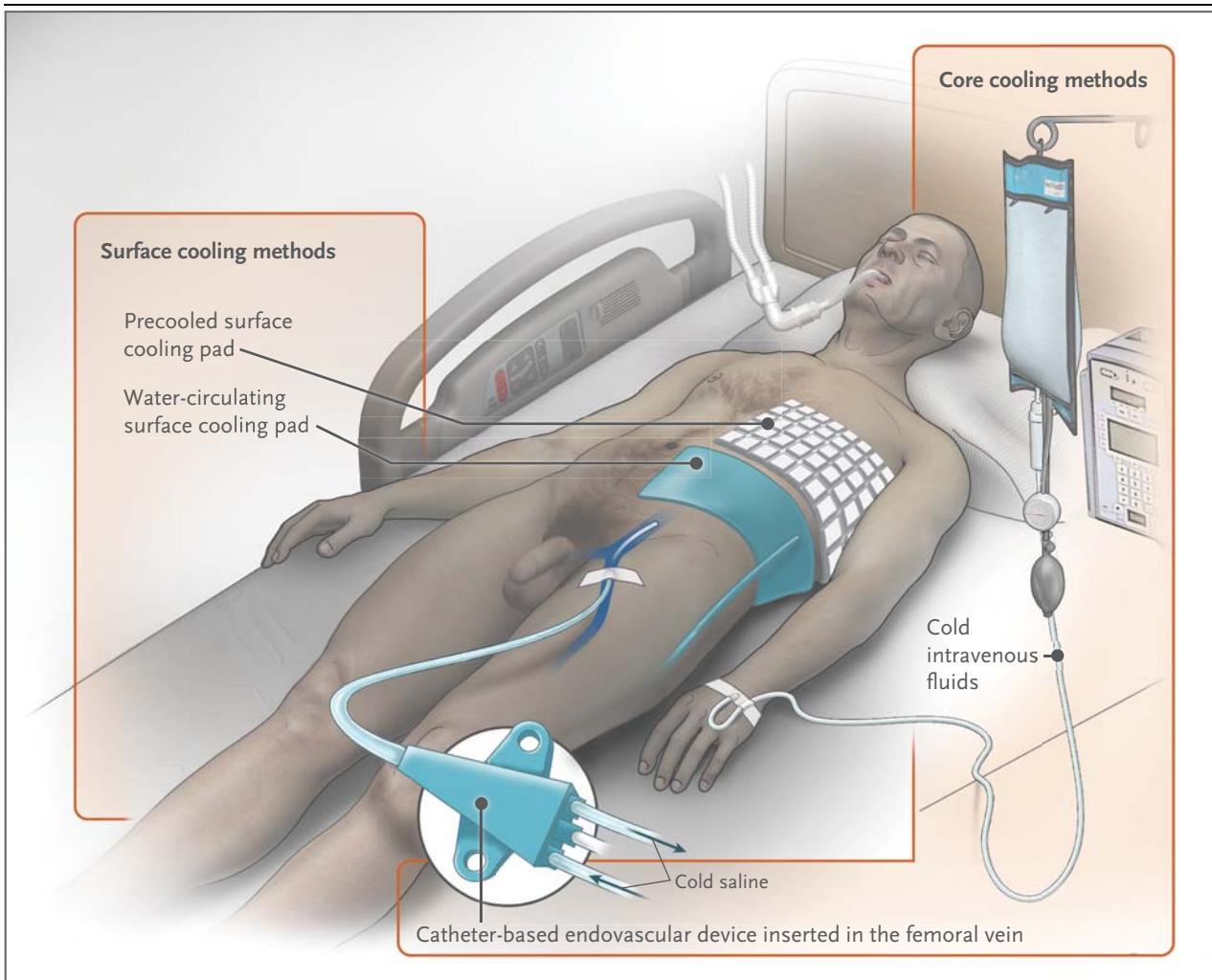
**Patients for whom therapeutic hypothermia should not be considered**

- Patients with tympanic-membrane temperature below 30°C on admission
- Patients who were comatose before the cardiac arrest
- Pregnant patients
- Patients who are terminally ill or for whom intensive care does not seem to be appropriate
- Patients with inherited blood coagulation disorders

the patient's temperature should be kept within the normal range for up to 48 hours, since hyperthermia could worsen the outcome.<sup>42</sup> After rewarming, sedatives, analgesics, and paralytic agents are discontinued and standard intensive care should be provided, including extubation when feasible.

Some patients may remain comatose for an extended period after resuscitation from cardiac arrest and yet have substantial neurologic recovery. The American Academy of Neurology has developed a prognostic algorithm to assist in predicting a poor outcome in this setting.<sup>43</sup> However, the use of therapeutic hypothermia may complicate this assessment, and the optimal approach to the prognostic evaluation of a patient treated with targeted temperature management has not been fully resolved (see Areas of Uncertainty). This is an issue of central importance, since it is ethically justifiable to limit care or withdraw support only when a poor prognosis is reasonably certain.<sup>44</sup>

The cost of treating a comatose patient with the post-cardiac arrest syndrome is dependent on the final clinical outcome, because most of the costs derive from the duration of the hospital stay and subsequent rehabilitation. In an analysis of cost-effectiveness, the incremental cost for an average patient treated with targeted temperature



**Figure 1. Cooling Methods Used in Clinical Practice.**

Surface cooling methods include the use of precooled (refrigerated) surface cooling pads and water-circulating surface cooling pads. Core cooling methods include the infusion of cold intravenous fluids and the use of catheter-based endovascular devices.

management was estimated to be approximately \$30,000 over the average cost for conventional care, which is estimated to be approximately \$100,000.<sup>7</sup>

#### ADVERSE EFFECTS

Adverse effects of targeted temperature management are either directly related to the cooling device or due to hypothermia itself. In 41 clinical trials of targeted temperature management that were conducted between 1997 and 2010, the overall rate of adverse events related to a cooling device was 1% (29 events in 3133 patients). These included 3 cases of bleeding, 8 cases of infection, and 10

cases of deep-vein thrombosis in patients who were cooled with the use of a catheter-based cooling device, as well as 8 cases of pulmonary edema in patients who were cooled with the use of cold intravenous fluid.

Adverse effects of targeted temperature management that were not related to a cooling device, as reported in the major comparative clinical trials,<sup>26,27,45-47</sup> occurred in 74% of the patients who were treated with hypothermia (223 events in 300 patients) and in 71% of the patients who were given standard treatment (201 events in 285 patients,  $P=0.31$ ) (Table 2). There were no reports in the randomized trials of thrombocytopenia, acute respiratory distress syndrome, cerebrovascular in-

sult, or bradycardia. In a recent observational study involving 986 patients, the most commonly observed adverse events were pneumonia (41%), hyperglycemia (37%), cardiac arrhythmias (33%), seizures (24%), and electrolyte disturbances (hypophosphatemia, 19%; hypomagnesemia, 18%; and hypokalemia, 18%).<sup>48</sup>

#### AREAS OF UNCERTAINTY

In the Australian<sup>26</sup> and European<sup>27</sup> trials discussed above, targeted temperature management was used almost exclusively in patients who had an out-of-hospital cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia. There are no data from studies of sufficient quality to recommend the use of this therapy in an adult who has had a cardiac arrest that is not due to ventricular fibrillation. However, since the pathophysiology of brain damage (global ischemia and reperfusion) is not different between patients with out-of-hospital arrests and those with in-hospital cardiac arrests or between cardiac arrests that are due to ventricular fibrillation and those that are not due to ventricular fibrillation, targeted temperature management may be a useful option for a broader population of patients than the populations in these two major trials.

The optimal regimen of sedation, analgesia, and relaxation is still a matter of debate, and many different protocols are used in clinical practice.<sup>33</sup> In the randomized trials, midazolam, fentanyl, pancuronium, or vecuronium was used to facilitate cooling and prevent shivering. A possible drawback of midazolam is that levels of the drug accumulate during hypothermia,<sup>49</sup> and the increased levels of the drug could result in a prolonged need for ventilation and intensive care. The use of paralytic agents has been questioned, since these agents are thought to increase the risk of myopathy associated with critical illness, although there has been no prospective trial so far that has shown such an association.<sup>50</sup> In any case, shivering should be avoided, since it increases the adrenergic response to induced hypothermia and systemic metabolic demands — a response that could lead to increased cardiac complications.<sup>51</sup>

The optimal time to initiate hypothermia, the optimal length of time that should be taken to reach the target temperature, the optimal level and duration of hypothermia, and the effect of the rewarming rate on the neurologic outcome after cardiac arrest are still unknown. Further study of

**Table 2. Adverse Events, Not Related to the Cooling Device, in Patients Who Received Targeted Temperature Management, as Compared with Adverse Events in Patients Who Received Standard Treatment.\***

| Adverse Event           | Targeted Temperature Management (N=300) | Standard Treatment (N=285) |
|-------------------------|---|----------------------------|
|                         | no. (%)                                 |                            |
| Arrhythmia              | 55 (18)                                 | 47 (16)                    |
| Hemodynamic instability | 14 (5)                                  | 15 (5)                     |
| Bleeding                | 26 (9)                                  | 19 (7)                     |
| Pneumonia               | 37 (12)                                 | 29 (10)                    |
| Sepsis                  | 13 (4)                                  | 7 (2)                      |
| Electrolyte disorder    | 17 (6)                                  | 0                          |
| Renal failure           | 17 (6)                                  | 19 (7)                     |
| Seizures                | 10 (3)                                  | 11 (4)                     |
| Pancreatitis            | 1 (<1)                                  | 2 (1)                      |
| Pulmonary edema         | 33 (11)                                 | 52 (18)                    |

\* Data are from major clinical trials comparing targeted temperature management with standard therapy after cardiac arrest.<sup>26,27,45-47</sup>

these components of targeted temperature management may provide information that would allow the tailoring of treatment to the individual patient, depending on the severity of the insult. Longer exposure to hypothermia might be required in the setting of more severe injury, as indicated in studies in rodents.<sup>52</sup> In addition, milder levels of hypothermia (e.g., 35°C) might have protective effects similar to those of the target temperatures used in current protocols (33°C).<sup>53</sup>

Determination of the prognosis after cardiac arrest may be difficult in patients undergoing therapeutic hypothermia.<sup>43,54</sup> The effect of hypothermia on the predictive value of various assessments, including somatosensory evoked potentials (SSEPs), magnetic resonance imaging, and serum markers of neuronal damage (e.g., neuron-specific enolase and S-100), remains uncertain.<sup>55-58</sup> Limited data suggest that hypothermia reduces the predictive value of motor responses and of the lack of N20 responses (the primary cortical component after median-nerve stimulation in SSEP readings) during SSEP testing early after cardiac arrest.<sup>44,57</sup>

#### GUIDELINES

After an advisory statement of the International Liaison Committee on Resuscitation (ILCOR) en-

dorsed the use of therapeutic hypothermia in 2003,<sup>59</sup> targeted temperature management was included in the 2005 guidelines for resuscitation and emergency cardiac care of the European Resuscitation Council<sup>60</sup> and the American Heart Association.<sup>61</sup> These guidelines recommend that the core body temperature of unconscious adult patients with spontaneous circulation after an out-of-hospital ventricular fibrillation cardiac arrest should be lowered to 32 to 34°C. Cooling should be started as soon as possible after the arrest and should be continued for at least 12 to 24 hours. The guidelines note that patients who have had a cardiac arrest due to nonshockable rhythms and patients who have had a cardiac arrest in the hospital may also benefit from induced hypothermia. In 2008, another statement from ILCOR incorporated targeted temperature management into the more comprehensive treatment bundle of therapy for the post-cardiac arrest syndrome.<sup>5</sup>

#### RECOMMENDATIONS

The patient described in the vignette is an appropriate candidate for targeted temperature management, given the diagnosis of the post-cardiac arrest syndrome with coma after successful resuscitation from an out-of-hospital cardiac arrest with a primary rhythm of ventricular fibrillation.

I would insert an additional temperature probe in the esophagus and initiate rapid cooling by the infusion of 2000 ml of cold lactated Ringer's solution with the use of a pressure bag through a large-bore cannula over the course of 30 minutes, combined with the application of refrigerated cooling pads (or the use of a catheter-based endovascular cooling device) to maintain a core temperature of 33°C for 24 hours. I would monitor the patient's hemodynamic status, oxygenation, electrolyte levels, and blood counts carefully during the period of hypothermia. After considering treatment options with respect to the cause of the cardiac arrest (e.g., cardiac catheterization in the case of acute myocardial infarction), I would rewarm the patient slowly, at a rate of 0.4°C per hour, until normothermia (36.5 to 37.5°C) was restored. I would then discontinue the sedatives, the analgesics, and the paralytic agent as tolerated and plan to initiate weaning from ventilatory support as soon as possible thereafter.

Dr. Holzer reports receiving fees for board membership from KCI Medical, consulting fees from EMCOOLS, and lecture fees from KCI Medical and Medivance. The Department of Emergency Medicine at the Medical University of Vienna received research grants from KCI Medical, Life Recovery Systems, and Velomedix on behalf of Dr. Holzer. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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