EDITORIAL

Temperature Management and Modern Post–Cardiac Arrest Care

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Modern cardiopulmonary resuscitation (CPR) began in 1960, when clinicians translated observations about external chest compressions from the laboratory to patients.[1] CPR increased survival for patients who had cardiopulmonary collapse outside of the operating room from none to a few. Incremental improvements in the survivorship from CPR occurred as more persons were trained in CPR and as defibrillators became portable and were deployed in more locations. Unfortunately, a cascade of brain injury begins within minutes after cardiac arrest, with the consequence that most patients who had return of cardiac activity did not survive to leave the hospital or did so in a neurologically devastated state. In the early 2000s, overall survival after cardiac arrest outside the hospital remained about 7 to 8%.[2] About one quarter of patients regained pulses after CPR, and about one third of the patients with those initial successes survived hospitalization.

The devastating effects of post-CPR brain injury stimulated decades of investigation into the pathophysiology of, and potential treatments for, global brain ischemia. Because cardiac arrest is an unpredictable emergency, clinically useful treatments for post-CPR brain injury must work not just as pretreatments but even when initiated after CPR or after restoration of circulation. To date, the only intervention robustly meeting these specifications is mild reduction of body temperature (from 37°C to between 32 and 35°C) for at least 5 hours after restoration of circulation.[3]

In 2002, two randomized, controlled trials showed that induction of mild hypothermia for 12 or 24 hours increased survival and improved neurologic outcomes for very select patients with out-of-hospital cardiac arrest.[4,5] Induced hypothermia after cardiac arrest gained widespread use and is now advocated by international guidelines.[6] Implementation of induced hypothermia increased survival, even when applied to less selected cohorts of patients than studied in the original trials.[7]

A new randomized trial now reported in the *Journal* by Nielsen et al.[8] questions whether lower temperatures actually benefit patients after cardiac arrest. When 939 patients with return of spontaneous circulation after CPR were assigned to targeted temperature management at either 33°C or 36°C after cardiac arrest, survival (51%) and a good neurologic outcome (47 to 48%) did not differ significantly between groups. This superbly executed study is more than twice the size of the original trials combined (which enrolled a total of 352 patients) and was conducted with meticulous attention to modern intensive care. The overall conclusion that there is no significant difference between a near-normal temperature (36°C) and induced hypothermia (33°C) seems to contradict the previous trials and implementation studies.

One of the greatest innovations in this trial is adoption of a protocol for withdrawal of life-sustaining treatment. Almost all prior studies of post–cardiac arrest care are tainted by the fact that the most common cause of death is withdrawal of life support because of perceived poor neurologic prognosis. This confounder is problematic in trials because there are almost no certain methods to establish long-term prognosis. The current authors have clearly delineated their approach for the 26% of patients who had withdrawal of care before hospital discharge.

There are multiple possible explanations for the absence of benefit from lower temperatures in patients with cardiac arrest. The population was less select than in previous trials, including

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patients with shockable rhythms and those with nonshockable rhythms. There has been evolution of intensive care over the past decade, and improvements in patient care may have reduced the potential incremental benefits of a single intervention. In addition, illness severity varies greatly among patients with cardiac arrest, and there may be subgroups of patients who do benefit from induced hypothermia but who were not designated in advance. Particularly if the degree or duration of hypothermia must be adjusted to match the severity of brain injury, the benefits to a subgroup may be missed in a trial of one regimen of hypothermia for all comers.

One interpretation of these results is that they reinforce the importance of controlling temperature, even while they question whether 33°C is the best temperature. For example, many patients in the "normothermia" group of the older trials actually became hyperthermic,[4,5] which is deleterious.[9,10] The exceptional rates of good outcomes in both the 33°C and 36°C groups in the present trial may reflect the active prevention of hyperthermia. Whatever the mechanisms, it seems clear that we should not regress to a pre-2002 style of care that does not manage temperature at all.

Perhaps the most important message to take from this trial is that modern, aggressive care that includes attention to temperature works, making survival more likely than death when a patient is hospitalized after CPR. In contrast to a decade ago, one half instead of one third of patients with return of spontaneous circulation after CPR can expect to survive hospitalization. Few medical situations have enjoyed such absolute improvement over the same time period. Future studies can continue to refine protocols, define subgroups that benefit from individual therapies, and clarify how to best adjust temperature or other interventions to each patient's illness.

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

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