Therapeutic Hypothermia After In-Hospital Cardiac Arrest: A Critique

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More than 210,000 in-hospital cardiac arrests occur annually in the United States. Use of moderate therapeutic hypothermia (TH) in comatose survivors after return of spontaneous circulation following out-of-hospital cardiac arrest (OOH-CA) caused by ventricular fibrillation or pulseless ventricular tachycardia is recommended strongly by many professional organizations and societies. The use of TH after cardiac arrest associated with nonshockable rhythms and after in-hospital cardiac arrest (IH-CA) is recommended to be considered by these same organizations and is being applied widely. The use in these latter circumstances is based on an extrapolation of the data supporting its use after out-of-hospital cardiac arrest associated with shockable rhythms.

The purpose of this article is to review the limitations of existing data supporting these extended application of TH after cardiac arrest and to suggest approaches to this dilemma. The data supporting its use for OOH-CA appear to this author, and to some others, to be rather weak, and the data supporting the use of TH for IH-CA appear to be even weaker and to include no randomized controlled trials (RCTs) or supportive observational studies. The many reasons why TH might be expected to be less effective following IH-CA are reviewed. The degree of neurologic injury may be more severe in many of these cases and, thus, may not be responsive to TH as currently practiced following OOH-CA. The potential adverse consequences of the routine use of TH for IH-CA are listed and include complications associated with TH, interference with diagnostic and interventional therapy, and use of scarce personnel and financial resources. Most importantly, it inhibits the ability of researchers to conduct needed RCTs. The author believes that the proper method of providing TH in these cases needs to be better defined.

Based on this analysis the author concludes that TH should not be used indiscriminantly following most cases of IH-CA, and instead clinicians should concentrate their efforts in conducting high-quality large RCTs or large-scale, well-designed prospective observation studies to determine its benefits and identify appropriate candidates.

KEY WORDS: cardiac arrest, therapeutic hypothermia

IT IS ESTIMATED that more than 210,000 in-hospital (IH) cardiac arrests (CA) occur annually in the United States and the rate is increasing.[1] A study by the American Heart Association (AHA) Get with the Guidelines (GWTG)–Resuscitation Investigators of 84,625 in-hospital cardiac arrests in 553 hospitals between 2001 and 2009 reported that only 17% survived to discharge and of the survivors 32.8% had clinically significant neurologic disability and 10.8% had severe neurologic disability. In 79.2% the initial rhythm was nonshockable (ie, asystole or pulseless electrical activity [PEA]), and this percentage increased over the 10-year period. Survival was about one-third as high in patients with nonshockable rhythms (about 12% *v* 35%).[2] This has led to the search for methods of improving these terrible results and to early adoption of the use of therapeutic hypothermia (TH) for in-hospital cardiac arrest (IH-CA). One jury of experts representing 5 professional organizations has opined that the term "therapeutic hypothermia" should be discarded in favor of "targeted temperature management" (TTM)[3] although in this paper the former terminology will be used.

Starting in 2003 moderate therapeutic hypothermia (TH) has been recommended strongly by many professional organizations after return of spontaneous circulation (ROSC) for patients who remain comatose after out-of-hospital (OOH) cardiac arrest (CA) because of "shockable rhythms" (ventricular fibrillation [VF] or pulseless ventricular tachycardia [PVT]). These organizations include the International Liaison Committee on Resuscitation[4]; the European Resuscitation Council[5]; the International Consensus on Cardiopulmonary Resuscitation[6]; the American Heart Association (AHA)[7]; the National Institute for Health and Clinical Excellence (NICE; www.nice.org.uk/guidance/IP/863/overview); a combined jury of representatives of the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the Societe de Reanimation de Langue Francaise[3]; the Australian Resuscitation Council[8]; the Scandinavian Society of Anaesthesiology and Intensive Care Medicine[9]; and the Canadian Association of Emergency Physicians.[10] Many of these organizations also have recommended that TH *be considered* after resuscitation from other cardiac rhythms and after in-hospital cardiac arrest (IH-CA), which probably is responsible for the widespread use of TH after CA in circumstances beyond those employed in the initial 2 major randomized controlled trials (RCTs).

The use of TH after IH-CA is based on the laudable effort to improve its poor prognosis (death and poor neurologic function) and extrapolation of the data supporting its use after out-of-hospital cardiac arrest (OOH-CA). Unfortunately, as

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will be reviewed later, even that evidence is weak.[11–13] This author believes that the evidence does not support the widespread use of TH after IH-CA and that this recommendation needs to be reassessed. The purpose of this article is to identify the limitations of the existing data supporting the use of TH after CA, especially after IH-CA, which often is associated with nonshockable rhythms and of noncardiac etiology, and to suggest possible responses to this limited evidence.

What is this author's justification for challenging the recommendations of these many professional organizations? First, because their recommendations largely are based on low quality and low level of evidence and on expert opinion, and second, because this would not be the first time that guidelines generated by prestigious societies have been wrong. Some examples include prophylactic perioperative beta-blockers, prophylactic aprotinin to reduce bleeding after cardiac surgery, intensive insulin therapy, and use of activated protein C (Xigris™; Eli Lilly, Indianapolis, IN) in severe sepsis.

But if the evidence is weak, then why has the use of TH after cardiac arrest been adopted so rapidly and widely? This likely is due to at least 4 factors: The strong desire to do something to improve the poor outcome after resuscitation from cardiac arrest, the enthusiasm and strong conviction of many investigators, practitioner and hospital competition, and promotion by the "medical-industrial complex." Hospitals and practitioners have published articles in the lay press "advertising" and promoting their use of this modality, often accompanied by dramatically successful case reports, but exaggerating the scientific evidence of its benefit. This is known as "spin," which has been explored by Yavchitz et al.[14]

The scientific hypothesis underlying the use of TH is that postarrest ischemia-reperfusion results in further neurologic injury and cerebral edema[15,16] and that postischemic hypothermia may minimize these adverse effects.[16–23] Animal experimental data strongly support the benefits of prophylactic (ie, prearrest) hypothermia.[24] However, the animal data are weaker and conflicting regarding whether postarrest hypothermia is beneficial. Several animal studies have demonstrated benefit from hypothermia induced during or immediately after resuscitation and even when initiated as long as 1 to 6 hours postresuscitation; however, other animal studies indicate that a delay of implementation of only 15 to 30 minutes may minimize or eliminate any benefit,[25,26] although other studies are more encouraging.[27,28] Whether the results in normal animals are applicable to "sick" patients, often with vascular disease, is problematic, and, further, animal data are low on the pyramid of evidence used to support clinical care.

First, the clinical evidence that supports the use of TH after OOH-CA because of "shockable rhythms" must be examined. According to the AHA 2010 guidelines,[7] this recommendation is supported only by level B evidence consisting of 1 good RCT,[29] 1 pseudo-randomized trial,[30] and 2 studies with historical controls.[31,32] Walters et al[33] conducted a systematic review of the evidence supporting the use of TH after CA. They found 77 studies evaluating effects in humans: 40 were uncontrolled observational studies, 15 were nonrandomized trials using historic controls, and 9 were nonrandomized trials using concurrent controls. They found only 5 independent RCTs (and no more have been found since this study was published). Unfortunately, all 5 RCTs had some limitations. These included a relatively small number of patients randomized (275, 77, 54, 42, and 30); the studies varied regarding details, including cardiac arrest rhythms included, how and when the patients were cooled, the depth and duration of cooling, and the primary outcome examined. All had methodologic problems, all had substantial risk of bias, and in all the care teams obviously were unblinded.[33] The second largest RCT (77 patients) actually only employed pseudo-randomization, and another of the RCTs only was published as an abstract more than 12 years ago. There have been 6 meta-analyses that included data from some or all of these 5 RCTs.[33–38] Disturbingly, in 3 of these meta-analyses, 2 of their authors were investigators in the RCTs included in the meta-analyses.

The best and the largest RCT was a multicenter (9) European study from the Hypothermia After Cardiac Arrest (HACA) study group.[29] In this study 273 patients were randomized, and markedly better incidences of favorable neurologic outcome (55% *v* 39%, relative risk [RR] 1.4, number needed to treat [NNT] 6; $p = 0.009$) and favorable 6-month survival (deaths 41% *v* 55%, RR 0.74, NNT 7; $p = 0.02$) were observed in those receiving TH after witnessed out-of-hospital (predominantly) CA caused by a shockable rhythm. But even this study had significant limitations, as identified by Nielsen et al.[37] These included baseline differences between the groups, the fact that not all outcomes were reported, that the authors did not define the withdrawal policy (which was not standardized and, therefore, exposed the study to risk of bias), that the study was terminated prematurely without predefined criteria, that baseline coma was not reported, that it was highly selective in terms of patients included (only included 7% of those screened), and, finally, that the investigators did not limit hyperthermia in the control group. Between 8 and 36 hours after ROSC the average temperature in the control group was above 37°C, whereas the patients in the therapeutic group were hypothermic (Fig 1). A similar observation was noted in the retrospective observational study reported by Testori and colleagues[39] (Fig 2). This is particularly disturbing because animal studies[24] and several observational clinical studies have reported that even modest degrees of hyperthermia are associated with worse survival and neurologic outcome in victims of cardiac arrest.[40–45] In a prospective observational study of the neurologic outcome of 151 patients with ROSC after cardiac arrest, Zeiner and colleagues observed that 49% had favorable neurologic recovery at 6 months.[45] They reported that favorable recovery was associated with a lower highest temperature during the first 48 hours (37.7°C *v* 38.3°C). For each degree Celsius higher than 37°C the risk of unfavorable neurologic recovery increased, with an odds ratio of 2.6 times (95% CI 1.2-4.1)![45]

The other highly cited and next largest RCT (77 patients) supporting the use of TH was the Australian study reported by Bernard et al.[30] They observed a higher incidence of good neurologic outcome (49% *v* 26%, RR 1.85, NNT 4; $p = 0.046$) and a lower mortality at discharge (51% *v* 68%, RR 0.76, NNT 6; $p = 0.145$) in unresponsive patients receiving TH after return of spontaneous circulation (ROSC) after OOH-CA