The American Academy of Neurology affirms the revival of cooling for the revived

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It is estimated that a cardiac arrest occurs approximately every minute in the United States.[1] Beyond the mere return of spontaneous circulation (ROSC) and gross survival at discharge, good neurologic function with minimal disability is the goal for revived cardiac arrest patients. Partnering with the cardiology and emergency and critical care communities, neurologists helped implement therapeutic hypothermia (TH) and targeted temperature management (TTM), major breakthroughs in post–cardiac arrest care.[2] Mitigating secondary brain injury after cardiac arrest (BICA) with TH is supported by 2 landmark randomized controlled trials (RCTs); supporting evidence came from nonrandomized studies, large registries, indirect evidence from pediatric trials, and animal studies.[3] TH to 33°C became standard for out-of-hospital cardiac arrest with a shockable rhythm, later endorsed in the 2015 guidelines of the American Heart Association (AHA).[2] Many experts were more liberal, cooling patients with all arrest rhythms and in-hospital cardiac arrests.[3]

In 2013, an RCT for unconscious survivors of out-of-hospital cardiac arrest from any rhythm revealed no difference between TTM to 36°C and TH to 33°C,[4] prompting a switch from TH to TTM; many adopted a cavalier approach to TTM, cooling long after the cardiac arrest, or cooling solely to control fever. These practices are without evidence of similar effectiveness.[3] A 2017 study found that 36°C caused more difficult management, poor therapeutic adherence, and worsened outcomes.[5] Therefore, the vast majority of the neurology, emergency and critical care physicians, who continue to treat cardiac arrest patients with TH,[3] will welcome the American Academy of Neurology (AAN) guidelines on management of BICA published in this issue of *Neurology*®.[6] With a particular attention to neurologic endpoints beyond survival, the AAN panel of experts examined all neuroprotective interventions published from 1966 to August 2016.[6]

The AAN recommends TH to 33°C for out-of-hospital cardiac arrest due to shockable rhythms, TTM to 36°C as an "acceptable alternative" if the rhythm is either shockable or not (TH to 33°C is still recommended as a first approach); further, TH to 33°C "may be offered" in case of nonshockable rhythms, and finally TH to 32°C is possibly better than 34°C, even if there is a "lack of statistical precision."[6] Overall, this suggests that the lower (the temperature), the better. In contrast, the 2015 AHA guidelines still allowed a choice (even a range) between 32°C and 36°C.[2] The keen semantic nuances used in these AAN guidelines[6] send the correct message to the neurologic community (*Yes we cool!*) to prevent ongoing misinterpretation of the study by Nielsen at al.[3,4] This set of recommendations[6] clearly favors 33°C, but if the AAN guidelines left it as an equipoise between 33°C and 36°C, it would have equated 1 RCT (Nielsen at al.[4]), with the bulk of opposing evidence from numerous other studies, including other RCTs, before-and-after studies, and large registries.[3] Favoring TTM to 36°C may be ill-advised,[3] being a more difficult approach with inferior consequences on outcomes.[5] The study results of Nielsen at al.[4] may only mean that there is equipoise between 36°C and 33°C only if you get to target temperature late (8–12 hours) after the cardiac arrest; however, animal experiments suggest that neither TH nor TTM can be fully effective when applied so late after ROSC. Recent molecular data suggesting that rapid ultramild hypothermia at 36°C induces neuroprotective changes[7] should not be interpreted as promoting TTM to 36°C, because this flash 36°C needs to happen very promptly after ROSC, which can be better achieved if targeting 33°C. The generalizability to human care from molecular studies would require further study.

The guidelines also suggest that expanding criteria for hypothermia to all cardiac arrest settings (out-of-hospital and in-hospital cardiac arrests, witnessed and unwitnessed), and all rhythms, even with known sepsis and shock, is likely safe[8] and judicious.[3]

Looking at prehospital cooling, the AAN guidelines[6] could have been more precise and should have only recommended against the methods that have been proven to be potentially deleterious: 4°C fluid loads or intranasal cooling. It is premature to close

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the door on all methods of prehospital TH induction.

The AAN guidelines are inconclusive regarding the comparison of different cooling methods and protocol use,[6] but recent data suggest that intravascular cooling is associated with faster, better cooling, as compared to traditional techniques,[9] corroborating the clinical experience of many, who would share that it is easier (if counterintuitive) to maintain a patient at 33°C than at 36°C.[3,5,8,9]

The authors of these guidelines[6] deserve praise for being comprehensive and meticulous. They have carefully compared nuanced definitions for coma, for the nebulous endpoint of neurologic outcome, and listed trials for which withdrawal of life support was controlled. Heterogeneity of outcome measures highlights the need for common data elements in cardiac arrest studies. Furthermore, preferred statistical approaches including sliding dichotomous, ordinal (shift-analysis), or continuous analyses would be interesting to reevaluate the role of neuroprotective interventions.

We concur with the AAN experts that less is not more and cooling should be *harder, better, faster, stronger*, in the sense that neurologists should be hardliners who embrace cooling as a default mode for nearly all cardiac arrest survivors, making it harder to exclude patients, while using cooling techniques that are the better ones, starting as quickly as possible after ROSC, and that 33°C is stronger than 36°C.

Finally, we suggest that we should find different TTM methods tailored to diverse subgroups, with nuanced indications based on the clinical severity of the acute brain injury, taking into account the arrest rhythm and time to ROSC, and we should steward the cooling dose to cerebral parenchymal metabolic signatures[10] and neuroimaging measures. We hope that the speed, depth, and length of cooling and rewarming will soon be informed by physiologic processes, trended biomarkers, and EEG responses, gathered for goal-directed therapy,[10] culminating in evidence-based individualized precision cooling.

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DISCLOSURE

Dr. Kapinos reports that he is copyright owner of the "Advanced Neurological Life Support" training program, course and manual, a patent outline deposited at the US Library of Congress (11/20/2009); and was trademark owner of "Advanced Neurological Life Support (ANLS)," serial number 77-887,057, with intent to use the mark in commerce on or in connection with the identified goods and/or services (12/5/2009), but with subsequent abandon with no use in commerce. Dr. Kapinos has no financial ties to any thermal modulation devices or pharmaceutical companies. Dr. Becker reports that he has worked closely with the NIH as a reviewer and grantee, and in a leadership role as the Chair of the Myocardial Protection Working Group for the NIH NHLBI's sponsored PULSE Conference and PULSE Leadership Group, which is dedicated to support of funding in resuscitation research. He also served as a member of the Food and Drug Administration (FDA) Device Evaluation panels and has appeared as an expert presenter before the FDA panels. Dr. Becker has institutional grant support from Philips Medical Systems (Seattle, WA), NIH (Bethesda, MD), Zoll Medical Corp. (Boston, MA), and Nihon Kohden (Tokyo, Japan). Dr. Becker has received honoraria and payments for serving as an external scientific advisor to the NIH Data Safety Monitoring Board and Protocol Review Committee (Bethesda, MD), the NIH Resuscitation Outcomes Consortium (Bethesda, MD), the NIH New York Mount Sinai K12 Training Grant Scientific Advisory Board (New York), and Nihon Kohden (Tokyo, Japan). Dr. Becker holds patents involving hypothermia induction and reperfusion therapies and oxygen consumption measurements. Dr. Becker is a longstanding volunteer member of the American Heart Association (currently serving on several committees), which has a financial interest selling training materials worldwide on resuscitation techniques. Go to Neurology.org for full disclosures.

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