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Temperature Management After Cardiac Arrest
An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation☆

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ABSTRACT

For more than a decade, mild induced hypothermia (32 °C–34 °C) has been standard of care for patients remaining comatose after resuscitation from out-of-hospital cardiac arrest with an initial shockable rhythm, and this has been extrapolated to survivors of cardiac arrest with initially nonshockable rhythms and to patients with in-hospital cardiac arrest. Two randomized trials published in 2002 reported a survival and neurological benefit with mild induced hypothermia. One recent randomized trial reported similar outcomes in patients treated with targeted temperature management at either 33 °C or 36 °C. In response to these new data, the International Liaison Committee on Resuscitation Advanced Life Support Task Force performed a systematic review to evaluate 3 key questions: (1) Should mild induced hypothermia (or some form of targeted temperature management) be used in comatose post–cardiac arrest patients? (2) If used, what is the ideal timing of the intervention? (3) If used, what is the ideal duration of the intervention? The task force used Grading of Recommendations Assessment, Development and Evaluation methodology to assess and summarize the evidence and to provide a consensus on science statement and treatment recommendations. The task force recommends targeted temperature management for adults with out-of-hospital cardiac arrest with an initial shockable rhythm at a constant temperature between 32 °C and 36 °C for at least 24 hours. Similar suggestions are made for out-of-hospital cardiac arrest with a nonshockable rhythm and in-hospital cardiac arrest. The task force recommends against prehospital cooling with rapid infusion of large volumes of cold intravenous fluid. Additional and specific recommendations are provided in the document.

Sudden cardiac arrest is one of the leading causes of death in adults around the world. Although the incidence varies from country to country, cardiac arrest affects several million people annually, with an average survival rate of <10%.[1,2] In patients who remain comatose after cardiac arrest, the post–cardiac arrest syndrome is a complex set of pathophysiological processes consisting of brain injury, myocardial depression, and systemic ischemia/reperfusion injury, as well as ongoing injury caused by the precipitating cause of the arrest.[3]

For more than a decade, mild induced hypothermia (32 °C–34 °C) has been the cornerstone of post–cardiac arrest care. Mild to moderate hypothermia induced after global brain ischemia or cardiac arrest was initially evaluated in animal models that showed improved neurological function for those receiving induced hypothermia.[4–7] After 2 human randomized trials published in 2002,[8,9] the International Liaison Committee on Resuscitation (ILCOR) recommended in 2003 that "unconscious adult patients with spontaneous circulation after out-of-hospital

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cardiac arrest (OHCA) should be cooled to 32 °C to 34 °C for 12 to 24 hours when the initial rhythm was [ventricular fibrillation] VF" and that "such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest" (IHCA).[10] Similar recommendations were provided in the "2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations."[11]

Recently, a prospective, randomized trial comparing a targeted temperature of 33 °C with 36 °C for a large group of patients with OHCA found that both groups had similar mortality (primary end point) and neurological outcome at 180 days.[12] As a result of that trial, there has been debate about the optimal target temperature for post–cardiac arrest patients.[13,14] To address the evolving science of targeted temperature management (defined as an active therapy to achieve and maintain a specific target temperature for a defined duration), the ILCOR Advanced Life Support (ALS) Task Force conducted an evidence review and created an updated position paper to address 3 key questions about temperature management in the post–cardiac arrest patient:

1. For patients who remain comatose after return of spontaneous circulation (ROSC), should targeted temperature management be used?
2. If targeted temperature management is used, what is the optimal timing of initiation?
3. If targeted temperature management is used, what is the optimal duration of therapy?

To address these questions, the ALS Task Force created formal Population, Intervention, Comparison, and Outcome (PICO) questions and performed a comprehensive literature search.[15] The task force evaluated, compiled, and summarized the evidence by using Grading of Recommendations Assessment, Development and Evaluation (GRADE; www.gradeworkinggroup.org) methodology and performed meta-analyses when appropriate. The task force then created a consensus statement by considering the available evidence and balancing benefits and harms to guide the final recommendations.

Methods

Overview

We conducted a systematic review and, when appropriate, meta-analyses for 3 distinct questions about temperature management (outlined in the Questions Asked section). We completed a bias assessment for all included studies and then used GRADE methodology to evaluate this evidence and to develop treatment recommendations. The outcomes of interest were defined and prioritized by the ILCOR ALS Task Force as part of the evidence review process for the 2015 ILCOR guidelines.

Questions Asked

The literature searches were designed to address the following 3 PICO questions:

1. Among patients with ROSC after cardiac arrest in any setting (P), does inducing mild hypothermia (target temperature, 32 °C–34 °C; I) compared with no targeted temperature management (C) change survival with favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days, or 1 year or survival only at discharge, 30 days, 60 days, 180 days, or 1 year (O)?
2. Among patients with ROSC after cardiac arrest in any setting (P), does induction of hypothermia before some time point (eg, 1 hour after ROSC or before hospital arrival; I) compared with induction of hypothermia after that time point (C) change survival with favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days, or 1 year or survival only at discharge, 30 days, 60 days, 180 days, or 1 year (O)?
3. Among patients with ROSC after cardiac arrest in any setting (P), does induction and maintenance of hypothermia for any duration other than 24 hours (I) compared with induction and maintenance of hypothermia for a duration of 24 hours (C) change survival with favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days, or 1 year or survival only at discharge, 30 days, 60 days, 180 days, or 1 year (O)?

Selection of Studies

Information specialists searched PubMed, EMBASE, and the Cochrane Library in December 2013 (questions 2 and 3) and January 2014 (question 1) and again in December 2014 by using the search terms outlined in Appendix A in the online-only Data Supplement.

Data Selection and Extraction

Two reviewers independently screened titles and abstracts that resulted from the search for studies that addressed the question posed by each PICO. Inclusion criteria within each question were chosen on the basis of the amount and type of evidence available. The entire task force approved each set of criteria. Disagreement on individual studies was settled via consensus between the reviewers and a facilitator from the task force.

- Question 1: For patient populations in which randomized, controlled trials (RCTs) were available (ie, shockable OHCA), only RCTs were included. Otherwise, observational studies were included for the 2 patient populations in which there were no RCT data: IHCA and OHCA with an initial nonshockable rhythm. We did not include studies without a comparator group, studies that did not report separate outcomes for shockable and nonshockable rhythms, or studies that only reported unadjusted outcomes. We chose to exclude studies with a pre-post design because of the significant changes in post–cardiac arrest care over the past several years and the consequent danger of significant confounding based on year of arrest.
- Question 2: Only human RCTs were included. Given the number of human RCTs available for review, observational data were excluded.
- Question 3: Given the lack of human RCT data, all studies with a comparator group were included. Case reports/series were not included.

Studies published only in abstract form were excluded from all 3 questions because of the risk of incomplete reporting. There were no exclusions based on language. Articles were initially included on the basis of title or abstract. Subsequently, the text was reviewed to determine whether the article addressed the PICO question and whether all inclusion and no exclusion criteria were met. Inclusion of animal studies was beyond the scope of the present document, although we recognize that animal studies have and will continue to provide valuable preliminary and mechanistic data.

Bias Assessment and GRADE Methodology

All included RCTs were assessed for bias on the basis of criteria from the *Cochrane Handbook for Systematic Reviews of Interventions*.[16] Briefly, RCTs were assessed on the adequacy of allocation generation, allocation concealment, blinding of participants,