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Cardiac arrest and therapeutic hypothermia

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ABSTRACT

Therapeutic hypothermia for patients who remain comatose following resuscitation from a cardiac arrest improves both survival and neurologic outcomes. Although this therapy has been incorporated into the guidelines for routine post-resuscitation care and has been in clinical use for over a decade, significant questions and controversies remain. In this review, we discuss these questions in the context of the current evidence and provide a practical framework to help guide clinicians.

Key words: Cardiac arrest, therapeutic hypothermia, targeted temperature management.

Introduction

Each year roughly 420,000 people in the United States suffer an out-of-hospital (OH) cardiac arrest (CA), and only 10% of those individuals survive to hospital discharge [1]. Although the in-hospital rate of survival for individuals hospitalized following OHCA improved by nearly 12% from 2001 to 2009, the in-hospital mortality rate remains close to 60% [2]. Even after successful return of spontaneous circulation (ROSC) following an OHCA, approximately 80% of patients remain comatose [3] and the majority of deaths following ROSC are attributable to neurological injury [4]. Many of the individuals who do survive have a wide range of subsequent neurologic impairments [5]. Therapeutic hypothermia (TH) for individuals who remain comatose following successful ROSC after CA has the potential to reduce mortality and neurologic morbidity. TH, which is now part of post-resuscitation care recommendations, has had variable uptake in use and remains controversial in its implementation. This review will discuss the indications, timing, and methods for implementing TH, as well as the care of patients during TH.

Indications for TH

The American Heart Association (AHA), European Resuscitation Council, and the International Liaison Committee on Resuscitation all provide post-resuscitation guidelines and recommendations that support the use of TH in patients with ROSC who remain comatose after CA as summarized in the Table [6–8]. These recommendations were initially based on 2 randomized control trials published in 2002 demonstrating improved neurologic outcome with TH compared with standard post-resuscitative care in a combined total of 352 patients who remained comatose following ROSC after ventricular fibrillation (VF) arrest [9,10] with recently updated recommendations based predominantly on the large Targeted Temperature Management (TTM) trial [11].

The larger of the 2 initial trials randomized 275 individuals with ROSC after VF OHCA to either TH (target temperature 32–34°C) over 24 h versus standard treatment [9]. The hypothermia group had an increased rate of favorable neurologic outcome at 6 months (55% in the TH group versus 39% in the control group) as measured by the Pittsburgh

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Table – Guidelines and recommendations for the use of therapeutic hypothermia following cardiac arrest.

2015 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care [6]	Comatose (i.e., lack of meaningful response to verbal commands) adult patients with ROSC after out-of-hospital ventricular fibrillation or pulse-less ventricular tachycardia (pVT) cardiac arrest should undergo targeted temperature management (TTM) with goal temperature 32-36°C (89.6-96.8°F) for at least 24h (class I, level of evidence B). Comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electric activity or asystole should undergo targeted temperature management (TTM) with goal temperature 32-36°C (89.6-96.8°F) for at least 24 h (class I, level of evidence C).
2015 Recommendations from the International Liaison Committee on Resuscitation [7]	Targeted temperature management with goal temperature 32-36°C (89.6-96.8°F) for at least 24 h should be part of a standardized treatment strategy for comatose survivors of cardiac arrest.
2010 European Resuscitation Council Guidelines for Resuscitation [8]	Use of therapeutic hypothermia should include comatose survivors of cardiac arrest associated initially with non-shockable rhythms and shockable rhythms. (The lower level of evidence for use after cardiac arrest from non-shockable rhythms is acknowledged.)

cerebral-performance category (CPC) score of 1 or 2 of 5 possible categories; 1 (good recovery), 2 (moderate disability), 3 (severe disability), 4 (vegetative state), and 5 (death). The TH group also had a lower 6-month mortality rate (41%) as compared with the group not undergoing temperature management (55%).

The other initial trial evaluated 77 patients with ROSC following VF OHCA assigned by day of presentation to either TH (target temperature 33°C within 2 h of ROSC) over 12 h versus no temperature management [10]. Similar to the other trial, the TH group had a higher rate of favorable neurologic outcome (49%) versus the control group (26%). There was a non-significant trend toward lower mortality in the TH group (51% with TH versus 68% with control).

Based on the results from these initial 352 patients, the number needed to treat (NNT) with TH for favorable neurologic outcome is between 5 and 6. Similarly, the NNT for mortality is roughly 6 [12]. Importantly, there was no difference in the rate of complications between the TH and control group in either study. In response to the TTM trial, which demonstrated similar survival in two groups of active temperature management (33 versus 36 degrees), the AHA has recently updated its recommendations that patients who remain comatose after ROSC following a ventricular fibrillation or pulse-less VT OHCA should undergo TTM with goal temperature 32-36°C (89.6-96.8°F) for at least 24 h [6].

In contrast, there are limited data for patients who remain comatose following a non-shockable rhythm or who have an in-hospital (IH) CA. Furthermore, the data from observational cohorts have been mixed; with some studies demonstrating benefit of TH in non-shockable rhythms [13], whereas others have not [14,15]. For patients experiencing an IHCA, observational data have not demonstrated benefit from TH [16,17]; however the use of TH for inpatients post-ROSC following IHCA is infrequent, with less than 3% of these individuals undergoing TH, and with only 50% of those undergoing TH achieving goal temperature [17,18]. The AHA acknowledges the limited data for TH in these clinical scenarios, and currently recommends TTM in individuals with ROSC following OHCA with initial rhythm of pulseless electric activity or asystole as well as IHCA with any rhythm (Class I) [6]. The AHA strengthened its recommendation for TTM in this group because the writing group felt that the option for TTM at 36°C decreased theoretical concerns about adverse effects from TTM. Additionally, the high rate of neurologic morbidity in prior cohorts that did not use TTM also influenced the writing group's decision. Given the uncertain benefit of TH in these groups, the decision to initiate TH in patients with IHCA or with non-shockable rhythms is challenging, and this group of individuals has a worse prognosis compared to patients with a shockable rhythm CA. However, because the pathophysiology for neurologic injury following CA is similar regardless of rhythm or location of arrest, the decision to initiate TH should be made on an individual patient basis considering the etiology of the arrest, time before initiation of CPR, duration of CPR prior to ROSC, and overall prognosis based on underlying comorbidities.

Timing of TH initiation

In the initial randomized control trials demonstrating benefit with TH, target temperature was achieved within 4–8 h post-ROSC [9,10]. However, the optimal timing for TH initiation as well as the time to goal target temperature remains uncertain. Data from animal models suggest that a delay in initiation of cooling (as short as 15 min post-ROSC) attenuates the benefit seen with TH [19]. Thus far, the data regarding optimal timing in human studies are mixed. Overall, 3 observational studies found worse outcomes with delayed TH [20–22]. Mooney et al. [20] demonstrated that among individuals undergoing TH post-CA (both shockable and non-shockable rhythms) there was a 20% increase in mortality for every hour that initiation of TH was delayed. Wolff et al. [21] demonstrated that time to coldest temperature was an independent predictor of good neurologic outcome. Additionally, Chiota et al. [22] demonstrated that reaching target temperature within 6 h (early group) was associated with a greater likelihood of favorable neurologic outcome when compared with individuals reaching target temperature after 6 h (delayed group). In contrast, Haugk et al. [23] found that shorter time to target temperature was associated with unfavorable neurologic outcomes (median duration 158 min—unfavorable versus 209 min—favorable).