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What is the proper target temperature for out-of-hospital cardiac arrest?

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The implementation of target temperature management (TTM) or therapeutic hypothermia has been demonstrated in several major studies to be an effective neuroprotective strategy in post-resuscitation care after cardiac arrest. Although several landmark studies found the promising results of lower targeted temperature (32–34 °C) in terms of survival and neurological outcomes, recent evidence showed no difference in either survival or long-term neurological outcome when compared with higher targeted temperature (36 °C). Thus, recent data suggest that avoiding hyperpyrexia, rather than cooling "per se," may be considered the main therapeutic target to avoid secondary brain damage after out-of-hospital cardiac arrest. Many questions are still debated about the exact protocol of TTM to be used, including whether temperature control is more beneficial than standard of care without active temperature control, the optimal cooling temperature, patient selection, and duration of cooling. The aim of this review article was to discuss the physiology of hypothermia, available

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cooling methods, and current evidence about the optimal target temperature and timing of hypothermia.

Introduction

Cardiac arrest is associated with the highest mortality in critically ill patients admitted to intensive care unit (ICU), and different outcomes have been reported among different countries. In Europe, the overall incidence for all-rhythms out-of-hospital cardiac arrest (OHCA) is 37.7 per 100,000 person-year with very low survival of 10.7% [1]. In United States, over the years, survival rate increased from 5.7% in the reference period of 2005–2006 to 8.3% in 2012 [2]. The poor survival rate to hospital discharge encouraged physicians and researchers to find new therapeutic approaches and implement post-cardiac care bundles to improve survival as well as post-cardiac arrest neurological outcomes [3–5]. Early cardiopulmonary resuscitation (CPR) performed before early medical services (EMS) arrival is associated with a 30-day survival rate, and that was more than 2 times as compared with no CPR before EMS arrival [6,7]. Following the successful initial resuscitation, the irreversible neurological dysfunction is the most common causes of death. This damage occurred both during the cardiac arrest period and during the phase of reperfusion by the generation of free oxygen radical species and releasing of other mediators. Physiologic evidence in experimental studies showed that the reduction of brain temperature decreases cerebral blood flow, cerebral oxygen consumption, the release of free radical species, as well as cell membrane destruction, and it led to the design of large clinical studies in patients. Target temperature management (TTM) or therapeutic hypothermia (TH) has been demonstrated in several major studies to be an effective neuroprotective strategy in postresuscitation care. In 2002, two landmark randomized control trials (RCTs) were published, and they investigated the use of TH after OHCA with an apparent cardiac cause. These two trials demonstrated the survival benefit of 32–34 °C induced hypothermia for OHCA with initial shockable rhythms [8,9]. Since 2003, hypothermia was implemented as the standard therapy for the unconscious survivors of OHCA in the guidelines for advance life support [3,4,10]. Nevertheless, recent meta-analysis and trial sequential analysis by Nielsen et al. including five randomized trials showed the lack of strong evidence for a beneficial effect [11]. Possible beneficial effects of targeted temperature of 33 °C and 36 °C on mortality and neurological outcome were investigated in an RCT including 950 unconscious patients after OHCA due to presumed cardiac showing no clear differences between groups [12]. Recently, the term "mild TH or "therapeutic hypothermia" has been replaced by the term "targeted temperature management" to underline the significance of defining complete temperature profile and intentionally manipulating the body temperature. In spite of uncertainties of the rate of rewarming, the target population, and temperature, new data were not able to demonstrate a strong level of evidence supporting induced hypothermia. The aim of this review article was to discuss mechanisms of hypothermia, available cooling methods, and current evidence about the optimal target temperature and timing of hypothermia.

The mechanisms of hypothermia

In cardiac arrest patients, there are three different phases of injury, namely (1) intra-arrest ischemic injury during no flow state, (2) immediate reperfusion injury, and (3) delayed postreperfusion injury [13]. After return of spontaneous circulation (ROSC), the cascades of injury during intra-arrest ischemia are amplified. The reactive oxygen species production, mitochondrial calcium overload, as well as mitochondrial permeability transition triggering program cell death signaling are increased [10,13]. The late stage of reperfusion injury is associated with neuronal calcium overload, altered gene expression, and releases of inflammatory cytokines [14]. Hyperthermia following cardiac arrest is caused by the release of endogenous catecholamine, the alteration of distribution of body heat by vasoconstriction, and infection associated with the translocation of bacteria following global ischemia especially gut ischemia [15]. The mechanisms of hyperthermia associated with poor neurological