Novel Uses of Targeted Temperature Management

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KEYWORDS

• Targeted temperature management • Hypothermia • Cardiac arrest • Prognosis • Methodology • Therapeutic hypothermia

KEY POINTS

- Compared with out-of-hospital cardiac arrest with ventricular tachycardia/ventricular fibrillation (VT/VF) as the initial rhythm, there is less benefit for targeted temperature management (TTM) after in-hospital cardiac arrest and for an initial rhythm of pulseless electrical activity/asystole.
- TTM has emerging evidence as a therapeutic modality for the critically ill patient with ischemia-reperfusion injury, refractory intracranial hypertension, and systemic inflammation.
- Maintaining normothermia may be as effective as deeper cooling in TTM. In addition, there is debate about the most effective method of TTM application as well as the optimal parameters for TTM.
- TTM is safe to use in a highly monitored setting in an experienced center. There seems to be an increased risk of pneumonia with TTM use, but no increased risk of bleeding or arrhythmia.
- TTM delays the ability of caregivers to accurately prognosticate in the comatose patient after cardiac arrest. The best estimates of prognosis take into consideration several of the following: patient factors, the clinical neurologic examination, neuroimaging, biomarkers, somatosensory-evoked potentials, and electroencephalogram.

INTRODUCTION

Historical Context and Current Practice

Over the past 200 years, purposefully lowering the body's temperature to improve health outcomes has evolved from anecdote to experimental therapy to widespread implementation. One of the first descriptions of medical hypothermia was by Russians in 1803, who would bury an individual to the neck in snow while trying for return of spontaneous circulation (ROSC).[1] This process of intentionally lowering a patient's core body temperature came to be known as therapeutic hypothermia (TH). However, in 2011, a statement by 5 critical care societies found this term too vague, especially pertaining to appropriate temperature targets.[2] They reasoned that targeted temperature management (TTM) was a more specific term that emphasized the importance of protocols having 3 explicitly stated phases: induction, maintenance, and rewarming.

The first clinical trial of TTM in human cardiac arrest was by Benson and colleagues in 1959.[3] Despite finding a survival advantage of TTM, large-scale studies were not undertaken until the early 2000s, when 2 major prospective randomized

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controlled studies set the framework for modern application of TTM in out-of-hospital cardiac arrest (OHCA). The HACA (Hypothermia after Cardiac Arrest Study Group) reported a relative risk (RR) of 0.74 (95% confidence interval [CI]: 0.58–0.95) for mortality at 6 months after TTM to 32°C for 24 hours was applied for ventricular fibrillation (VF) arrest. The number needed to treat was 7 to save one life and 6 to achieve one favorable neurologic outcome.[4] A favorable neurologic outcome was defined as a 1 or 2 on the Pittsburgh Cerebral-Performance Category scale (**Box 1**).[5] This scale is the most used of the TTM outcomes literature. In the same issue of *New England Journal of Medicine*, Bernard and colleagues[6] found a higher likelihood of a good neurologic outcome defined as normal, mild, or moderate neurologic deficit, allowing discharge to home or short-term rehabilitation facility in the intervention group. These landmark studies changed how those with OHCA are managed and suggested that inducing moderate hypothermia could improve outcomes.

These 2 studies provided the evidence that led to the American Heart Association (AHA) rating TTM after VF OHCA for adults as a "class 1, level of evidence B" recommendation in 2010.[7] Perhaps in part helped by widespread adoption of post-cardiac arrest care that included TTM, OHCA outcomes have been improving. In 2014, the large CARES (Cardiac Arrest Registry to Enhance Survival) study reported an improvement in risk-adjusted survival in OHCA to hospital discharge from 5.7% in 2005 to 2006 to 7.2% in 2008 to 2009 and finally to 8.3% by 2012 to 2013, along with better neurologic outcomes of survivors.[8] In short, a patient with OHCA was 47% more likely to survive in 2011–2012 compared with 2005–2006.

Box 1
Cerebral performance category

Category	
1	Good cerebral performance • Conscious, independent on ADL, IADL • Work full time • Minor neurologic impairment
2	Moderate cerebral disability • Conscious, independent ADL, IADL • Work part time
3	Severe cerebral disability • Conscious but dependent on others for ADL, IADL
4	Coma/vegetative state • Unconscious, unaware of surroundings • No cognition
5	Brain death • Unconscious • Traditional criteria by certified practitioners

Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living.

Data from Blondin NA, Greer DM. Neurological prognosis in cardiac arrest patients treated with therapeutic hypothermia. Neurologist 2011;17:241–8.

Purpose of the Review

There are excellent comprehensive reviews on TTM.[9–11] The remainder of this review focuses on uncertainties intensivists face when making decisions regarding application of TTM to the adult patient other than for the class 1B application in OHCA. Selected landmark prospective randomized trials of TTM in these novel clinical situations are summarized in **Table 2**. The following clinical questions are addressed: Which patients might benefit from TTM? Which modality is best? At what temperature and for what duration should TTM be applied? What are the adverse events related to TTM and how can one monitor for them or prevent these complications? These questions are addressed in the context of emerging TTM evidence.

Targeted Temperature Management Mechanisms of Cellular Protection

Neurologic injury during cardiac arrest is a well-studied paradigm of ischemia-reperfusion injury. Classically described are 3 phases. Initially, lack of tissue perfusion results in primary cellular energy failure wherein anaerobic metabolism predominates, membrane potentials are lost, intracellular calcium accumulates, and excitatory neurotransmitters become abundant.[12] During the second phase (after ROSC), there is reperfusion injury. Here, injured, swollen mitochondria produce reactive oxygen species that cause direct cellular damage and activate pro-apoptotic pathways and intracellular proteases. During a delayed third phase, a pro-inflammatory state causes secondary cell injury.[10–12]

During ischemia-reperfusion, TTM reduces injury through multiple mechanisms. For every 1°C temperature drop, cerebral metabolism reduces 6%