Targeted Temperature Management After Cardiac Arrest

Position Statement of the Hong Kong Society of Critical Care Medicine

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Definition[1,2]

Elevated temperature is common after cardiac arrest and is associated with a worse prognosis, but this can be improved by accurate, active temperature control. Reflecting that a variety of temperature targets are now used, the term targeted temperature management (TTM) has been adopted to refer to induced hypothermia as well as to active control of temperature at any target. It is an active treatment that tries to achieve and maintain a specific body temperature in a person for a specific duration of time. It is often used in neurocritical care to minimise secondary neurologic injury and improve outcome.

Recommendations on the use of TTM after cardiac arrest[3-8]

Initiation

It is recommended selecting and maintaining a constant temperature between 32°C and 36°C during TTM (strong recommendation, moderate-quality evidence). It should be started as soon as possible after ROSC[9].

From a recent systemic review published in 2021, mild (35-36°C), moderate (33-34°C), or deep hypothermia (31-32°C) may not improve survival or functional outcome after OHCA, as compared to normothermia (37-37.8°C). Moderate and deep hypothermia were associated with higher incidence of arrhythmia. Routine use of moderate or deep hypothermia in comatose survivors of OHCA may potentially be associated with more harm than benefit[10].

Specific features of the patient may favour selection of one temperature over another for TTM. Higher temperatures might be preferred in patients for whom lower temperatures convey some risks (e.g., patients with mild brain injury, higher bleeding risk, trauma, recent surgery as higher temperature lower the risk of bleeding, arrhythmia and electrolyte disturbance), and lower temperatures might be preferred when patients have clinical features that are worsened at higher temperatures (e.g., patients with stroke, severe brain injury or hepatic encephalopathy as greater degree of hypothermia may help reduce seizures and cerebral edema).

TTM is recommended for adults after either OHCA or IHCA (with any initial rhythm) who remain unresponsive after ROSC[5].

TTM should be initiated as soon as possible after ROSC.

Maintenance

It is suggested that if targeted temperature management is use, duration should be at least 24 hours, as in the 2 largest previous RCTs (weak recommendation, very low-quality evidence)[11,12].

Rewarming
It is suggested to rewarm gradually at a rate not faster than 0.25-0.5°C per hour until normothermia[11,13], as rapid rewarming has been associated with complications, including hypotension, electrolyte changes and dysrhythmias.
Actively or rapidly warming patients is not suggested.

Fever prevention
It is reasonable to actively prevent fever (>37.7°C) for at least 72 hours after ROSC in patients who remain in coma (weak recommendation, very low-quality evidence)[5].

Optimal temperature measurement site[2]
Patient undergoing TTM should have their core temperature continuously or frequently monitored by rectal, oesophageal, bladder or pulmonary artery temperature. The device must be designed to measure temperatures in the targeted temperature range. Axillary or tympanic membrane measurements should not be used since they do not adequately measure core temperature.

Pregnancy population
Targeted temperature management should be considered in pregnancy on an individual basis (Class IIb; Level of Evidence C)[14].

Mechanism of Action of TTM

Induced hypothermia decreases the metabolic rate by 6-7% for every 1°C decrease in temperature, hence improved the oxygen supply and reduces oxygen consumption in the ischaemic brain. There are three phases of cerebral injury after hypoxic insult: early, intermediate, and late. Besides, therapeutic hypothermia is considered to be neuroprotective by acting at each of the three stages of injury.

Cardiac arrest immediately decreases cerebral blood flow despite ongoing consumption of oxygen, ATP, and glucose. In this early stage, hypothermia decreases energy utilization, consumption of oxygen, and glucose.

The intermediate or latent phase occurs in the hours post-arrest. Excitatory amino acids and glutamate are released in the brain, activating cytotoxic cascades including free radicals and nitric oxide. Hypothermia decreases the release of excitatory amino acids and other neurotoxic mediators. Cooling lessens nitric oxide production and delays the peak of nitric oxide.

The latent phase of cerebral injury can occur up to 24 hours after cardiac arrest. At this stage, the blood-brain barrier breaks down and cerebral edema worsens; seizures and neuronal death may occur. Hypothermia slows the deterioration of the blood-brain barrier and decrease cerebral edema.

Background and scientific evidence

Induction of moderate hypothermia (28-32°C) has been successfully used since 1950s to protect the brain against global ischemia that occurs during some open heart surgeries.

In animal studies, induction of hypothermia after return of spontaneous circulation (ROSC) has been associated with improved functional recovery and reduced cerebral histological deficits.

In 2002, two prospective randomized clinical trials[11,15] were published that found therapeutic hypothermia (TH) to be effective in reducing the risk of neurological disability in patients with out-of-hospital cardiac arrest (OHCA) due to an initial shockable rhythm who were comatose post-arrest[11,15]. In summary, therapeutic hypothermia reduced mortality by 41% and increase functional survivors by 55%. These trials led to a rapid adoption of TH into clinical practice. Major limitations of the studies included a small patient population (a total of 352 patients) and temperature in the control arm was not actively managed. Moreover, treatment was not blinded and protocols for neuro-prognostication were not standardised.

In 2003 the American Heart Association[16] recommended that unconscious adult patients with spontaneous circulation after an out-of-hospital cardiac arrest should be cooled to 32-34°C for 12-24 hours when the initial rhythm was Ventricular Fibrillation (VF). Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest (IHCA).

The Targeted Temperature Management (TTM) trial[12] in 2013 randomised 950 subjects with an OHCA with a presumed cardiac cause to two different temperature targets: 33°C versus 36°C, with active temperature management in both groups. No significant difference in mortality (50% vs. 48%; P=0.51), or a composite of mortality and poor neurological outcome at 6 months (54% vs. 52%; P=0.78). It was to note that the body temperature was actively managed in both treatment arms using similar cooling techniques and the study did not compare "no cooling" with active cooling.

In 2015 the American Heart Association[4] recommended TTM for adults with OHCA with an initial shockable rhythm at a constant temperature between 32°C and 36°C for at least 24 hours. Similar suggestions were made for OHCA with a non-shockable rhythm and IHCA.

The HYPERION trial[17] in 2019 randomised 581 subjects with an OHCA and IHCA with non-shockable rhythms to two different temperature targets: 33ºC versus normothermia of 37.5°C. The trial found a significant benefit in favour of 33°C for the primary end point of 90-day survival with a favourable neurological outcome (10.2% vs. 5.7%; 95% [CI], 0.1 to 8.9, p= 0.04), but no difference in overall mortality.

The TTM-2 trial[18] in 2021 randomised 1861 subjects with an OHCA with a presumed cardiac cause to TH of 33°C versus targeted normothermia with early treatment of fever (goal temperature: <37.5°C). Overall, there was no difference in survival at 6 months (50% vs. 48%, P=0.37) and no difference in survival with severe disability on the modified Rankin Scale (55% vs. 55%; RR 1.00; 95% CI, 0.92-1.09). Arrhythmia resulting in hemodynamic compromise was more common in the hypothermia group than in the normothermia group (24% vs. 17%, P=<0.001). However, it should be noted that the "normothermic" arm required use of sedation for 40 h in all patients and active temperature management (i.e., cooling devices with temperature-feedback control; relatively slow rewarming and avoidance of fever for 72 h) in almost 50% of them.

Who is going to benefit from TTM?

- Age above 18
- TTM is recommended for selected adults after either OHCA or IHCA (with any initial rhythm) who remain unresponsive after ROSC[5]
- Extracorporeal cardiopulmonary resuscitation (commonly known as ECPR)

Who should not get TTM?

- Coma unrelated to arrest e.g. head trauma, hypovolemic shock, stroke or sepsis
- Patient's condition not suitable for TTM e.g. documented intracranial hemorrhage, severe hemorrhage leading to exsanguination, hypotension refractory to multiple vasopressors and severe sepsis[19]
- Exclusion to ICU admission
- Pre-existing illness that precludes meaningful recovery
- Known limitation of therapy or Do Not Resuscitate status
- Pregnancy (may need to discuss on case-to-case basis)
- Rapid neurological recovery

How to apply TTM?

Methods: Combination of methods could be used to achieve the goal. Example: Ice Packs, Cooling Mattresses, Cooling Blanket, Intra-vascular cooling catheter, Ice cold IV Saline. Temperature control can be achieved by exposing the patient, using anti-pyretic drugs, or if this is insufficient, by using a cooling device with a target temperature set[8]. There is insufficient evidence to recommend one cooling modality over another[20]

Monitoring: Routine monitoring plus continuous temperature monitoring and monitor for shivering. Neuromuscular blockade may be used if shivering continues

What are the potential side effects during TTM[13]?

- Cardiovascular: e.g. hypotension and bradycardia/arrhythmias, patient may require rewarming, pacing +/- pressors
- Shivering: it should be recognised and controlled early, as it increases metabolic demand and prevents or delays achievement of target temperatures. Sedation and analgesia +/- paralytic agents may help to reduce shivering.
- Infections: pneumonia and sepsis have been found to be increased during hypothermia, and recognition of fever is not possible owing to the active cooling process.
- Endocrine effect: hypothermia decreases insulin secretion and increases insulin resistance, causing hyperglycaemia in patients receiving TTM. The glucose level can fall precipitously during rewarming.
- Renal: electrolyte shifts (namely Phos, Mag, Ca, K) during cooling and rewarming. Close monitoring of electrolytes during TTM is crucial.
- Gastrointestinal: GI motility is reduced during TTM and there may be an increased likelihood of stress ulcers.
- Haematological: platelet counts, platelet function and other clotting factors of the patient can be affected by hypothermia. Consider stopping TTM if there is uncontrolled bleeding.
- Pharmacological: drug metabolism is impaired during hypothermia owing to reduced hepatic clearance, and the effects may be prolonged.
- Hyperthermia: it should be prevented for at least 72 hours after rewarming.
- Peripheral complications: direct cold injury and peripheral vasoconstriction leading to skin necrosis, gangrene of digits/ limbs and infections.

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