Dozens of observational studies published over the past 2 decades have shown that fever in patients with acute neurological injury, regardless of its cause, is independently linked to higher mortality, poor neurological outcome, and increased length of stay in the intensive care unit and hospital. This has been demonstrated for traumatic brain injury, acute ischemic stroke, subarachnoid hemorrhage, intracranial hemorrhage, and cardiac arrest (CA). Therefore, therapeutic temperature management is a key goal of care in all patients with acute brain injury. In most cases the goal is strict fever control, ie, controlled normothermia; in patients with hypoxic injuries, the goal is often to achieve below-normal core temperature, ie, to induce therapeutic hypothermia.

Therapeutic hypothermia has been studied extensively in newborns with neonatal asphyxia and in adults with hypoxic injury following witnessed CA. A “heated” debate is currently going on regarding optimal target temperature after CA. Current guidelines recommend 32°C to 34°C, based on numerous before-after studies, and indirect evidence from 7 multicenter RCTs in perinatal asphyxia. A small RCT published in 2012 comparing 2 temperature regimens after witnessed CA reported significantly better outcomes with 32.0°C in comparison with 33.0°C. The conclusions of this study have been criticized by various authors (including the undersigned) for problems such as potential selection bias, prolonged time (10 hours) to target temperature, temperature fluctuations during the maintenance phase, excessively rapid rewarming, and other issues. This topic continues to be debated; however, although there is disagreement on the optimal temperature (32, 33, or 36°C), there is general consensus on the importance of temperature management after CA per se.

In this regard, the efficacy of temperature control devices is becoming increasingly important. Attempts to lower or maintain temperature by using external or internal cooling methods will be complicated by vigorous countermeasures, ie, attempts by the patient’s body to raise core temperature through various mechanisms. Of note, these warming mechanisms tend to be more active when the aim is to control fever or to maintain very mild (36.0°C) hypothermia than is the case when the patient is hypothermic (see below). Temperature can be increased by conserving heat (mainly through vasoconstriction of arteries in the skin) and by generating heat (mainly through shivering). Under normal circumstances, vasoconstriction begins at a core temperature of around 36.5°C; the reduction in heat loss resulting from cutaneous vasoconstriction is ±25%. Heat generation through shivering is usually much more active, and therefore more effective, at temperatures close to the normal range than at temperatures that are several degrees below normal. In patients with a normal hypothalamic set point the shivering threshold is ±1°C below the vasoconstriction threshold, so ±35.5°C. The shivering response peaks at core temperatures ≈35°C, and decreases significantly at temperatures <33.5°C to 34°C; in most patients, shivering ceases completely at core temperatures ≈31°C, although there is a wide variability between patients, and even within the same patient if and when the hypothalamic set point changes (see below).

Shivering can cause multiple problems in patient management. Sustained shivering can double the metabolic rate, thereby preventing effective temperature management. In addition, it significantly increases oxygen consumption (by 40%–100%), the work of breathing, and heart rate; it induces a stresslike response with tachycardia, hypertension, and elevated intracranial pressure; and it has been linked to an increased risk of morbid cardiac events and adverse outcome in the perioperative setting. Therefore, shivering should be aggressively and preemptively controlled, and shivering management should be an integral part of the temperature management strategy. Some common antishivering measures are listed in the Figure.

Thus, whether the aim is fever control or hypothermia, the physiological defenses of the body have to be overcome; and, as explained above, these defenses are generally most active at temperatures ≥2°C below the hypothalamic set point (1°C below the skin vasoconstriction threshold). Of note, febrile patients with acute brain injury are likely to have an elevated hypothalamic set point. The cause of hyperthermia very often is so-called central fever, which is a direct consequence of the brain injury itself. However, brain-injured patients are also at a very high risk for infections; this applies to all types of brain injury, including posthypoxic injury after CA. Apart from the risk of complications such as aspiration pneumonia
Figure. A (adapted from11). Temperature management with set target of 32°C. For the induction phase, the aim is to get temperature to <34°C and down to the target temperature as quickly as possible. A small overshoot (≤1°C) should be regarded as acceptable provided temperature remains >30°C. For the maintenance phase, the target is tight control of core temperature, with minimal fluctuations (ideally never >0.3°C). The rewarming phase should be slow and controlled (warming rate 0.2°C–0.25°C/h).

B. Temperature management with set target of 36°C. For the induction phase, the aim is to get the temperature to 36.0°C as quickly as possible. For the maintenance phase, the target is tight control of core temperature, with minimal fluctuations (ideally never >0.2–0.3°C). More shivering is likely, because the target temperature is closer to normal, leading to an enhanced shivering response. There is greater risk of slipping into a supranormal (febrile) temperature range, especially because brain temperature exceeds core temperature by 1.0°C to 2.0°C at this temperature. temp indicates temperature; and TTM, therapeutic temperature management.
Whatever the cause, the result is that the temperature set point combination of both, either simultaneously or sequentially.

The effectiveness of heat conservation and heat generation decreases with age; this is attributable to a less effective vascular response (ie, less vasoconstriction), decreased ability to detect small temperature changes (leading to a slower counter-regulatory response), and a lower basal metabolic rate. This means that, in general, fever control and the induction of hypothermia are easier to achieve and maintain in older patients is elevated, triggering the body’s mechanisms to increase core temperature, and that the patient develops fever.

### Basic Information on Cooling Methods and Devices Commonly Used or Discussed in the Literature

<table>
<thead>
<tr>
<th>Method</th>
<th>Description and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface cooling: air</td>
<td>Easy, inexpensive. Skin exposure without water/alcohol sprays: induction speed = 0.5°C/h. With water/alcohol sprays (alcohol sprays more effective); induction speed = 1.0°C/h. Advantage: easy, cheap. Disadvantage: labor intensive; not reliable for maintenance; cannot be used for rewarming.</td>
</tr>
<tr>
<td>Cooling fans</td>
<td>Induction speed = 1.0°C/h. Advantages: easy, inexpensive. Disadvantages: not reliable for maintenance; cannot be used for rewarming; possible increase in infection risk.</td>
</tr>
<tr>
<td>Air-circulating cooling blankets (Polar Air and Bair Hugger)</td>
<td>Should not be used for cooling, only for skin counterwarming. Even at lowest temperature setting the induction speed is no higher than simple skin exposure (=0.5°C/h).</td>
</tr>
<tr>
<td>Air cooling bed (Deltatherm)</td>
<td>Cooling rates = 1°C/h. Used for the HACA trial; no longer commercially available.</td>
</tr>
<tr>
<td>Ice packs</td>
<td>Induction speed = 1°C/h. Advantages: easy, inexpensive. Downsides: risk of skin lesions and burns; not reliable for maintenance; cannot be used for controlled rewarming.</td>
</tr>
<tr>
<td>Immersion in ice-cold water</td>
<td>Induction speed = 3°C/h–10°C/h. Advantage: fast, inexpensive. Disadvantages: uncomfortable, impractical, cannot be used for reliable maintenance or controlled rewarming.</td>
</tr>
<tr>
<td>Continuous cold water spraying/immersion device (LRS ThermoSuit system)</td>
<td>Induction rate = 3°C/h. Advantage: relatively fast. Disadvantages: potentially uncomfortable, cannot be used for reliable maintenance or controlled rewarming.</td>
</tr>
<tr>
<td>Pre-refrigerated cooling pads</td>
<td>Pads precooled in a freezer, then used for surface cooling. Cooling activity ≤ 2 h. Few clinical data available. Advantage: ease of use, potentially more effective than ice packs, lower risk of skin burns. Downsides: not reliable for maintenance; cannot be used for rewarming. Theoretical risk of skin injury.</td>
</tr>
<tr>
<td>Surface cooling: water-circulating blankets and pads</td>
<td>Induction rate = 1.0°C–1.5°C/h. Advantages: reusable, significantly lower costs compared to other devices. Disadvantages: relatively labor-intensive during induction; potential contamination issues (reusable).</td>
</tr>
<tr>
<td>Blanketroll II</td>
<td>Induction rate = 1.5°C/h. Advantages: targeted neck cooling possible; inexpensive in comparison with other disposable devices. Disadvantages: less cooling capacity than some other devices.</td>
</tr>
<tr>
<td>Blanketroll III, CoolBlue, CritiCool, and CureWrap</td>
<td>Hydrogel-coated water-circulating pads. Induction rate = 1.5°C–2.0°C/h. Advantages: high cooling capacity, user friendly, less labor intensive than water-circulating blankets; less surface area required for cooling. Disadvantages: slight risk of skin lesions if used at maximum setting; higher costs than other systems.</td>
</tr>
<tr>
<td>Arctic Sun</td>
<td>Hydrogel-coated water-circulating pads. Induction rate = 1.5°C–2.0°C/h. Advantages: high cooling capacity, user friendly, less labor intensive than water-circulating blankets; less surface area required for cooling. Disadvantages: slight risk of skin lesions if used at maximum setting; higher costs than other systems.</td>
</tr>
<tr>
<td>Invasive cooling: endovascular</td>
<td>Quattro, Icy, Solex, and CoolLine, catheters; Innercool standard and Accutrol catheters</td>
</tr>
<tr>
<td>Fortius</td>
<td>Large bore catheter for very rapid TH induction. Induction rate = 5°C–10°C. Limited experience so far (although the precursor of this catheter type, the Reprieve, was marketed for several years and used in clinical trials for AMI). Disadvantages: invasive procedure required for placement; very large size, not for prolonged temperature control.</td>
</tr>
<tr>
<td>Velomedix Automated Peritoneal Lavage System (APLS)</td>
<td>Continuous circulation of refrigerated fluid in the peritoneal cavity. Induction rate = 5°C–9°C/1h (awake nonintubated patients) = 14.0°C/1h in CA patients. Reliable maintenance and rewarming. Limited data available, manufacturing company went bankrupt, so not commercially available. Invasive procedure required for placement.</td>
</tr>
<tr>
<td>Extracorporeal circulation, ECMO</td>
<td>extracorporeal membrane oxygenation; HACA, Hypothermia after Cardiac Arrest; NSAID, nonsteroidal anti-inflammatory drug; and TH, therapeutic hypothermia.</td>
</tr>
<tr>
<td>CWH, Antipyretic circulation (acetaminophen, aspirin, NSAIDs, others)</td>
<td>Fever control only, cannot be used for TH induction (including 36.0°C). Average temperature decrease 0.3°C–0.7°C. Usually less effective for central fever, more effective for infectious fever.</td>
</tr>
</tbody>
</table>

AM1 indicates acute myocardial infarction; CA, cardiac arrest; CVVH, continuous venovenous hemofiltration; ECMO, extracorporeal membrane oxygenation; HACA, Hypothermia after Cardiac Arrest; NSAID, nonsteroidal anti-inflammatory drug; and TH, therapeutic hypothermia.
than in younger ones. In addition, the doses of opiates and sedatives required to effectively suppress the body’s warming mechanisms are usually much higher in younger patients.

Another important parameter affecting ease and speed of cooling is body mass; obese patients are more difficult to cool, especially with surface cooling, because of the insulating properties of adipose tissue and the greater mass that needs to be cooled.

Finally, an issue that often confounds studies dealing with efficacy of temperature management is that severe brain injury can significantly diminish or even obviate the thermoregulatory response; it is therefore much easier to cool patients with very severe brain injury (and absent shivering response) than those with less severe injury. Thus, easy temperature control is, paradoxically, often a poor prognostic sign, whereas increased workload of cooling devices predicts better neurological outcome.11,15

These issues have complicated trials assessing the importance of early and rapid cooling, and studies on the efficacy of different cooling technologies, as well. These technologies can be broadly divided into invasive (core cooling) and noninvasive (surface cooling) methods (Table). Figure depicts optimal central temperature control for a target of 32.0°C (Figure A) and a target of 36.0°C (Figure B), respectively.

The (theoretical) advantages of invasive cooling over surface cooling are as follows:

1. Some studies suggest greater speed of hypothermia/nor-mothermia induction when core cooling is used; however, it is unclear whether more rapid induction improves outcome.
2. Possibly, endovascular cooling has fewer and smaller temperature fluctuations in the maintenance phase (Figure A and B).
3. Some types of endovascular catheter allow continuous central (blood) temperature measurement.
4. No risk of surface cooling-induced skin lesions.
5. Patient easily accessible, ie, no need to cover large areas of the skin to achieve cooling.
6. Less medication may be needed to control shivering because there is more effective shivering suppression with skin counterwarming (ie, the entire surface area can be warmed using warm air, leading to a significantly diminished shivering response).11,12,16 In a related issue, there may be better tolerance/less shivering with endovascular cooling when therapeutic hypothermia is used in awake, nonintubated patients (eg, for treatment of acute ischemic stroke, or acute myocardial infarction to reduce infarct size).

The theoretical advantages of surface cooling over invasive cooling are as follows:

1. Ease of use; can be applied by nurses without a physician being present.
2. No invasive procedure required; therefore, no risk of mechanical complications.
3. Can be started immediately, without waiting for a catheter insertion procedure, so potentially less delay in the initiation of cooling.
4. No risk of catheter-induced thrombus formation.
5. Can be more easily applied outside the intensive care unit setting.
6. Combines better with infusion of refrigerated fluids (because this allows simultaneous cooling of both the core compartment and peripheral compartment of the body).

The available data on safety and efficacy of different cooling technologies are limited.11 Most published studies were small and have evaluated only a single cooling device or method; comparative studies were mostly retrospective or nonrandomized, or have enrolled only small numbers of patients.11 Some had methodological flaws, or noncomparable study groups. None have found statistically significant differences in patient outcomes between different cooling technologies, although some have reported trends in favor of invasive cooling.11,17,18 Of note, 1 study reported that therapeutic hypothermia in CA patients could be induced and maintained with low-technology methods (refrigerated fluids and ice packs) only, without cooling devices, and that outcomes were comparable to studies using more sophisticated cooling technology.19 However, controlling temperature in this way significantly increases nursing workload, and it is difficult to prevent temperature variation during the maintenance phase and to effectively control rewarming.11

Now there is compelling new evidence on this issue from a study by Deye and coworkers,20 who compared endovascular with surface cooling in a prospective, multicenter RCT, the results of which are published in this issue of Circulation. The authors enrolled 400 patients; 203 were treated with endovascular cooling (using Zoll femoral Icy catheters) and 197 were treated with external cooling (ice packs, fans, and a homemade tent). The main findings were as follows: significantly shorter time to target temperature (33.0°C), greater stability of temperature (defined as time within target ±1°C) in the maintenance phase, and reduced nursing workload (10 versus 38 minutes, \( P<0.001 \)) in the endovascular group; more minor side effects (likely attributable to more effective cooling) in the endovascular group (\( P=0.009 \)); a nonsignificant trend toward more favorable outcome at 28 days (36.0 versus 28.4%, odds ratio 1.41 [0.93–2.16], \( P=0.107 \); for shockable rhythm 53.7% versus 37.1%, odds ratio 1.97 [0.99–3.9], \( P=0.269 \)) and at 90 days (34.6% versus 26.0%, odds ratio 1.51 [0.96–2.35], \( P=0.07 \)) in the endovascular group; and fewer cases of severe overshoot (below 30°C) in the endovascular group (\( n=0 \) versus \( n=3 \)).20 Of note, strict fever control was maintained for a minimum of 3 days following rewarming in both groups.

This is the first major study to directly compare the 2 fundamental cooling methodologies, ie, surface versus core cooling, in a prospective RCT; the authors are to be congratulated. Their study has some limitations, especially the fact that newer and more powerful surface-cooling devices such as the Arctic Sun system were not used; surface cooling was accomplished by using fairly basic tools and devices. Other water-circulating blankets such as the Meditherm and Blanketrol systems (Table) were also not evaluated. In addition, at 90 days, a significant number of patients (18% in the endovascular and 34% in the surface-cooling group) had been lost to follow-up; if all patients could have been followed, the differences might well
have reached statistical significance. Another potential weakness of the study is that shivering management strategies were not well defined.

Nevertheless, the study addresses important clinical questions. The results show that better temperature control can be achieved by using modern cooling technologies, and that this was associated with a clear trend to better neurological outcomes, although the numbers did not reach statistical significance. The numbers are similar to those reported in a fairly large (167 patients) retrospective study from Norway, where survival with good neurological outcome was 38% (surface cooling) versus 45% (core cooling), \( P=0.345 \). Similarly, a retrospective study using a Korean registry for CA patients compared 559 patients cooled with surface-cooling devices (including Blanketrol, MediTherm, and Arctic Sun) with 244 patients cooled with endovascular catheters; good neurological outcome was 23.6% for surface cooling versus 35.4% for endovascular cooling (\( P=0.01 \)). However, the groups were not well matched; after propensity score matching in 360 patients (180 in each group), rates of favorable neurological outcome were 30% for surface cooling versus 35% for endovascular cooling (\( P=0.31 \)). As in the study by Deye et al, the risk of overcooling was greater in the surface-cooling group (17.8% versus 7.8%, \( P=0.01 \) after propensity score matching). There was also a higher risk of rebound hyperthermia (13.5% versus 5.9%, \( P=0.02 \)) and other adverse events during rewarming in patients treated with surface cooling.18

When these studies and the robust prospective trial by Deye et al are examined, the data suggest (although they do not conclusively prove) that a quicker induction with less overshoot and (probably of greater importance) more stable temperature maintenance and better control during rewarming may improve neurological outcomes. Although the outcome data did not reach statistical significance, the technical data on cooling success are clinically relevant, and potentially useful to clinicians seeking information on the efficacy of cooling technologies (and on temperature management without using a cooling device), regardless of which temperature is targeted.

The side effects of both cooling strategies were closely monitored in the study by Deye et al, and these were relatively minor. Of note, the number of deaths related to therapeutic hypothermia was zero, again underlining the safety of therapeutic temperature management. Patients were not systematically screened for catheter-related thrombosis, but no patient developed clinical signs of thrombosis that would have triggered an evaluation.

Precision of temperature control may become even more important if centers decide to switch target temperature following CA from 32°C, 33°C or 34°C to 36.0°C, based on the findings in the Nielsen trial.7 The reason for this is that at a core temperature of 36.0°C, an increase in temperature of 1.5°C attributable to (for example) a shivering episode would immediately put the patient in febrile territory. Moreover, in patients with acute brain injury and a normal core temperature, brain temperature typically exceeds core temperature by 1.0°C to 2.0°C, with even higher temperatures in injured areas of the brain.2,11,12 Therefore, even a small increase in core temperature >36.0°C would immediately lead to brain hyperthermia. In contrast, at a core temperature of 32.0°C brain temperature usually equals core temperature,11,12 after a 1.5°C increase in core temperature, the patient would still be hypothermic, with no risk for brain hyperthermia. Therefore, maintaining a stable temperature is likely more important, and more difficult, at a core temperature of 36.0°C than at 32.0°C to 33.0°C.

In summary, the study by Deye and coworkers demonstrates the capacity of newer cooling devices, specifically endovascular cooling, to control temperature safely and effectively. As in previous (retrospective) studies, better temperature control was associated with a clear trend to improved outcome, although this did not reach statistical significance. Further studies will be needed to assess cooling efficacy for fever management, which is likely to be more difficult because the patients’ heat-generating abilities will be greater at temperatures that are closer to normal. In this regard, it may be harder to be (and stay) normothermic than to be (and stay) cool in the intensive care unit.

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References


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Kees H. Polderman

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