The narrative of induced hypothermia presents a compelling topic for neurocritical care, yet the approach to its application remains nuanced. The practice of induced hypothermia has been advocated for its potential benefits in minimizing neurological injury following cardiac arrest, traumatic brain injury, stroke, and other critical neurological events. However, the evidence for its efficacy is mixed, and the risks associated with hypothermia, such as hypotension and thrombocytopenia, must be carefully considered.

The initial narrative introduces the context of induced hypothermia, emphasizing its role in neurocritical care. It highlights the importance of monitoring patients undergoing hypothermia to prevent complications such as hemorrhage and thrombocytopenia. The text concludes by emphasizing the need for continuous monitoring and adjustment of the hypothermia protocol to ensure patient safety.

The second narrative delves into the mechanisms of action underlying the therapeutic effects of hypothermia. It discusses the potential benefits of hypothermia in reducing brain edema, improving cerebral blood flow, and decreasing metabolic demand. The narrative also acknowledges the challenges associated with hypothermia, such as the risk of hypotension and the need for careful monitoring to prevent complications.

Repetition of key points: The narrative concludes by summarizing the main points, emphasizing the importance of individualizing the hypothermia protocol based on patient-specific factors. It reinforces the need for close monitoring and adjustment of the hypothermia protocol to ensure patient safety.

Table 1: Examples of interventions shown to improve outcomes in randomized, controlled trials (or meta-analyses) that have not become routinized in neurocritical care

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeSmet et al.</td>
<td>Selective gut decontamination</td>
</tr>
<tr>
<td>Koeppen et al.</td>
<td>Immunoabsorption for patients with severe sepsis</td>
</tr>
<tr>
<td>Prieskorn et al.</td>
<td>Omnipaque (a contrast agent) for severe sepsis</td>
</tr>
<tr>
<td>Pontes-Arruda et al.</td>
<td>Diet enriched with essential amino acids and probiotics in critically ill patients with acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Gallerani et al.</td>
<td>Use of gastric tonometric measurement of gastric intramural pHi to titrate fluid and nutrition therapy</td>
</tr>
</tbody>
</table>

Table 2: Examples of interventions shown to improve outcomes in randomized, controlled trials (or meta-analyses) that have not become routinized in neurocritical care

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akasaka et al.</td>
<td>Reduction in reperfusion injury after cardiac arrest</td>
</tr>
<tr>
<td>Menon et al.</td>
<td>Reduction in hospital mortality rate</td>
</tr>
<tr>
<td>Katayama et al.</td>
<td>Reduction in hospital mortality rate</td>
</tr>
<tr>
<td>Koeppen et al.</td>
<td>Reduction in hospital mortality rate</td>
</tr>
<tr>
<td>Pontes-Arruda et al.</td>
<td>Reduction in mortality rate</td>
</tr>
<tr>
<td>Gallerani et al.</td>
<td>Use of gastric tonometric measurement of gastric intramural pHi to titrate fluid and nutrition therapy</td>
</tr>
</tbody>
</table>

The narrative concludes by summarizing the main points, emphasizing the importance of individualizing the hypothermia protocol based on patient-specific factors. It reinforces the need for close monitoring and adjustment of the hypothermia protocol to ensure patient safety.
Successful use of therapeutic temperature management requires:

- Awareness of physiology of cooling
- Awareness of potential side effects
- Understanding of underlying mechanisms

Well, we are trying to prevent/treat:

**Ischemia-reperfusion injury**

and/or

**Injury caused by brain edema.**
Hypothermia: effects on ICP

Additional studies where ICP decreases were reported but not quantified:

- Clifton et al., NEJM 2001. Normalization of ICP (15.7 mmHg during cooling), baseline values not registered (7)
- Shiozaki et al., J Neurosurgery 1998. Significant decrease in ICP and in percentage of patients with intracranial hypertension; values not reported
- Tokutomi T et al., Neurosurgery 2003. Significant decrease in ICP, values not reported

Additional 292 patients.

There is one exception: NABISH II, Clifton et al., Lancet Neurol 2011. HIGHER ICP in the hypothermia group (rebound effect during re-warming?).


Ischemia/reperfusion

Diseases where edema/ICP control may play a key role:

- Acute disseminated encephalomyelitis
- Immune response, neuroexcitotoxicity
- Ischemia/reperfusion injury and endothelin & TxA2;
- Local generation of cytotoxic edema, formation of cytotoxic edema, intracellular acidosis
- Production of free radicals (O2, NO, H2O2, OH•)

These processes are all temperature-dependent.

Now, let’s move quickly to the clinical evidence.

Mild hypothermia works in:
- Cardiac arrest models;
- Asphyxia models;
- Traumatic brain injury models;
- Stroke models;
- SAH models.

In fact, it works in all types of neurological injury (although time windows differ).

Works in:
- The brain (prevents/decreases brain injury);
- The heart (prevents/decreases myocardial injury);
- The kidney, other organs.

### Potential indications for induced hypothermia

- Acute disseminated encephalomyelitis (ADEM)
- Cardiac arrest due to coronary causes
- Intracranial hypertension
- Sepsis, septic encephalopathy
- Preventing/I Delaying cardiac arrest, severe hypoxicischemic encephalopathy
- Postcardiac arrest syndrome
- Post-resuscitative encephalopathy
- Post-asphyxial encephalopathy
- Ayspetal/PEA
- Traumatic brain injury: reducing outcome
- Mitigating myocardial ischemia during ischemia/reperfusion
- Level III
- Brain death (Level I)
- Brain death (Level II)
- Stroke – improving outcome
- Stroke – reducing outcome
- Traumatic brain injury: reducing ICP
- Preventing/reducing radiological cerebral edema
- Hepatic ischemia (reducing ICP)
- Bacterial meningitis
- Spinal cord contusion
- Level IV
- ARDS
- Improve oxygenation
- Cardiac arrest

Fever in neurological injury:

- Is associated with worse outcome.
  - Higher mortality;
  - Increased length of stay;
  - Worse neurological outcome.


- This difference persists when multivariate analysis is performed, i.e. patients are matched for other variables;
- Applies to all types of neurological injury.

Fever in ischemic stroke:

- Fever was associated with a 3.4-fold increase in risk for adverse outcome (95% CI 1.2-9.5) in a prospective observational study
- Fever within 24 hours after onset of stroke was independently related to larger infarct volumes (OR 3.23, 95% CI 1.63-6.43) and higher neurological deficits (OR 3.06, 95% CI 1.70-5.53) at 3 months.
  Castillo J et al., Stroke 1998;29:2455-60
- Each °C increase of admission body temperature independently predicted a 30% relative increase in long term mortality risk (95% CI 4%-57%)
  Kammersgaard LP et al., Stroke 2002;33:1759-62

Fever in hemorrhagic stroke:

- Subarachnoid Hemorrhage
  - Fever burden is independently associated with mortality and poor functional outcome
    Fernandez A et al., Neurology 2007;68:1013-19
- Intracerebral Hemorrhage
  - Duration of fever (>37.5° C) within the first 72 hours is independently associated with poor outcome
    Schwarz S et al., Neurology 2000;54:354-61

Fever following out-of-hospital cardiac arrest (OHCA):

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-refusion duration (measured in minutes)</td>
<td>1.54 (1.34-1.75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Low-flow duration (measured in minutes)</td>
<td>1.05 (1.01-1.09)</td>
<td>.01</td>
</tr>
<tr>
<td>Age</td>
<td>1.32 (1.26-1.38)</td>
<td>25</td>
</tr>
<tr>
<td>Sex</td>
<td>1.36 (1.06-4.35)</td>
<td>56</td>
</tr>
<tr>
<td>Out-of-hospital cardiac arrest</td>
<td>0.97 (1.11-1.8)</td>
<td>.07</td>
</tr>
<tr>
<td>pH level on admission to the emergency department</td>
<td>0.96 (0.90-1.01)</td>
<td>40</td>
</tr>
<tr>
<td>Location level on admission to the emergency department (measured in millimeters per liter)</td>
<td>1.93 (1.52-2.46)</td>
<td>.003</td>
</tr>
</tbody>
</table>


Fever following in-hospital cardiac arrest (IHCA):


- Fever in neurological injury:
  - Is associated with worse outcome.
  - This difference persists when multivariate analysis is performed, i.e. patients are matched for other variables;
  - Applies to all types of neurological injury.

- Fever in ischemic stroke:
  - Fever was associated with a 3.4-fold increase in risk for adverse outcome (95% CI 1.2-9.5) in a prospective observational study
  - Fever within 24 hours after onset of stroke was independently related to larger infarct volumes (OR 3.23, 95% CI 1.63-6.43) and higher neurological deficits (OR 3.06, 95% CI 1.70-5.53) at 3 months.
    Castillo J et al., Stroke 1998;29:2455-60
  - Each °C increase of admission body temperature independently predicted a 30% relative increase in long term mortality risk (95% CI 4%-57%)
    Kammersgaard LP et al., Stroke 2002;33:1759-62

- Fever in hemorrhagic stroke:
  - Subarachnoid Hemorrhage
    - Fever burden is independently associated with mortality and poor functional outcome
      Fernandez A et al., Neurology 2007;68:1013-19
  - Intracerebral Hemorrhage
    - Duration of fever (>37.5° C) within the first 72 hours is independently associated with poor outcome
      Schwarz S et al., Neurology 2000;54:354-61

- Fever in neurological injury:
  - Is associated with worse outcome.
  - This difference persists when multivariate analysis is performed, i.e. patients are matched for other variables;
  - Applies to all types of neurological injury.
Elevated body temperature was associated with a dose-dependent:
- ICU & Hospital LOS
- Mortality rate
Elevated body temperature was associated with 3.2 additional ICU days and 4.3 additional hospital days
ICU LOS was predicted by the number of complications and elevated body temperature

Of course, observational data cannot conclusively prove that this is a cause-and-effect relationship.

However, animal data and the persistence of the relationship after multivariate analysis strongly suggests that this is the most likely explanation.

Fever in neurological injury:
- In all animal models for stroke, global ischemia, TBI and intracranial haemorrhage:
  - Active warming is harmful (even a little warming, say 1°C above normal);
  - Spontaneous development of hyperthermia is harmful;
  - Maintaining normothermia is protective;
  - And mild hypothermia significantly decreases the extent of injury

Hyperthermia is especially harmful during periods of ischemia (i.e., during secondary injury)
Why is this effect so large???

Some of these processes GENERATE HEAT.

Brain-, blood- and rectal temperature in TBI:

Brain and bladder temperature in stroke
So, even if core temperature is normal, the brain will be running a fever;

Temperature will be highest in injured area’s of the brain;

The higher the core temperature, the greater the difference between core and brain.

Range of this phenomenon:

- In healthy individuals: 0.1-1°C
- In injured brains:
  - Uninjured area's: 1-2°C
  - Injured area’s: up to 4°C!

Now, let’s move from fever control to induced hypothermia.

Cooling for cardiac arrest...
It is NOT just about cooling....

- Promote awareness, use of bystander CPR, availability of defibrillators;
- New emphasis on the importance of chest compressions, at the expense of breaths, especially in BLS;
- Prevent hypotension, [additional] hypoxia, hyper/hypocapnia, hypovolemia, and electrolyte disorders in the ER and ICU;
- Immediate cardiac revascularisation (at least in witnessed arrest patients);
- Etc. etc.
- And of course, use induced hypothermia!

Increased survival despite a reduction in out-of-hospital ventricular fibrillation in north-east Italy

Methods and results: The area investigated, Piedmont province, is representative of the entire region studied in 1994. In the 1994 FACS study, the heterogeneous ambulance personnel, ranging from volunteers to registered nurses and physicians, were not all trained in basic life support and early defibrillation. In 2003 all resuscitators had advanced cardiac life support (ACLS) skills. Moreover, in 2003 dispatch-guided CPR was used. The time from dispatch to defibrillation of victims of OOH-CA from cardiac aetiology was comparable between 1994 and 2003. However, the rate of ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) as presenting rhythm decreased significantly between 1994 and 2003 from 30.2% to 20.1% (p < 0.05). Despite this, survival to hospital discharge for VF/VT almost tripled (5.4%) versus 1.0% (p < 0.05). Hospital discharge for asystole or pulseless electrical activity remained dismal (3.1% and 1.7%).

CPR - % good outcome

Randomised controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypothermia</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>HACA 2002</td>
<td>61% (N=273)</td>
<td>57% (N=77)</td>
</tr>
<tr>
<td>Bernard 2002</td>
<td>19% (N=33)</td>
<td>19% (N=33)</td>
</tr>
</tbody>
</table>

Number needed to treat to achieve good neurological outcome in one extra patient: 6
ERC: “Class I evidence”. AHA: “Class IIa evidence”.

Formally adopted by the ERC and by the AHA in December 2005

ERC: “Class I evidence”. AHA: “Class IIa evidence”.

Formally adopted by the ERC and by the AHA in December 2005

**“Upgraded” to Class 1 evidence in the 2010 version of the AHA guidelines.**

Part 9: Post–Cardiac Arrest Care
2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

In summary, we recommend that comatose (ie, lack of meaningful response to verbal commands) adult patients with ROSC after out-of-hospital VF cardiac arrest be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours (Class I, LOE B). Induced hypothermia also may be considered for 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 (Class Ib, LOE B).

**“Upgraded” to Class 1 evidence in the 2010 version of the AHA guidelines.** With Class Ib for asystole/PEA...

Providers should closely monitor patient core temperature after ROSC and actively intervene to avoid hyperthermia (Class I, LOE C).

...and a recommendation for strict fever management in the resuscitation phase following hypothermia.

**Why this change in the AHA perspective?**

<table>
<thead>
<tr>
<th>HN 6-month outcome</th>
<th>N=998 patients, outcome data for n=975</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good outcome</td>
</tr>
<tr>
<td>All patients</td>
<td>(CPC 1-2)</td>
</tr>
<tr>
<td></td>
<td>46 %</td>
</tr>
<tr>
<td>&quot;HACA&quot;</td>
<td>68 %</td>
</tr>
<tr>
<td>All VF/VT</td>
<td>54 %</td>
</tr>
<tr>
<td>Asyst/PEA</td>
<td>26 %</td>
</tr>
</tbody>
</table>

2010 saw the publication of:

- The new AHA guidelines for resuscitation
- Five new studies looking at hypothermia for witnessed cardiac arrest

Remember, these results are from regular, run-of-the-mill hospitals; not research centers.

HN 6-month outcome
N=998 patients, outcome data for n=975

<table>
<thead>
<tr>
<th></th>
<th>Good outcome (CPC 1-2)</th>
<th>Bad outcome (CPC 3-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>46 %</td>
<td>54 %</td>
</tr>
<tr>
<td>&quot;HACA&quot;</td>
<td>68 %</td>
<td>32 %</td>
</tr>
<tr>
<td>All VF/VT</td>
<td>54 %</td>
<td>46 %</td>
</tr>
<tr>
<td>Asyst/PEA</td>
<td>26 %</td>
<td>74 %</td>
</tr>
</tbody>
</table>


CPR - % good outcome

CPR - % good outcome VT/VF only
Regional Variation in Out-of-Hospital Cardiac Arrest Incidence and Outcome

Conclusion: In this study involving 10 geographic regions in North America, there were significant and important regional differences in out-of-hospital cardiac arrest incidence and outcome.

We can, and must, do better!
And we should lose the pessimism surrounding patients with (witnessed) cardiac arrest!

2005 Induced hypothermia is underused after resuscitation from cardiac arrest: a current practice survey
Benjamin S. Abella, June W. Bao, Kwan-Ning Huang, Tony L. Vander Heide, Lance C. Becker
Emergency Resuscitation Team, Department of Emergency Medicine, University of California, San Francisco, CA. 13%

Conclusion: Despite compelling data supporting its use, hypothermia has yet to be broadly incorporated into physician practice.

2006 Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest
Rohit M. Mehta, MD; Joannet Saur, MD; Markus B. Skrifvars, MD, MS; Edmund J. Tornheim, MD; Tami H. Plutcker, MD; David P. Edelman, MD; Fawaz Ahmed, GA; Kwan-Ning Huang; Monica Khan, Tony L. Vander Heide, MD; Lance B. Bichler, MD; Benjamin S. Abella, MD, MPH

Conclusion: Physician utilization of cooling after cardiac arrest remains low.
Of respondents! So this will overestimate actual use!
N= 6326 patients
- Hyperoxia (PaO2/FiO2 ≥300) was seen in 1156 (18%)
- Hypoxia (PaO2/FiO2 ≤60) was seen in 3999 patients (63%)
- 1171 (19%) had normoxia

Another limitation worthy of note is that our study did not capture which or not therapeutic hypothermia was attempted. However, only 6% of patients had a low body temperature under 34°C in the first 24 hours after arrival in the ICU, indicating that therapeutic hypothermia was not widely applied in this cohort.
Cooling may protect the heart also...

- Animal studies have reported reductions in infarct size of **30-90%** (!) of area at risk, depending on region of the heart and the timing of cooling.

- Number needed to treat to achieve good neurological outcome in one extra patient: **6**

- Cooling started only after 5-6 hours!

- Potentially, significant room for improvement (similarly to the story in adult CPR studies)
**COOL MI and ICE-IT Trials**

168 + 105 patients (total n=273) enrolled

- **Primary PCI**
- **PCI + Cooling**

Target temp = 33°C

1st Infarct Size (SPECT)
2nd MACE

---

**COOL MI and ICE-IT**

Measured SPECT Infarct Size at 30-Days – whole group

<table>
<thead>
<tr>
<th>Control</th>
<th>Hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.9</td>
<td>13.2</td>
</tr>
<tr>
<td>10.8</td>
<td>10.2</td>
</tr>
</tbody>
</table>

Target temperature NOT ACHIEVED before reperfusion in large majority of patients.


---

**Core temperature at reperfusion**

Anterior MI Group – mean infarct size by subgroup

<table>
<thead>
<tr>
<th>COOL-MI</th>
<th>ICE-IT</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.9</td>
<td>16.3</td>
</tr>
<tr>
<td>10.6</td>
<td>10.6</td>
</tr>
</tbody>
</table>

All Cool <35 C >35 C Control

<table>
<thead>
<tr>
<th>COOL-MI</th>
<th>ICE-IT</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.9</td>
<td>18.2</td>
</tr>
<tr>
<td>17.6</td>
<td>16.7</td>
</tr>
</tbody>
</table>

All Cool <35 C >35 C Control

p=0.09

(n=54) (n=16) (n=38) (n=59) (n=36) (n=10) ((n=26) (n=38)

---

**A Pilot Study of Rapid Cooling by Cold Saline and Endovascular Cooling Before Reperfusion in Patients With ST-Elevation Myocardial Infarction**

- Rapid Intravascular Cooling in Myocardial Infarction as Adjunctive to Percutaneous Coronary Intervention study (RAPID-M-I-ICE)
- Combination of endovascular cooling (cooling catheter, Celsius Control System, Innercool Therapies, San Diego) with cold fluid infusion (average volume 1540±430 ml)
- N=18 patients (9 cooled, 9 controls; 1 patient treated with cold fluids only because catheter could not be placed)


---

**Cooling speed**

Controls

Hypothermia
Use of hypothermia in *ischemic stroke*:

**Automated peritoneal lavage**
*Using the Peritoneal Cavity for ultra-rapid heat exchange. Velomedix Systems Inc.*

**Use of hypothermia in ischemic stroke:**

<table>
<thead>
<tr>
<th>Authors</th>
<th>No of pts</th>
<th>Target temp</th>
<th>Time from injury to start of cooling</th>
<th>Time to target temp</th>
<th>Duration</th>
<th>Ref. cooling rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Guluma et al.</em> 2006</td>
<td>10 (10 / 0)</td>
<td>33°C</td>
<td>1.7 ± 0.7 hrs</td>
<td>&lt;6 hrs</td>
<td>24 hrs</td>
<td>0.3°C/hr</td>
</tr>
<tr>
<td><em>Hemmen et al.</em> 2010 ICTuS-L*</td>
<td>58 (28 / 30)</td>
<td>33°C</td>
<td>1.1 hrs (median)</td>
<td>&lt;6 hrs</td>
<td>24 hrs</td>
<td>0.33°C/hr</td>
</tr>
<tr>
<td><em>Lyden et al.</em> 2006*</td>
<td>18 (18 / 0)</td>
<td>33°C</td>
<td>7 hrs</td>
<td>12-24 hrs</td>
<td>7 hrs</td>
<td>7.7 ± 3.1 hrs</td>
</tr>
<tr>
<td><em>Els et al.</em> 2006</td>
<td>25 (12 / 13)</td>
<td>33°C</td>
<td>15 ± 6 hrs</td>
<td>&lt;6 hrs</td>
<td>36-37°C</td>
<td>0.25-0.5°C/hr</td>
</tr>
<tr>
<td><em>Krieger et al.</em> 2001*</td>
<td>19 (10 / 9)</td>
<td>32 ± 1°C</td>
<td>3.5 ± 1.56 hrs</td>
<td>&lt;6 hrs</td>
<td>32°C</td>
<td>0.25°C/hr</td>
</tr>
<tr>
<td><em>Kammersgaard et al.</em> 2000</td>
<td>73 (17 / 56)</td>
<td>35.5°C</td>
<td>4 hrs</td>
<td>6 hrs</td>
<td>6.2 ± 1.3 hrs</td>
<td>0.25-0.5°C/hr</td>
</tr>
<tr>
<td><em>De Georgia et al.</em> 2004*</td>
<td>40 (18 / 22)</td>
<td>33°C</td>
<td>Variable; 8'59'' ± 2'52''</td>
<td>24 hrs</td>
<td>Variable; 8'59'' ± 2'52''</td>
<td>0.2oC/hr</td>
</tr>
<tr>
<td><em>Georgiadis et al.</em> 2002</td>
<td>36 (19 / 17)</td>
<td>33°C</td>
<td>3.5 ± 1 hrs, range 2-4.5</td>
<td>48-72 hrs</td>
<td>3.5 ± 1 hrs, range 2-4.5</td>
<td>0.12-0.2°C/hr</td>
</tr>
<tr>
<td><em>Georgiadis et al.</em> 2004*</td>
<td>22 (range 18-24)</td>
<td>33°C</td>
<td>48-72 hrs</td>
<td>4 ± 1 hrs, range 2-6</td>
<td>48-72 hrs</td>
<td>0.12-0.2°C/hr</td>
</tr>
<tr>
<td><em>Jian S et al.</em> 2003</td>
<td>50 (50 / 0)</td>
<td>33°C</td>
<td>48 hrs</td>
<td>2 ± 1 hrs, range 1.5-3.5</td>
<td>48 hrs</td>
<td>0.2°C/hr</td>
</tr>
<tr>
<td><em>Schwab et al.</em> 2001</td>
<td>50 (50 / 0)</td>
<td>33°C</td>
<td>24 hrs</td>
<td>72 hrs</td>
<td>3.5-11 hrs</td>
<td>Passive</td>
</tr>
<tr>
<td><em>Steiner T et al.</em> 2001</td>
<td>15 (15 / 0)</td>
<td>33°C</td>
<td>2-7 hrs</td>
<td>72-96 hrs</td>
<td>3.5-6.2 hrs</td>
<td>0.25-0.5°C/hr</td>
</tr>
<tr>
<td><em>Schwab et al.</em> 1998</td>
<td>20 (20 / 0)</td>
<td>33°C</td>
<td>48-72 hrs</td>
<td>2-7 hrs</td>
<td>4-8.4 hrs, median 17</td>
<td>32-33°C</td>
</tr>
<tr>
<td><em>Naritomi H et al.</em> 1996</td>
<td>4 (4 / 0)</td>
<td>33°C</td>
<td>&lt;5 hrs</td>
<td>72-96 hrs</td>
<td>&lt;5 hrs</td>
<td>0.25-0.5°C/hr</td>
</tr>
</tbody>
</table>

**Use of hypothermia in ischemic stroke:**

**Late cooling, mainly/purely for edema control**

Total number of cooled patients reported so far: 270.
Use of hypothermia in ischemic stroke:

Clinical studies (total number of patients 157):
- Cooling continued for 24-72 hours
- Effective in decreasing brain edema/controlling ICP
- Decreased mortality in the largest study by Schwab et al. 2001, n=50 patients; 38% vs. 78% in historical controls in malignant MCA infarction
- Most frequently reported adverse event (apart from bradycardia, which is a physiological consequence of cooling): increased rate of pneumonia
- Many deaths occurred during re-warming
- Most frequently effective in decreasing brain edema/controlling ICP
- Increases in ICP can apparently be prevented by slower and controlled re-warming
- Mostly (very) long time intervals between onset of stroke and initiation of hypothermia (22 ± 9 hours in largest study)

Patient with large MCA infarction:
- 24 hrs after 1st symptoms
  - Core temperature 37.0°C
- 36 hrs after 1st symptoms
  - Core temperature 33.0°C

Use of hypothermia in malignant MCA infarction, no reperfusion:

Clinical studies (total number of patients 157):
- Cooling continued for 24-72 hours
- Effective in decreasing brain edema/controlling ICP
- Decreased mortality in the largest study by Schwab et al. 2001, n=50 patients; 38% vs. 78% in historical controls in malignant MCA infarction
- Most frequently reported adverse event (apart from bradycardia, which is a physiological consequence of cooling): increased rate of pneumonia
- Many deaths occurred during re-warming, following rebound increases in ICP
- Increases in ICP can apparently be prevented by slower and controlled re-warming
- Mostly (very) long time intervals between onset of stroke and initiation of hypothermia (22 ± 9 hours in largest study)

Table 3. Outcome Measures Between HY and NT Patients

<table>
<thead>
<tr>
<th>HY (Groups 2, 5, 6)</th>
<th>NT (Groups 1, 3, 4)</th>
<th>Fisher Exact Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=28</td>
<td>n=30</td>
<td>P</td>
</tr>
<tr>
<td>mRS 0–1 at 90 days</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>NIHSS at 90 day (mean±SD)</td>
<td>6.3 (±6.6)</td>
<td>3.8 (±3.0)</td>
</tr>
<tr>
<td>At least one SAE (%)</td>
<td>75</td>
<td>43.3</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>All ICH (%)</td>
<td>28.6</td>
<td>20</td>
</tr>
<tr>
<td>Symptomatic ICH (%)</td>
<td>3.6</td>
<td>10</td>
</tr>
<tr>
<td>Mortality by 90 days (%)</td>
<td>21.4%</td>
<td>16.7</td>
</tr>
</tbody>
</table>

SAE indicates serious adverse event; ICH, intracerebral hemorrhage.

Hemmen TM et al. Stroke 2010; 41(10):2265-70
Use of hypothermia in moderately severe stroke:

Combined with thrombolysis:
- 74 patients in four studies;
- Average time to target temperature >6 hours in 2 studies (28 patients), <6 hours in 46 patients
- Thrombolysis within 6 hours; within 3 hours in majority of these patients
- No apparent increased risk of adverse events except pneumonia

No thrombolysis:
- N=57 patients in four studies;
- No increased risk of adverse events except pneumonia

Planned/ongoing studies:

Ongoing:
- Mild Hypothermia in Acute Ischemic Stroke Safety/Efficacy Study; n=36 patients, target core temperature of 35°C for 12 hours by means of a non-invasive temperature management system and cold i.v. fluids. No controls

Planned:
- The Intravascular Cooling in the Treatment of Stroke 2/3 (ICTuS 2/3) Trial (combining cooling with t-PA); RCT, planned enrolment 400 patients, controls: tPA & normothermia.

Counter-indications?

- Persistent hypotension?
- Arrhythmia’s?
- Active bleeding?
- Pregnancy?
- Severe pre-admission morbidity?
- High age?

Successful outcome utilizing hypothermia after cardiac arrest in pregnancy: A case report

Jon C. Rittenberger, MD, MS; Elizabeth Kreis, MD; David Jorg, MD; Kenneth Green, MD; Alan Herfin, MD

Case: We present the case of a 35-yr-old woman, 13 wks pregnant, who had a witnessed out-of-hospital ventricular fibrillation cardiac arrest. She was resuscitated by prehospital personnel yet remained comatose at arrival to the hospital. Therapeutic cooling (33°C) was initiated for 24 hrs, and she was discharged home with mild neurologic deficits (Cerebral Performance Category 2) on hospital day 6. The infant was delivered via cesarean section.

Conclusion: This is the first case of therapeutic hypothermia applied to postarrest care of a pregnant woman followed by a successful delivery. This therapy should be considered in pregnant patients with cardiac arrest. (Crit Care Med 2008; 36:1354-1356)
Everything!!

changes when we induce hypothermia in a patient.

**Effects on metabolism**

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Oxygen consumption</th>
<th>CO₂ production</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-35°C</td>
<td>↓7-10% / °C↓ in core temp</td>
<td>↓7-10% / °C↓ in core temp</td>
<td>↓7-10% / °C↓ in core temp</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

↑Fat metabolism: ⇒ ↑Glycerol, free fatty acids, ketonic acids, lactate; metabolic acidosis

≤35°C  
↓Insulin sensitivity ↓Insulin secretion

**Strategy:**

- Adjust ventilator settings
- Adjust feeding rate
- Accept slight acidosis and slightly elevated lactate levels
  (it has been shown that intracellular pH increases rather than decreases, even if a mild acidosis develops extracellularly).
- A reduced metabolism is a good thing in most of these cases! Less oxygen consumption/demand in (injured area’s of) the brain, less demand on the myocardium.
Acute head injury (6 hrs post impact)
Areas in red show regions with rCBF < 20 ml/100g/min)


Effects on \textit{metabolism}

\begin{itemize}
\item \(36-38^\circ\text{C}\): \downarrow\text{Oxygen consumption}
\item \(\leq 35^\circ\text{C}\): \downarrow\text{CO}_2\text{ production}
\item \(\downarrow\text{Metabolism:}\)
\item \(\uparrow\text{Fat metabolism: } = \uparrow\text{Glycerol, free fatty acids, ketonic acids, lactate, metabolic acidosis}\)
\item \(\leq 35^\circ\text{C}\): \downarrow\text{Insulin sensitivity, } \downarrow\text{Insulin secretion}\)
\end{itemize}

Effects on the \textit{cardiovascular system}

\begin{itemize}
\item \(\leq 36-35^\circ\text{C}\): Tachycardia
\item \(35^\circ\text{C}\): Bradycardia
\item \(34^\circ\text{C}\): Stable or slightly increased blood pressure (average increase 5-10 mmHg)
\item \(32^\circ\text{C}\): Mild arrhythmias in some patients
\item \(33^\circ\text{C}\): EKG changes: increased PR-interval, widening of QRS-complex, increased QT interval
\item \(32-30^\circ\text{C}\): \(\uparrow\uparrow\) Risk of tachyarrhythmia’s, beginning with atrial fibrillation
\item \(35^\circ\text{C}\): \(\uparrow\text{CVP and } \downarrow\text{CO}\)
\item \(35^\circ\text{C}\): \(\uparrow\text{ or } \text{mixed venous saturation}\)
\end{itemize}

\begin{itemize}
\item Use insulin therapy.
\item (We target glucose values of 3.8-8.5 mmol).
\item Realize that high doses of insulin may be needed.
\item Of particular importance: realize that insulin requirements are likely to decrease during re-warming! So hypoglycemia can easily occur in this phase.
\item This is another reason for slow re-warming strategies.
\end{itemize}
### Effects on the Cardiovascular System

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤38→35°C</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>≤35°C</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>≤34°C</td>
<td>Stable or slightly increased blood pressure (average increase 5-10 mmHg)</td>
</tr>
<tr>
<td>≤33°C</td>
<td>Mild arrhythmias in some patients</td>
</tr>
<tr>
<td>≤32°C</td>
<td>EKG changes: increased PR-interval, widening of QRS-complex, increased QT interval.</td>
</tr>
<tr>
<td>≤28-30°C</td>
<td>Risk of tachyarrhythmia's, beginning with atrial fibrillation</td>
</tr>
<tr>
<td>≤35°C</td>
<td>CVP and CO ↓</td>
</tr>
<tr>
<td>≤35°C</td>
<td>Mixed venous saturation</td>
</tr>
</tbody>
</table>

Mild hypothermia does not increase the risk of arrhythmia's. Indeed mild hypothermia increases membrane stability and can decrease the risk of arrhythmias.

### Effects on the Cardiovascular System

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤38→35°C</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>≤35°C</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>≤34°C</td>
<td>Stable or slightly increased blood pressure (average increase 5-10 mmHg)</td>
</tr>
<tr>
<td>≤33°C</td>
<td>Mild arrhythmias in some patients</td>
</tr>
<tr>
<td>≤32°C</td>
<td>EKG changes: increased PR-interval, widening of QRS-complex, increased QT interval.</td>
</tr>
<tr>
<td>≤28-30°C</td>
<td>Risk of tachyarrhythmia's, beginning with atrial fibrillation</td>
</tr>
<tr>
<td>≤35°C</td>
<td>CVP and CO ↓</td>
</tr>
<tr>
<td>≤35°C</td>
<td>Mixed venous saturation</td>
</tr>
</tbody>
</table>

Mild hypothermia does not increase the risk of arrhythmia's. Indeed mild hypothermia increases membrane stability and can decrease the risk of arrhythmias. However, more profound hypothermia (<28°C; sometimes 30°C if electrolyte disorders and/or ischemia are present) can increase the risk of arrhythmias. In addition, such arrhythmia's are harder to treat, as the myocardium becomes less responsive to anti-arrhythmic drugs.

### Hypothermia Improves Defibrillation Success and Resuscitation Outcomes From Ventricular Fibrillation

**Kimberly A. Boddicker, MD, Yi Zhang, MD, PhD; M. Bridget Zimmerman, PhD; Loyd R. Davies, BS; Richard E. Kerber, MD**

![Graph](image)

**Figure 5.** Record-first shock success rate, defined as termina-
tion of VT after first electrode shock, is in a yield in each
control temperature condition (n=8 per group).

**Figure 3.** Total number (mean) shock delivered during resuscitations at all patient under each tempe-
rate condition (n=8 per group).


### Clinical Observations (5 case series, n=28 patients):


---

Moderate hypothermia increases the chance of spiral wave collision in favor of self-termination of ventricular tachycardia/shock

Effects on the cardiovascular system

≤35°C
- Tachycardia
- Bradycardia

Bradydardia is a normal consequence of hypothermia (though there is wide inter-individual variability — “normal” heart rate at 32°C may range from 30-60 BPM). If the heart rate is higher there are probably other factors involved.

≤28-30°C
- EKG changes: increased PR-interval, widening of QRS-complex, increased QT interval.
- Risk of tachyarrhythmias, beginning with atrial fibrillation.

≤35°C
- CVP and ↓ CO
- or = mixed venous saturation

Greater hypothermia (≤30°C) is associated with a decreased left ventricular ejection fraction and cardiac output.

Human data

At 33°C increasing heart rate from 80 to 120 BPM decreases contractility.

Effects on the cardiovascular system

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤36-35°C</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>≤35°C</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>≤34°C</td>
<td>Stable or slightly increased blood pressure (average increase 5-10 mmHg)</td>
</tr>
<tr>
<td>≤32°C</td>
<td>Mild arrhythmias in some patients</td>
</tr>
<tr>
<td>≤33°C</td>
<td>EKG changes: increased PR-interval, widening of QRS-complex, increased QT interval.</td>
</tr>
<tr>
<td>≤28-30°C</td>
<td>↑↑ Risk of tachyarrhythmia's, beginning with atrial fibrillation</td>
</tr>
<tr>
<td>≤35°C</td>
<td>↑ CVP and ↓ CO</td>
</tr>
<tr>
<td>≤36°C</td>
<td>↑ or = mixed venous saturation</td>
</tr>
</tbody>
</table>

In summary, our results confirm that contractility falls with temperature if HR is artificially maintained. Increasing HR at low temperature causes a fall in contractility. Care should be taken when increasing a hypothermic patient's HR either through pacing or the use of chronotropic agents.

Does Head Cooling With Mild Systemic Hypothermia Affect Requirement for Blood Pressure Support?

CONCLUSIONS: Mild systemic hypothermia did not affect arterial blood pressure or initial treatment with inotropes or volume in infants with moderate-to-severe encephalopathy, but there was an apparent change in physician behavior, with slower withdrawal of therapy in cooled infants.

What This Study Adds

- Mild systemic hypothermia did not affect arterial blood pressure or initial treatment with inotropes or volume in infants with moderate-to-severe encephalopathy.
Cooling has been used to treat cardiac shock.

3 case series in pediatric patients (n=127)
2 case series in adult patients (n=18)

- Deakin CD et al. Anaesthesia 1998;53: 848–53 (n=50)

---

**Induced hypothermia in the management of refractory low cardiac output states following cardiac surgery in infants and children**

N=20 Infants with refractory cardiac shock; long-term survival n=10.


**Graph:**
- Blood pressure
- Heart rate

- N=20 infants with refractory cardiac shock; long-term survival n=10.

**Table:**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before cooling</th>
<th>After cooling</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure, mmHg</td>
<td>115 (16)</td>
<td>109 (15)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean right atrial pressure, mmHg</td>
<td>58 (4)</td>
<td>53 (16)</td>
<td>0.001</td>
</tr>
<tr>
<td>Core temperature difference, °C</td>
<td>6.1 (2.1)</td>
<td>6.1 (2.1)</td>
<td>0.72</td>
</tr>
<tr>
<td>Intravascular pH</td>
<td>7.38 (0.03)</td>
<td>7.38 (0.07)</td>
<td>0.011</td>
</tr>
<tr>
<td>Plasma bicarbonate, mmol/L</td>
<td>49.2 (15.7)</td>
<td>22.7 (13.1)</td>
<td>0.028</td>
</tr>
<tr>
<td>Base excess, mmol/L</td>
<td>-1.0 (3.0)</td>
<td>-2.8 (3.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Platelet count, x10^9/L</td>
<td>251.7 (72.9)</td>
<td>72 (47.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>White blood cell count, x10^9/L</td>
<td>11.8 (3.5)</td>
<td>10.9 (5.9)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

**No serious adverse effects reported**


---

**Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock**

Outcome in 23 cardiac arrest patients with refractory cardiac shock treated with hypothermia compared to 27 patients without cardiac shock.
Good outcome 61% vs. 74%


---

**Induction of mild hypothermia in cardiac arrest survivors presenting with cardiogenic shock syndrome**

N=56; 28 hemodynamically stable, 28 unstable. Good outcome 39.3% vs. 71.4%

But if this is true, why do we often see hypotension during cooling?

Renal function

| ≤35°C | ↑Diuresis, tubular dysfunction, electrolyte loss & electrolyte disorders |

If uncorrected this can lead to hypotension and hypovolemia, as well as severe electrolyte disorders.

The solution is fairly simple; just give sufficient (cold) fluids and supplement electrolytes!

Coagulation

| ≤35°C | Platelet count, impaired platelet function. |

| ≤33°C | Impaired coagulation cascade |

Strategy:

- Although the effect is real the risk of severe bleeding seems to be small. None of the numerous clinical studies in cardiac arrest patients has reported significant bleeding problems.
- The same applies to other hypothermia studies, including studies in TBI patients with brain contusions.
- NB: actively bleeding patients were excluded from most studies.
- What we do: if there is an indication for cooling but the patient is actively bleeding, and if we cannot (surgically) control the source of bleeding (e.g. liver laceration), we keep the temperature at 35°C. If there is a (moderately) increased risk of bleeding we will typically go down to 33°C instead of 32°C (our normal target temperature according to protocol). A temperature of 32°C affects platelet function & platelet count but not coagulation factors.
**Inflammation & immune function**

| ≤35°C | Impaired neutrophil and macrophage function; suppression of pro-inflammatory mediator release; ➞ increased risk of infection (mainly pneumonia & wound infections) |
|≤33°C | ↓ White blood cell count and impaired leucocyte function |

**Strategy:**

- This is a significant risk. Many (though not all) of the hypothermia studies have reported (trends toward) increased rates of infection, especially pneumonia.
- High risks reported especially in studies in stroke patients treated with cooling for prolonged periods.
- Studies on accidental hypothermia have shown an increased risk of wound infections and airway infections.
- On the other hand, most authors reported that final outcomes were not adversely affected even if infections occurred and the infection risk appears fairly low if cooling is continued for only 24 hours (as is currently recommended for cardiac arrest patients).

**What to do:** consider antibiotic prophylaxis (SDD); other prophylactic measures; careful monitoring including daily blood cultures, assessment of "machine workload", etc.

---

**This problem IS manageable, even with prolonged cooling...**
Pharmacokinetics

Altered clearance of various medications (data available for muscle paralyzers, propofol, fentanyl, morphine, phenytoin, pentobarbital, verapamil, propranolol and volatile anaesthetics (reduced clearance). In all likelihood this applies to many other types of medication, though effect of temp on clearance has not been studied for many drugs.

Speed of re-warming

Strategy:
- This effect will definitely occur. The magnitude is variable.
- What we do: adjust drug doses. Make sure that your medical & nursing staff is well aware of this phenomenon.
  As a rule we tend to use high bolus doses and low maintenance doses during hypothermia treatment.
In addition, combating fever/maintaining normothermia after hypothermia treatment may be extra important.
Physiologic attempts to increase temperature:

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-35°C</td>
<td>Generation of heat: shivering, peripheral vasoconstriction, etc.</td>
</tr>
<tr>
<td>30-33°C</td>
<td>‘Hibernation’: shivering ceases, marked decrease in rate of metabolism.</td>
</tr>
</tbody>
</table>

Shivering:
- Can increase oxygen consumption by 40-100%.
  - This is certainly an undesirable effect in patients with neurological and/or post-anoxic injury; but in ventilated and sufficiently sedated patients it is less of a problem, as these patients will have sufficient oxygen supplies and no work of breathing!
- Can be counteracted by administration of (preferably) opiates, sedatives, or other drugs (see next slide).
- Sedation and anaesthesia also increase peripheral blood flow, thereby increasing transfer of heat from the core to the periphery.
- Paralysis is usually not necessary! Certainly not once target temperature has been reached.

List of alternatives to combat shivering:
- Magnesium (MgSO4, MgCl, etc.)
- Meperidine/pethidine
- Quick-acting opiates (fentanyl, remi-fentanyl) (or slow-acting opioids such as Morphine)
- Propofol
- Benzodiazepines (midazolam, temazepam, diazepam, etc. etc.)
- Clonidine
- Ketanserin
- Tramadol
- Dexmedetomidine
- Others: Doxapram, Urapidil, Physostigmine, etc.

Also, SKIN COUNTERWARMING can be a highly effective anti-shivering strategy.

Conclusions: Surface CW provides beneficial control of shivering and improves the metabolic profile during TTM. (Crit Care Med 2009; 37:1893–1897)
Also, SKIN COUNTERWARMING can be a highly effective anti-shivering strategy.

Blowing hot and cold? Skin counter warming to prevent shivering during therapeutic cooling?

Arthur R. H. van Zanten, MD, PhD
Department of Intensive Care
Gelderse Vallei Hospital
Ede, The Netherlands
Kees H. Polderman, MD, PhD
Department of Intensive Care
Utrecht University Medical Center
Utrecht, The Netherlands


Air cooling blankets
Cooling rates lower than exposure of the patient; no good for cooling!

Blanketrol II and III
(CSZ company, United States)

Wrapping garments
(Gaymar company, MTRE company)

Arctic sun system
(Medivance Inc, United States)
A comparison of intravascular and surface cooling techniques in comatose cardiac arrest survivors (Crit Care Med 2011; 39:443–449)

Brynn Tamme, MD; Tomas Dragee, RN; Arild Morkneschiu, MD, PhD; Erlig Jacobsen, MD, PhD; Bjørn Ausvåt, PhD; Kjetil Sunde, MD, PhD

Coolgard system
Zoll Medical system
(formerly Alsius)

Celsius control system
Philips systems
(formerly Innercool)

In this setting, both cooling strategies resulted in a similar time of approximately 4.5 hrs from time of arrest or approximately 3 hrs from initiation of cooling to reach 34°C.

Table 2. Therapeutic hypothermia timing and outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Surface Cooling (n = 829)</th>
<th>Core Cooling (n = 756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial temperature (°C), n = 54, 57</td>
<td>35.8 (34.6, 36.5)</td>
<td>35.5 (34.6, 36.2)</td>
</tr>
<tr>
<td>Arrest to initiation of cooling (hrs), n = 68, 61</td>
<td>60 (44, 91)</td>
<td>65 (56, 99)</td>
</tr>
<tr>
<td>Arrest to 34°C (min), n = 90, 49</td>
<td>273 (196, 339)</td>
<td>279 (199, 340)</td>
</tr>
<tr>
<td>Initiation of cooling to 34°C (min), n = 81, 36</td>
<td>17 (63, 240)</td>
<td>186 (86, 256)</td>
</tr>
<tr>
<td>Available initial cooling</td>
<td>56 (92, 63)</td>
<td>58 (92, 70)</td>
</tr>
<tr>
<td>Maintained hypothermia (hours)</td>
<td>24 (23, 24)</td>
<td>24 (23, 24)</td>
</tr>
<tr>
<td>Postcooling fever (&gt;38°C)</td>
<td>43 (25, 60)</td>
<td>58 (25, 69)</td>
</tr>
<tr>
<td>Time in intensive care unit, primary hospital stay</td>
<td>136 (78, 232)</td>
<td>138 (74, 213)</td>
</tr>
<tr>
<td>Time in hospital, primary hospital stay</td>
<td>7 (1, 13)</td>
<td>6 (1, 13)</td>
</tr>
<tr>
<td>Time on respirator, all hospitals (hrs), n = 24, 46</td>
<td>124 (51, 215)</td>
<td>89 (44, 239)</td>
</tr>
<tr>
<td>Survived to first hospital discharge with good neurologic function (CPC 1–2)</td>
<td>34 (27, 45)</td>
<td>34 (25, 45)</td>
</tr>
<tr>
<td>Survived to follow-up*</td>
<td>39 (23, 47)</td>
<td>33 (25, 41)</td>
</tr>
<tr>
<td>CPC 1 at follow-up*</td>
<td>32 (23, 41)</td>
<td>31 (25, 41)</td>
</tr>
<tr>
<td>CPC 2 at follow-up*</td>
<td>2 (68) (2)</td>
<td>5 (72) (3)</td>
</tr>
<tr>
<td>CPC 3 at follow-up*</td>
<td>2 (68) (2)</td>
<td>1 (74) (1)</td>
</tr>
<tr>
<td>CPC 4 at follow-up*</td>
<td>2 (68) (2)</td>
<td>1 (74) (1)</td>
</tr>
<tr>
<td>CPC 5 at follow-up* (dead)</td>
<td>2 (68) (2)</td>
<td>1 (74) (1)</td>
</tr>
</tbody>
</table>


Review Article

Therapeutic hypothermia and controlled normothermia in the intensive care unit: Practical considerations, side effects, and cooling methods

Kees H. Polderman, MD, PhD; Ingolf Kerst, MD

Conclusions: Temperature management and hypothermia induction are gaining importance in critical care medicine. Intensive care unit physicians, critical care nurses, and others (emergency physicians, neurologists, and cardiologists) should be familiar with the physiologic effects, current indications, techniques, complications, and practical issues of temperature management, and induced hypothermia. In experienced hands the technique is safe and highly effective. (Crit Care Med 2009; 37:1101–1120)

Conclusions

Hypothermia is the first neuroprotective strategy that has been shown to work in clinical practice.

It affects all of the 20+ mechanisms underlying ischemia/reperfusion.

It reduces brain edema.

Conclusions

At the very, very least, controlling fever should be a key goal of therapy in patients with neurological injury (level IIA-IIB evidence).

- Fever seems to be toxic for any brain that is severely injured.

Conclusions

Should you use cooling in post-cardiac arrest patients?

- Certainly in witnessed arrest with VT/VF (level I evidence)
- Very probably in witnessed arrest with asystole/PEA (level III evidence)

Conclusions

Induced hypothermia can definitely be used to control intracranial hypertension, and is highly effective for this purpose (Level I evidence).
Conditions for effective use of cooling in TBI:

- Patients should **NEVER** be re-warmed while they (still) have brain edema!!

Conclusions

- There are numerous reasonably effective cooling methods; you should select one that fits in your setting.
- I think cold fluid infusion should be part of your strategy for induction of hypothermia.
- I recommend using a temperature management device with feedback loop to control temperature in the maintenance and re-warming phase (and thereafter).

Temperature is an important physiological parameter in critically ill patients. Should be regarded in the same way as blood pressure, heart rate, etc.

For temperature, usually, normal is good; maybe sometimes, high = good (e.g. some cases of severe infection (??)).

But sometimes, below-normal is better.
A good analogy might be the use of a β-blocker following myocardial infarction.

Thank you for your attention!