Targeted temperature management to treat post-ischemic injuries

Kees H. Polderman

The Essex Cardiothoracic Centre, Basildon and Thurrock University Hospitals; Anglia Ruskin School of Medicine, London-Essex, United Kingdom; and United General Hospital, Houston, USA
First:
😊 Thanks for inviting me here!
Disclosures

✓ My trip here is being sponsored by BD medical.
✓ A honorarium will be paid to a research foundation.
✓ The slides and opinions presented here are my own.
Topics of my lecture:

1: Introduction
2: (Briefly): physiology/underlying mechanisms
3. Fever
4: Cardiac arrest - which temperature target?
5: Perspective & conclusions
Temperature is an important physiological parameter in critically ill patients. It should be regarded in the same way as blood pressure, heart rate, etc. So you should have a core temperature target for each patient, and a range that you are willing to accept; and if the temperature is outside that range you should react just as aggressively as you would for hypo/hypertension, or hyper/hypocapnia, or hypoxia/hyperoxia.
Destructive processes following ischemia/reperfusion.

Blue lettering = early mechanisms
Red lettering = late mechanisms

They are all stimulated by fever...
↓Mitochondrial injury and dysfunction
↓Cerebral metabolism (decrease 6-10% per °C below 37°C)
↓Ion pump dysfunction, ↓influx of calcium into cell, decreased neuroexcitotoxicity
↓Cell membrane leakage, ↓formation of cytotoxic edema, ↓intracellular acidosis
↓Production of free radicals (O₂, NO₂, H₂O₂, OH⁻)
↓Reperfusion injury
↓Apoptosis, ↓calpain-mediated proteolysis, ↓DNA injury

Suppression of epileptic activity & seizures
↓Local generation of endothelin & TxA2; ↑generation of prostaglandins
Improved cerebral repair, ↓acidosis, ↓production of toxic metabolites
"Cerebral thermo-pooling" and local hyperthermia
Decreased vascular permeability, ↓edema formation
↓Activation of protective “Early genes”

↓Immune response, ↓neuroinflammation
↓Coagulation activation, ↓formation of micro-thrombi
↓Permeability of the blood-brain barrier, ↓edema formation
↓Spreading depression-like depolarizations
↓Improved cerebral repair, ↓vascular permeability, ↓edema formation

...and inhibited by hypothermia!
Some of these processes **GENERATE HEAT.**
Brain-, blood- and rectal temperature in TBI:

Romano et al., Brain temperature exceeds systemic temperature in head-injured patients. Critical Care Medicine 1998;562-567
Brain and bladder temperature in stroke

In cardiac arrest patients:

- N=11 patients with severe injury
- Brain temperature compared to esophageal or rectal
- On average brain temperature was 0.34°C higher than core temperature.
- The difference varied, and brain temperature exceeded measured core temperature by ≥1°C for 7% of the time.
- OF NOTE, these patients were all being cooled to 32-33°C, which decreases the brain-core gradient!

Coppler PJ et al. Ther Hypothermia Temp Manag 2016;6:194-197
Sources of fever in neuro patients

**Infectious**
- **Infectious**
  - Pneumonia
  - Central lines infection
  - (Urinary Tract Infection)
  - NG Tubes
  - etc.

- **Miscellaneous**
  - Drugs, medications

**Non-Infectious**
- **Neurogenic or Central**
  - Activation of the inflammatory cascade
  - Damage to the thermoregulatory center in the hypothalamus
  - Trauma or intracranial lesions
  - Presence of ICP monitor
Sources of fever in neuro patients

Infectious

- Infectious
  - Pneumonia
  - Central lines infection
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  - NG Tubes
  - etc.

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  - Drugs, medications

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- Neurogenic or Central
  - Activation of the inflammatory cascade
  - Damage to the thermoregulatory center in the hypothalamus
  - Trauma or intracranial lesions
  - Presence of ICP monitor

- Miscellaneous
  - Drugs, medications

In addition, patients with acute brain injury have immune dysfunction, mediated through the vagal nerve and cytokine release. This has been shown for TBI but likely also occurs in other types of brain injury.
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

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)

Neurologic function

% Neurologic Function

Temperature (°C)

37°C

38°C

39°C

Wass CT et al. Anesthesiology 1995;83:325-35
Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest.

John Bro-Jeppesen, Christian Hassager, Michael Wanscher, Helle Søholm, Jakob H. Thomsen, Freddy K. Lippert, Jacob E. Møller, Lars Køber, Jesper Kjaergaard

Poor outcome when fever develops after hypothermia treatment after CA....

**Fig. 2.** Kaplan–Meier 30-days mortality plot. The curves represent mortality rates according to development of PHF (≥38.5°C), log-rank 0.02. OHCA, PHF, Post-hypothermia fever.
Fever following out-of-hospital cardiac arrest (OHCA):

Table 5. Multivariate Logistic Regression Analysis Relating Known Influencing Factors and Temperature to Neurologic Recovery*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-flow duration (measured in minutes)</td>
<td>1.34 (1.16-1.55)</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>1.02 (0.98-1.06)</td>
<td>.25</td>
</tr>
<tr>
<td>Sex</td>
<td>1.39 (0.46-4.25)</td>
<td>.56</td>
</tr>
<tr>
<td>Out-of-hospital cardiac arrest</td>
<td>0.12 (0.11-1.18)</td>
<td>.07</td>
</tr>
<tr>
<td>pH level on admission to the emergency department</td>
<td>0.16 (0.00-10.81)</td>
<td>.40</td>
</tr>
<tr>
<td>Lactate level on admission to the emergency department (measured in millimoles per liter)</td>
<td>1.10 (0.93-1.29)</td>
<td>.26</td>
</tr>
<tr>
<td>Maximum temperature†</td>
<td>2.26 (1.24-4.12)</td>
<td>.008</td>
</tr>
</tbody>
</table>
Fever following in-hospital cardiac arrest (IHCA):

Survival to Discharge (%)

- 36.1-37.0
- 37.1-38.0
- 38.1-39.0
- 39.1-40.0
- >40.0

Epidemiology and Outcomes of Fever Burden Among Patients With Acute Ischemic Stroke

Michael S. Phipps, MD; Rani A. Desai, PhD; Charles Wira, MD; Dawn M. Bravata, MD

Dose dependent risk of adverse outcome with fever burden in AIS.

Figure. In-hospital mortality or discharge to hospice and fever burden.

Table 3: Factors significantly associated with good outcome by univariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>0.95</td>
<td>0.93, 0.98</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DND</td>
<td>0.37</td>
<td>0.18, 0.77</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fever</td>
<td>0.12</td>
<td>0.05, 0.32</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Infection</td>
<td>0.21</td>
<td>0.09, 0.46</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fisher grade*</td>
<td></td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.58</td>
<td>0.06, 5.79</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.20</td>
<td>0.02, 1.69</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.13</td>
<td>0.02, 1.03</td>
<td></td>
</tr>
<tr>
<td>Number of days febrile category*</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1-2</td>
<td>0.19</td>
<td>0.06, 0.57</td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>0.13</td>
<td>0.04, 0.41</td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>0.08</td>
<td>0.02, 0.23</td>
<td></td>
</tr>
<tr>
<td>Number of infections category*</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1</td>
<td>0.29</td>
<td>0.11, 0.76</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.24</td>
<td>0.08, 0.66</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>0.10</td>
<td>0.04, 0.32</td>
<td></td>
</tr>
</tbody>
</table>

*Compared to Fisher grade 1.

*Compared to a reference of zero days febrile.

*Compared to a reference of zero infections.

Poor outcome in SAH with increasing fever burden....
Influence of Fever and Hospital-Acquired Infection on the Incidence of Delayed Neurological Deficit and Poor Outcome after Aneurysmal Subarachnoid Hemorrhage

Table 5: Predictors of good outcome* by multivariate analysis.

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<td></td>
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</tr>
<tr>
<td>1-2</td>
<td>0.19</td>
<td>0.06, 0.62</td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>0.13</td>
<td>0.04, 0.41</td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>0.08</td>
<td>0.02, 0.24</td>
<td></td>
</tr>
</tbody>
</table>

* Good outcome = GOS 4 or 5

¥ Compared to a reference of zero days febrile.
This is not really new....

- Greer et. al. (2008)
- Meta-analysis in 14,431 patients
- Fever was significantly associated with worse outcomes
Fever in a mixed neuro-ICU:

Diringer M et al. Crit Care Med 2004; 32;1489-93

- 4,295 patients with LOS >1 day
- 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

Diringer M et al. Crit Care Med 2004; 32;1489-93
Fever in hemorrhagic stroke:

- **Subarachnoid Hemorrhage**
  - Fever burden is independently associated with mortality and poor functional outcome

- **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
Does controlling fever improve outcome?
Impact of Induced Normothermia on Outcome After Subarachnoid Hemorrhage: A Case-Control Study

**FIGURE 1.** Graph showing average temperature burden for advanced fever control (AFC) and conventional fever control (CFC) patients. SE, standard error.

Impact of Induced Normothermia on Outcome After Subarachnoid Hemorrhage: A Case-Control Study

**TABLE 3. Predictors of 12-month Outcome After Subarachnoid Hemorrhage**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced fever control</td>
<td>0.2</td>
<td>0.1–0.6</td>
<td>.004</td>
</tr>
<tr>
<td>Hunt and Hess grade</td>
<td>1.6</td>
<td>1.03–2.4</td>
<td>.04</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.1</td>
<td>1.2–7.7</td>
<td>.02</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>2.6</td>
<td>0.9–8.1</td>
<td>.1</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.1</td>
<td>0.9–5.3</td>
<td>.1</td>
</tr>
<tr>
<td>Age</td>
<td>1.2</td>
<td>0.9–1.4</td>
<td>.2</td>
</tr>
</tbody>
</table>

*OR, odds ratio; CI, confidence interval.*

But don’t we need a febrile response to fight infections?
Fever Control Using External Cooling in Septic Shock
A Randomized Controlled Trial

Frédérique Schortgen1,2, Karine Clabault3, Sandrine Katsahian4, Jerome Devaquet5, Alain Mercat6, Nicolas Deye7, Jean Dellamonica8, Lila Bouadma9, Fabrice Cook10, Olfa Beji1, Christian Brun-Buisson1, François Lemaire1, and Laurent Brochard1,2,11

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**TABLE 4. SECONDARY OUTCOMES**

<table>
<thead>
<tr>
<th></th>
<th>Cooling (n = 101)</th>
<th>No Cooling (n = 99)</th>
<th>Between-Group Absolute Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressor requirement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients requiring a vasopressor dose increase during the study-treatment period, n</td>
<td>35</td>
<td>52</td>
<td>-18 (-31 to -4)</td>
<td>0.011</td>
</tr>
<tr>
<td>Shock reversal in the ICU, n</td>
<td>87</td>
<td>72</td>
<td>13 (2 to 25)</td>
<td>0.021</td>
</tr>
<tr>
<td>Time course of organ failures on Day 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA&lt;sub&gt;max&lt;/sub&gt; score, mean (SD)</td>
<td>11.4 (3.7)</td>
<td>12.3 (3.6)</td>
<td>-0.9 (-1.9 to 0.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>ΔSOFA score, mean (SD)</td>
<td>0.2 (2.1)</td>
<td>1.1 (2.7)</td>
<td>-0.9 (-1.6 to -0.2)</td>
<td>0.010</td>
</tr>
<tr>
<td>Mortality rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 14, n</td>
<td>19</td>
<td>34</td>
<td>-16 (-28 to -4)</td>
<td>0.013</td>
</tr>
<tr>
<td>ICU discharge, n</td>
<td>35</td>
<td>43</td>
<td>-9 (-22 to 5)</td>
<td>0.20</td>
</tr>
<tr>
<td>Hospital discharge, n</td>
<td>43</td>
<td>48</td>
<td>-6 (-19 to 8)</td>
<td>0.40</td>
</tr>
<tr>
<td>Length of stay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the ICU (d), mean (SD)</td>
<td>17 (14)</td>
<td>16 (17)</td>
<td>1 (-3 to 5)</td>
<td>0.67</td>
</tr>
<tr>
<td>Among ICU survivors</td>
<td>17 (14)</td>
<td>19 (16)</td>
<td>-2 (-6 to 2)</td>
<td>0.38</td>
</tr>
<tr>
<td>In the hospital (d), mean (SD)</td>
<td>36 (40)</td>
<td>28 (31)</td>
<td>9 (-1 to 19)</td>
<td>0.09</td>
</tr>
<tr>
<td>Among hospital survivors</td>
<td>43 (39)</td>
<td>35 (26)</td>
<td>8 (-2 to 17)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: ICU = intensive care unit.*
Figure 5. Kaplan-Meier survival curve for mortality until Day 14.
Induced hypothermia in patients with septic shock and respiratory failure (CASS): a randomised, controlled, open-label trial

Theis Skovgaard Itenov*, Maria Egede Johansen*, Morten Bestle, Katrin Thorner, Lars Hein, Louise Gyldensted, Anne Lindhardt, Henrik Christensen, Stine Estrup, Henrik Planck Pedersen, Matthew Harmon, Uday Kant Soni, Silvia Perez-Proto, Nicolai Wesche, Ulrik Skram, John Asger Petersen, Thomas Mohr, Tine Walsau, Lone Musaeus Poulsen, Ditte Strange, Nicole P. Juffermans, Daniel I. Sessler, Else Tennesen, Kirsten Møller, Dennis Karsten Kristensen, Alessandra Cozzi-Lepri, Jens D. Lundgren, Jens-Ulrik Jensen, for the Cooling and Surviving Septic Shock (CASS) Trial Collaboration

- N=436 patients.
- Age >50.
- Septic shock.
- Routine thermal management vs. 24 hours of TH 32-34°C.
- No benefit: 0-day mortality 44.2% vs. 35.8% (p=0.07).

Figure 3: Kaplan-Meier plot
No patients were censored. HR=hazard ratio.
OK. So, *how* can we control fever?
Overview of Cooling Methods

➢ Conventional

– Antipyretic drugs

– Evaporation:
  • Water sprays, sponge bath

– Conduction
  • Ice, water circulation, water blanket, immersion

– Convection
  • Fans, air circulating cooling blanket

– Radiation
  • Exposure

➢ Advanced

– Non-invasive core cooling

– Intravascular

Ok. So we start by giving Tylenol, or NSAID’s.
Efficacy of oral (or IV) antipyretics:

- The effectiveness of these drugs is very limited, especially in patients with neurological (central) fever.
- In large studies the average decrease in temperature during treatment with high doses (4000-6000 mg/day) of acetaminophen is only 0.3-0.4°C.\(^1\text{-}^8\)
- Similar results have been reported in smaller studies using high doses of aspirin, Ibuprofen and metamizole.\(^5\text{-}^7\)

Shivering Management

- Counter warming is the first line therapy for shivering treatment\(^1\)

- Sedation prevents increased metabolism\(^1\)

- Paralytic agents affect shivering\(^1-3\)
  - Precautions: difficult to identify seizures, select agent with anticonvulsant properties, continuous EEG may be utilized, drug metabolism is affected, appropriate dosing must be tailored to the specific conditions of the patients and must be tightly monitored

Skin counterwarming

- May reduce incidence of shivering
- Tricks skin receptors into believing the body is warm
- Warm air circulating may be used to cover these areas

Medications to combat shivering:

**Non-sedating**
- Magnesium (MgSO4, MgCl2)
- Buspirone
- Ondansetron
- Nefopam
- Clonidine
- Ketanserin
- Urapidil
- Physostigmine
- Doxapram

**Sedating**
- Meperidine/pethidine
- Opiates quick-acting: fentanyl, remi-fentanyl; or slow-acting, e.g. tramadalo or morphine)
- Propofol
- Benzodiazepines (midazolam, temazepam, diazepam, etc.)
- Dexmedetomidine
- Ketamine

**Paralytic agents**

Adapted from: Polderman KH et al. Critical Care Med 2009; 37:1101-20
So, cooling for cardiac arrest....
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.

JAMA. 2008;300(12):1423-1431

Table 5. Incidence and Outcome of Ventricular Fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Alabama (n = 65)</th>
<th>Dallas (n = 195)</th>
<th>Iowa (n = 135)</th>
<th>Milwaukee (n = 165)</th>
<th>Ottawa (n = 429)</th>
<th>Pittsburgh (n = 102)</th>
<th>Portland (n = 249)</th>
<th>Seattle (n = 297)</th>
<th>Toronto (n = 614)</th>
<th>Vancouver (n = 478)</th>
<th>Overall (n = 2729)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted incidence rate per 100,000</td>
<td>9.9</td>
<td>12.8</td>
<td>12.4</td>
<td>18.7</td>
<td>10.4</td>
<td>9.3</td>
<td>15.1</td>
<td>19.0</td>
<td>11.4</td>
<td>15.2</td>
<td>12.8</td>
</tr>
<tr>
<td>Adjusted mortality rate per 100,000</td>
<td>8.8</td>
<td>10.7</td>
<td>8.9</td>
<td>13.7</td>
<td>8.6</td>
<td>7.2</td>
<td>11.3</td>
<td>11.5</td>
<td>9.5</td>
<td>10.9</td>
<td>9.8</td>
</tr>
<tr>
<td>Case-fatality rate, %</td>
<td>69.2</td>
<td>82.7</td>
<td>72.9</td>
<td>74.0</td>
<td>83.1</td>
<td>77.5</td>
<td>73.9</td>
<td>59.8</td>
<td>83.0</td>
<td>74.7</td>
<td>76.5</td>
</tr>
<tr>
<td>Survival to discharge, %</td>
<td>7.7</td>
<td>9.5</td>
<td>22.7</td>
<td>26.0</td>
<td>14.8</td>
<td>21.5</td>
<td>22.5</td>
<td>39.9</td>
<td>15.7</td>
<td>25.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Vital status data missing, %</td>
<td>3.1</td>
<td>7.9</td>
<td>4.4</td>
<td>0</td>
<td>2.1</td>
<td>1.0</td>
<td>3.6</td>
<td>0.3</td>
<td>1.3</td>
<td>3.3</td>
<td>2.6</td>
</tr>
</tbody>
</table>

*a All rates were unequal across sites at P < .001.
Outcomes from out-of-hospital cardiac arrest in Detroit

Robert B. Dunne, Scott Compton, R.J. Zalenski, Robert Swor, Robert Welch, Brooks F. Bock

Results: During this study timeframe, there were 538 confirmed out-of-hospital cardiac arrests within the City of Detroit, of which 67 were excluded for being dead on scene [51 (12.5%)] or having no available hospital records [16 (3.0%)]. Of the remaining 471 patients, 443 (94.1%) died before hospital admission. Only 44 (9.9%) of the 471 patients had a first recorded rhythm of ventricular fibrillation (VF), and 339 (76.5%) were asystolic. Of the 28 patients who survived to hospital admission, only 2 (7.1%) were noted to have a first rhythm of VF, and 15 (53.6%) were asystolic. Only one patient survived to hospital discharge.

Conclusions: In this urban setting, out-of-hospital cardiac arrest is an almost uniformly fatal event.
3 major changes compared to 2010:

1. ☀️☀️☀️ Recommendation for strict fever management after initial period of hypothermia;
2. ☀️☀️☀️ Recommendation to treat all CA arrest patients with TTM (strong recommendation for shockable rhythms, weak recommendation for non-shockable rhythms and IHCA);
3. ☀️☀️☀️ Widening of temperature range for hypothermia from 32-34°C to 32-36°C.
AAN guidelines 2017: TTM 32-34°C recommended

Conclusions and recommendations. For patients who are comatose after an initial cardiac rhythm of VT/VF, TH (32–34°C for 24 hours) is highly likely to be effective in improving neurologic outcome and survival compared with non-TH (2 Class I studies) and should be offered (Level A).
ENLS guidelines update 2015 and 2017: no change in recommended target temperature, remains at 32-34°C
Disclosure:
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D., David Erlinge, M.D., Ph.D., Yvan Gasche, M.D., Christian Hassager, M.D., D.M.Sc., Janneke Horn, M.D., Ph.D., Jan Hovdenes, M.D., Ph.D.,

CONCLUSIONS

In unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac cause, hypothermia at a targeted temperature of 33°C did not confer a benefit as compared with a targeted temperature of 36°C.

Nicole P. Juffermans, M.D., Ph.D., Matty Koopmans, R.N., M.Sc., Lars Kober, M.D., D.M.Sc., Jørund Langørgen, M.D., Gisela Lilja, O.T., Jacob Eifer Møller, M.D., D.M.Sc., Malin Rundgren, M.D., Ph.D., Christian Rylander, M.D., Ph.D., Ondrej Smid, M.D., Christophe Werer, M.D., Per Winkel, M.D., D.M.Sc., and Hans Friberg, M.D., Ph.D., for the TTM Trial Investigators*
No significant difference between 36 and 33 degree group.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>33°C Group</th>
<th>36°C Group</th>
<th>Hazard Ratio or Risk Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome: deaths at end of trial</strong></td>
<td>235/473 (50)</td>
<td>225/466 (48)</td>
<td>1.06 (0.89–1.28)</td>
<td>0.51</td>
</tr>
<tr>
<td>Neurologic function at follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPC of 3–5</td>
<td>245/469 (52)</td>
<td>239/464 (52)</td>
<td>1.01 (0.89–1.14)</td>
<td>0.87</td>
</tr>
<tr>
<td>Modified Rankin scale score of 4–6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths at 180 days</td>
<td>226/473 (48)</td>
<td>220/466 (47)</td>
<td>1.01 (0.87–1.15)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

The only difference in favor of 33°C compared to 36°C.....

<table>
<thead>
<tr>
<th>Variable</th>
<th>33°C Group</th>
<th>36°C Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPC at follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>469</td>
<td>464</td>
</tr>
<tr>
<td>Category — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>195 (42)</td>
<td>183 (39)</td>
</tr>
<tr>
<td>2</td>
<td>23 (5)</td>
<td>39 (8)</td>
</tr>
<tr>
<td>3</td>
<td>17 (4)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>4</td>
<td>6 (1)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>5</td>
<td>228 (49)</td>
<td>220 (47)</td>
</tr>
<tr>
<td>P value for trend</td>
<td>0.85</td>
<td></td>
</tr>
</tbody>
</table>
So, why do I feel that this study doesn´t settle the case?
Argument 1: **physiology.**

Destructive processes following ischemia/reperfusion.

**Blue lettering = early mechanisms**

**Red lettering = late mechanisms**

They are all stimulated by fever...

↑Mitochondrial injury and dysfunction

↑Cerebral metabolism (increase 6-10% per °C below 37°C)

↑Ion pump dysfunction, ↑influx of calcium into cell, decreased neuroexcitotoxicity

↑Cell membrane leakage, ↑formation of cytotoxic edema, ↑intracellular acidosis

↑Production of free radicals (O₂, NO₂, H₂O₂, OH⁻)

↑Reperfusion injury

↑Apoptosis, ↑calpain-mediated proteolysis, ↑DNA injury

↑Increase of epileptic activity & seizures

↑“Cerebral thermo-pooling” and local hyperthermia

↑Local generation of endothelin & TxA₂; ↓generation of prostaglandins

More depressed cerebral repair, ↑acidosis, ↑production of toxic metabolites

Decreased tolerance for ischemia

↑Immune response, ↑neuroinflammation

↑Coagulation activation, ↑formation of micro-thrombi

↑Permeability of the blood-brain barrier, ↑edema formation

↑Spreading depression-like depolarizations

↑Activation of protective “Early genes”

Decreased vascular permeability, ↑edema formation

↑“Cerebral thermo-pooling” and local hyperthermia
↓Production of free radicals ($O_2$, $NO_2$, $H_2O_2$, $OH^-$)

↓Mitochondrial injury and dysfunction

↓Cerebral metabolism (decrease 6-10% per °C below 37°C)

↓Ion pump dysfunction, ↓influx of calcium into cell, decreased neuroexcitotoxicity

↓Cell membrane leakage, ↓formation of cytotoxic edema, ↓intracellular acidosis

↓Reperfusion injury

Suppression of epileptic activity & seizures

↓Local generation of endothelin & TxA2; ↑generation of prostaglandins

Improved cerebral repair, ↓acidosis, ↓production of toxic metabolites

↓“Cerebral thermo-pooling” and local hyperthermia

Decreased vascular permeability, ↓edema formation

↓Immune response, ↓neuroinflammation

↓Coagulation activation, ↓formation of micro-thrombi

↓Permeability of the blood-brain barrier, ↓edema formation

↓Spreading depression-like depolarizations

↓Activation of protective “Early genes”

...and inhibited by hypothermia!
✓ This is a LINEAR relationship. In general, fever control is protective, but hypothermia is more protective.

✓ For example, the metabolic rate decreases by 7-10% per °C
Arguments 2 & 3.
Dose-dependent effects of temperature on brain injury (and injury to other organs) have been demonstrated in hundreds of experiments, in every species used for experiments.
Group A (controls);

Group D (cold fluids & surface cooling)

Group E (rapid cooling with cardiac device)
Dose dependent

Fig. 3. Scattergram of infarct size (% of LV) plotted against AAR (% of LV) in normothermic controls (○; n = 11) and hypothermia (●; n = 11) groups.

Argument 4.

The baby studies....

Cooling for neonatal asphyxia.
Perinatal asphyxia - Multicenter RCT's
% Favourable outcome; n=1329 patients

N=65
+32%
+210%
P=0.01

N=208
+20%
+46%
P=0.01

N=218
+11%
+32%
P=0.05

N=325
+16%
+53%
P=0.003

N=194
+32%
+160%
P=0.001

N=111
+15%
+53%
P=0.03

N=208
+18%
+48%
P=0.01

Eicher DJ et al. Ped Neurol 2005
Gluckman PD et al. Lancet 2005
Zhou W et al. J Pediatr 2010
Simbruner G et al. Pediatr 2010
Temperature control was applied in controls in all of these studies.
Target temp in controls 36.5°C-37.0°C (active temperature management).
N=325
Target temp in controls $37.0 \pm 0.2^\circ C$ (active temperature management).

Motto: N=194

Target temp in controls 36.5-37.0 (active temperature management).

✓ Criticisms of the HACA trial and Bernard trial....
Patients assigned to normothermia were also sedated and paralyzed initially, but the target core temperature was 37°C.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TREATMENT GROUP</th>
<th>ADMISSION TO ED</th>
<th>ADMISSION TO ICU</th>
<th>6 HR</th>
<th>12 HR</th>
<th>18 HR</th>
<th>24 HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>Hypothermia</td>
<td>43</td>
<td>39</td>
<td>39</td>
<td>39</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td>24</td>
<td>23</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>Hypothermia</td>
<td>35.0±1.18</td>
<td>33.3±0.98†</td>
<td>32.7±1.19†</td>
<td>33.1±0.89†</td>
<td>36.0±1.24†</td>
<td>37.4±0.85†</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td>35.5±0.90</td>
<td>36.0±0.76†</td>
<td>37.1±0.75</td>
<td>37.4±0.58†</td>
<td>37.3±0.56†</td>
<td>37.3±0.59†</td>
</tr>
<tr>
<td>P value‡</td>
<td>0.02</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.60</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>Hypothermia</td>
<td>90.4±18.89</td>
<td>108.7±20.89†</td>
<td>97.0±14.92</td>
<td>89.5±13.16</td>
<td>88.8±9.17</td>
<td>89.1±12.9</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td>87.2±21.46</td>
<td>94.4±18.80</td>
<td>92.2±13.00</td>
<td>90.8±14.16</td>
<td>91.3±12.96</td>
<td>92.1±11.76</td>
</tr>
<tr>
<td>P value‡</td>
<td>0.51</td>
<td>0.02</td>
<td>0.16</td>
<td>0.82§</td>
<td>0.38</td>
<td>0.24</td>
<td></td>
</tr>
</tbody>
</table>

*Values with † are significantly different from normothermia at the 0.05 level.
Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children

Frank W. Moler, M.D., Faye S. Silverstein, M.D., Richard Holubkov, Ph.D., Beth S. Slomine, Ph.D., James R. Christensen, M.D., Vinay M. Nadkarni, M.D., Kathleen L. Meert, M.D., Amy E. Clark, M.S., Brittan Browning, M.S., R.D., C.C.R.C.,

N=260, 138 treated with TH (temp 33.0°C) and 122 controls (temp 36.6°C)
Table 2. Primary and Secondary Outcomes.*

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia</th>
<th>Normothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in survival</td>
<td>9% (relative 31%); p=0.14</td>
<td></td>
</tr>
<tr>
<td>Difference in good neurologic outcome: 8% (relative 53%), p=0.13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Primary outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hypothermia</th>
<th>Normothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive with VABS-II score ≥70 at 1 yr</td>
<td>27/138 (20)</td>
<td>15/122 (12)</td>
</tr>
<tr>
<td>Detailed supportive analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>87/138 (63)</td>
<td>88/122 (72)</td>
</tr>
<tr>
<td>Disability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profound§</td>
<td>16/138 (12)</td>
<td>11/122 (9)</td>
</tr>
<tr>
<td>Moderate-to-severe¶</td>
<td>8/138 (6)</td>
<td>8/122 (7)</td>
</tr>
<tr>
<td>Good functional status</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Secondary outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hypothermia</th>
<th>Normothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive at 1 yr</td>
<td>57/151 (38)</td>
<td>39/136 (29)</td>
</tr>
<tr>
<td>1-yr change in VABS-II score from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>94/151 (62)</td>
<td>97/134 (72)</td>
</tr>
</tbody>
</table>
5. The TTM trial was FLAWED. It almost seems designed to prove that TH doesn’t work.
How Low Should We Go? Hypothermia or Strict Normothermia After Cardiac Arrest?

Kees H. Polderman, MD, PhD; Joseph Varon, MD, FACP, FCCP, FCCM, FRSM

Interpreting the results of the therapeutic temperature management trial in cardiac arrest

We should not abandon therapeutic cooling after cardiac arrest

Kees H Polderman¹ and Joseph Varon²,³,⁴

Targeted Temperature Management after Cardiac Arrest

What Is the Use of Hypothermia for Neuroprotection After Out-of-Hospital Cardiac Arrest?

Francis Kim, MD; Paco E. Bravo, MD; Graham Nichol, MD

Target Temperature Management for Postcardiac Arrest Patients

Weaknesses....

- It took up to **4 hours** to randomize; no temperature management during that time
- **10 hours** to target in the 33°C group. (In animal studies the time window for TH is up to ±6 hours)
- Many other problems: potential selection bias, rapid rewarming rate, etc. etc.

Øresund bridge
INCOMPETENCE

When you truly believe that you can compensate for lack of skill by doubling your efforts, there's no end to what you can't do.
Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest

N. Nielsen\textsuperscript{1,2}, J. Hovdenes\textsuperscript{3}, F. Nilsson\textsuperscript{4}, S. Rubertsson\textsuperscript{5}, P. Stammet\textsuperscript{6}, K. Sunde\textsuperscript{7}, F. Valsson\textsuperscript{8}, M. Wanscher\textsuperscript{9} and H. Friberg\textsuperscript{1,10}, for the Hypothermia Network

\textsuperscript{1}Department of Clinical Sciences, Lund University, Lund, Sweden, \textsuperscript{2}Departments of Anaesthesiology and Intensive Care, Helsingborg Hospital, Helsingborg, Sweden, \textsuperscript{3}Rikshospitalet, Oslo, Norway, \textsuperscript{4}Competence Centre for Clinical Research, Lund University, Lund, Sweden, \textsuperscript{5}Uppsala University Hospital, Uppsala, Sweden, \textsuperscript{6}Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg, \textsuperscript{7}Department of Anaesthesiology and Institute for Experimental Medical Research, Ullevål University Hospital, Oslo, Norway, \textsuperscript{8}Departments of Anaesthesiology and Intensive Care, Landspitali University Hospital, Reykjavik, Iceland, \textsuperscript{9}Rigshospitalet, Copenhagen, Denmark and \textsuperscript{10}Sweden and Lund University Hospital, Lund, Sweden

Time to initiation of TH was 90 min (60–165 min) and to achievement of the target temperature (≤ 34 °C) was 260 min (178–400 min)
Weaknesses....

- It took up to 4 hours to randomize; no temperature management during that time
- 10 hours to target in the 33°C group. (In animal studies the time window for TH is up to ±6 hours)
- Pre-screening of patients by the ER physician, who decided whether patients would receive the routine treatment (=TH), or whether treatment should be withheld and the study coordinator called to screen them for the study. This almost guarantees selection bias.
- This explains the enrollment rate of 65.6%, the highest in any study that I have ever seen
- Enrolment number of 1 per center/month (or 1.5, according to a subsequent publication by the authors); ≠ all CA patients admitted in the study period; = selection for sure, possible selection bias
Weaknesses....

- Small imbalances between groups, mostly in favor of the 36°C group
- Rapid rewarming rate of 0.5°C/hr; why???? Why not 0.25°C which was standard in most centers?
- No temperature data beyond 36 hours; in contrast to all other studies looking at temperature in CA and the 7 multicenter RCT’s in neonatal asphyxia. Why was this never provided in any of the 60+ publications resulting from this study, or any of the rebuttals to the published criticisms by myself and others??