Cooling After Cardiac Arrest

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Disclosures

NO FINANCIAL CONFLICT OF INTEREST

• Research Grants:
  – NINDS K23NS075363

• American Heart Association (Volunteer)
  – Get with The Guidelines Resuscitation Pediatric Task Force, Past Chair
  – Emergency Cardiovascular Care Pediatric Emphasis Group, Member
  – Emergency Cardiovascular Care
Disclosures
I am a Pediatric Intensivist
Adults are Just Big Children.....

Objectives
• Review targeted temperature management guidelines and supporting data
• Discuss basics of targeted temperature management
19 year old boy playing basketball

- Collapses in the middle of the court
- **Bystander** CPR performed with AED administered **defibrillation** twice
- EMS arrival
  - asystole with ongoing bystander CPR
- Intubated and transported to emergency department

What temperature do you want?

- In the field?
- In the ambulance?
- In the ED?
- In the ICU?
The Chain of Survival
When does the Resuscitation end?

Post Arrest Care

Systemic Inflammatory-like response: similar to sepsis
- Brain injury
- Myocardial dysfunction
- Ischemia/reperfusion response
- Persistent precipitating pathophysiology

Kronick et al., Circulation, 2015

Post Cardiac Arrest Syndrome. Epidemiology, Pathophysiology, Treatment, and Prognostication: A Consensus Statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and
Post Cardiac Arrest Care: Brain - Goal Directed Therapy

- Blood Pressure
- Temperature
- Oxygen
- Ventilation
- Seizures
- Metabolism/Glucose
Targeted Temperature Management

THEN

NOW

AHA: Targeted Temperature Management

- We recommend comatose adults with ROSC to have TTM for VF/pVT and non-VF/pVT OHCA and IHCA
- We recommend selecting and maintaining a constant temperature between 32°C and 36°C during TTM, for at least 24 hours...
- It may be reasonable to actively prevent fever in comatose patients after TTM

Callaway, Circulation, 2015
Bladder Temperature Course

Normothermia (n = 124)

Hypothermia (n = 123)
### Mild Therapeutic Hypothermia

**Out-of-hospital VF Cardiac Arrest**

<table>
<thead>
<tr>
<th>6 months</th>
<th>Hypothermia</th>
<th>Control</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Neuro</td>
<td>75/136**</td>
<td>54/137**</td>
<td><strong>1.40 (1.08-1.81)</strong></td>
</tr>
<tr>
<td></td>
<td>*(53%)</td>
<td><em>(36%)</em></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>56/137*</td>
<td>76/138*</td>
<td><em>0.74 (0.58-0.95)</em></td>
</tr>
<tr>
<td></td>
<td>*(41%)</td>
<td><em>(55%)</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>P = 0.02</strong></td>
<td><strong>P = 0.009</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Good Neuro = CPC 1 or 2  Hypothermia = 32-34 °C for 24 hrs

HACA, *NEJM* 2002

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### Mild Therapeutic Hypothermia

**Out-of-hospital VF Cardiac Arrest**

<table>
<thead>
<tr>
<th>Good Outcome</th>
<th>Hypothermia</th>
<th>Control</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21/43*</td>
<td>9/34*</td>
<td><strong>5.25 (1.47-18.76)</strong></td>
<td></td>
</tr>
<tr>
<td><em>(49%)</em></td>
<td><em>(26%)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P = 0.046</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Good outcome = discharged to home  Hypothermia = 33 °C for 12 hrs

Bernard, *NEJM* 2002
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Niklas Nielsen, M.D., Ph.D., Jarn 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.,
Jesper Kjaergaard, M.D., D.M.Sc., Michael Kuiper, M.D., Ph.D., Tommaso Pellis, M.D.,
Pascal Stamment, M.D., Michael Wünscher, M.D., Ph.D., Matt P. Wise, M.D., D.Phil.,
Anders Åneman, M.D., Ph.D., Nawaf Al-Subaie, M.D.,
Søren Boesgaard, M.D., D.M.Sc., John Bro-Jeppesen, M.D., Iole Brunetti, M.D.,
Jan Frederik Bugge, M.D., Ph.D., Christopher D. Hingston, M.D.,
Nicole P. Juffermans, M.D., Ph.D., Matty Koopmans, R.N., M.Sc.,
Lars Kéber, M.D., D.M.Sc., Jarund Langergan, 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*

TTM-trial – 2010-2013

- 950 patients randomized
- 36 hospitals
- 10 countries
- Europe and Australia

Funded by:
Swedish Heart Lung Foundation
AFA-insurance Foundation, Sweden
Swedish Research Council
Governmental and Regional funding within the Swedish National Health System
TrygFoundation, Denmark
Zoega, Krapperup, Thure Carlsson, Trolle-Wachtmeister foundations, Sweden

From Ben Abella
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>33°C</th>
<th>36°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>473</td>
<td>466</td>
</tr>
<tr>
<td>Age</td>
<td>64+/-12</td>
<td>64+/-13</td>
</tr>
<tr>
<td>Male sex</td>
<td>83%</td>
<td>79%</td>
</tr>
<tr>
<td>Arrest in place of residence</td>
<td>52%</td>
<td>55%</td>
</tr>
<tr>
<td>Arrest in public place</td>
<td>42%</td>
<td>40%</td>
</tr>
<tr>
<td>Bystander witnessed</td>
<td>89%</td>
<td>90%</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>73%</td>
<td>73%</td>
</tr>
<tr>
<td>Shockable rhythm</td>
<td>79%</td>
<td>81%</td>
</tr>
<tr>
<td>Arrest to ROSC (min)</td>
<td>25 [18-40]</td>
<td>25 [16-40]</td>
</tr>
<tr>
<td>Circulatory shock</td>
<td>15%</td>
<td>14%</td>
</tr>
<tr>
<td>Lactate mmol/L</td>
<td>6.7±4.5</td>
<td>6.7±4.5</td>
</tr>
<tr>
<td>ST-elevation infarction</td>
<td>40%</td>
<td>42%</td>
</tr>
<tr>
<td>GCS</td>
<td>3 [3-4]</td>
<td>3 [3-4]</td>
</tr>
</tbody>
</table>

From Ben Abella

The TTM Trial – Nielsen et al

No difference in survival

Survival

Kaplan-Meier estimates for time to death in TTM-trial intervention groups

P=0.51

From Ben Abella
Making Sense of the Differences

<table>
<thead>
<tr>
<th>Condition</th>
<th>No Cooling</th>
<th>33°C</th>
<th>36°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cooling</td>
<td>36%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>33°C</td>
<td>26%</td>
<td>49%</td>
<td>50%</td>
</tr>
<tr>
<td>36°C</td>
<td>33%</td>
<td></td>
<td>52%</td>
</tr>
</tbody>
</table>

How can this be?

Nielsen et al                           HACA study
~36.0°C                                ~37.6°C

Nielsen et al
Bernard et al: ~37.3°C

Large difference in maintenance temperatures
AHA: Pre-hospital Hypothermia

- We recommend against the routine prehospital cooling of patients after ROSC with rapid infusion of cold intravenous fluids.

Callaway, Circulation, 2015

Effect of Prehospital Induction of Mild Hypothermia on Survival and Neurological Status Among Adults With Cardiac Arrest: A Randomized Clinical Trial

- RCT of cooling prehospital standard of care
  - **VF**: 62.7% vs 64.3%, p = 0.69
  - **Non-VF**: 19.2% vs 16.3%, p = 0.3
- Outcomes: survival to discharge
  - Intervention group had more re-arrest in the fields, increased pulmonary edema and diuretic use in the first 24 hours post arrest
AHA PALS Guidelines 2015: Temperature

- If comatose after OHCA it is reasonable
  - 5 days of normothermia (36°C to 37.5°C)
  OR
  - 2 days of hypothermia (32°C to 34°C)
    followed by 3 days of continuous normothermia
- If comatose after IHCA, insufficient evidence to recommend cooling over normothermia

Fever (≥ 38°C) should be aggressively treated

de Caen et al., Circulation, 2015
Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children

Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children

- U01 HL094345
- U01 HL094339
- R21 HD044599
- R34 HD050531

Supported by funding from HRSA/MCHB/EMSC

Moler, NEJM 2015

THAPCA: Out of Hospital Cardiac Arrest

- 2 days to 18 years old
- Motor GCS < 5
- CPR > 2 minutes
- Randomized within 6 hours of ROSC
- Hypothermia: 155 subjects
- Normothermia: 140 subjects

Moler, NEJM, 2015

0→ 120 hours
THAPCA Outcomes

CONCLUSIONS

OHCA
In comatose children who survived out-of-hospital cardiac arrest, therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit in survival with a good functional outcome at 1 year. (Funded by the National Heart, Lung, and Blood Institute and others; THAPCA-OH ClinicalTrials.gov number, NCT00878644.)

IHCA

RESULTS

PATIENTS
The trial was stopped on February 27, 2015, because of futility after a review of interim efficacy analyses by the data and safety monitoring board.

Does Treatment Change Outcome?

Maybe for some
Stratify Degree of Brain Injury on Admission

0-6 hours

mild / none → Good outcome with any treatment
moderate → Aggressive personalized post-resuscitation care
severe → Poor outcome with any treatment
Hypothermia side effects:

**Induction**

- Insulin resistance
- Hyperglycemia
- Insulin infusion

**Hypotension**

- Hypokalemia
- Hypophosphatemia
- Hypomagnesemia

**Fluid bolus**

- Increased venous return
  - ↑ ANP
  - ↓ ADH
- ↓ Heart rate
  - ↑ SVR
  - ↓ Cardiac output

**Hypertension Bradycardia**

**Electrolyte replacement**

- intracellular shift of potassium

**Hypothermia side effects**

- ↓ platelet count
  - ↑ bleeding time
  - clotting dysfunction

- ↑ bleeding risk

- ↓ white cell function
  - ↓ inflammation
  - ↓ phagocytosis

- ↑ infection risk
Other side effects

• Skin breakdown
• EKG changes
  – Prolonged PR
  – Widened QRS
  – Increased QT
• Shivering
• Altered drug metabolism
• Blood gas analysis
• Increased ketone and lactate production
• Mild increase amylase, ALT, AST

• 61 TH vs. 58 HC
• Multiple interventions implemented at one time:
  – TH (33°C for 24 hours)
  – PCI
  – Hemodynamic optimization (MAP>65
  – Treat seizures, optimize, SaO2, CO2, urine output
  – 30% absolute mortality reduction
• “A resuscitation bundle can improve outcomes in comatose post-arrest patients”

Sunde et al. Resuscitation, 2007
Aspects of the care bundle

Table 3: Inhospital treatment in the control (1996–1998) and intervention (2003–2005) periods, presented as absolute numbers (percentage) or means±5.0. (Fluid balance)

<table>
<thead>
<tr>
<th></th>
<th>Control period (n= 50)</th>
<th>Intervention period (n= 61)</th>
<th>OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reperfusion treatment</td>
<td>2 (2)</td>
<td>30 (49)</td>
<td>27.10 (6.06, 121.09)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Therapeutic hypothermia</td>
<td>0</td>
<td>40 (66)</td>
<td>n.a.</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Inotropic agents</td>
<td>29 (50)</td>
<td>43 (80)</td>
<td>2.39 (1.13, 5.08)</td>
<td>0.022</td>
</tr>
<tr>
<td>Intra aortic balloon pump</td>
<td>0</td>
<td>8 (15)</td>
<td>n.a.</td>
<td>0.004*</td>
</tr>
<tr>
<td>Glyceryl trinitrate</td>
<td>31 (53)</td>
<td>0</td>
<td>n.a.</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fluid balance 1st day (ml)</td>
<td>2300 ± 1211</td>
<td>3435 ± 1594</td>
<td>10.72 (3.45, 33.33)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Insulin</td>
<td>4 (7)</td>
<td>27 (44)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reperfusion treatment was only by PCI in the intervention period and by thrombolitics in the control period. n.a. not applicable.
a, Fisher’s exact test.
b, Two sided p-values for continuous variables from Student’s t-test.

Sunde et al, Resuscitation, 2007

Should you Cool?

- Fever is harmful and should be prevented
- Optimal temperature target is not clear and may depend on patient level factors
- Stratifying brain injury severity early may allow targeted temperature depth and duration to be personalized in the future
- Treat the other derangements of the post cardiac arrest syndrome including hypotension

YES, TTM!
How Do You Do All of This?

- Debrief and set goals for next steps
- Define who the key team members are
- Continuously monitor temperature
- Have a plan to preempt and respond

ILCOR Post Arrest Checklist

Table 1: Postarrest Checklist

<table>
<thead>
<tr>
<th>Oxygenation and ventilation</th>
<th>Peds</th>
<th>ALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure oxygenation and target normoxemia.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Avoid hypoxia.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Measure Paco₂, and target a clinically appropriate value.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Avoid hypoxemia.</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Hemodynamic monitoring

- Monitor blood pressure.
- Set hemodynamic goals during postresuscitation care.
- Use parenteral fluids and/or inotropes or vasopressors to maintain a systolic blood pressure

Targeted temperature management

- Measure and monitor core temperature; prevent and treat fever.
- In children, apply TTM (22°C-34°C or 36°C-37.5°C) for at least 24 hours if unresponsive after ROSC.
- In adults, select and maintain a constant target temperature between 32°C and 36°C if unresponsive after ROSC; if used, apply for at least 24 hours.
- Prevent fever after rewarming.

Neuromonitoring

- Treat clinical seizures.
- Do not routinely use pharmacologic prophylaxis for seizures.

Glucose control

- Measure glucose.
- Avoid hypoglycemia.
- In adults, follow standard glucose control protocols.

Prognosis

- Always consider multiple modalities (clinical and other) over any single predictor factor.
- EEG may be useful within the first 7 days.
- Somatosensory evoked potentials may be useful after 72 hours.
- Blood biomarkers may be measured repeatedly over 72 hours.
- Neuroimaging such as CT in the initial hours and MRI during the first 6 days may be valuable.
- Remember that assessments may be modified by TTM or induced hypothermia.

ALS indicates advanced life support; CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; ROSC, return of spontaneous circulation; and TTM, targeted temperature management.

de Caen and Maconchie, Circulation, 2015
Thank you
**Too Hot?**

Temperature patterns in the early postresuscitation period after pediatric inhospital cardiac arrest

- 549 children
- 43% at least 1 temperature > 38°C
- 5% had persistent hyperthermia
- **Hyperthermia associated with worse neurologic outcomes**

Bembea, PCCM, 2010

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**Too Cold?**

Influence of hypothermia, barbiturate therapy, and intracranial pressure monitoring on morbidity and mortality after near-drowning

- 40 children suffered non-fatal drowning
- Phenobarbital, paralysis, ICP < 15, hyperventilation
- **Hypothermia 30-33°C for 24-36 hours**
- **No benefit of hypothermia and severe neutropenia**

Bohn, CCM, 1986