Therapeutic Hypothermia

A Piece of the Northland in the ICU

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St. Luke’s Cardiology Associates
Duluth, Minnesota
Disclosures

- None
Case

- 65-year-old male
  - At home working in his garden
  - Loses consciousness
  - Wife
    - Calls 911
    - Initiates CPR

- EMS arrives
  - Ventricular fibrillation
  - Perfusing rhythm within 10 minutes
  - Repeated episodes of VF resulting in multiple shocks and CPR
Case

- Unresponsive after restoration of spontaneous circulation (ROSC)
- Initial ECG: inferior STEMI
- Further VT/VF in ED
- Taken to cath lab for PCI
- ER personnel
  - IV iced saline
  - Ice packs
ECG

PR 157
QRSD 99
QT 378
QTc 404

---AXIS---
P 64
QRS 36
T 87

ABNORMAL ECG

Confirmed By: Scott Mikesell DO 07/16/2013 14:19:42
Case

- Cath Lab – RCA culprit
- ICU
  - Surface cooling pads applied
  - Therapeutic hypothermia x 24 hours
  - Rewarmed
- Day 7 – awake, alert, interactive
- Discharged home
Outline

Epidemiology
Biology
Evidence
Management, expectations, side effects
Patient selection
Epidemiology & Hypothermia History
Epidemiology – Cardiac Arrest

Out-of-hospital cardiac arrest (OHCA)
- 300,000 – 450,000 people annually in the US
- 40,000 survive to hospitalization
- Systemic, neurologic & cardiac sequelae
- One third survive to hospital discharge


Epidemiology – Cardiac Arrest

- 80% remain comatose for >1 hour post-resuscitation
- < 50% recover good neurologic activity as defined by the Cerebral Performance Category scale (CPC), range 1-5, higher scores = worse

CPC Scale

- 1 = Good recovery
- 2 = Moderate disability (independent ADLs)
- 3 = Severe disability (dependent daily support)
- 4 = Coma or vegetative state
- 5 = Brain death

Hypothermia History

- 1950s - cardiac and neurologic surgeries
- Late 1950s - after cardiac arrest
  - uncertain benefits
  - difficulties with implementation
- 1990s - studies in animal models
  - histological benefits
  - functional benefits
- 2002 - randomized clinical trials of TH
Biology
Hypothermia

A condition in which an organism's temperature drops below that required for normal metabolism and body function.

- Stratified into four categories:
  - Mild (32 - 35°C or 90 - 95°F)
  - Moderate (28 - 32°C or 82.4 - 90°F)
  - Severe (20 - 28°C or 68 - 82.4°F)
  - Profound (< 20°C or < 68°F)
Brain stores of oxygen lost in seconds
Glucose, ATP lost within 5 minutes
Loss of transmembrane electrochemical gradient
Loss of synaptic, axonal function
Glutamate is released leading to excitotoxic cell death
Intracellular calcium accumulates leading to cell death (necrosis and apoptosis)
Vulnerable areas = hippocampus, neocortex, cerebellum, corpus striatum, thalamus

Holzer, M. Targeted Temperature Management for Comatose Survivors of Cardiac Arrest. 
NEJM 2010; 363:1256-64.
Biology

Restoration of circulation, reperfusion and reoxygenation – further neuronal damage due to -

- Microcirculation failure – transient hyperemia
- Followed by prolonged global/microfocal hypoperfusion
- Reactive oxygen species (lipid peroxidation, oxidative damage)
- Inflammatory response leading to endothelial activation, leukocyte infiltration → tissue injury
- Brain edema limiting perfusion

Mechanisms

- Hypothermia
  - Lower metabolic rate
  - Less oxygen consumption

- Ischemia
  - Glutamate release
  - Calcium shifts
  - Excitotoxicity
  - Inflammatory cascades
  - Cell death
  - Blood brain barrier disruption & cerebral edema

- Reperfusion
  - Mitochondrial dysfunction
  - Oxygen-free radicals

Limit neurologic injury

- Reduction in brain metabolism (less oxygen and ATP utilization)
- Inhibition of release of glutamate and dopamine
- Induction of brain-derived neurotrophic factor (less glutamate)
- Inhibition of calcium overload & pro-apoptotic factors
- Induction of anti-apoptotic factors
- Limited inflammation/edema

Management of TH

1. Initiation
   - Start cooling immediately
   - Analgesia/Sedation
   - Recognize/treat shivering

2. Maintenance
   - Close attention to BP, O₂ sat, volume, glucose, K⁺, seizures

3. Rewarming
   - Begin 24h after induction
   - 0.25°/hr
   - Watch BP, glucose, K⁺

4. Normothermia
   - Avoid fevers

Scirica B M Circulation. 2013;127:244-250
Evidence
Multicenter, randomized, controlled trial with blinded assessment of outcome.

Inclusion -

▪ Positive ROSC
▪ Witnessed VT/VF arrest
▪ Age 18 – 75 years old
▪ Estimated time to resuscitation of 5 – 15 minutes by EMP
▪ Interval no greater than 60 minutes from collapse to restoration of spontaneous circulation

Holzer, M. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. NEJM 2002; 346:549-56.
Multicenter, randomized, controlled trial with blinded assessment of outcome.

Exclusion -

- Temperature < 30° C on admission
- Comatose state prior to arrest d/t drug administration
- Pregnancy
- Hypotension (MAP < 60 mmHg) for > 30 min. post-ROSC
- Hypoxemia (SpO₂ < 85% for > 15 min. post-ROSC)
- Terminal illness
- “Factors that made participation in follow-up unlikely”
- Enrollment in another study
- Cardiac arrest post-EMP arrival
- Known coagulopathy

Holzer, M. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. NEJM 2002; 346:549-56.
Hypothermia after Cardiac Arrest Study Group

Primary outcome

- Favorable neurologic outcome within 6 months
  
  CPC Scale
  
  - 1, 2, 3, 4, 5
  
  - Blinded assessment

Secondary end points

- Mortality at 6 months
- Rate of complications during the 1st 7 days post-ROSC
- Bleeding of any severity, pneumonia, sepsis, pancreatitis, renal failure, pulmonary edema, seizures arrhythmias and pressure sores were all recorded

Hypothermia after Cardiac Arrest Study Group

Therapies –

– ACS management
– Standard ICU management
– Sedation + paralysis (shivering), mechanical ventilation
– Temperature monitoring via bladder
– Cooling via TheraKool device (cooling blanket) to 32 – 34° C within 4 hours post-ROSC
– Ice packs if not at goal
– 24 hours at target temperature
– Passive rewarming

Holzer, M. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. NEJM 2002; 346:549-56.
Inclusion –
- Initial rhythm of VT/VF
- Successful ROSC

Exclusion –
- Age < 18 for men, < 50 for women
- Cardiogenic shock (SBP < 90 mmHg despite Epi)
- Coma due to other causes
- No ICU bed

Therapies –

- Hypothermia versus normothermia
- EMPs initiated hypothermia in the field with cold packs
- Sedation, paralysis, mechanical ventilation
- Standard ICU management
- ACS therapy
- Lidocaine bolus followed by infusion
- PRN KCl for levels < 4.0
- Insulin
- Aspirin
- PA catheter
- Cooling via ice packs
- Active rewarming

**Australian Group**

**Table 1. Clinical Characteristics of the 77 Patients with Anoxic Brain Injury Who Were Eligible for Randomization.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypothermia (N=43)</th>
<th>Normothermia (N=34)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td>0.55</td>
</tr>
<tr>
<td>Median</td>
<td>66.8</td>
<td>65.0</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>49–89</td>
<td>41–85</td>
<td></td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>58</td>
<td>79</td>
<td>0.05</td>
</tr>
<tr>
<td>Arrest witnessed (%)</td>
<td>05</td>
<td>94</td>
<td>0.81</td>
</tr>
<tr>
<td>Bystander performed cardiopulmonary resuscitation (%)</td>
<td>49</td>
<td>71</td>
<td>0.05</td>
</tr>
<tr>
<td>Time from collapse to emergency-medical-services call (min)</td>
<td>2.1±1.9</td>
<td>2.7±3.0</td>
<td>0.32</td>
</tr>
<tr>
<td>Time from call to emergency-medical-services arrival (min)</td>
<td>7.9±3.1</td>
<td>8.3±2.8</td>
<td>0.60</td>
</tr>
<tr>
<td>Time from arrival to first DC shock (min)</td>
<td>2.5±2.2</td>
<td>2.0±1.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Time from first shock to return of spontaneous circulation (min)</td>
<td>13.6±11.2</td>
<td>12.1±7.9</td>
<td>0.48</td>
</tr>
<tr>
<td>Time from collapse to return of spontaneous circulation (min)</td>
<td>26.5±12.9</td>
<td>25.0±8.9</td>
<td>0.54</td>
</tr>
<tr>
<td>Number of DC shocks</td>
<td>4.2±3.0</td>
<td>4.1±3.2</td>
<td>0.87</td>
</tr>
<tr>
<td>Dose of epinephrine (mg)</td>
<td>2.2±2.1</td>
<td>2.2±1.9</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. DC denotes direct current.*

Good outcome of hypo- to normothermia = 49% to 26%; p = .046

Unadjusted odds ratio = 2.65 (1.02 – 6.88; p = .046)

Adjusted odds ratio (age, time to ROSC) = 5.25 (1.47 – 18.76; p = .011)
Is there a time window for initiation of mild hypothermia?

- Delay in initiation of cooling negates beneficial neurologic effects (glutamate)
- Cardiac arrest in mice with intra-arrest cooling, improved outcome as compared to post-arrest
- Cardiac arrest in dogs with cooling while in VF for 40 minutes preserved organ viability and improved outcome
- Clinical trials demonstrate at least 60 minutes to cooling goals in the community clinical scenario

Is there a time window for initiation of mild hypothermia?

Is there a time window for initiation of mild hypothermia?

Is there a time window for initiation of mild hypothermia?

<table>
<thead>
<tr>
<th></th>
<th>Delayed hypothermia</th>
<th>Early hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPC 5 or death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>OPC 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>OPC 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>OPC 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>OPC 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NDS (%)</td>
<td>[0]</td>
<td>5.5 (0.57)</td>
</tr>
<tr>
<td>HDS</td>
<td>[32, 38, 45]</td>
<td>0 (0.98)</td>
</tr>
<tr>
<td>MDS (%)</td>
<td>68.5 (47-93)</td>
<td>58.5 (43-93)</td>
</tr>
</tbody>
</table>

**Resuscitation Variables**

<table>
<thead>
<tr>
<th>Group</th>
<th>DH</th>
<th>EH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countershocks, total</td>
<td>13 (1-58)</td>
<td>1 (1-8)</td>
<td>0.125</td>
</tr>
<tr>
<td>Countershocks, total energy, J</td>
<td>2755 (150-14 770)</td>
<td>185 (150-1510)</td>
<td>0.125</td>
</tr>
<tr>
<td>ROSC, min of CPB</td>
<td>51 (15-235)</td>
<td>16.5 (15-80)</td>
<td>0.395</td>
</tr>
<tr>
<td>Total bicarbonate, mEq</td>
<td>107 (55-175)</td>
<td>95 (40-230)</td>
<td>0.908</td>
</tr>
<tr>
<td>Total epinephrine, mg</td>
<td>2.45 (1.3-4.3)</td>
<td>0.75 (0.2-3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total NE, mg</td>
<td>13.86 (5.22-26.64)</td>
<td>17.80 (2.47-112.94)</td>
<td>0.674</td>
</tr>
<tr>
<td>Duration of NE infusion, h</td>
<td>5.3 (2.9-25.6)</td>
<td>20.5 (0.0-85.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Survival, h</td>
<td>21 (4-96)</td>
<td>96 (48-96)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

NE indicates norepinephrine. Data are given as median (range).

Hypothermia and Defibrillatory Success

- Patients with cardiac arrest are at increased risk for refibrillation
- Concern for refibrillation while cooled as well as increased risk for arrhythmias while hypothermic
- Previous investigation demonstrated improved defibrillation with severe hypothermia (30°C) with less post-defibrillation ventricular asystole

Hypothermia and Defibrillatory Success

**TABLE 1. Hemodynamic Data at Baseline and After Induction of Hypothermia**

<table>
<thead>
<tr>
<th></th>
<th>Normothermia</th>
<th>Mild Hypothermia</th>
<th>Moderate Hypothermia</th>
<th>Severe Hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>65.3±1.4</td>
<td>70.7±2.4</td>
<td>66.4±1.5</td>
<td>61.3±1.0</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>145.6±6.5</td>
<td>140.5±10.1</td>
<td>145.6±9.1</td>
<td>128.9±6.4</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>6.3±0.6</td>
<td>6.9±0.3</td>
<td>6.9±0.4</td>
<td>7.3±0.4</td>
</tr>
<tr>
<td>CO, L/minute</td>
<td>5.4±0.3</td>
<td>5.2±0.2</td>
<td>6.1±0.3</td>
<td>4.8±0.5</td>
</tr>
<tr>
<td>CPP, mm Hg</td>
<td>46.0±1.1</td>
<td>50.4±2.6</td>
<td>46.6±1.5</td>
<td>40.6±0.8</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>37.0±0.3</td>
<td>36.9±0.2</td>
<td>37.0±0.2</td>
<td>37.3±0.2</td>
</tr>
<tr>
<td><strong>Hypothermia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>68.3±2.6</td>
<td>64.9±1.6</td>
<td>63.4±1.8</td>
<td>56.6±2.4‡</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>150.5±5.7</td>
<td>138.5±12.6</td>
<td>132.1±6.1</td>
<td>120.3±9.6</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>6.8±0.5</td>
<td>6.1±0.4</td>
<td>6.6±0.3</td>
<td>6.5±0.6</td>
</tr>
<tr>
<td>CO, L/minute</td>
<td>5.5±0.5</td>
<td>4.7±0.3</td>
<td>4.7±0.3</td>
<td>3.0±0.3‡</td>
</tr>
<tr>
<td>CPP, mm Hg</td>
<td>48.9±2.3</td>
<td>46.0±1.3</td>
<td>45.6±1.8</td>
<td>41.6±1.8†</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>37.0±0.2</td>
<td>34.9±0.0</td>
<td>33.0±0.0</td>
<td>30.0±0.0</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *P* value is from test of mean contrast in linear mixed model analysis.
*After induction of hypothermia in 3 groups or equivalent time in normothermia group, before induction of VF.
†*P*≤0.05, ‡*P*≤0.01, hypothermia vs normothermia.

Hypothermia and Defibrillatory Success

Hypothermia and Defibrillatory Success

Should hypothermia be induced intra-arrest?

- Cooling improves neurologic outcome post-ROSC
- Post-reperfusion injury rapidly evolves post-ROSC
- Earlier cooling improves outcomes in animal models
- Earlier and moderate hypothermia improves successful defibrillation and prevents post-ROSC arrhythmias in animal models
Retrospective analysis of patients with out-of-hospital cardiac arrest (OHCA)

- Included if experienced non-traumatic OHCA and ≥ 18 years old
- Excluded if pregnant, arrest secondary to drowning, DNR order or obvious signs of death

Should hypothermia be induced intra-arrest?

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Total population</th>
<th>Normothermic</th>
<th>IATHa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, 95% confidence interval)</td>
<td>64.5 (63.0–66.0)</td>
<td>63.9 (62.0–65.7)</td>
<td>65.9 (63.6–68.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>212 (39.1%)</td>
<td>127 (38.0%)</td>
<td>85 (40.9%)</td>
</tr>
<tr>
<td>Male</td>
<td>330 (60.9%)</td>
<td>207 (62.0%)</td>
<td>123 (59.1%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minority</td>
<td>264 (48.7%)</td>
<td>161 (48.2%)</td>
<td>103 (49.5%)</td>
</tr>
<tr>
<td>White</td>
<td>278 (51.3%)</td>
<td>173 (51.8%)</td>
<td>105 (50.5%)</td>
</tr>
<tr>
<td>Presenting rhythm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-VF/VTb</td>
<td>423 (78.0%)</td>
<td>259 (77.5%)</td>
<td>164 (78.8%)</td>
</tr>
<tr>
<td>VF/VT</td>
<td>119 (22.0%)</td>
<td>75 (22.5%)</td>
<td>44 (21.2%)</td>
</tr>
<tr>
<td>Witnessed arrest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>252 (46.5%)</td>
<td>148 (44.3%)</td>
<td>104 (50.0%)</td>
</tr>
<tr>
<td>Yes</td>
<td>290 (53.5%)</td>
<td>186 (55.7%)</td>
<td>104 (50.0%)</td>
</tr>
<tr>
<td>Bystander CPRc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>377 (69.6%)</td>
<td>232 (69.5%)</td>
<td>145 (69.7%)</td>
</tr>
<tr>
<td>Yes</td>
<td>165 (30.4%)</td>
<td>102 (30.5%)</td>
<td>63 (30.3%)</td>
</tr>
</tbody>
</table>

a IATH = intra-arrest therapeutic hypothermia.
b VF/VT = ventricular fibrillation/ventricular tachycardia.
c CPR = cardio-pulmonary resuscitation.

Should hypothermia be induced intra-arrest?


<table>
<thead>
<tr>
<th>Association between IATH and ROSC, survival to admission, and discharge.</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehospital ROSC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>Unadjusted OR&lt;sup&gt;b&lt;/sup&gt; (95% confidence interval)</td>
<td>Adjusted&lt;sup&gt;c&lt;/sup&gt; OR (95% confidence interval)</td>
</tr>
<tr>
<td>Normothermic</td>
<td>90 (26.9%)</td>
<td>244 (73.1%)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>IATH&lt;sup&gt;d&lt;/sup&gt;</td>
<td>76 (36.5%)</td>
<td>132 (63.5%)</td>
<td>1.56 (1.07–2.26)</td>
<td>1.83 (1.19–2.81)</td>
</tr>
<tr>
<td>Survival to admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normothermic</td>
<td>78 (23.4%)</td>
<td>256 (76.6%)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>IATH</td>
<td>59 (28.4%)</td>
<td>149 (71.6%)</td>
<td>1.30 (0.88–1.93)</td>
<td>1.50 (0.96–2.36)</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normothermic</td>
<td>40 (12.0%)</td>
<td>294 (88.0%)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>IATH</td>
<td>26 (12.5%)</td>
<td>182 (87.5%)</td>
<td>1.05 (0.62–1.78)</td>
<td>1.03 (0.54–1.98)</td>
</tr>
</tbody>
</table>

<sup>a</sup> ROSC = return of spontaneous circulation.

<sup>b</sup> OR = odds ratio.

<sup>c</sup> OR adjusted for confounding variables age, gender, race, initial presenting rhythm, witnessed arrest, and bystander CPR.

<sup>d</sup> IATH = intra-arrest therapeutic hypothermia.
Should hypothermia be induced intra-arrest?

Frequency of ROSC per initial rhythm

Volume of chilled saline versus likelihood of ROSC

A cardiac arrest is a cardiac arrest, right???

- PEA/asystole may not behave similar to VT/VF
- No harm, no foul
- No evidence for benefit in PEA/asystole
A cardiac arrest is a cardiac arrest, right???

- OHCA in Paris, France is managed by at least 1 physician, firefighters, paramedics
- Post-ROSC, ICU or cardiac catheterization laboratory

A cardiac arrest is a cardiac arrest, right???

A cardiac arrest is a cardiac arrest, right???

<table>
<thead>
<tr>
<th></th>
<th>VF/Vt</th>
<th>P*</th>
<th>PEA/Asystole</th>
<th>Overall (n=437)</th>
<th>TMH</th>
<th>No TMH</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=708)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>218 (35)</td>
<td>155 (38)</td>
<td>63 (29)</td>
<td>0.02</td>
<td>148 (38)</td>
<td>101 (42)</td>
<td>47 (31)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>77 (12)</td>
<td>53 (13)</td>
<td>24 (11)</td>
<td>0.42</td>
<td>76 (19)</td>
<td>52 (22)</td>
<td>24 (16)</td>
</tr>
<tr>
<td>Smoker</td>
<td>261 (48)</td>
<td>168 (47)</td>
<td>93 (48)</td>
<td>0.80</td>
<td>124 (38)</td>
<td>85 (42)</td>
<td>39 (31)</td>
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<tr>
<td>Men</td>
<td>562 (79)</td>
<td>359 (79)</td>
<td>203 (81)</td>
<td>0.47</td>
<td>275 (63)</td>
<td>164 (63)</td>
<td>111 (63)</td>
</tr>
<tr>
<td>Age, y†</td>
<td></td>
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<tr>
<td>&lt;49</td>
<td>188 (27)</td>
<td>111 (24)</td>
<td>77 (31)</td>
<td>0.05</td>
<td>105 (24)</td>
<td>59 (23)</td>
<td>46 (26)</td>
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<tr>
<td>49-59</td>
<td>201 (28)</td>
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<td>77 (31)</td>
<td></td>
<td>95 (22)</td>
<td>55 (21)</td>
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<tr>
<td>59-71</td>
<td>163 (23)</td>
<td>109 (24)</td>
<td>54 (21)</td>
<td></td>
<td>111 (25)</td>
<td>71 (27)</td>
<td>40 (23)</td>
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<td>≥71</td>
<td>156 (22)</td>
<td>113 (25)</td>
<td>43 (17)</td>
<td></td>
<td>126 (29)</td>
<td>76 (29)</td>
<td>50 (28)</td>
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<td>Cardiac arrest cause</td>
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<tr>
<td>Cardiac cause</td>
<td>386 (55)</td>
<td>247 (54)</td>
<td>139 (55)</td>
<td>0.73</td>
<td>51 (12)</td>
<td>28 (11)</td>
<td>23 (13)</td>
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<tr>
<td>Extracardiac cause</td>
<td>322 (45)</td>
<td>210 (46)</td>
<td>112 (45)</td>
<td></td>
<td>386 (88)</td>
<td>233 (89)</td>
<td>153 (87)</td>
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<tr>
<td>Location</td>
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<td>Public area</td>
<td>171 (24)</td>
<td>105 (23)</td>
<td>66 (27)</td>
<td>0.25</td>
<td>113 (26)</td>
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<td>53 (30)</td>
</tr>
<tr>
<td>Home</td>
<td>251 (36)</td>
<td>158 (35)</td>
<td>93 (37)</td>
<td></td>
<td>233 (53)</td>
<td>146 (56)</td>
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<tr>
<td>Other</td>
<td>284 (40)</td>
<td>194 (42)</td>
<td>90 (36)</td>
<td></td>
<td>91 (21)</td>
<td>55 (21)</td>
<td>36 (21)</td>
</tr>
<tr>
<td>Time from collapse to BLS‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 minutes</td>
<td>333 (50)</td>
<td>219 (51)</td>
<td>114 (50)</td>
<td>0.89</td>
<td>193 (49)</td>
<td>110 (46)</td>
<td>83 (55)</td>
</tr>
<tr>
<td>Time from BLS to ROSC‡</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤15 min</td>
<td>297 (44)</td>
<td>192 (43)</td>
<td>105 (48)</td>
<td>0.23</td>
<td>188 (47)</td>
<td>110 (44)</td>
<td>78 (55)</td>
</tr>
</tbody>
</table>

A cardiac arrest is a cardiac arrest, right ???

Duluth Cold vs. Minneapolis Cold
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest


ABSTRACT

BACKGROUND

Unconscious survivors of out-of-hospital cardiac arrest have a high risk of death or poor neurologic function. Therapeutic hypothermia is recommended by international guidelines, but the supporting evidence is limited, and the target temperature associated with the best outcome is unknown. Our objective was to compare two target temperatures, both intended to prevent fever.

METHODS

In an international trial, we randomly assigned 990 unconscious adults after out-of-hospital cardiac arrest of presumed cardiac cause to targeted temperature management at either 33°C or 36°C. The primary outcome was all-cause mortality through the end of the trial. Secondary outcomes included a composite of poor neurologic function or death at 180 days, as evaluated with the Cerebral Performance Category (CPC) scale and the modified Rankin scale.

RESULTS

In total, 990 patients were included in the primary analysis. At the end of the trial, 50% of the patients in the 33°C group (235 of 473 patients) had died, as compared with 40% of the patients in the 36°C group (222 of 446 patients) (hazard ratio with a temperature of 33°C: 1.06; 95% confidence interval [CI], 0.89 to 1.28; P=0.51). At the 180-day follow-up, 54% of the patients in the 33°C group had died or had poor neurologic function according to the CPC, as compared with 52% of patients in the 36°C group (risk ratio, 1.03; 95% CI, 0.88 to 1.16; P=0.78). In the analysis using the modified Rankin scale, the comparable rate was 52% in both groups (risk ratio, 1.01; 95% CI, 0.89 to 1.14; P=0.87). The results of analyses adjusted for known prognostic factors were similar.

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. (Funded by the Swedish Heart-Lung Foundation and others; TTM Clinical Trials.gov number, NCT01302091.)
Targeted Temperature Management

- Multicenter RCT (36 hospitals, 10 countries, Europe and Asia)
- N=939
  - T = 33°C = 473
  - T = 36°C = 466
- Standardized rules for prognostication
- Standardized rules for withdrawal of life support
- Blinded prognostication and outcome assessment
Inclusion criteria
- Age ≥ 18y
- OHCA of presumed cardiac cause
- Sustained ROSC for 20 minutes
- GCS < 8 after sustained ROSC

Exclusion criteria
- Pregnancy
- Known bleeding diathesis (other than medical coagulopathy, eg, warfarin)
- Suspected/confirmed ICH or stroke
- Unwitnessed cardiac arrest with initial rhythm asystole
- DNR or known prognosis < 6 months
- Pre-arrest CPC 3 or 4
- > 4 hrs from ROSC to screening
- SBP < 80 despite pressor, inotrope, IABP
- Temp < 30 °C on admit
Targeted Temperature Management, Nielsen et al, *NEJM* 2013

- **Intervention Group**
  - Target Temp at 33°C
  - Intervention period of 36 hrs commenced at randomization
  - Mandatory sedation
  - Cooled to target in < 6 hrs after randomization
  - Maintained at 33°C until 28 hours after screening, then rewarmed at 0.5°C/hr
  - Mandatory sedation stopped/tapered at 36 hrs
  - Maintain temp below 37.5°C until 72 hrs after CA

- **Comparison Group**
  - Target Temp at 36°C
  - Similar treatment to intervention group
Body Temperature during the Intervention Period.

Outcomes

Primary: mortality at 180 days

Secondary

- Composite of poor neurologic function or death
  - CPC 3-5
  - Modified Rankin scale 4-6
- At or around 180 days
Probability of Survival through the End of the Trial.

Results

No difference in mortality
- $T=33^\circ C$: 235/473 died (50%)
- $T=36^\circ C$: 225/466 died (48%)
- HR=1.06 (95% CI 0.89-1.28), $P = 0.51$

No difference in composite mortality/poor neurologic outcomes
- CPC: $T=33^\circ C$: 54%, $T=36^\circ C$: 52%, RR=1.02 (0.88-1.16), $P = 0.78$
- mRS: $T=33^\circ C$: 52%, $T=36^\circ C$: 52%, RR=1.01 (0.89-1.14), $P = 0.87$

Serious adverse events were common, and slightly higher in $T=33^\circ C$ (93%) vs $T=36^\circ C$ (90%), RR=1.03 (1.00-1.08), $P = 0.09$
Conclusions

- No difference found between Target Temp at $T=36^\circ\text{C}$ compared to $T=33^\circ\text{C}$
- Good outcomes in both groups may reflect active prevention of hyperthermia
- Modern aggressive care that includes attention to temperature works
  - Makes survival more likely than death when a patient hospitalized after CPR
Remaining Issues

- Patient selection
- Optimum target temperature
- Timing of cooling initiation
- Duration of therapy
- Rate of rewarming
- In versus out-of-hospital
- VT/VF versus non-VT/VF
Patient selection, equipment, induction & maintenance
# Patient Selection

<table>
<thead>
<tr>
<th>Table 1. Indications and Contraindications for Targeted Temperature Management in Comatose Patients after Cardiac Arrest.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients for whom therapeutic hypothermia should be considered</strong></td>
</tr>
<tr>
<td>Adult patients successfully resuscitated from a witnessed out-of-hospital cardiac arrest of presumed cardiac cause (patients after in-hospital cardiac arrest may also benefit)(^2)</td>
</tr>
<tr>
<td>Patients who are comatose (i.e., patients with a score on the Glasgow Coma Scale of less than 8 or patients who do not obey any verbal command at any time after restoration of spontaneous circulation and before initiation of cooling)</td>
</tr>
<tr>
<td>Patients with an initial rhythm of ventricular fibrillation or nonperfusing ventricular tachycardia (patients presenting with other initial rhythms such as asystole or pulseless electrical activity may also benefit)(^2)</td>
</tr>
<tr>
<td>Patients whose condition is hemodynamically stable (retrospective data suggest that patients in cardiogenic shock may also safely undergo hypothermia treatment)(^29,30)</td>
</tr>
<tr>
<td><strong>Patients for whom therapeutic hypothermia should not be considered</strong></td>
</tr>
<tr>
<td>Patients with tympanic-membrane temperature below 30°C on admission</td>
</tr>
<tr>
<td>Patients who were comatose before the cardiac arrest</td>
</tr>
<tr>
<td>Pregnant patients</td>
</tr>
<tr>
<td>Patients who are terminally ill or for whom intensive care does not seem to be appropriate</td>
</tr>
<tr>
<td>Patients with inherited blood coagulation disorders</td>
</tr>
</tbody>
</table>
American Heart Association post–cardiac arrest care algorithm.

Scirica B M Circulation. 2013;127:244-250
Prognosis after TH

No brain stem reflexes
Or
Day 1
Myoclonus
Status Epilepticus
Or
Day 1-3
SSEP
Absent N20 responses
Or
Day 1-3
High serum NSE (> 80 µg/L)
Or
Day 3
Absent pupil or corneal reflexes
Or
Day 6
Absent or extensor motor responses
Or
Day 3-5
Moderate to severe cortical abnormalities on DWI/FLAIR; >10% of brain with ADC <650x10^4 mm^2/sec

Yes
Almost certainly brain dead

Yes
Probably poor outcome

Yes
Probably poor outcome

Yes
Poor outcome

Yes
Probably poor outcome

Yes
Poor outcome

Yes
Poor outcome

From the 8th New York Symposium on Neurocritical Care, 2011
Equipment

Cincinnati Sub-Zero Blankerol III

Artic Sun
Side Effects

- Bradycardia
- Oozing
- Hypotension
- Diuresis
- Arrhythmias
- Hypokalemia
- Hyperglycemia
- Prolonged drug metabolism
Physician signature OR telephone/verbal order (with verbal read back) required for implementation.

- Admit to ICU after cath lab as inpatient
- Admit to ICU as inpatient

**Diagnosis:**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Potential Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pre hospital or inpatient VT/VF Cardiac Arrest</td>
<td>• Less than 18 years of age</td>
</tr>
<tr>
<td>• Return of Spontaneous Circulation (ROSC) and Protocol Initiated</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Within 6 Hrs of VT/VF Cardiac Arrest</td>
<td>• GCS greater than 7</td>
</tr>
<tr>
<td>• Unconscious Adult Patients (18 Years Old or Greater)</td>
<td>• Trauma</td>
</tr>
<tr>
<td>• Glasgow Coma Scale less than 7</td>
<td>• Systemic infection/Sepsis</td>
</tr>
<tr>
<td>• Hemodynamically Stable MAP greater than 50, with or without the support of pressors</td>
<td>• Terminal Illness- Pre-arrest life expectancy less than 6 months</td>
</tr>
<tr>
<td>• Known INR less than 4, unless otherwise directed, consider correction of coagulation</td>
<td></td>
</tr>
</tbody>
</table>

**INDUCTION PHASE:**

Achieve goal temp of 32º to 34º C quickly as possible

☐ Establish 3 peripheral access sites
  - A Presep Central Line Catheter and Arterial line may be inserted in the ED
☐ Infuse refrigerated Normol Saline 30cc/kg IV bolts over one hour via 2 IV sites
☐ Insert temperature sensing catheter, obtain core temperature, baseline vital signs, labs, post arrest ECG and baseline neuro assessment
☐ Apply defibrillator pads (date and time)
☐ Call ICU if Cincinnati Sub Zero Blanket III to be delivered to Cath Lab

**LAB/DIAGNOSTICS:**

☐ CBC w/o Diff Stat
☐ CMP Stat (Includes: LDH, Tbil, Creatinine, CO2, CI, Alk Phos, ALT, AST, Urea Nioragen)
☐ Hepatic Panel Stat (Includes: Alb, Tbil, DBil, ALK Phos, T Prot, ALT, AST)
☐ CKMB Stat (Reflex to CK, total & % CKMB if CKMB greater than 1ng/ml)
☐ Troponin I Stat
☐ Lactic Acid Stat
☐ ABG Stat (temperature corrected)
☐ PT/PTT Stat (temperature corrected)
☐ Type & Screen Stat (Includes: ABG, Rh & AB Screen, pos AB identification reflexes to 2 units set up on inpts)
☐ Blood cultures ≤ 2 peripherally Stat
☐ Sputum Culture Stat
☐ EKG Stat
☐ Portable Chest X-ray Stat
☐ Other

**MISCELLANEOUS**

☐ Notify Cardiology- clarify if they want to manage hypothermia protocol
☐ Notify Pulmonologist if Cardiology not managing protocol
☐ Notify Primary Care MD

**Physician Signature:**

**Date/Time:**
Physician signature OR telephone/verbal order (with verbal read back) required for implementation.

- Admit to ICU as inpatient

**Diagnosis:**

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<tr>
<td>Glasgow Coma Scale less than 7</td>
<td>Systemic infection/Sepsis</td>
</tr>
<tr>
<td>Hemodynamically Stable MAP greater than 60, with or without the support of pressors</td>
<td>Terminal Illness- Pre-arrest life expectancy less than 8 months</td>
</tr>
<tr>
<td>Known INR less than 4, unless otherwise directed, consider correction of coagulation</td>
<td></td>
</tr>
</tbody>
</table>

**PHASE ONE-INITIATION**

- Initiation Time of Cooling: ______________ Achieve goal temp of 32° to 34° C quickly as possible

**CONSULT:**
- Consult to Intensivist
- Consult to Cardiologist (Clarify if Cardiologist is managing patient)

**NURSING:**
- Vital signs every 15 minutes including temperature and ScvO2 (pulse oximetry may be unreliable due to peripheral vasoconstriction)
- Apply Defib pads. Date and time. Change every 24 hours and/or prior to rewarming.
- Maintain MAP 60mmHg
- Document time of Goal Temperature met
- Maintenance Phase begins at the time of goal temperature met
- Rewarming begins 24 hours after goal temperature met
- Mepilex Coccyx dressing
- Pillow heel protectors
- Turn q two hours as tolerated

**ACTIVITY:**
- Bedrest

**NUTRITION:**
- NPO

**PROCEDURES:**
- Insert Arterial Line. Prewrap Catheter and Esophageal Probe
- Insert OG/NG and place on intermittent suction.
- Insert Indwelling catheter with Bladder Temperature Probe

**RESPIRATORY:**
- Initiate Ventilator Management Order set (RESP04)

**COOLING:**
- Cincinnati Sub Zero Blanket IV with head wrap, vest and blanket
- Set goal temperature to 34°C
- If temp goal not achieved in 4 hours add ice packs to groins, chest, axilla and side of neck.
- Once 34°C temperature achieved decrease goal temperature to 32° C with a 20° gradient

**MEDICATIONS:**
- IV’s
  - 1000 mL Normal Saline IV X 2 refrigerated and infuse rapidly (obtain from pharmacy)
  - IV fluids _________ at ___________ ml/hr

**HYPOTHERMIA ORDER SET**

| HOSP 89 | REV 4/6/11 | Page 1 of 2 |
Sedation, Analgesia and Paralytic

- Midazolam IV per Adult Critical Care Analgesia and Sedation (HOSP48)
- Fentanyl IV per Adult Critical Care Analgesia and Sedation (HOSP48)
- Vecuronium (Norcuron) bolus 0.1 mg/kg q 1hr PRN (train of four (TOF) not accurate use shivering or other indicators for administrations)

Electrolyte

- Potassium 20mEq IVPb X 1 if Potassium level 3 - 3.4 Check Potassium 1hr after infusion
- Discontinue all intravenous Potassium 6 hours prior to rewarming

Insulin Drip

- Insulin Drip per Insulin Infusion (Hosp 71) start if glucose is _______
- Use Arterial Line for Glucose checks

Vasopressors

- DOProine IV Drip to keep MAP at 60-90
- Phenylephrine IV Drip to keep MAP at 60-90
- Other (Specify): _______________________________
- Other (Specify): _______________________________

LAB/DIAGNOSTICS:

- CBC w/o Diff Stat
- CMP Stat (Includes Alb, TBil, Calcium total, CO2, CL Creat, Gluc, Alk Phos, K, Tot Prot, Na, ALT, AST, Urea Nitrogen)
- Hepatic Panel Stat (Includes Alb, TBil, DBlil, Alk Phos, Tot Prot, ALT, AST)
- ABG Stat (Record patient temperature on blood sample)
- CKMB Stat (Reflexes to CK, total and % CKMB if CKMB greater than 5ng/ml)
- Troponin I Stat
- Lactic Acid Stat
- Type and Screen Stat (Includes ABO, Rh & AB Screen, pos AB identification reflexes to 2 units set up on inpts)
- Blood Cultures x2 peripherally Stat
- Sputum Culture Stat
- PT/PTT Stat then every 6 hours after initiation
- HGB 12 hours after initiation
- Electrolyte Panel q 4hrs after initiation (Includes CO2, CL, K, Na)
- EKG Stat
- Portable Chest X-ray Stat
- Other __________________________

Call Physician if:

- SBP is less than 90 mmHg or MAP is less than 60 mmHg
- Core temperature less than 32 °C
- Inability to reach target temperature within 6 hours with the added ice application
- Urine output is less than 30mL/hr
- ST elevation or depression is noted

PHASE TWO

Pre rewarming

- Stop all IV Potassium 6 hours prior to rewarming
- Check Potassium prior to rewarming

Rewarming Phase:

- IV Fluids
- Rewarm at a patient temp rate of 0.25 - 0.5 °C per hour with a 10° gradient
- Discontinue Vecuronium (Norcuron) boluses when patient temperature reaches 36 °C
- Slowly Wean Versed and Fentanyl per Adult Critical Care Analgesia and Sedation Protocol (HOSP48) when patient temperature reaches 36° C.

Physician Signature: ____________________________

Date/Time: ____________________________

HYPOTHERMIA ORDER SET
HOSP89

REV 4/6/11

St. Luke's

Page 2 of 2
Mild hypothermia improve neurologic outcomes in *witnessed VT/VF arrest*

Intra-arrest hypothermia may be beneficial for improved ROSC

Neurologic outcomes after intra-arrest may be improved, randomized evidence is lacking