How to Optimize Therapeutic Hypothermia and What to Expect

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Associate Professor of Medicine, U of Minnesota

David Hildebrandt, RN
Director, CV Emergencies Program
Cardiac Arrest

- Out-of-hospital cardiac arrest (OOHCA) affects 295,000 people annually in the US
- 7.9% median survival rate
- Anoxic encephalopathy and neurologic deficits are common and disabling - among survivors
- Enormous public health issue - personal, family & societal burdens

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INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

# Hypothermia Trials: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia (%)</th>
<th>Normothermia (%)</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alive at hospital discharge with favourable neurological recovery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HACA</td>
<td>72/136 (53%)</td>
<td>50/137 (36%)</td>
<td>1.51 (1.14-1.89)</td>
<td>0.006</td>
</tr>
<tr>
<td>Bernard</td>
<td>21/43 (49%)</td>
<td>9/34 (26%)</td>
<td>2.65 (1.0-6.88)</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Alive at 6 months with favourable neurological recovery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HACA</td>
<td>71/136 (55%)</td>
<td>50/137 (39%)</td>
<td>1.44 (1.11-1.76)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
- New Guidelines – more aggressive, 30’ CPR
- Full recoil. 30:2
- Less defib use
- Hypothermia Level 1A recommendation
Unconscious adult patients with ROSC after out-of-hospital VF cardiac arrest should be cooled to 32°C - 34°C for 12 - 24 hours.

Possible benefit for other rhythms or in-hospital cardiac arrest.
Surprising TTM Results

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

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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., Tormaso Pellis, M.D.,
Pascal Stammet, M.D., Michael Wanscher, M.D., Ph.D., Matt P. Wise, M.D., D.Phil.,
Anders Áneman, 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.,
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Lars Kober, M.D., D.M.Sc., Jörund 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*
TTM Trial: Body Temperature during the Intervention Period.

Probability of Survival through the End of the Trial
TTM Trial.

Note excellent outcome in Both groups.

So why Good results

• Tertiary care – shock, EEG, neuro-critical care
• Early angio, PCI, advanced team approach
• Hypothermia-prevention of fever and delayed neuro prognostication
• Formal neuro-prognostication protocol
• Major benefit = system of care and not necessarily hypothermia
Neuro-prognostication Protocol

• How to tell when u are dead – not easy
• Very rigid .. Many false shrines ie early exam or imaging or EEG or serum markers – none used
• If u say that hope is gone- the patient dies
TTM neuro prognostication

• Brain death due to cerebral herniation.

• Severe myoclonus status in the first 24 hours after admission and a bilateral absence of N20-peak on median nerve SSEP.

• Minimum 72 hours after the intervention period: persisting coma with a Glasgow Motor Score 1-2 and bilateral absence of N20-peak on median nerve SSEP.

• Minimum 72 hours after the end of the intervention period: persisting coma with Glasgow Motor Score 1-2 and a treatment refractory status epilepticus.
Resuscitation and Evaluation
- Establish: Stable rhythm
- Stable airway
- MAP > 65mmHg
- Neurological Examination
- Cardiac evaluation

Therapeutic Hypothermia
- Induction:
  - Goal core temperature 33°C
  - Replace potassium to > 3.8
  - Evaluate and treat seizures
  - Infuse 30-40cc IVF at 4°C
  - Sedate, place cEEG and BIS
  - Vecuronium or cisatricurium
  - Surface or intravascular cooling

72h Re-evaluation
- Neuroprognostication

Decoiling
- Decool at 0.25-0.33°C/hr
- Volume repletion
- Follow potassium
- Maintain MAP > 65
- Discontinue paralytic
- Wean sedation if T > 36°C
- Extubate if appropriate
- Shivering protocol
- Maintain T<37.5°C until 72h after ROSC

Maintenance
- Core temperature 33°C x 18-24h
- Ventilate to normal pH
- Normal electrolytes
- cEEG if available
- Blood glucose 100-150mg/dl
- MAP 65-95mmHg
- Verify adequate systemic perfusion
- Antibiotics for pulmonary infiltrates
- Dose medications for hypothermia
- Skin care

Seder, Crit Care Med 2009;37 (Suppl):S211-S222
Regional Variation in Out-of-Hospital Cardiac Arrest Incidence and Outcome

Graham Nicol, MD, MPH
Elizabeth Thomas, MSc
Cintron W. Gallaway, MD, PhD
Jerrie Hodges, MD, MS
Judy L. Powell, BSN
Tom P. Audheide, MD
Tom Rea, MD
Robert Lowe, MD, MPH
Todd Brown, MD
John Dreyer, MD
Dan Davis, MD
Ahamed Idris, MD
Ian Stiell, MSc

It remains to be determined how often out-of-hospital cardiac arrest (OHCA) occurs. Recent sources indicate that about 166,000 to 310,000 Americans per year experience an OHCA, although resuscitation is not attempted in many of these cases. The reported incidence of OHCA is

Table 5. Incidence and Outcome of Ventricular Fibrillation

<table>
<thead>
<tr>
<th>Location</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>89.2</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>71.7</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>2.5</td>
</tr>
</tbody>
</table>

All rates were unequal across sites at P < .001.

1428 JAMA, September 24, 2008—Vol 300, No. 12 (Reprinted) ©2008 American Medical Association. All rights reserved.
TH can be integrated as part of a comprehensive cardiac arrest program into existing STEMI networks to achieve a broad dispersion of this essential therapy for cardiac arrest
STEMI Program at MHI and 33 hospital since 2003
Initial Rhythm

CPC at discharge based on initial rhythm.

<table>
<thead>
<tr>
<th>CPC</th>
<th>Vfib/Vtach</th>
<th>PEA</th>
<th>Asystole</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPC 1</td>
<td>38.8%</td>
<td>12.5%</td>
<td>19.4%</td>
<td>25%</td>
</tr>
<tr>
<td>CPC 2</td>
<td>19.7%</td>
<td>3.1%</td>
<td>6.5%</td>
<td>37.5%</td>
</tr>
<tr>
<td>CPC 3</td>
<td>4.5%</td>
<td>9.4%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>CPC 4</td>
<td>2.2%</td>
<td>0%</td>
<td>3.2%</td>
<td>0%</td>
</tr>
<tr>
<td>CPC 5</td>
<td>34.8%</td>
<td>75%</td>
<td>70.9%</td>
<td>37.5%</td>
</tr>
</tbody>
</table>
Non-Cardiac in Origin Arrest Data (n=31)

<table>
<thead>
<tr>
<th>CPC Score at Hospital Discharge</th>
<th>1 (n=1)</th>
<th>2 (n=6)</th>
<th>3 (n=1)</th>
<th>4 (n=0)</th>
<th>5 (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Cardiac Cardiac Arrests</td>
<td>3.2%</td>
<td>19.4%</td>
<td>3.2%</td>
<td>0%</td>
<td>74.2%</td>
</tr>
</tbody>
</table>

* Cerebral Performance Category (CPC) Score

<table>
<thead>
<tr>
<th>CPC Score at 6 Month Follow Up*</th>
<th>1 (n=4 (50.0%))</th>
<th>2 (n=1 (12.5%))</th>
<th>3 (n=1 (12.5%))</th>
<th>4 (n=0)</th>
<th>5 (n=1 (12.5%))</th>
<th>Lost to f/u (n=1 (12.5%))</th>
</tr>
</thead>
</table>

* Allina Health
* Abbott Northwestern Hospital
* Minneapolis Heart Institute
* Creating a world without heart disease
STEMI

- 39.7% (98/247) of patients had ST elevation greater than 1 mm in 2 contiguous leads or evidence of posterior MI. Of those with STEMI, the culprit artery on angiogram was:
  - RCA 27.6%
  - LAD 31.6%
  - Cx 9.2%
  - L Main 2.0%
  - None 29.6%
Of the 138 survivors, CPC score at discharge and 6 months:

<table>
<thead>
<tr>
<th>CPC</th>
<th>At Discharge</th>
<th>At 6 month F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPC 1</td>
<td>81 (58.6%)</td>
<td>107 (79.8%)</td>
</tr>
<tr>
<td>CPC 2</td>
<td>41 (29.7%)</td>
<td>19 (13.8%)</td>
</tr>
<tr>
<td>CPC 3</td>
<td>11 (8.0%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>CPC 4</td>
<td>5 (3.6%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>CPC 5</td>
<td></td>
<td>9 (6.5%)</td>
</tr>
</tbody>
</table>

- Of survivors, 88.3% DC’d with good neuro outcome (CPC 1 or 2)
- At 6 months, 93.6% of patients had good neuro outcome (CPC 1 or 2)
Level 1 STEMI Outcomes

STEMI = Blue line, others = Red line

Fraction surviving

Days Arrest to Death or Last Known Alive
Transfer Outcomes

Transfer = Blue line, ANW = Red line

Fraction surviving

Days Arrest to Death or Last Known Alive
Transfer Hospital – What is Important

- For many .. Get hypothermia started and refer
- Have a protocol and transfer process in place
- Consider head CT if no ST elevation
- Repeat EKG often
- Undress and apply surface cooling
- consider early angio for VF
1. Direct to cath lab
2. Equipment in Cath Lab
3. Pads ready
4. Pads applied
5. Groin access
6. Leg application
7. Drape as usual
8. Machine on

Average time: 6 minutes
Decision tree for referring physicians

Resuscitated Cardiac Arrest

Continue resuscitation per appropriate protocol

Pt meets criteria for
Therapeutic Hypothermia

Expose Pt

Obtain EKG

Obtain Core Temp

< 34°C

- Continued temp checks every 10 minutes

> 34°C

- Apply ice packs to neck, groin and axilla

Contact Minneapolis Heart Institute® (612-863-3900)

If meets Level One STEMI criteria and cardiac arrest, transfer directly to cath lab.

YES

- Aspirin 300 mg rectally
- Heparin loading dose of 60 units/kg (max 4,000 units IV push).
- Heparin continuous infusion at 12 units/kg/hr (max 1,000 units/hr).
- Plavix 600 mg per OG tube, if placement verified per chest x-ray.
- No thrombolytics.
- Tranexamic Acid (TXA), if not contraindicated

NO

Repeat 12 lead EKG every 15 minutes

24/7 Cardiologist
612-863-3900
Care After Hypothermia Treatment for Cardiac Arrest
ANW/SKRI “Cool it” Rehabilitation Approach

Our challenges:

- Don’t let relief of survival overshadow need to focus on rehab-relevant adverse outcomes
- Select array of tests with validity and reliability in this population, acceptably easy to administer, broad yet focused
  - Screening model: find survivors with any cognitive dysfunction after Cool-it knowing:
    - would over-identify dysfunction
    - not all dysfunction identified would necessarily be due to effects of CA-related global cerebral ischemia
Hot Load training by Air
Mercy Medical Center

Level 1 Sites ★ Mercy - DM
Deep River (188 Km)

Pembroke (141 Km)

Renfrew (90 Km)

St. Francis (183 Km)

Arnprior (64Km)

Almonte (48Km)

Carleton Place (48Km)

Kemptville (54Km)

Hawkesbury (112Km)

Glengarry (98Km)

Cornwall (104 Km)

Regional Code STEMI Hospitals- Ottawa- Champlain LHIN District
Resuscitation Center

Tertiary Center
PCI Center

Community Education
Awareness

Pre Hospital EMS
Educational support
Ongoing feedback
Data assistance

Ability and resources
To perform continuous
High quality human
or mechanical CPR
for 30-60 min

Cath Lab 24/7
meets min
standards and experience
for performing TH in Lab in
combination
with appropriate Dx/Interventional
procedures

Lurie et al 2009
Community Education Awareness

“BAR” Neurocognitive Recovery plan

Support Neurology, CT surgery to provide Supportive Care available within 30 min of notification

Head CT perfusion And/or MRI on 24 hr basis with Rapid radiology interp

Electrophysiologist “Shock” Cardiologist

In house Intensivist/Cardiologist Team 24/7 for comprehensive Inhouse management

Surgical intervention Emergent Cardiac bypass/ VAD/ECMO Within 1 hour Of determination of need

Able to perform high quality Human or mechanical CPR fpr 30-60 min

Cath Lab 24/7 meets standards and experience for performing TH in Lab in combination

Ability to perform TH within 1 hour of pt evaluation Clinical Pharm D

Able to perform high quality Human or mechanical CPR fpr 30-60 min

Allina Health
ABBOTT NORTHWESTERN HOSPITAL

MINNEAPOLIS HEART INSTITUTE
Creating a world without heart disease®
Dr Ebbert 2 months after anterior MI and “Cool-It”

Michael R. Mooney, MD
Suite 301
920 East 28th Street, Minneapolis, MN 55407
(612) 775-3030

Dear Dr. Mooney,

A little more than two months ago I was a patient in your facility at Abbott-Northwestern Hospital. I had collapsed with a fatal arrhythmia at Minneapolis Airport flying back from Massachusetts to my home in South Dakota. This involved an almost unbelievable amount of luck to have this happen at a place where I was able to be immediately defibrillated, then taken to your hospital where I had superb care. I also was treated with your hypothermia program, which I know preserved brain function. In South Dakota I live alone about fifteen miles outside of Rapid City, so my chances for survival would have been very small. In Rapid City we are using hypothermia, but it is not routine and I think this would inject some delay into the treatment, and I think time is of the essence. I retired from my medical oncology practice a year ago, but I am now planning to return to work part-time at the VA here. Actually, my recovery was very rapid and I was back to my normal routine about a week after discharge.

In late August I went to Alaska with some friends, and part of our activities involved a four day backpacking-camping trip in the Wrangell-St. Elias National Park. I won’t say I led the pack, but I didn’t hold people back either. I am sending you three pictures from this trip. Thank you for your care and keep up the good work.

Larry P. Ebbert
TH and STEMI
Insights from animal studies

Hypothermia:

• Inhibits necrosis of cardiomyocytes and apoptotic cell death\textsuperscript{1}
• Protects the myocardium through a reduction in metabolism\textsuperscript{1}
• Protects during ischemia\textsuperscript{2}
• Reduces reperfusion injury\textsuperscript{3}
• Has minimal effect when initiated after reperfusion\textsuperscript{3}
• Improves survival in cardiogenic shock\textsuperscript{4}

\textsuperscript{1}Verma et al. \textit{Circulation}, 2002; Tissier et al. \textit{Cardiovascular Research}, 2010
\textsuperscript{3}Götberg et al. \textit{Basic Research in Cardiology}, 2011
\textsuperscript{4}Götberg et al., \textit{Resuscitation}, 2010
Early clinical trials

**COOL-MI**

- 49% of patients cooled to ≤35°C at the time of reperfusion achieved a reduction in infarct size.

**ICE-IT**

- 43% of patients cooled to ≤35°C at the time of reperfusion achieved a reduction in infarct size.

- Primary endpoints not achieved in the studies.
- Only 1/3 of the patients reached ≤35°C at the time of reperfusion.
- In anterior STEMI patients cooled to ≤35°C before reperfusion, a trend for reduction in infarct size was observed in both trials.

1 O’Neill, *TCT 2003*
2 Grines, *TCT 2004*
Combination Hypothermia for Rapid Cooling

• Pressurized cold saline (4°C) IV infusion to ”kick start” cooling
• Endovascular cooling catheter with temperature sensor placed in vena cava

Anterior: 10 mL/kg
Inferior: 20 mL/kg

InnerCool RTx Endovascular Cooling System (Philips Healthcare)
RAPID MI-ICE Pilot Study

Infarct size (IS)/Myocardium at Risk (MaR) measured with cardiac MRI was reduced by cold saline and endovascular cooling.

MRI

A. Normothermia, duration of ischemia: 152 min

B. Hypothermia, duration of ischemia: 164 min

Δ = 38%
p = 0.04

Götberg et al. Circulation Cardiovascular Interventions, 2010
CHILL-MI: Study Design

Anterior and Inferior STEMI
120 Patients
< 6 hrs of symptom onset

Primary Endpoint:
Infarct size/myocardium at risk (IS/MaR)
assessed by cardiac MRI at 4±2 days

Key Secondary Endpoints:
IS/MaR in patients with anterior and inferior infarctions
IS/MaR assessed by cardiac MRI at 6 months
Death & Heart Failure within 45 days

Safety Endpoints:
Incidence of heart failure, pulmonary edema, infections and bleeding
(TIMI definition) within 45 days
CHILL-MI: Primary endpoint
Infarct Size/Myocardium at Risk at 4±2 days

All patients
RR = 13%

P=0.15

Control
n=48

Hypothermia
n=49

Median (IQR)
**CHILL-MI: Infarct size by location**

Symptom onset to PCI of 0-4 hrs

**Exploratory analysis**

<table>
<thead>
<tr>
<th>Location</th>
<th>IS%/MaR</th>
<th>Control (n)</th>
<th>Hypothermia (n)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients &lt;4h</td>
<td>RR = 21%</td>
<td>n=40</td>
<td>n=42</td>
<td>0.049</td>
</tr>
<tr>
<td>Inferior &lt;4h</td>
<td>RR = 13%</td>
<td>n=20</td>
<td>n=30</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior &lt;4h</td>
<td>RR = 33%</td>
<td>n=19</td>
<td>n=12</td>
<td>0.046</td>
</tr>
</tbody>
</table>
CHILL-MI: Adjudicated Death & Heart Failure

Main Clinical endpoint

No mortality; HF in anterior patients only

P=0.047

%Death & Heart Failure

Days elapsed

Control (8 events)
Hypothermia (2 events)
2008 Survivors
MHI@ Abbott
Northwestern Hospital
System of CV Emergency Care

Clinical Support Services

- Advanced Imaging
- Vascular Surgeons
- Hemodynamic Support
- 24/7 Intensivists Hospitalists
- Cardiac/Transplant Surgeons
- Rehabilitation

DATA COLLECTION/ ANALYSIS

Post-Hospital Discharge Coordination

Research Education Publications

Administrative Support Services

- CV Emergency Program Manager
- Nurse Educator
- Administrative Assistant
- Clinical Assistants

Extensive Education for Patients, Community & Providers
Sudden Cardiac Arrest Association Medical Leadership Award 2011
Conclusions

• Systems of care are the cornerstone for any successful Cardiac Emergency Program

• TH in the treatment of Acute MI has yet to establish important efficacy

• TH is current standard of care in cardiac arrest but neuro-prognostication may be more important

• Integration of cardiac arrest CV emergencies into existing STEMI networks is now recommended by ACC/AHA

• Establishing systems of care for cardiac arrest should be a priority for every community. This is a Mission Lifeline goal.
Thank You