Post–Resuscitation Care and EMS initiated Therapeutic Hypothermia (TH)

Mohamud Daya MD, MS
Hypothermia – Definitions

- Mild
  - 32 to 34
- Moderate
  - 28 to 32
- Severe
  - 28 and below
Acknowledgments

- Jon Rittenberger
- Shervin Ayati
- Protocol Development Committee Hypothermia Working Group
  - Lynn Wittwer
  - Jon Jui
  - John Stouffer
  - Scott Sullivan
- Many others
TH – Brief History

- Few things represent new discoveries, most are re-discoveries (Peter Safar)
- Napoleon’s surgeon Baron Dominique Jean Larrey (1814)
  - Benefits of hypothermia in trauma
- Cold water drowning
- Hypothermia used therapeutically in the 1950’s but abandon due to complications
  - Coagulopathy, infection
- 1990’s pilot trials with mild hypothermia beneficial
INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

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

Inclusion Criteria

HACA

- In ED after ROSC
- Witnessed
- VF / VT
- Presumed cardiac
- 18–75 years old
- <60 min since collapse
- 5–15 min collapse to resuscitation

Bernard

- Arrival at participating ED
- VF / VT
- ROSC
- Coma after ROSC
Exclusions

**HACA**
- Responds to verbal commands
- MAP $<$ 60 mmHg $\times$ 30 min
- SaO2 $<$ 85% $\times$ 15 min
- Coagulopathy
- Tympanic temp $<$ 30 C
- Arrested after EMS arrival
- Pregnancy
- Coma before cardiac arrest
- Terminal illness

**Bernard**
- Systolic BP $<$ 90 despite pressors (epinephrine)
- $<$ 18 yrs old for men
- $<$ 50 years old for women (surrogate for pregnancy)
- Alternative cause of coma (Drug OD, head trauma, CVA)
- No ICU bed available
Treatment

HACA

- Normothermia (N=138)
  - Standard hospital bed and kept warm
- Hypothermia (N=137)
  - 32–34 C (tympanic and bladder) for **24 hours**
  - TheraKool mattress/blanket
  - If not at goal within 4 hours, added ice packs

Bernard

- Normothermia (N=34)
  - Usual care with passive rewarming to 37 C
- Hypothermia (N=43)
  - In field, expose, cold packs to head/torso
  - In ED / ICU, further ice-packs
  - Core temperature of 33 C for **12 hours**.
**Outcome**
- Favorable Outcome 1.81
- Death at 6 months 0.95

**Risk Ratio**
- Favorable Outcome 1.40 (1.08 –
- Death at 6 months 0.74 (0.58 – 1.00)

**NNT (Favorable Outcome)** = 6.4

**Outcome**
- Good Outcome 6.88
- Good Outcome 18.76

**Odds Ratio**
- Good Outcome 2.65 (1.02 – 6.88)
- Good Outcome 5.25 (1.47 – 18.76)

**NNT (Good Outcome)** = 4.5
## Comparison of ICU Strategies
(Gropper, Anesth Analg 2004: 99:566)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NNT (mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Goal-directed therapy</td>
<td>7</td>
</tr>
<tr>
<td>Low-dose steroid</td>
<td>10</td>
</tr>
<tr>
<td>ARDSnet low TV ventilation</td>
<td>12</td>
</tr>
<tr>
<td>Activated protein C</td>
<td>17</td>
</tr>
<tr>
<td>Intensive glycemic control</td>
<td>28</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>6.1–7.0</td>
</tr>
</tbody>
</table>
Unconscious adult patients with ROSC after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours when the initial rhythm was VF (Class IIa).

Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (Class IIb).
Chemical cascades of reoxygenation injury.

Hypothermia
TH – Mechanisms

- Decrease in cerebral metabolism
  - 6% reduction for every 1°C drop in temperature

- Suppression of reperfusion injury
  - Decreased free radical production
  - Reduction in excitatory neurotransmitters
  - Suppression of Ca$^{+2}$ mediated cell death
  - Anti-inflammatory effects

Nolan et al. (2003) Circulation
When to start cooling?

Probably as soon as possible

Cardiac Arrest

ROSC

0     1     2     3     4     5     6     7     8

Time

Intra-arrest

Abella, 2004
Katz, 2000

Soon after ROSC

Sterz, 1991
Kuboyama, 1993

HACA, 2002
Is Early Better?

- Ischemic injury occurs in neuronal tissue within minutes.

- Reperfusion injury may begin within minutes and is followed by a period of hypoperfusion which persists for 12 hours or more.

- Reducing demand during periods of ischemia while mitigating reperfusion injury makes intuitive sense.
HACA patients required 4–16 hours to reach target temperature and still demonstrated benefit.

Animal data suggest early induction of hypothermia improves outcome.
- Stertz et al. (1991) Crit Care Med
- Kuboyama et al. (1993) Crit Care Med

Limited data comparing early versus delayed hypothermia in humans.
Does Early Cooling Matter?

Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest

Birger Wolff\textsuperscript{a,*}, Klaus Machill\textsuperscript{a}, Detlef Schumacher\textsuperscript{a}, Ilona Schulzki\textsuperscript{a}, Dierk Werner\textsuperscript{b}

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Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest

Birger Wolffa,*, Klaus Machilla, Detlef Schumachera, Ilona Schulzik, Dierk Wernerb

Table 3
Variables with predictive value for the neurologic outcome of CA patients after MTH

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% Confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per increment by 1 year)</td>
<td>.86</td>
<td>.76–.97</td>
<td>.012</td>
</tr>
<tr>
<td>BMI (per increment by 1.0 kg/m²)</td>
<td>.49</td>
<td>.30–.79</td>
<td>.004</td>
</tr>
<tr>
<td>Asystole as initial rhythm (yes/no)</td>
<td>.01</td>
<td>.00–.32</td>
<td>.010</td>
</tr>
<tr>
<td>Thrombolysis during CPR (yes/no)</td>
<td>.02</td>
<td>.00–.71</td>
<td>.031</td>
</tr>
<tr>
<td>TCT (per increment by 1 h)</td>
<td>.73</td>
<td>.45–.98</td>
<td>.013</td>
</tr>
<tr>
<td>TTT (per increment by 1 h)a</td>
<td>.69</td>
<td>.51–.98</td>
<td>.037</td>
</tr>
</tbody>
</table>

maximum NSE levels. Finally, in multivariate analyses, any hour delay till the coldest T or the target T tended to worsen the likelihood for a favourable outcome by approximately 27% or 31%, respectively.
Other benefits of Hypothermia

- It prevents HYPERTHERMIA
  - For each 1°C over 37°C for $T_{\text{max}}$ during the first 48 hours, likelihood of poor outcome increased with

$$\text{Odds Ratio (Poor)} = 2.26 \ (1.24 - 4.12)$$
Other benefits of Hypothermia

- May decrease vasopressor use!
- 10 pigs survived to 1 hour after arrest
- 5/6 pigs that did not require pressors were cooled

Norepinephrine (mcg/kg) after ROSC

![Chart showing comparison of norepinephrine levels between Normothermia and Hypothermia.]
Decreasing temperature increases myocardial contractility
- ↑isometric twitch force in isolated muscle
- ↑dP/dT, ↑stroke volume in vivo
- ↓heart rate in vivo (like β-blockade)
- ↑cardiac output
- No real change in SVR, PVR in this temp range

Decreasing temperature may save myocardium
Mild hypothermia reduces ultimate infarct size.
- LAD occlusions in 60–80 kg swine for 60 minutes
- Endovascular cooling to 34°C from 20–75 minutes.

Optimizing Therapeutic Hypothermia

HCASG, 2002
Bernard, 2002

55% Good Outcome
49% Good Outcome

? Outcome
How to cool out-of-hospital?

- Cold Saline infusion
- Surface cooling
- Nasal cavity PFC infusion
What is the Best Method of Prehospital Cooling?

- Busch et al. demonstrated successful cooling in Norway with ice packs and towels.

- In controlled environments, ice packs and exposure reduce temperature by $0.1^\circ C$ per hour.

- Forced air systems similar to HACA study cool at $0.3^\circ C$ per hour.
Bernard’s initial protocol relying on surface cooling decreased temperature by 0.9°C per hour.

Catheter based systems may be more efficient but are invasive and require equipment not available to prehospital providers.
What is the Best Method of Prehospital Cooling?
Induction of therapeutic hypothermia after cardiac arrest in prehospital patients using ice-cold Ringer’s solution: a pilot study

Ilkka Virkkunen\textsuperscript{a,b,\ast}, Arvi Yli-Hankala\textsuperscript{b,c}, Tom Silfvast\textsuperscript{a,d}

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\textsuperscript{d} Department of Anaesthesia and Intensive Care, Helsinki University Hospital, Helsinki, Finland

Received 28 November 2003; received in revised form 29 March 2004; accepted 8 April 2004
Clinical studies – Out-of-hospital cooling

Induction of therapeutic hypothermia after cardiac arrest in prehospital patients using ice-cold Ringer’s solution: a pilot study

Ilkka Virkkunen\textsuperscript{a,b,*}, Arvi Yli-Hankala\textsuperscript{b,c}, Tom Silfvast\textsuperscript{a,d}

30 ml/kg of 4°C RA i.v. 100 ml/min
Clinical studies – Out-of-hospital cooling

Pilot Randomized Clinical Trial of Prehospital Induction of Mild Hypothermia in Out-of-Hospital Cardiac Arrest Patients With a Rapid Infusion of 4°C Normal Saline

Francis Kim, MD; Michele Olsufka, RN; W.T. Longstreth, Jr, MD; Charles Maynard, PhD; David Carlbom, MD; Steven Deem, MD; Peter Kudenchuk, MD; Michael K. Copass, MD; Leonard A. Cobb, MD

*(Circulation. 2007;115:1&NA;-.*)

<table>
<thead>
<tr>
<th>TABLE 2. Esophageal Temperatures</th>
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</thead>
<tbody>
<tr>
<td>Randomized to Field Cooling (n=63)</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Temperature at randomization, °C</td>
</tr>
<tr>
<td>Temperature at hospital arrival, °C</td>
</tr>
<tr>
<td>Difference (hospital minus initial), °C</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD (n).
*Based on t test.
## Cold Fluid Studies (RL or NS)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Initial Temp</td>
<td>35.5</td>
<td>35.4</td>
<td>35.6</td>
</tr>
<tr>
<td>Mean Temp Decrease</td>
<td>1.7</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Fluid</td>
<td>RL</td>
<td>NS</td>
<td>RL</td>
</tr>
<tr>
<td>Amount</td>
<td>30 ml/kg</td>
<td>2L</td>
<td>2L</td>
</tr>
</tbody>
</table>
Clinical studies – Out-of-hospital cooling

Limitations of cold i.v. infusion

Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest☆

Andreas Kliegel, Andreas Janata, Cosima Wandaller, Thomas Uray, Alexander Spiel, Heidrun Losert, Matthias Kliegel, Michael Holzer, Moritz Haugk, Fritz Sterz, Anton N. Laggner

☆ This is a note or footnote indicating a special condition or exception, but the specific details are not provided in the text.
Clinical studies – *Out-of-hospital cooling*

Limitations of cold i.v. infusion

*Pilot Study of Rapid Infusion of 2 L of 4°C Normal Saline for Induction of Mild Hypothermia in Hospitalized, Comatose Survivors of Out-of-Hospital Cardiac Arrest*

Francis Kim, MD; Michele Olsufka, RN; David Carlbom, MD; Steven Deen, MD; W.T. Longstreth, Jr, MD; Margret Hanrahan, RN; Charles Maynard, PhD; Michael K. Copass, MD; Leonard A. Cobb, MD

![Graph showing temperature difference over time with various interventions such as fans, lowered room temperature, and cooling blanket.](image-url)
Clinical studies – *Out-of-hospital cooling*

Limitations of cold i.v. infusion

Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest—a feasibility study

Andreas Kliegel\(^a\), Heidrun Losert\(^a\), Fritz Sterz\(^a,\ast\), Matthias Kliegel\(^b\), Michael Holzer\(^a\), Thomas Uray\(^a\), Hans Domanovits\(^a\)
Concerns with ICE PACKS and COOLING BLANKETS

Therapeutic hypothermia after cardiac arrest: Unintentional overcooling is common using ice packs and conventional cooling blankets

Raina M. Merchant, MD; Benjamin S. Abella, MD, MPhil; Mary Ann Peberdy, MD; Jasmeet Soar, MD; Marcus E. H. Ong, MBBS, MPH; Gregory A. Schmidt, MD; Lance B. Becker, MD; Terry L. Vanden Hoek, MD

(Crit Care Med 2006; 34[Suppl.]:S490–S494)
HACA cooling device
Other benefits of cold saline

- Post–cardiac arrest is a sepsis like syndrome
  - Goal directed therapy
    - Fluids
  - Glucose control
Prehospital Surface Cooling – Emcools
TEMP CHANGE 3°C per hour
2010 Regional EMS HT Protocol

Purpose:

- To define the procedures for induced hypothermia following post-resuscitation from sudden cardiac arrest, with the aim to reduce body temperature to 32°–34° C.
Indications

- Patients with a sustained return of spontaneous circulation (ROSC) $>5$ minutes post-cardiac arrest.
- Unconscious and without purposeful response to pain or verbal stimuli.
- Systolic BP $\geq 100$ mmHg (may use vasopressors to maintain pressure)
2010 Regional EMS HT Protocol

Contraindications

- Age <15 years old.
- Traumatic cardiac arrest or suspected significant hemorrhage.
- Hypothermia already present.
- Pulmonary edema.
- Known pregnancy.
- Refractory or recurrent VF/VT, 2nd° or 3rd° heart blocks.
Cooling Methods

- Exposure combined with chemical ice packs, and/or
- Chilled normal saline (NS); stored at a temperature of approximately 4°C (39°F).
Procedure

- Remove patient’s clothing (undergarments may remain)
- Obtain a 12-lead ECG if feasible. If STEMI identified, follow STEMI protocol
- Begin the cooling process with chemical ice packs applied to the groin and axilla, (wet towels may be used along with the ice packs)
- If feasible, establish a large-bore IV. Using a high-pressure bag or other method, rapidly infuse up to 2 L of chilled NS
- Do not administer medications at the same time through the same IV line as the chilled saline
- If patient begins to shiver, move, or have an increased level of consciousness
  - Administer 5.0 mg midazolam IV or IO. May repeat to a maximum of 10 mg as long as Systolic BP is ≥100 mmHg.
- Transport to a hospital that is capable of continuing induced hypothermia.
Unresolved Issues – Temperature Monitoring

- Prehospital
  - Tympanic
  - Esophageal
  - Nasal

- Hospital
  - Bladder
  - Rectal
  - Esophagus
  - PA catheter
Unresolved Issues

- All rhythms or just those with initial rhythm of VF
- How long to cool for (12 vs. 24 hours)
- Intra-arrest cooling or only post-resuscitation
**HT – Complications**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Normothermia</th>
<th>Hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding of any severity†</td>
<td>26/138 (19)</td>
<td>35/135 (26)</td>
</tr>
<tr>
<td>Need for platelet transfusion</td>
<td>0/138</td>
<td>2/135 (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>40/137 (29)</td>
<td>50/135 (37)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>9/138 (7)</td>
<td>17/135 (13)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>2/138 (1)</td>
<td>1/135 (1)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>14/138 (10)</td>
<td>13/135 (10)</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>6/138 (4)</td>
<td>6/135 (4)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>5/133 (4)</td>
<td>9/136 (7)</td>
</tr>
<tr>
<td>Seizures</td>
<td>11/133 (8)</td>
<td>10/136 (7)</td>
</tr>
<tr>
<td>Lethal or long-lasting arrhythmia</td>
<td>44/138 (32)</td>
<td>49/135 (36)</td>
</tr>
<tr>
<td>Pressure sores</td>
<td>0/133</td>
<td>0/136</td>
</tr>
</tbody>
</table>

*None of the comparisons between the two groups, performed with the use of Pearson’s chi-square test, indicated significant differences.*

†The sites of bleeding were mucous membranes, the nose, the urinary tract, the gastrointestinal tract, subcutaneous tissue, and skin, as well as intracerebral and intraabdominal sites.
End of Life Decision Making

- Hypothermic patients
  - “All bets are off” early on
  - Many place patients into a “neurological black box” for up to 2 days after the event
  - No data on how fast the brain is expected to reach maximal predictive recovery after hypothermia
  - If forced to decide, it is reasonable to add 3–5 days to the standard decision making process
  - ? Role of EEG or neurological markers as predictor
Bernard – AHA ReSS 2008

- RCT
- Field cooling vs. no cooling
- Once at hospital, initiation or continuation of cooling left to the discretion of the treating physician
- No differences in outcome
1964: ABC’s of resuscitation “hypothermia should be started within 30 minutes if there is no sign of CNS recovery”

Potential applications
- Traumatic Brain Injury
- Spinal Cord Injury
- Cardiac Arrest
- Stroke
- Myocardial Infarction
- Refractory Septic Shock
Final Thoughts

“Any fool can make a good decision with abundant data. The art of medicine becomes important when you are forced to make good decisions with little data.”

Anonymous