Therapeutic Hypothermia

The cold, hard facts

Acute Coronary Syndrome Summit
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Disclosures

• No conflicts of interest
• Nothing to disclose
Incidence of Out-of-Hospital Cardiac Arrest (OHCA):

326,000 in the U.S. in 2011

196,000 EMS treated OHCA, 10.6% survived

(Holzer. NEJM 2010)
(Bernard. NEJM 2002)
Primary Cause of Cardiac Arrest

- 65-70% due to Coronary Disease
ROSC!!

... now what?!
Post-Resuscitation Syndrome

- Energy Store Depletion
- Inflammation/Edema
- Excitotoxic neuronal cell death
- Free radical production
- Re-oxygenation injury
- Reperfusion injury

Recovery without neurologic damage is rare.
“The idea is to slow the cellular reactions that can cause brain and other organ damage after the heart restarts.”
AHA Guidelines

Hypothermia after ROSC + coma recommended

2005

2010

Post-resuscitation Algorithm

2015

STAY TUNED
Current use of TH

- Routinely implemented for post-cardiac arrest care
- Initiated ASAP
- Surface cooling or Intravascular cooling
- Maintain mild hypothermia (33°C) for 24 hours
Shivering is the ENEMY of hypothermia

Increases metabolic demand

↑ Oxygen consumption (40-100%)!!

Slows/prevents achievement of temp goal
Shivering control

Initiation:
• “Shiver cocktail”
  Magnesium
  Buspirone
  Acetaminophen
  Ativan
  Fentanyl
  Vecuronium

Maintenance:
• Bedside Shivering Assessment Scale
**Maintenance Phase**

- Target temperature of 33°C or 36°C for 24 hours

- Aggressive monitoring:
  - Electrolytes/glucose
  - Intravascular volume status
  - Hemodynamics
  - Awareness of potential adverse events

- Family communication
  - Unexpected, chaotic situation
  - “no straight answers”
  - Difficult prognostication

Re-warming Phase

• Controlled and active process
  Goal of ~ 0.25°C/hr, should take about 12 hours
  Avoid rebound HYPERthermia

• Monitoring:
  Electrolytes
  Hemodynamics

• Discontinuation of sedation and paralytics
## Complications

<table>
<thead>
<tr>
<th>Deleterious effects of hypothermia</th>
<th>Mitigated by</th>
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<tbody>
<tr>
<td>Shivering, thermogenesis</td>
<td>Sedation, analgesia, paralysis</td>
</tr>
<tr>
<td>Catecholamine release</td>
<td>Sedation</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>Maintaining temp above 32°C</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Monitor bradycardia, Maintain temp above 28 ° to avoid VF</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Heparin DVT prophylaxis</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Monitor, treat</td>
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<tr>
<td>Infection</td>
<td>Monitor, consider antibiotics</td>
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</table>
EKG in hypothermia

J-waves, or Osborne Waves
RECENT RESEARCH
33 versus 36

- Nielsen, et al, December 2013 NEJM
- Randomized 950 post-arrest patients to either 33 or 36 degrees Celsius
- End points of survival and neuro status at 180 days
- No statistically significant difference between groups.
Clinical implications

• Other trials did not control for fever. Control group was allowed to run higher temperatures (38 degrees)
• Were these patients as sick?
• Target temperature still up for debate
• Danger of fever may be more important
Pre-hospital Cooling

• Studies have been done to show cooling by EMS with ice bags and chilled saline are “safe and effective”

• Considerations
  Transport time
  Patient selection
  Inadvertent re-warming
  Logistics (ice, coolers, thermometers)

• More recent studies have failed to show outcome benefit to pre-hospital cooling

Prognostication

• No reliable prognostic test within 24 hours of arrest

• “Durations of observation greater than 72 hours after ROSC should be considered before predicting poor outcome in patients treated with hypothermia (Class I, Level C).”

*Circulation. 2010; 122: S768-S786 doi: 10.1161/CIRCULATIONAHA.110.971002*
When do we go to the lab?

• Considerations
  EKG immediately after ROSC not always reliable
  Shockable or non-shockable?
  Good story?
  Survivable?

• STEMI ➔

• Shockable with a good story? ➔

2015 AHA Guidelines

• Targeted Temperature Management
• 32-36
• No pre-hospital cooling
• Wait 72 hours to predict
Reperfusion injury

Ischemia followed by reperfusion

Oxidative stress, inflammation, vasoconstriction of capillaries

Accelerated apoptosis and endothelial damage, secondary injury
If hypothermia can mitigate reperfusion injury in the brain, what about the myocardium?
Rats, rabbits, pigs

Reduction in infarct size

Prior to ischemia
During ischemia
At reperfusion
After reperfusion
Real life?

- Reperfusion is the essential treatment for MI

Our Mantra: Time is MUSCLE
## Human research

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>Result</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>O’Neill, 2004 COOL-MI Transcath CV Therapeutics</td>
<td>Intravascular cooling in STEMI patients</td>
<td>No difference in MACE or IS overall. <strong>Patients who reached &lt;35° prior to reperfusion and had an anterior STEMI had a 49% relative reduction in IS</strong></td>
<td>0.05</td>
</tr>
</tbody>
</table>
| Gotberg, 2010 Rapid-MI-ICE Circ | 20 patients Intravascular cooling prior to PCI in MI pts | 38% RR in IS  
No delay in D2B time  
All patients were <35°                                                                                                                                  | 0.041    |
| Erlinge, 2014 CHILL-MI JACC     | 120 patients Intravascular cooling prior to PCI in STEMI | 14% RR in IS  
33% RR in IS in anterior STEMI                                                                                                                                  | 0.15 0.046 |
Patient characteristics

- Average temp at reperfusion: 34.7°
- 80% of patients were less than 35.0° at reperfusion
- Door to balloon time
  - Control group 34 minutes
  - Hypothermia group 42 minutes
Subanalysis

Patients with the largest anterior infarcts reaped the most benefit from hypothermia with a 24% reduction in infarct size.

Patients with the shortest duration of symptoms prior to presentation had the best outcomes, with those <4 hours having a 31% reduction in infarct size.
Who should we cool?

- Inclusion/exclusion criteria
  Not sick enough?
  Too sick?
  Not “evidence based”
DYING PROHIBITED
Remember that one time...

• Patient woke up while cooling
  Sedated and kept on cooling

• Patient’s family wanted to withdraw care
  Re-warmed early and extubated

• Patient hypotensive at time to re-warm
  Maintained hypothermia until stable, then re-warmed extra slowly

• Took over 4 hours to get to goal temp
  Paralyze for micro-shivering
  Start antibiotics for infection (spiking a fever?)
  EEG for subclinical seizure
Don't fool with the cool.