Yin and Yang of Hypothermia in Trauma and Adult Critical Care

Raeanna C. Adams, MD
Assistant Professor
Trauma and Surgical Critical Care
Department of Surgery
Vanderbilt University Medical Center
Before medicine...
Financial Disclosures

None
Objectives

- Definitions
- Lessons learned
- Physiology/pitfalls
- History of IH
- Uses of hypothermia
- Future

Clipart courtesy FCIT
# Definitions of Hypothermia

<table>
<thead>
<tr>
<th>Type</th>
<th>Induced (°C)</th>
<th>Exposure (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>33-36</td>
<td>33-36</td>
</tr>
<tr>
<td>Moderate</td>
<td>28-32</td>
<td>28-32</td>
</tr>
<tr>
<td>Deep/ Severe</td>
<td>16-27</td>
<td>&lt;28</td>
</tr>
<tr>
<td>Profound</td>
<td>6-15</td>
<td></td>
</tr>
</tbody>
</table>
“Not dead until warm and dead”

Lowest temp documented in survivor:

- Infant - 15.2° C (59.4° F)
- Adult - 13.7° C (56.8° F)
“Not dead until warm and dead”

- Not reliable in hypothermia:
  - Tissue decomposition
  - Apparent rigor mortis
  - Dependent lividity
  - Fixed/dilated pupils

- Series: 9/27 patients CPR in field, 6/14 survived

ED CPR

Lessons from Primary Hypothermia

- Passive vs Active rewarming
  - External-truncal
  - Core
    - Warmed IVF
    - Heated, humidified ventilation
    - Lavage-gastric, colonic, mediastinal, thoracic, peritoneal
    - VV or AV extracorporeal
    - CPB

- Physiology

- For each 1°C ↓ = 6-7% ↓ in cerebral metabolism

Auerbach, Wilderness Medicine, 5th ed.
Lessons Learned

- Intermittent flow may be preferable to no flow
- Difference between warm and cold ischemia time

<table>
<thead>
<tr>
<th>N</th>
<th>Avg Age (y)</th>
<th>Long-term survival (# pts)</th>
<th>Presentation esophageal temp (mean)</th>
<th>Time to CPB (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>25.3</td>
<td>15</td>
<td>21.8°C</td>
<td>141 min</td>
</tr>
</tbody>
</table>

Survival of Hypothermia

Predictors of survival:
- Rapid cooling
- VF during cardiac arrest
- Narcotic/ethanol intoxication

Poor prognostic factors:
- Severe hyperkalemia (>10meq/dL)
- Pre-hypothermia asphyxiation

Auerbach, Wilderness Medicine, 5th ed.
Schaller MD. JAMA 1990.
Cardiovascular

- **Bradycardia**
- Prolonged QT
- Osborn waves
- Arrhythmias $<32^\circ$C
- Most vasopressors relatively ineffective
## Hemodynamics

<table>
<thead>
<tr>
<th>Hypothermia</th>
<th>HR</th>
<th>SVR</th>
<th>CO</th>
<th>CVP</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-mod</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↔</td>
</tr>
</tbody>
</table>

- **Bradycardia unresponsive to atropine**
- **Atrial/ventricular fibrillation**
Respiratory

- Initial tachypnea → hypopnea
- CO2 prod = ↓ 50% / 8°C ↓
- Decreased ciliary motility and airway reflexes
- VQ mismatch
  - atelectasis
  - bronchorrhea
Renal

- **Cold diuresis**
  - Increased with EtOH
  - Electrolyte loss

- **Renal tubular dysfunction**
  - ↓ creatinine clearance—drug dosing

- **Hypokalemia – loss and intracellular shift**

Macintosh TK. Brain Res. 1989.
Coagulopathy

- Enzyme inhibition
  - Increased PT, possibly PTT
  - Clotting cascade affected below 34°C
- Decreased plt count/function
- Fibrinolysis
- If due to hypothermia: not reversed with FFP, easily reversed with rewarming
- Clinically significant?

Watts DD. J Trauma 1998
Sessler DI. NEJM. 1997.
Infectious

- ↓ function of neutrophils and macrophages
- ↑ pneumonia-esp if IH>48hr
- Wound infxn: local vasoconstriction and suppression immune function

Neurologic

- Mild hypothermia – confusion, ataxia
- Moderate – obtundation
- Hyperreflexia at 32°C
- <27°C, loss of pupillary light reflex and DTR

## Spontaneous vs Induced Hypothermia

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous</th>
<th>Induced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
<td>Severe ischemia, ↓ cellular reserve</td>
<td>Deliberate, controlled</td>
</tr>
<tr>
<td></td>
<td>Unable to thermoregulate</td>
<td>Poss more cellular reserve</td>
</tr>
<tr>
<td></td>
<td>Environmental exposure</td>
<td></td>
</tr>
<tr>
<td><strong>Significance</strong></td>
<td>Advanced tissue ischemia</td>
<td>↓ metab rate</td>
</tr>
<tr>
<td></td>
<td>↓ cellular substrates</td>
<td>Preservation of substrates</td>
</tr>
<tr>
<td></td>
<td>Failure of homeostasis</td>
<td>↓ free radical</td>
</tr>
<tr>
<td></td>
<td>Shivering worsens mismatch of tissue supply/demand</td>
<td>↓ oxidative stress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ vasc permeability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active shivering prevention</td>
</tr>
<tr>
<td><strong>Clinical Implication</strong></td>
<td>Lethal triad</td>
<td>Therapeutic strategy with potential benefit</td>
</tr>
<tr>
<td></td>
<td>Poor prognostic sign</td>
<td></td>
</tr>
</tbody>
</table>

**Metabolism is reduced 5-8% for each ↓ 1° C**
Does Cold Kill?

  - N=57, randomized
  - Trauma pt with T ≤ 35.5°C
  - Rewarming with CAVR vs standard
  - 7% vs 43% mortality
  - Pt who did not rewarm died
- ?Chicken or egg?
“All bleeding stops...eventually”

- Lethal Triad/Damage control
  - Hypothermia
  - Coagulopathy
  - Acidosis
- Marker of severity
- ? Animal models of better outcome with IH in exanguination

Why We Warm in Trauma

- (Spontaneous) hypothermia tripled chance of death
- ↓ 2°C increased EBL by 500cc
- 3x SSI with periop hypothermia
- Important to realize:
  - Marker of severity of injury
  - Benefits vs risk

George ME. J Trauma. 2010.
Ireland S. Resuscitation. 2010.
Sessler. NEJM. 1997.
Kurtz. NEJM. 1996.
How We Warm
“Cold injures the body while heat injures the spirit…”

-from the *Yellow Emperor's Classic of Medicine*
History of IH Research

- Hippocrates – snow to wounds
- Baron Larrey
- 1939- Dr. Temple Fay pain control, metastatic disease
- 1954-1959- used in TBI
- 1964 – in CPR algorithm (Safar)
- 1960-1970’s- ↓ interest
- 1980’s - animal studies with IH in cardiac arrest
  - Mild/moderate vs deep IH
Who Do We Cool?
Cardiac Arrest with Return of Spontaneous Circulation

- 350K / yr with OHCA in USA
- 25% survive to the hospital
- 70%-80% in-hospital mortality
- Overall survival 5-8% at 1yr
- Good neurologic recovery 20-30% of survivors
Neurologic Injury After Cardiac Arrest

Post-Cardiac Arrest Syndrome

- Primary and post-arrest brain injury
- Post-arrest myocardial dysfunction
- Systemic ischemia-reperfusion response

Don’t forget the initial cause of arrest!

Circulation 2008;118:2452
Brain Injury Continues After Reperfusion

Increased:

- Oxygen free radicals
- Neutrophil infiltration
- Calcium sequestration in mitochondria
- Cellular membrane ATPase pump dysfunction
- Metabolic rate/demand
- Vascular permeability
- Loss of autoregulation / Cerebral edema
-She's only mostly dead.
MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP

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


NEJM, February 21, 2002
Neurologic Injury in Out-of-Hospital Arrest

- Multi-center, prospective, randomized
- VF/VT arrest with neuro inj
- IH 32-34°C (12hr for Bernard; 24hr for HACA)
- HACA - 6mo outcomes, screened >3500 pt

<table>
<thead>
<tr>
<th></th>
<th>N=pts</th>
<th>+Neuro (%)</th>
<th>p</th>
<th>Mortality (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IH</td>
<td>C</td>
<td>IH</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>HACA</td>
<td>137</td>
<td>138</td>
<td>55</td>
<td>39</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41</td>
<td>55</td>
</tr>
<tr>
<td>Bernard</td>
<td>43</td>
<td>34</td>
<td>49</td>
<td>26</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51</td>
<td>68</td>
</tr>
</tbody>
</table>

HACA. NEJM 2002.
European HACA Trial

OUTCOME MEASURE

- Survival with min or mod disability at 6 mo
- 55% IH; 39% C
- Risk ratio for good outcome 1.40 (1.08-1.81)

- Number needed to treat = 6
- Sooner = better
- Complications not statistically significant

HACA Study Group, NEJM
## Why We Cool

### Compare ICU Strategies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NNT (mortality)</th>
</tr>
</thead>
<tbody>
<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>Stroke Aspirin</td>
<td>33</td>
</tr>
<tr>
<td>AMI Thrombolytics</td>
<td>37–91*</td>
</tr>
<tr>
<td><strong>Hypothermia</strong></td>
<td><strong>6.1-7.0</strong></td>
</tr>
</tbody>
</table>

*Depending on age

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NEJM 2002;346:549
HYPOTHERMIA: Mechanisms of Ischemic Neuroprotection

- **Improved**
  - BBB stability
  - Protection against cytoskeletal proteolysis

- **Decreased:**
  - Metabolic demand-active and basal
  - Cellular apoptosis
  - Oxygen free radical production
  - Neutrophil infiltration
  - Cytokine and leukotriene production

Lancet 2008;371:1955
“Unconscious patients with spontaneous circulation after out of hospital arrest should be cooled to 32-34°C for 12-24 hours when the initial rhythm is ventricular fibrillation.”

AND

“Such cooling may also be beneficial for other rhythms or in-hospital arrest.”

Nolan, JP, Resuscitation, 2003
Lessons

- Animal and clinical studies
- Earlier is better
- Preservative > Resuscitative
- Resuscitative > not at all
- Fever = worse outcomes
How To Cool

• NS +/- chilled
  • Safety of chilled NS, rapid cooling
• Truncal cooling
• Localized
  • Not quite ready for prime-time
• Intravascular
• External pads

***MUST CONTROL COOLING***
How We Cool
VUMC Induced Hypothermia Protocol

- **Induction**
  - Rapid to 32-34°C
  - Sedation, paralyze if necessary to prevent shivering

- **Maintenance**
  - Goal temperature 33°C
  - Standard 24 hr after ROSC
  - ***Suppress shivering***

- **Rewarming**
  - Most dangerous period: hypotension, brain swelling, hyperkalemia
  - Goal 37°C over 12-24h
  - Stop all sedation when normal body temperature is achieved
Cardiac Arrest Patients with STEMI: VUMC

January 2007-May 2010:

- 23 pts with OHCA + STEMI
- All emergent PCI, treated with hypothermia
- 13/23 (57%) survivors
- Support with IABP or VAD required in 10 pts
  - Survival rate 2/10 in this group
- Survival 85% in pts not requiring mechanical support
- Good neurologic outcome - 92% of survivors

Information from McPherson J, MD. 2010
Traumatic Brain Injury

- TBI deaths = 50,000 pt/yr in US
- 30%-70% mortality severe TBI
- Direct neuronal inj
- Secondary inj
- Fever worsens outcome
- Hypothermia decreases ICP

Sydenham, E. Cochrane review. 2009
Traumatic Brain Injury

- **Mixed results of RCTs**
  - Single center trials gen with positive benefit
  - Multi-center trials not replicated benefit

- **Criticisms: Poor control of variables**
  - ICU care, complications
  - Hydration/resuscitation
  - Hypotension and rewarming

- **No increase in mortality**

Fox JL. CJEM. 2010.
Sydenham, E. Cochrane review. 2009
Hypothermia in Traumatic Brain Injury

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>IH</th>
<th>F/U</th>
<th>Good Outcome (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiozaki, 1993</td>
<td>33</td>
<td>34C/48h</td>
<td>6mo</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>Clifton, 1993</td>
<td>46</td>
<td>33C/48hr</td>
<td>3mo</td>
<td>52</td>
<td>36</td>
</tr>
<tr>
<td>Marion, 1993</td>
<td>82</td>
<td>33C/24hr</td>
<td>6mo</td>
<td>56</td>
<td>33</td>
</tr>
<tr>
<td>Jiang, 2000</td>
<td>87</td>
<td>34C/3-14d</td>
<td>1yr</td>
<td>47</td>
<td>27</td>
</tr>
<tr>
<td>Shiozaki, 2001</td>
<td>91</td>
<td>34C/48hr</td>
<td>3mo</td>
<td>46</td>
<td>59</td>
</tr>
<tr>
<td>Clifton, 2001</td>
<td>392</td>
<td>33C/48hr</td>
<td>6mo</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Gal, 2002</td>
<td>30</td>
<td>34C/72hr</td>
<td>6mo</td>
<td>87</td>
<td>47</td>
</tr>
<tr>
<td>Zhi, 2003</td>
<td>396</td>
<td>33C/1-7d</td>
<td>6mo</td>
<td>62</td>
<td>38</td>
</tr>
<tr>
<td>Qiu, 2005</td>
<td>86</td>
<td>34C/3-5d</td>
<td>2yr</td>
<td>65</td>
<td>37</td>
</tr>
<tr>
<td>Qiu, 2007</td>
<td>80</td>
<td>34C/4d</td>
<td>1yr</td>
<td>70</td>
<td>48</td>
</tr>
</tbody>
</table>
Traumatic Brain Injury

- Adult RCT ongoing – Japan
- Eurotherm3235 Trial
- AANS Guidelines – consider:
  - Control of refractory ↑ICP
  - Early induction
  - ≥48hr IH

Traumatic Spinal Cord Injury

- September, 2007
- NFL player: incomplete cervical SCI
- Tackling player during kick-off return
- Systemic cooling en route to hospital, early decompression, successful recovery
Traumatic Spinal Cord Injury

- Animal models only, studies – 1970s-80s
  - Suggested improved outcomes
  - Mixed studies

- Suggestion of protection as prophylaxis before SC surgery/aortic repair
  - Mixed data, human studies
  - No convincing evidence of benefit

- To date, no RCTs
  - Not enough evidence to recommend for/against

Future

- Cold ischemia time in IH
  - Mild – 15min
  - Mod – 20min
  - Deep – 30min
  - Profound – 60min

- Preservative

- Resuscitative

- Suspended animation

Safar PJ. Curr Opin Anaesthesiol. 2002.
And the Future is Now…

- Trauma patient with hypotension
  - Delay vascular collapse, surgical control
  - Animal models-improved mortality, fluid limitation+mild IH

- EPR-CAT: Emergency Preservation and Resuscitation for Cardiac Arrest from Trauma - multicenter trial
  - Pulseless trauma patient, exsanguinating cardiac arrest
  - ED thoracotomy, aortic cannula, 10°C, repair, CPB rewarming

Wu X. J Cereb Blood Flow Metab. 2008
Summary

- Double-edged sword in trauma
- IH for neuro injury after OHCA
- Careful control of challenges of IH
- Possible TBI
- Risks/benefits
- Need for ongoing research
- Further areas of application