Hypothermia in Medicine

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Denver Health and Hospitals
Hypothermia in Trauma Victims

Man is a homeotherm. . .

- Maintains constant temperature
- Tolerates deviation poorly

- 37.0 °C under the tongue
- 38.0 °C rectal
- 32.0 °C skin
- 38.5 °C liver
## Causes of Hypothermia

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accidental</td>
<td>Environmental exposure, immersion</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>Organ preservation; cardiac surgery</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Alcohol, anesthetics, narcotics, etc.</td>
</tr>
<tr>
<td>Hypothalamic</td>
<td>Wernicke’s; anorexia nervosa; pinealoma</td>
</tr>
<tr>
<td>CNS Dysfunx</td>
<td>CVA, cord transection, hypopituitary</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hypo - glycemic, thyroid, adrenal</td>
</tr>
<tr>
<td>Trauma</td>
<td>Severe injury; altered thermoregulation; combinations</td>
</tr>
</tbody>
</table>
Hypothermia in Medicine

- Solid Organ Transplantation
- Cryo-preservation
- Stroke
- Drowning
- Brain Injury
- Cardiac Arrest
- Trauma
Hypothermia in Trauma

“Lack of Effect of Induction of Hypothermia after Brain Injury”

• Prospective, randomized, multi-center trial of cooling head injured patients to 33°C for 48 hrs.
• Planned sample size: 500 patients
• Blunt head trauma, GCS 3-8 after resuscitation
• Surface cooling techniques
• Excluded if other severe injuries, shock, bleeding, or if not cooled within 6 hours

Clifton et al, NEJM, Feb 2001
Nation Acute Brain Injury Study

Hypothermia in Trauma
Hypothermia & Brain Injury

“Lack of Effect of Induction of Hypothermia after Acute Brain Injury”

Results:

• Stopped early, n = 392
• Injury to randomization: 4 hrs
• Injury to target temperature: 8.4 hrs
• Not effective in improving outcomes
• Overall equal mortality (28% vs. 27%)
• More complications in cold patients

Clifton et al, NEJM, Feb 2001

Hypothermia in Trauma
Hypothermia & Brain Injury

Results (cont.):

• No difference in outcome confounders

• More vasopressors in cold pts. (80% vs. 69%)

• More fluid in cold patients (3L vs. 1.9L)

• More hospital days with complications in cold patients (78 d vs. 70 d)

• More ICU interventions (TISS score) in hypothermic patients

Clifton et al, NEJM, Feb 2001
Hypothermia & Brain Injury

Results (subgroup analyses):

- Hypothermic patients > 45 yrs old had 1.3 RR (CI 1.0-1.7) of poor outcome
- Patients ≤ 45 years old, who arrived with core body temperature ≤ 35°C, had a 0.7 RR (CI 0.5-1.0) of poor outcome
- Suggests: very early cooling, or not rewarming, young patients, might be helpful; but . .
- Induced hypothermia is not helpful

Clifton et al, NEJM, Feb 2001

Hypothermia in Trauma
Hypothermia & Cardiac Arrest

- Small study from Japan, SCCM, 2001
- Better neurological outcome in hypothermic patients if...
- GCS > 5 initially
- < 20 minutes CPR
Hypothermia & Cardiac Arrest

“Clinical Trial of Induced Hypothermia in Comatose Survivors of Out-of-Hospital Cardiac Arrest”

- **N=22 adults, acute cardiac event**
- **Unconscious following successful CPR**
- **Surface cooling in ED to 33°C, maintained for 12 hrs in ICU**
- **Retrospective control group**

Victoria, Australia*
Hypothermia in Trauma

"Clinical Trial of Induced Hypothermia in Comatose Survivors of Out-of-Hospital Cardiac Arrest"

Results:

• No adverse effects, no septic complications
• Slowing of heart rate, no change in BP
• Slight acidosis, hyperkalemia at 18 hrs
• Improved Glasgow Outcome Coma Scale
• Lower Mortality: 45% vs. 77%

Victoria, Australia
European Hypothermia Study Group

**Hypothermia After Cardiac Arrest Study Group**

- Vienna, Austria
- Multi-center European study
- 275 patients (equal distribution)
- 24 hours of mild hypothermia ($32^0\text{C}-34^0\text{C}$) after ventricular fibrillation arrest and resuscitation
- Outcome analysis blinded to treatment
- 6 month neurologic outcome 1^0 endpoint

*NEJM 2002; 346(8), 550.*
Hypothermia after Cardiac Arrest

**NEJM, 2002**

- **Graph**: Shows the bladder temperature over time after restoration of spontaneous circulation in two groups: normothermia (n=124) and hypothermia (n=123).

- **X-axis**: Hours after restoration of spontaneous circulation.

- **Y-axis**: Bladder temperature (°C).
## Neurologic Outcome & Mortality

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Normoth.</th>
<th>Hypoth.</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Neuro</td>
<td>54/137</td>
<td>75/136</td>
<td>1.4 (1.08-1.81)</td>
</tr>
<tr>
<td></td>
<td>39%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>76/138</td>
<td>56/137</td>
<td>0.74 (0.58-0.95)</td>
</tr>
<tr>
<td></td>
<td>55%</td>
<td>41%</td>
<td></td>
</tr>
</tbody>
</table>

*NEJM Feb 21 2002*
Hypothermia after Cardiac Arrest  

**NEJM, 2002**

**Graph:**
- **Survival (%)** vs **Days**
- Two lines: Hypothermia and Normothermia
- Number of patients at risk:
  - Hypothermia: 137, 92, 86, 83, 11
  - Normothermia: 138, 74, 66, 64, 9
Cardiac Arrest & Hypothermia

More complications in the hypothermic group

- Bleeding
- Pneumonia
- Sepsis
- Edema

---

**TABLE 4. Complications during the First Seven Days after Cardiac Arrest.**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Normothermia</th>
<th>Hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td>no./total no. (%)</td>
</tr>
<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.
ILCOR Advisory Statement (2002)

Circulation 108, 2003

• International Liaison Committee on Resuscitation

• Recommendation: for unconscious adults with spontaneous circulation after out-of-hospital arrest:

• Cool to 32°C - 34°C for 12-24 hrs when initial rhythm was vent. fibrillation.

• Such cooling might be beneficial for other rhythms or in-hospital cardiac arrest.
Hypothermia in Trauma: Problems

• Very time dependent: must be accomplished within 1-3 hours of arrest
  » Rosomoff et al, SG&O, 1960

• Very temperature dependent: only mild range (33°C-36°C), tight temp. control needed
  » Safar et al, Stroke, 1996

• Rewarming: timing & technique

• How to assure poikilothermia

• Mechanism unknown
Hypothermia & Cardiac Arrest: Not so fast

• Targeted temperature management after cardiac arrest (33 vs 36 degrees)
• European and Australian multi-center prospective randomly assigned trial
• 950 pts, unconscious, out of hospital cardiac arrest
• No benefit: mortality & neurologic outcome

Nielsen et al, NEJM, Nov 2013
Immediate cooling, for 30 hours

Hypothermia in Trauma

Nielsen et al: NEJM 2013
Shown are Kaplan–Meier estimates of the probability of survival for patients assigned to a target temperature of either 33°C or 36°C and the number of patients at risk at each time point. The P value was calculated by means of Cox regression, with the effect of the intervention adjusted for the stratification variable of study site.
In conclusion, our trial does not provide evidence that targeting a body temperature of 33°C confers any benefit for unconscious patients admitted to the hospital after out-of-hospital cardiac arrest, as compared with targeting a body temperature of 36°C."

Now what? Maybe keeping euthermia is the ideal (eg: preventing fevers)
Hypothermia and Trauma

• Hypothermia occurs frequently
  ▶ Blood loss
  ▶ Prolonged environmental exposure
  ▶ Cold fluid resuscitation
  ▶ Open body cavities
  ▶ Shivering ablated
  ▶ Anesthetic and paralyzing agents
Incidence: Jurkovich et al

- 71 patients, ISS > 25
- 42% < 34 °C
- 23% < 33 °C
- 13% ≤ 32 °C, and all died
- Incidence directly related to
  - Injury severity
  - Massive fluid resuscitation
  - Presence of shock

J Trauma 1987
Hypothermia and Mortality

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Zones of Hypothermia

**Safe/Mild**
- 98.6°F (37°C)
- Hyperdynamic cardiovascular, pulmonary, and metabolic response
- Shivering, and vasoconstriction

**Transitional**
- 91.4°F (33°C)
- Confusion, ataxia, amnesia
- Severe shivering
- Bradycardia, falling cardiac output, irrigable myocardia
- Hypoventilation
- Cold diuresis
- Muscle rigidity
- Complex acid-base status
- Progressive loss of consciousness and reflexes
- Pupils dilated, slow or absent light response
- Flaccid appearance
- Hypotension, hypoperfusion, acidosis

**Critical Temperature in Trauma Victims**
- 86°F (30°C)
- Critical temperature in trauma victims
Hypothermia and Coagulation

- platelet count
- platelet function
- partial thromboplastin time
- prothrombin time
- thrombin time
Hypothermia and Coagulation

Prothrombin time (secs)

Temperature (°C)

Normal

Coagulopathy
INR and Factor Levels
## Hypothermia and Coagulation

<table>
<thead>
<tr>
<th>Temp.</th>
<th>35(^\circ) C</th>
<th>33(^\circ) C</th>
<th>31(^\circ) C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor IX Activity</td>
<td>39%</td>
<td>16%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Johnston, 1989
<table>
<thead>
<tr>
<th>Hypothermic Baboons (32°C)</th>
<th>Normothermic Baboons</th>
</tr>
</thead>
<tbody>
<tr>
<td>arm temp (°C)</td>
<td>bleeding time (sec)</td>
</tr>
<tr>
<td>27.3</td>
<td>5.8</td>
</tr>
<tr>
<td>34.0</td>
<td>2.4</td>
</tr>
<tr>
<td>38.9</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Valeri Ann Surg 1987
<table>
<thead>
<tr>
<th></th>
<th>&lt; 35°C</th>
<th>&gt; 35°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>trauma score</td>
<td>15.4</td>
<td>15.7</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>17.6</td>
<td>16.5</td>
</tr>
<tr>
<td># abdominal organs injured</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>blood loss</td>
<td>1820</td>
<td>540</td>
</tr>
</tbody>
</table>

Bernabei, 1992
Hypothermia and Blood Loss

Bernabei 1992
Hypothermia and Oxygen Consumption

VO$_2$ mls/min

Zwischenberger, 1987
Hypothermia and Oxygen Consumption

- 24 adult surgical patients studied in PACU
- Small decreases in core temperature (0.3-1.2°C) associated with a 92% increase in oxygen consumption

Roe, 1966
Rewarming

- Hypothermia in trauma has specific detrimental effects
  - Coagulopathy
  - Ablation of shivering
  - Increased energy consumption to rewarm
  - Immunosuppressive
Now King David was old and stricken in years; and they covered him with clothes, but he gat no heat. Wherefore his servants said unto him, “Let there be sought for my lord the king a young virgin; and let her stand before the king, and let her cherish him, and let him lie in her bosom, that the lord my king get heat.”

I Kings 1: 1-2
Spontaneous Rewarming

- heat production is proportional to VO$_2$
- with normal VO$_2$ = 1 kcal/kg/hr (70 kcals/hr)
- body temperature increases by 1.2$^\circ$C per hour
- increases to 3.6$^\circ$C per hour with shivering
Hypothermia and Oxygen Consumption

- 70 kcals produced at rest per hour
- 280 kcal heat deficit equals 4 hours total heat production
- patient must double heat production for 4 hours to pay back “heat deficit”
- requires consumption of additional 55,440 mls of oxygen
Hypothermia and Oxygen Consumption

- 24 adult surgical patients studied in PACU
- small decreases in core temperature (0.3-1.2°C) associated with a 92% increase in oxygen consumption

Roe, 1966
Hypothermia and Oxygen Consumption

VO$_2$ mls/min

- Shivering
- Paralyzed

Zwischenberger, 1987

Hypothermia in Trauma
Rewarming

• Hypothermia in trauma has specific detrimental effects
  ➢ Coagulopathy
  ➢ Ablation of shivering
  ➢ Increased energy consumption to rewarm

• How best to rewarm the cold trauma patient?
Specific Heat: the amount of heat required to raise the temperature of 1 kg of a substance by 1°C.

- 32°C to 37°C
- 5°C
- 5 kcal
- 70 kgs Water X 5°C = 350 kcal
Hypothermia and Rewarming

Specific Heat of Man = 0.8 kcals/kg/°C

0.8 kcals/kg/°C $\times$ 70 kgs = 56 kcals/°C

37°C - 32°C $\times$ 56 kcals/°C = 280 kcals

280 Kcals
Warm Intravenous Fluids

10 kcals increases body temperature by 0.17 ºC

28 liters required to provide 280 kcals

Hypothermia in Trauma
Airway Rewarming

latent heat of vaporization = 0.56 kcals/ml

41 ºC air
0.05 mls H₂O/L

32 ºC air
0.03 mls H₂O/L

0.02 mls H₂O/L X 600 L air/hr = 12 mls/hr

0.56 kcals/ml X 12 mls H₂O/hr = 6.7 kcals/hr
Convective Blankets

specific heat of air = 0.24 kcals/kg/°C

- air flow 24,000 L hr
- density of air = .0012 kg/L
- equals 28.8 kg air/hr

28.8 kg/hr \times 0.24 \text{ kcals/kg/°C} = 6.9 \text{ kcals/hr}

will raise body temperature by 0.12°C/hr

_Hypothermia in Trauma_
specific heat of H₂O = 1 kcal/kg/°C

42°C water enters

5 kcals

37°C water exits

raises body temperature 0.09 °C/L

56 liters required to transfer 280 kcals
Cardiopulmonary Bypass

specific heat of blood = 0.9 kcals/L/°C

9°C X 0.9 kcals/L/°C X 2.5 L/min = 1200 kcals/hr

Hypothermia in Trauma
CAVR: Continuous A-V Rewarming

No Pump!

8 kcals X 0.9 X 225-350 mls/min = 96-150 kcals/hr
will raise body temperature by 1.7-2.6ºC/hr
CAVR Technique

[Diagram showing the CAVR technique with labels for femoral artery, subclavian vein, cold blood, rewarmed blood, and water flow.]
Countercurrent Rewarmer

Warm blood
in
out

Cold blood
in

Hot water
in

Cold water
out
CAVR Complications

No Anticoagulation: but no clot observed

Arterial injury: 1.0%
<table>
<thead>
<tr>
<th>Technique</th>
<th>Heat Transfer (kcals/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>airway rewarming</td>
<td>6.7</td>
</tr>
<tr>
<td>convective warming</td>
<td>6.9</td>
</tr>
<tr>
<td>warm IV fluids</td>
<td>35-70</td>
</tr>
<tr>
<td>CAVR</td>
<td>96-150</td>
</tr>
<tr>
<td>Total</td>
<td>145-234</td>
</tr>
</tbody>
</table>
Is Hypothermia in the Major Trauma Victim Protective or Harmful?

LM Gentilello, GJ Jurkovich, MS Stark, SA Hassantash, GE O’Keefe

American Surgical Association, 1996
Annals of Surgery, 1997
Patient Allocation

62 eligible hypothermic patients

5 not randomized

57 randomized patients

- CAVR
- All the same standard techniques

29 CAVR

28 SR

- airway rewarming
- convective air blanket
- aluminized hat
- warm IV fluids
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>SR</th>
<th>CAVR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>45.6</td>
<td>47.5</td>
<td>0.85</td>
</tr>
<tr>
<td>ICU temp</td>
<td>33.3</td>
<td>33.6</td>
<td>0.10</td>
</tr>
<tr>
<td>blood pressure</td>
<td>112</td>
<td>120</td>
<td>0.18</td>
</tr>
<tr>
<td>ISS</td>
<td>32</td>
<td>31</td>
<td>0.39</td>
</tr>
<tr>
<td>blunt mechanism</td>
<td>86%</td>
<td>83%</td>
<td>0.75</td>
</tr>
<tr>
<td>severe injury AIS &gt; 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>head injury</td>
<td>52%</td>
<td>52%</td>
<td>0.48</td>
</tr>
<tr>
<td>chest injury</td>
<td>71%</td>
<td>59%</td>
<td>0.31</td>
</tr>
<tr>
<td>abdominal injury</td>
<td>36%</td>
<td>35%</td>
<td>0.92</td>
</tr>
<tr>
<td>laparotomy</td>
<td>36%</td>
<td>69%</td>
<td>0.01</td>
</tr>
</tbody>
</table>
24 Hour Fluid Requirements

- Historical control study: 26 liters
- Randomized study: 32 liters

- CAVR
- SR

33 liters
24 Hour Fluid Requirements

- CAVR: 25 liters
- SR: 33 liters
Clotting Factor Requirements:

20% less in rewarmed patients

<table>
<thead>
<tr>
<th></th>
<th>SR</th>
<th>CAVR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-8 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fresh frozen plasma</td>
<td>1,412</td>
<td>1,123</td>
<td>-</td>
</tr>
<tr>
<td>cryoprecipitate</td>
<td>208</td>
<td>139</td>
<td>-</td>
</tr>
<tr>
<td>platelets</td>
<td>449</td>
<td>353</td>
<td>-</td>
</tr>
<tr>
<td>total clotting products</td>
<td>2,069</td>
<td>1,615</td>
<td>0.17</td>
</tr>
<tr>
<td>0-24 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fresh frozen plasma</td>
<td>2,120</td>
<td>1,699</td>
<td>-</td>
</tr>
<tr>
<td>cryoprecipitate</td>
<td>387</td>
<td>280</td>
<td>-</td>
</tr>
<tr>
<td>platelets</td>
<td>535</td>
<td>392</td>
<td>-</td>
</tr>
<tr>
<td>total clotting products</td>
<td>3,042</td>
<td>2,371</td>
<td>0.22</td>
</tr>
</tbody>
</table>
Figure 2. Time to rewarming to 36ºC for CAVR and SR patients. Twelve SR and two CAVR patients failed to rewarm to 36ºC, and are not included.
Rewarming Failures

- 12 of 28 standard technique patients failed to rewarm to 36°C
  - Failure to rewarm: 43%
  - Mortality: 100%

- 2 of 29 CAVR patients failed to rewarm to 36°C
  - Failure to rewarm: 7%
  - Mortality: 100%
Kaplan-Meier Survival

% survival vs survival duration, hours

- CAVR
- SR

\( p = 0.059 \)
\( ^* p = 0.047 \)
Summary

- CAVR reduced the duration of hypothermia and affects resuscitation
  - decreased fluid requirements
  - decreased risk of early death
- Rewarming alters the natural history of resuscitation
  - Shifts the survival curve to new problems
Conclusions

Hypothermia is not protective in trauma patients during resuscitation, and independently increases the risk of early mortality.
Trauma Hypothermia

- Specific and unique detrimental effects
  - Coagulopathy
  - Ablation of shivering
  - Increased energy consumption to re-warm
  - Immunosuppressive
Hypothermia in Neurotrauma

- Induction hypothermia following head injury does not improve survival
  - Coagulopathy
  - Infection
  - BP control
  - Perhaps beneficial in certain ages, settings
  - No current clinical trials
Hypothermia in Cardiac Arrest

- Induction hypothermia in acute cardiac arrest
  - Difficult to induce and maintain
  - Mixed clinical evidence of efficacy
  - Ongoing clinical trials
  - Most recent trial shows no benefit to 33 deg C vs. holding at 36 deg C