The Physiologic Effects of Mild Hypothermia

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Director, Emergency Intensive Care
Washington Hospital Center
Disclosure

- Gaymar Industries
- Inverness Medical
- NIH-NHLBI co-PI ALI in severe sepsis
- Beatrice Wind Gift Fund
Outline

• Accidental Hypothermia
• Historic Perspective
• Physiologic Effects versus Adverse Effects
  – Organ Systems Approach
  – Experience in Randomized Clinical Trials
  – Experience From Hypothermia Registry
• Conclusions
Accidental Hypothermia

Accidental Hypothermia: Unintentional decline in core temperature below 35°C

**Severity Based on Body Temperature on Arrival:**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90.0-95° F</td>
<td>82.4-90° F</td>
<td>&lt; 82.4° F</td>
</tr>
<tr>
<td></td>
<td>32.2-35° C</td>
<td>28-32.2° C</td>
<td>&lt; 28° C</td>
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</table>

# Physiologic Changes Associated with Hypothermia

<table>
<thead>
<tr>
<th>Severity of Hypothermia</th>
<th>Body Temperature</th>
<th>Central Nervous System</th>
<th>Cardiovascular</th>
<th>Respiratory</th>
<th>Renal and Endocrine</th>
<th>Neuromuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>35°C (95°F) to 32.2°C (90°F)</td>
<td>Linear depression of cerebral metabolism; amnesia; apathy; dysarthria; impaired judgment; maladaptive behavior</td>
<td>Tachycardia, then progressive bradycardia; cardiac-cycle prolongation; vasoconstriction; increase in cardiac output and blood pressure</td>
<td>Tachypnea, then progressive decrease in respiratory minute volume; declining oxygen consumption; bronchorrhea; bronchospasm</td>
<td>Cold diuresis; increase in catecholamine, adrenal steroids, triiodothyronine, and thyroxine; increase in metabolism with shivering</td>
<td>Increased preshivering muscle tone, then fatiguing shivering-induced thermogenesis; ataxia</td>
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<td>Electroencephalographic abnormalities; progressive depression of level of consciousness; pupillary dilatation; paradoxical undressing; hallucinations</td>
<td>Progressive decrease in pulse and cardiac output; increased atrial and ventricular arrhythmias; nonspecific and suggestive (J-wave) electrocardiographic changes; prolonged systole</td>
<td>Hypoventilation; 50% decrease in carbon dioxide production per 8°C drop in temperature; absence of protective airway reflexes; 50% decrease in oxygen consumption</td>
<td>50% increase in renal blood flow; renal autoregulation intact; no insulin activity</td>
<td>Hyporeflexia; diminishing shivering-induced thermogenesis; rigidity</td>
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<td>Severe</td>
<td>&lt;28°C (82.4°F)</td>
<td>Loss of cerebrovascular autoregulation; decline in cerebral blood flow; coma; loss of ocular reflexes; progressive decrease in electroencephalographic activity</td>
<td>Progressive decreases in blood pressure, heart rate, and cardiac output; reentrant dysrhythmias; decreased ventricular arrhythmia threshold; asystole</td>
<td>Pulmonary congestion and edema; 75% decrease in oxygen consumption; apnea</td>
<td>Decrease in renal blood flow parallels decrease in cardiac output; extreme oliguria; poikilothermia; 80% decrease in basal metabolism</td>
<td>No motion; decreased nerve-conduction velocity; peripheral areflexia</td>
</tr>
</tbody>
</table>

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Early Translation Failure

- 1950’s Hypothesis
- Lower Temp $\Rightarrow$ Lower Metabolism
- Temp Dependent Metabolic Processes
- Decreased O$_2$ Demand
- Decreased Glucose Demand by Brain
- Therefore, Lower = Better

Polderman, KH. CCM 2009; 37: S186-202
• “It has been repeatedly demonstrated that hypothermia will protect the brain against anoxic injury. This protection appears related to the demonstrable reduction in cerebral oxygen consumption and cerebral blood flow present in hypothermic individuals.”


<table>
<thead>
<tr>
<th>Case Number</th>
<th>Date</th>
<th>Age</th>
<th>Cause of arrest</th>
<th>Duration of arrest</th>
<th>Neurologic damage</th>
<th>Hypothermia: Range</th>
<th>Duration</th>
<th>Residual neurologic defect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>Jan. 1957</td>
<td>5 yr. C. M.</td>
<td>5 minutes</td>
<td>Severe</td>
<td>32–34°C</td>
<td>72 hours</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Aug. 1957</td>
<td>9 yr. C. F.</td>
<td>5 minutes</td>
<td>Severe</td>
<td>30–32°C</td>
<td>24 hours</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Sept. 1957</td>
<td>38 C. M.</td>
<td>5 minutes</td>
<td>Severe</td>
<td>32–33°C</td>
<td>48 hours</td>
<td>None</td>
</tr>
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<td></td>
<td>4</td>
<td>Nov. 1957</td>
<td>39 C. F.</td>
<td>5 minutes</td>
<td>Severe</td>
<td>32–34°C</td>
<td>72 hours</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Hypothermia has been shown to protect the brain against anoxia. There is a reduction in the cerebral oxygen consumption and cerebral blood flow with body cooling.

Benson DW et al. Anesthesia and Analgesia 1959; 38: 423-428
HEART-LUNG RESUSCITATION

I. FIRST AID: OXYGENATE THE BRAIN IMMEDIATELY

- Airway - Tilt head back
- Breathe - Inflate lungs 3-5 times, maintain head tilt
- Circulate - Compress heart once a second, alternate 2-3 lung inflations with 15 sternal compressions until spontaneous pulse returns.

II. START SPONTANEOUS CIRCULATION

- Drugs: EPISTEMEPHINE: 1.0 mg (10 cc of 1:1000) I.V. or 0.5 mg INTRACARDIAC, repeat larger dose if necessary. SODIUM BICARBONATE: Approximately 2.5 g/50 cc (1/2 dose in children) I.V., repeat every 5 minutes if necessary.
- E.K.G.: Fibrillation: External electric defibrillation, repeat shock every 1.5 minutes until fibrillation reversed. If asystole or weak beats: Epinephrine or Calcium I.V.
- Fluids: I.V. Plasma, Dextran, Saline. Do not interrupt cardiac compressions and ventilation. Tracheal intubation only when necessary. After return of spontaneous circulation use vasopressors as needed, e.g. Norepinephrine (Levophed) I.V. drip.

III. SUPPORT RECOVERY

- Gauge: Evaluate and treat cause of arrest. Start within 30 minutes if no sign of CNS recovery.

Post-Arrest Care: Gauge
Hypothermia
Intensive Care

Peter Safar: Journal of the Iowa Medical Society, November, 1964
Problems Leading to Abandonment of Hypothermia

• Clinical application at Pittsburgh in the 60s
• Complications:
  – Bleeding
  – Arrhythmias, including bradycardia
  – Hypotension
• But...
  – Cooling to 30°C (moderate)
  – Overshoot (into severe range)
  – Labor Intensive
  – Applied to heterogeneous patient population
• 1980s, 1990s: Focused on cardiac arrest; animal studies; pilot studies; randomized trials
Insights from Animal Experiments

• Mild versus Moderate Hypothermia
• Protective Effects not primarily result of decreased metabolism ($O_2$ and glucose consumption)
• Ischemia and Reperfusion are complex cascades of injury and repair
• Negovsky coins phrase “Post-Resuscitation Disease”
The second step in resuscitation—the treatment of the ‘post-resuscitation disease’

V. A. NEGOVSKY

Laboratory of Experimental Resuscitation, Academy of Medical Sciences of the U.S.S.R., 9, October 25th Street, Moscow, U.S.S.R.

In the first stages of the development of the science of resuscitation, ‘reanimatology’, research workers have been limited mainly to the study of the pathology of death, and to the elaboration of a series of techniques of resuscitation. We now have at our disposal some knowledge of the process of disintegration of physiological functions during the dying of an organism, and of their restoration during resuscitation. We also have at our disposal a number of methods available to a large circle of practising doctors. Extensive experimental studies and clinical findings have clearly proved that after the first step in resuscitation when heart function and respiration have been restored, the second step in resuscitation arises—the more complicated problems of treating the after-effects of a general hypoxia. There are characteristic disturbances in the functions of the central nervous system and internal organs, in metabolism and in homeostasis among other systems.

There is much evidence that the organism experiences a specific pathological condition after resuscitation. We are inclined to call this condition ‘the post-resuscitation disease’, and to examine it as an independent nosological form. Indeed, irreversible changes occur during clinical death and after resuscitation.
Destructive processes following ischemia/reperfusion that can be prevented or significantly mitigated by hypothermia.

**Black lettering = early mechanisms**

**Gray lettering = late mechanisms**

![Diagram showing mechanisms of hypothermia](image)

Figure 1. Schematic depiction of the mechanisms underlying the protective effects of mild to moderate hypothermia. TxA2, thromboxane A2.

Polderman, KH. CCM 2009; 37: S186-202
Destructive Processes

• Cellular Injury
  – Necrosis
  – Full or Partial Recovery
  – Apoptosis (programmed cell death):
    • 7 Day Window
    • Membrane Dysfunction $\rightarrow$ ↑ LA, ↑ Ca into cells
    • Dysfunction of ATP-dependent ion pumps
    • Caspase activation
    • Increased glutamate

Polderman, KH. CCM 2009; 37: S186-202
Ning, XH. J Appl Physiol 2002; 92: 2200-2207
Destructive Processes

• Free radical generation
  – Release of oxygen free radicals by ischemia, amplified by reperfusion
    • Superoxide (O2-)
    • Peroxynitrite (NO2-)
    • Hydrogen Peroxide (H2O2)
    • Hydroxyl Radicals (OH-)
  – Produce oxidation, irreversible injury to cell membranes, mitochondria, endothelium, lipids, proteins, nucleic acids

Destructive Processes

• **Blood Brain Barrier:**
  - Ischemia/Reperfusion increases permeability

• **Vasoactive Mediators:**
  - Ischemia $\rightarrow$ ↑ Thromboxane A2 (TxA2)
    • Vasoactive
    • ↑ increased platelet aggregation
  - Local vasoconstriction, hypoperfusion, microthrombi

Huang, ZC. Can J Neurol Sci 1999; 26: 298-304
Hypothermia’s Role

• All of these processes are temperature dependent
• Hypothermia can blunt, reverse, or prevent these destructive processes
• For example, hypothermia blunts early apoptosis
• Hypothermia decreases permeability of BBB

Huang, ZC. Can J Neurol Sci 1999; 26: 298-304
Polderman, KH. CCM 2009; 37: S186-202
Safar: Dog model of VF arrest

- Normothermic VF of 11 minutes
- Defibrillation and controlled reperfusion
- Controlled ventilation for 20 hrs; ICU to 96 hrs
- Control group (n=8)
  - Normothermic (37.5°C), Normotensive, Hypocapnic
- Experimental group (n=8)
  - Mild hypothermia (34°C) from 10 minutes to 12 hours
  - Cerebral blood flow promotion w/ induced moderate HTN
  - Mild hemodilution, Normocapnia

Safar, P. Stroke 1996; 27:105-113
Dog model of VF arrest: Results

• All 16 dogs in the protocol survived

• Control group (n=8):
  – All OPC 3 (severe disability) or 4 (coma)

• Experimental group (n=8):
  – 6/8 (75%) dogs OPC 1 (normal)
  – 1/8 (12.5%) OPC 2 (moderate disability)
  – 1/8 (12.5%) OPC 3

(P<.001)

Safar, P. Stroke 1996; 27:105-113
Physiologic Effects

- Decreased Metabolic Rate
- CNS
- Cardiovascular
- Respiratory
- Renal/Electrolytes
- Musculoskeletal
- Endocrine/Metabolic
- Gastrointestinal
- Infectious Disease
- Hematologic

Myths About Adverse Effects of Mild Therapeutic Hypothermia

- Hypotension
- Decreased myocardial contractility
- Reason: Misinterpretations of “cold diuresis”, myocardial stunning, and “sepsis-like syndrome”
- Corollary: Can’t use in patients with cardiogenic shock
- Marked coagulopathy
- Increased arrhythmias
Decreased Metabolic Rate

• Cerebral metabolism decreases 6-10%/°C decrease in core T°
• At core T of 33°C, metabolic rate drops by 25-40%
• O₂ consumption and CO₂ production decrease by same amount
• This is an important protective effect but only one of dozens

Central Nervous System

- Confusion/Delirium
- Slurred speech
- Impaired judgment
- Amnesia
- Apathy

Not applicable in comatose, sedated, sometimes paralyzed post-arrest patients
Cardiovascular

- Tachycardia, then bradycardia when T < 35°C
- Increased contractility
- Cardiac cycle prolongation (PR, QRS, QT)
- Vasoconstriction – Stable or Increased BP
- ↑ CVP due to venoconstriction
- Decreased CO 25-40%
- Arrhythmias very rare at Temp > 30°C
  - At 32-34°C, ↑ rate of conversion of VF (in swine)

Boddicker, KA. Circulation 2005; 111: 3195-3201
Respiratory

- In accidental hypothermia
  - tachypnea, then progressive ↓ in MV
- In TH after OHCA, ventilation controlled
- ↑ Solubility of O₂ & CO₂ → ↓ PaO₂, PaCO₂
- Bronchorrhea, bronchospasm
- Left shift of Oxy-Hgb dis curve → ↓ DO₂
- Ventilator settings require frequent changes during induction
Renal/Electrolytes

• Cold diuresis
  – Increased venous return 2/2 venoconstriction
  – ↑ANP, ↓ADH, & tubular dysfunction
  – If uncorrected, causes hypovolemia, hemoconcentration
• ↓ electrolytes (K, Mg, Phos) due to
  – diuresis-induced ↑ renal excretion
  – intracellular electrolyte shifts

Polderman, KH. J Neurosurg 2001; 94: 697-705
Musculoskeletal

• Induction of hypothermia $\rightarrow$ activation of counter-regulatory mechanisms
  – Vasoconstriction begins @ $\approx 36.5^\circ$C
  – Shivering begins @ $\approx 35.5^\circ$C
  – In awake patients
    • increased VO2 (40-100%); $\uparrow$ MyocardialVO$_2$
    • increased metabolic rate; $\uparrow$ WOB, $\uparrow$ HR
  – These are suppressed with sedatives
  – Removed with paralytics

Lopez M, Anesthesiology, 1994; 80: 780-788
Polderman KH, Crit Care Med, 2009; 37: 1101-1120
Endocrine/Metabolic

• ↑ Drug levels/effects
  – ↓ hepatic clearance 2/2 ↓ speed of enzymatic reactions
  – ↓ blood flow, bile excretion
  – Affected drugs: pressors, sedatives, analgesics, NRB, etc

• Hyperglycemia
  – Decreased insulin sensitivity
  – Decreased insulin secretion by pancreatic islet cells
  – Hyperglycemia is damaging to the injured brain

• ↑ lactate, ketones, free fatty acids

Povlishock, JT. Acta Neurochir Suppl (Wein) 1999; 73: 15-20
Gastrointestinal

- Ileus: impaired bowel function
- Delayed gastric emptying
- Gastric stress ulcers
- Hepatic dysfunction – LFT’s (transaminitis)
- Pancreatic dysfunction – ↑amylase, but no clinical pancreatitis
Infectious Disease

• Impairs immune/inflammatory response (mechanism of improved CNS outcome)
• Inhibition of leukocyte migration, phagocytosis
• ↑ Risk of PNA when hypothermia > 24 hrs
• ↑ Wound infections
  – ↓ WBC migration, ↑ skin vasoconstriction
  – Contact point of cooling pads
Hematologic

• ↑ HgB
• ↓ platelet & WBC count (>24 hrs)
• Mild hypothermia ➔ Mild Coagulopathy
  – ↓ platelet function, count (@ < 35°C)
  – ↓ function of plasma proteins (@ < 33°C)
  – Risk of spontaneous bleeding is very low
Etiology and Exacerbation of the Metabolic Phase

Ischemia → ROSC → Reperfusion

- Reactive oxygen species (ROS)
- Inflammatory cascades
- Mitochondrial dysfunction

Hypothermia

Vascular dysfunction/hypotension
Apoptosis – organ dysfunction
Cerebral edema

ICU Care Bundle
Hypothermia-induced Physiologic Changes

- Cooling Curve
  - ROSC
  - Shivering
  - Electrolyte Losses
  - Hyperglycemia
  - Decreased HR, VO2
  - Sepsis-like Syndrome
  - Decreased CO, diuresis

Potential for "rebound hyperthermia"

- Hemodynamic recovery, increased O2 consumption
- Increased K, decreased glucose

Rewarming Begun

34°C

32°C
33 years pass...

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

Study objective: To examine the effects of moderate hypothermia (33°C), induced by surface cooling in the ED and maintained for 12 hours in the ICU, on patients with anoxic brain injury after out-of-hospital cardiac arrest.

- 22 OHCA, comatose, prospectively treated w/ mild TH to 33°C for 12 hours
- 22 OHCA, comatose, from historic chart review treated with normothermia

Bernard, SA. Annals Emerg Med 1997; 30: 146-153
Table 2.
Results of analyses obtained in hypothermic (IH) and normothermic (control) patients during the 24 hours after arrival at the ED.

<table>
<thead>
<tr>
<th>Parameters (Mean±SD)</th>
<th>Time Since Arrival in ED (Hours)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Temp (°C)</strong></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>35.6±1.2</td>
</tr>
<tr>
<td>IH</td>
<td>35.3±1.0</td>
</tr>
<tr>
<td><strong>MAP (mm Hg)</strong></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>83±38</td>
</tr>
<tr>
<td>IH</td>
<td>79±41</td>
</tr>
<tr>
<td><strong>Pulse</strong></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>91±39</td>
</tr>
<tr>
<td>IH</td>
<td>88±43</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7.23±.16</td>
</tr>
<tr>
<td>IH</td>
<td>7.20±.17</td>
</tr>
<tr>
<td><strong>Potassium (mmol/L)</strong></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.8±.8</td>
</tr>
<tr>
<td>IH</td>
<td>3.6±.6</td>
</tr>
<tr>
<td><strong>Total leukocyte count (×1,000/mm³)</strong></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>13.5±6.2</td>
</tr>
<tr>
<td>IH</td>
<td>15.1±7.2</td>
</tr>
<tr>
<td><strong>Platelet count (×1,000/mm³)</strong></td>
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</tr>
<tr>
<td>Control</td>
<td>270±85</td>
</tr>
<tr>
<td>IH</td>
<td>266±76</td>
</tr>
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*<i>P</i> <.05, comparison within treatments against arrival.
†<i>P</i> <.05, comparison between treatments at comparative times.
Results

• Good Outcome:
  – IH: 11/22
  – Control: 3/22 \( p < 0.05 \)

• Mortality:
  – IH: 10/22
  – Control: 17/22 \( p < 0.05 \)

Bernard, SA. Annals Emerg Med 1997; 30: 146-153
Experience From RCT’s

*NEJM, 2002*

- HACA and Bernard et al:
  - Different cooling techniques
  - Different durations of hypothermia
  - Different degrees of invasive monitoring
  - Different outcome measures for adverse events
  - Many lessons to learn OTHER THAN TH
Hypothermia:
- No differences in complications
- Trend towards more infectious complications (pneumonia, sepsis)
- Trend toward more bleeding, but not statistically significant

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<th>COMPLICATION</th>
<th>NORMOTHERMIA</th>
<th>HYPOTHERMIA</th>
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<tbody>
<tr>
<td>no./total no. (%)</td>
<td></td>
<td></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>
Hypothermia: ↓ HR, ↑ SVR, trend toward ↓ CO, no significant arrhythmias
Hypothermia Effects:

- K ↓ initially, then ↑ significantly w/ rewarming
- Trend toward ↑ LA
- Significant ↑ Glucose

**Table 3. Biochemical Values.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TREATMENT GROUP</th>
<th>ADMISSION TO ED</th>
<th>ADMISSION TO ICU</th>
<th>6 Hr</th>
<th>12 Hr</th>
<th>24 Hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>Hypothermia</td>
<td>43</td>
<td>39</td>
<td>39</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td>34</td>
<td>33</td>
<td>32</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Potassium (mmol/liter)</td>
<td>Hypothermia</td>
<td>3.8 (2.5–7.8)</td>
<td>3.6 (2.6–6.9)</td>
<td>3.6 (2.7–6.3)</td>
<td>4.1 (2.6–7.6)</td>
<td>4.5 (2.9–7.1)†</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td>3.9 (2.2–6.4)</td>
<td>3.9 (2.5–5.1)</td>
<td>4.0 (2.7–5.7)</td>
<td>4.2 (3.3–5.7)</td>
<td>3.9 (3.9–4.6)</td>
</tr>
<tr>
<td></td>
<td>P value$^$</td>
<td>0.84</td>
<td>0.98</td>
<td>0.05</td>
<td>0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate (mmol/liter)</td>
<td>Hypothermia</td>
<td>8.3 (2.2–14.9)</td>
<td>2.7 (0.9–11.6)†</td>
<td>3.7 (1.2–11.8)†</td>
<td>4.4 (1–11.1)†</td>
<td>2.5 (0.7–11.4)†</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td>7.5 (2–14)</td>
<td>2.6 (0.9–8.4)†</td>
<td>3.3 (1.1–9.3)†</td>
<td>3.5 (1–12.4)†</td>
<td>1.6 (0.6–11)†</td>
</tr>
<tr>
<td></td>
<td>P value$^$</td>
<td>0.75</td>
<td>0.46</td>
<td>0.79</td>
<td>0.67</td>
<td>0.08</td>
</tr>
<tr>
<td>Glucose (mmol/liter)$^|$</td>
<td>Hypothermia</td>
<td>13.3 (9.0–33.0)</td>
<td>16.2 (7.4–26.8)</td>
<td>16.0 (7.1–36.7)</td>
<td>16.1 (4.2–28)</td>
<td>8.0 (1.6–27.8)†</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td>12.6 (4.8–22.7)</td>
<td>10.5 (6.6–17.9)</td>
<td>12.1 (5.8–25)</td>
<td>11.6 (6.2–28)</td>
<td>7.5 (3.5–15.1)†</td>
</tr>
<tr>
<td></td>
<td>P value$^$</td>
<td>0.13</td>
<td>0.002</td>
<td>0.02</td>
<td>0.14</td>
<td>0.92</td>
</tr>
</tbody>
</table>
Hypothermia:
- No impact on platelet or WBC counts
- "No clinically significant infections were noted"

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TREATMENT GROUP</th>
<th>ADMISSION TO ED</th>
<th>12 HR</th>
<th>24 HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>Hypothermia</td>
<td>43</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td>34</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Platelet count (×10^9/mm³)</td>
<td>Hypothermia</td>
<td>209±65.7</td>
<td>193±60.2†</td>
<td>190±63.3†</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td>221±63.4</td>
<td>217±63.0</td>
<td>199±54.2†</td>
</tr>
<tr>
<td></td>
<td>P value‡</td>
<td>0.46</td>
<td>0.24</td>
<td>0.82</td>
</tr>
<tr>
<td>White-cell count (×10^3/mm³)</td>
<td>Hypothermia</td>
<td>10.9 (5.7–21.5)</td>
<td>14.5 (5.5–30.4)§</td>
<td>14.6 (7.1–35.3)§</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td>11.1 (6.3–25.3)</td>
<td>14.6 (8.5–29)§</td>
<td>15.8 (9.8–25.3)§</td>
</tr>
<tr>
<td></td>
<td>P value‡</td>
<td>0.46</td>
<td>0.12</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Experience from Individual Centers

**Table 8. Rate of infections and arrhythmias**

<table>
<thead>
<tr>
<th></th>
<th>Therapeutic Hypothermia</th>
<th>Standard Resuscitation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>19/55 (34.5)</td>
<td>23/54 (42.6)</td>
<td>.38</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>20/55 (36.4)</td>
<td>23/54 (42.6)</td>
<td>.51</td>
</tr>
</tbody>
</table>

*aTherapeutic hypothermia: pneumonia n = 16, sepsis n = 2, urinary tract infection n = 1.*

Standard resuscitation: pneumonia n = 19, central venous catheter infections n = 2, sepsis n = 2; 

*bunsustained ventricular tachycardia or atrial fibrillation. Data are presented as number of patients/total with complications according to treatment group (%).*

<table>
<thead>
<tr>
<th></th>
<th>Control period (n = 58)</th>
<th>Intervention period (n = 61)</th>
<th>OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>37 (64)</td>
<td>44 (72)</td>
<td>1.47 (0.68–3.19)</td>
<td>0.44</td>
</tr>
<tr>
<td>Sepsis</td>
<td>33 (57)</td>
<td>29 (48)</td>
<td>1.28 (0.69–2.40)</td>
<td>0.43</td>
</tr>
<tr>
<td>Severe arrhythmias</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>2.33 (0.21–26.21)</td>
<td>0.60</td>
</tr>
<tr>
<td>Brady-arrhythmias</td>
<td>0</td>
<td>3</td>
<td>1.90 (0.80–4.53)</td>
<td>0.14</td>
</tr>
<tr>
<td>Tachy-arrhythmias</td>
<td>9</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>16 (28)</td>
<td>11 (18)</td>
<td>0.63 (0.28–1.39)</td>
<td>0.34</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>3 (5)</td>
<td>5 (8)</td>
<td>1.98 (0.46–8.56)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Pulse rate >120 min or <40 min lasting for > 5 min was defined as severe arrhythmias.
Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest

- Hypothermia Network Registry
- 986 OHCA pts > 18 yo; 34 centers, 7 countries
- OHC to ROSC:
  - 20 (14–30) minutes
- OHCA to initiation of hypothermia:
  - 90 (60–165) minutes
- OHCA to goal temperature (≤34°C):
  - 260 (178–400) minutes

Table 6

(a) Adverse events: all 34 centres and (b) adverse events: 22 reporting centers.

<table>
<thead>
<tr>
<th>Event</th>
<th>(a) Count (Percentage)</th>
<th>(b) Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia &lt; 40 beats/min</td>
<td>127 (13)</td>
<td></td>
</tr>
<tr>
<td>Tachycardia &gt; 130 beats/min</td>
<td>57 (6)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>88 (9)</td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>89 (9)</td>
<td></td>
</tr>
<tr>
<td>VF</td>
<td>71 (7)</td>
<td></td>
</tr>
<tr>
<td>Any combination of arrhythmia</td>
<td>325 (33)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>407 (41)</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>35 (4)</td>
<td></td>
</tr>
<tr>
<td>Other infection</td>
<td>41 (4)</td>
<td></td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>44 (4)</td>
<td></td>
</tr>
<tr>
<td>Intracerebral bleeding</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>233 (24)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>(b) Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycaemia &lt; 3 mmol/l</td>
<td>42 (6)</td>
</tr>
<tr>
<td>Sustained hyperglycaemia &gt; 8 mmol/l &gt; 4 h</td>
<td>278 (37)</td>
</tr>
<tr>
<td>Hypokalaemia (&lt; 3.0 mmol/l)</td>
<td>133 (18)</td>
</tr>
<tr>
<td>Hypomagnesaemia (&lt; 0.7 mmol/l)</td>
<td>132 (18)</td>
</tr>
<tr>
<td>Hypophosphataemia (&lt; 0.7 mmol/l)</td>
<td>143 (19)</td>
</tr>
</tbody>
</table>

Data presented as absolute numbers and percentages. TH, therapeutic hypothermia; VT, ventricular tachycardia; VF, ventricular fibrillation.
Summary

• Hypothermia is associated with numerous adverse physiologic effects in the setting of accidental hypothermia
• Therapeutic hypothermia produces numerous side effects, some advantageous, some disadvantageous
• However, the incidence of significant adverse events is low from clinical trials and institutional experience
• Be vigilant for hypokalemia, hypovolemia, hyperglycemia, shivering, and infection
PATH

• Penn Alliance for Therapeutic Hypothermia
• A Post-Arrest Therapeutic Hypothermia Registry
• A quality assurance and research tool
• Secure on-line, web-accessible database of post-arrest patients treated with therapeutic hypothermia
• Scheduled to go live 2/15/10
• For questions contact:
  – gaieskid@uphs.upenn.edu
  – www.med.upenn.edu/resuscitation/hypothermia/