Therapeutic Hypothermia: How to Chill Out

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Disclosures

- None

Therapeutic Hypothermia = Targeted Temperature Management (TTM)
Learning Objectives
- Evolution of therapeutic hypothermia
- Use in ACLS guidelines
- Methods of cooling
- Various temperature management
- What to watch clinically during hypothermia procedure
- Uses beyond cardiac arrest

Cardiac Arrest
- 450,000 Americans/year
- 80% occur at home
- Rate of death is 90%
- In-hospital arrests have slightly better outcomes
  - Restoration of circulation in 44%
  - Survival to discharge in 17%


Cardiac arrest: Fundamentals of therapy

“Chain of Survival”

Prompt Access  Early CPR  Early Defib  ACLS Care

It still has not increased survivability or improved neurological outcomes
Cerebral Ischemia: What Happens?

Ischemic Event Triggers Chemical Cascade

- Electrical depolarization
- Activation of protein kinase enzymes
- Cytoskeleton breakdown
- Oxygen radicals production
- Release of neurotransmitters
- Blood/brain barrier breakdown

Lowering core temperature can suppress the inflammation process.

Basic principle

- Temperature dependent reductions in metabolism
- Decreased demand for oxygen and glucose
- Cerebral metabolism decreases by 6% to 10% for each 1°C reduction in body temperature
- When core body temperature drops to 32°C, the metabolic rate drops to 50%-65% of normal

Hippocrates

- The Greek physician Hippocrates advocated the packing of wounded soldiers in snow and ice


Shortcomings of initial trials

- Believed needed large reduction in temperature to achieve efficacy
- Most treated with deep hypothermia (<30°C)
- Core temperature difficult to maintain
- Duration of cooling ranged from 2-10 days
- Rewarming methods not reliable
- Intensive care facilities not widely available

Back again

- Positive studies in the early 80’s
- Realized outcomes could be improved with mild to moderate hypothermia (31-35°C)
- Advancements in technology
- Evolution of critical care units
- Understanding and anticipating side effects of cooling

2 Landmark Clinical Trials

**European: HACA Trial**
- 275 patients randomized to cooling or normal temps
- Cooling time: 6.5 hrs to 34°C using surface cooling

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Outcome</td>
<td>55%</td>
<td>39%</td>
<td>0.009</td>
</tr>
<tr>
<td>Mortality</td>
<td>41%</td>
<td>55%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Australian Study:**
- 77 patients randomized
- Used ice packs to cool; Cooling rate 3°C/hour

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Outcome</td>
<td>49%</td>
<td>26%</td>
<td>0.046</td>
</tr>
<tr>
<td>Mortality</td>
<td>51%</td>
<td>68%</td>
<td>NS</td>
</tr>
</tbody>
</table>

For every six patients treated, one life saved

The New England Journal of Medicine, 2002 Vol 346, no.8
What are the current Standards of care for cardiac arrest? (2005)

Evidence-based Practice

ROSC from VT/VF Cardiac arrest

> 32-34 degrees
> 12-24 hours

American Heart Association (AHA) Recommendations

Class Ia: Unconscious adult patients with return of spontaneous circulation (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 ventricular fibrillation (VF).

Class Ib: Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest.

Level of Evidence

A: Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32-34°C for 12-24 hours when the initial rhythm was ventricular fibrillation (VF).

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

International Liaison Committee on Resuscitation (ILCOR) Recommendations

Level I evidence

Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32-34°C for 12-24 hours when the initial rhythm was ventricular fibrillation (VF).

Part 8: Post–Cardiac Arrest Care

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

- Induce hypothermia for unconscious adult patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest when the initial rhythm was ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) (class I, level of evidence: B-R).

- Similar therapy may be beneficial for patients with non-VF arrest out-of-hospital or in-hospital arrest (class I, level of evidence: C-EQ).

- The temperature should be maintained between 32°C and 36°C (class I, level of evidence: B-R).

- It is reasonable to maintain TTM for at least 24 hours (class IIa, level of evidence: C-EQ).
The 2015 American Heart Association (AHA) guidelines:

- Routine prehospital cooling of patients with ROSC with intravenous (IV) rapid infusion is not advised (class III: no benefit; level of evidence A)
- It is reasonable to prevent fever in comatose patients after TTM (class IIb, level of evidence C-LD)
- Hemodynamically stable patients with spontaneous mild hypothermia (>33°C) after resuscitation from cardiac arrest should not be actively rewarmed

Inclusion criteria:

- Age greater than 18 years
- Intubated patients with treatment initiated within 6 hours after cardiac arrest (nonperfusing VT or VF)
- Patients able to maintain a systolic blood pressure above 90 mm Hg, with or without pressors, after cardiopulmonary resuscitation (CPR)
- Patients in a coma at the time of cooling

Exclusion criteria:

- The patient can follow verbal commands
- Recent major surgery within 14 days - Possible risk for infection and bleeding
- Systemic infection/sepsis - Small increase in risk of infection
- Coma from other causes (drug intoxication, preexisting coma prior to arrest)
- Known bleeding diathesis or with active ongoing bleeding - Hypothermia may impair the clotting system (however, patients may receive chemical thrombolysis, antipatelet agents, or anticoagulants if deemed necessary in the treatment of the primary cardiac condition)
- In addition, hypothermia is inappropriate in patients with a valid do not resuscitate order (DNR).
Goals of the optimal cooling procedure:
- Rapid cool the body core to the target temperature
- Maintain target temperature for 24 hours
- Controlled rewarming
- Maintain normothermia (<37.5°C) until 72 hours after ROSC
- Proper management and prevention of known side effects

Mechanisms of Cooling
- Conduction: Thermal energy transfer between materials within direct contact with one another (ice packs)
- Convection: Thermal energy transferred by molecular movement within a gas or fluid (fans)
- Radiation: Heat transfer via electromagnetic radiation (cold room)
- Evaporation: Heat transfer with liquid to gas phase change (sweating)

How to Cool? - surface cooling
- Must be able to control all 4 phases
- Tight control within 32-34°C range
- Slow, controlled rewarm to avoid rebound increased ICP
Limitations of Surface Cooling

- Difficult to achieve target temperature
  - 14% never achieved target and 70% of patients required additional cooling methods (the HACA study)¹
- Difficult to maintain target temperature– overshoot
  - a 63% chance of overcooling when using surface cooling methods²

¹HACA, New Eng J Med, 2002
²Raina M. Merchant, MD; Benjamin S. Abella, MD MPhil' Mary Ann Peberdy, MD; Marcus E. H. Ong, MBBS, MPH; Gregory A. Schmidt, MD; Lance B. Becker, MD; Terry L. Vanden Hoek, MD: Therapeutic Hypothermia After Cardiac Arrest: Unintentional Overcooling is Common Using Ice Packs and Conventional Cooling Blankets. Crit Care Med 2006 Vol. 34, No. 12
³Mayer, Neurocrit Care. 2005

(Overcooling increases Mortality)

Death Rate: Overcooling vs. Not Overcooling

<table>
<thead>
<tr>
<th></th>
<th>Overcooling</th>
<th>Not Overcooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival (%)</td>
<td>30%</td>
<td>58%</td>
</tr>
<tr>
<td>Death (%)</td>
<td>70%</td>
<td>42%</td>
</tr>
</tbody>
</table>

References
¹HACA, New Eng J Med, 2002
²Raina M. Merchant, MD; Benjamin S. Abella, MD MPhil' Mary Ann Peberdy, MD; Marcus E. H. Ong, MBBS, MPH; Gregory A. Schmidt, MD; Lance B. Becker, MD; Terry L. Vanden Hoek, MD: Therapeutic Hypothermia After Cardiac Arrest: Unintentional Overcooling is Common Using Ice Packs and Conventional Cooling Blankets. Crit Care Med 2006 Vol. 34, No. 12
³Mayer, Neurocrit Care. 2005

Limitations of Surface Cooling

- Difficult to achieve target temperature
- Difficult to maintain target temperature– overshoot
- Uncontrolled rewarming – rebound ICP and hyperthermia
- Hindered access to patient (i.e during PCI procedure)
- Very nurse "Labor" intensive: often 2:1 ratio (nurses/pt)
- Skin monitoring and care required
- Increased shivering and paralytic usage ***

¹HACA, New Eng J Med, 2002
²Raina M. Merchant, MD; Benjamin S. Abella, MD MPhil' Mary Ann Peberdy, MD; Marcus E. H. Ong, MBBS, MPH; Gregory A. Schmidt, MD; Lance B. Becker, MD; Terry L. Vanden Hoek, MD: Therapeutic Hypothermia After Cardiac Arrest: Unintentional Overcooling is Common Using Ice Packs and Conventional Cooling Blankets. Crit Care Med 2006 Vol. 34, No. 12
³Mayer, Neurocrit Care. 2005
Cooling the Patient’s Skin
- Skin is a temperature receptor for brain
- Brain/Hypothalamus tries to maintain homeothermia
- Therefore, cold applied to skin sends “cold” stress message to hypothalamus:
  - Triggers shivering → generates heat
  - Causes vasoconstriction → stops heat loss
  - May cause thermal damage

Counterproductive cooling Therapy

Shivering is the Enemy
- Increased oxygen consumption
- Metabolic rate up to 600%
- Fights the cooling process
- Increasing Heart rate (HR), Respiratory rates (RR), Intracranial pressure (ICP)
  Result in hypoxemia, myocardial ischemia
- Use of high doses of sedation and paralytics
  Hypotension – ischemia
  Cardiac depression – AMI
  Prolong on ventilator – ARDS and Ventilator Associated Pneumonia
  Reduced muscle tone is further associated with risk for skin breakdown

Cold IV Fluid
- Good way to get jump started
- Can be initiated pre-hospital, at ED or during transportation
- 30-40 cc/kg of 4°C NS
- Difficult to reach target temperature
- Difficult to maintain target temperature for 24 hours
- Limitation on the fluid quantities – due to heart condition

Intravascular Temperature Management (IVTM™) For Precise Core Cooling or Warming

Vein Placement options:
- Femoral
- Subclavian
- Internal jugular

Alsius catheters provide triple-lumen central venous access.

Philips Electronics InnerCool RTx System for endovascular modulation of body temperature. The system gives surgeons and critical care specialists the ability to rapidly alter a patient’s body temperature through the use of a catheter with an integrated temperature sensor, called Innercool Accutrol. Its closed-loop design circulates warm or cold saline without introducing liquid to the patient, and it provides faster cooling and warming rates than any currently available temperature management system, short of going on bypass.

Inflow
Outflow

3 infusion lumens

Heat exchange

designed for insertion in the jugular vein and combined central venous capabilities (multiple infusion ports)
• Cool or warm saline flows within the balloons
• Blood is cooled or warmed as it passes by each balloon
• Closed-loop system – no fluid infusion to the patient

How the Cooling Catheter Works

Esophageal Cooling Device

PowerPoint Presentation
**Key Benefits**

- Rapid and precise core body temperature management
- System automatically maintains target temperature
- Software enables real-time temperature display, storage and download
- Easy-to-use, multi-function catheters
- "Hands free" operation reduces nursing time
- Improved access to patient
- Less shivering

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**Less shivering and less paralytics needed**

Shivering occurs through a narrow band of temperature

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**The esophageal cooling device: A new temperature control tool in the intensivist's arsenal**

Hegazy, Ahmed F. et al.

Heart & Lung: The Journal of Acute and Critical Care, Volume 46, Issue 3, 143 – 148

May-June, 2017

- A mean cooling rate of 0.42 °C/hr (SD ± 0.26) was observed. An average of 4 hr 24 min (SD ± 2 hr 6 min) was required to reach target temperature.
Shivering Rate Comparison

<table>
<thead>
<tr>
<th></th>
<th>Medivance1</th>
<th>Medivance2</th>
<th>Cincinnati</th>
<th>A lsius3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>86%</td>
<td>39%</td>
<td>8%</td>
<td>3.70%</td>
</tr>
</tbody>
</table>

1. Treatment of Refractory Fever in the Neurosciences Critical Care Unit Using a Novel, Water-Circulating Cooling Device; Meratee et al.; Journal of Neurosurgical Anesthesiology; vol 15, No. 4, 313-318.
2. Clinical trial of a novel surface cooling system for fever control in neurocritical care patients; Commichau et al; Critical Care Medicine 2004; vol.32; No 12.
3. Fever control (Diringer)

Advantages of Esophageal TM

- Compatible with multiple chiller brands
- Reduced risk of skin complications
- Reduced risk of needle sticks
- Reduced risk of CLABSI
- Reduced risk of blood clots (DVT and PE)
- Unobtrusive and maintains easy access to patient
- Non-sterile placement procedure
- Reduced shivering compared to surface devices
- Rapid placement via single provider

Targeted temperature management using the “Esophageal Cooling Device” after cardiac arrest (the COOL study): A feasibility and safety study

Cooling rate to reach the Target Temperature (33 °C-TT) was 0.26 °C/h [0.19-0.36].

Resuscitation 2017 121, 54-61DOI: (10.1016/j.resuscitation.2017.09.021)
Tight control at target temperature


Targeted temperature management using the "Esophageal Cooling Device" after cardiac arrest (the COOL study): A feasibility and safety study.

- Temperature deviation outside the TT during TTM-maintenance was 0.10 °C [0.03–0.20]. Time with deviation >1 °C was 0 h. Rewarming rate was 0.20 °C/h [0.18–0.22].

Control rebound hyperthermia

Rew: 1/30/2018
Better Temperature Management = Saves Nursing Time

43% Reduction in nursing time required for patient management

Better Temperature Management = Reduce Hospital Costs

IVTM reduces length of ICU stay
- IVTM group: 8.8±3 days
- Surface cooling group: 12.9±6 days

4 extra ICU days = $20,000

Potential complications of Therapeutic Hypothermia
What to Watch For Clinically During Therapeutic Hypothermia

**Hypothermia induction-maintenance phase**

**Avoid shivering**
- Increases the metabolic demands of the brain, \( \text{O}_2 \text{ consumption} \) and decreases rate of cooling.
- Sedating and chemical paralyzing patient prior to cooling.

**Avoid hypovolemia**
- Hypothermia-induced diuresis

**Avoid arrhythmia**
- Bradycardia is common, transient, at early phase of cooling induction
- Do not let temperature go less than 32°C – lead to ventricular fibrillation

**Osborn wave**
### What to Watch For Clinically During Therapeutic Hypothermia

#### Hypothermia induction-maintenance phase

**Avoid hyperglycemia**
- Hypothermia ↓ insulin sensitivity and secretion
- Tight glucose regulation with high dose of insulin to maintain at normal level
- Finger stick is not reliable, draw blood from CVC or A line

**Altered clearance of medications**
- Clearance of various drugs ↓
  - Known drugs: muscle paralyzers, propofol, fentanyl, phenytoin, pentobarbital, verapamil, propanol and volatile anesthetics

**Prevent electrolyte disorders**
- Potassium shifts intra cellular, monitoring and correct Potassium level

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### Ventilator management

- When core body temperature drops to 32°C, the metabolic rate drops to 50%-65% of normal
- Oxygen consumption and CO2 production will decrease by the same percentage
- If vent settings left unchanged, then will lead to hyperventilation (resp alkalosis) which will cause cerebral vasoconstriction
- Need to adjust vent accordingly

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- Arterial line done ASAP
- Goal is normal pH
- Do not temperature correct ABG
- If can’t get good finger pulse ox, try forehead
- Incidence of pneumonia is 30-50%
  - Usually due to aspiration at time of arrest
  - Immunosuppressive effects of hypothermia
  - If suspected, give prophylactic antibiotics
What to Watch For Clinically During Therapeutic Hypothermia

**Rewarming phase**
- Slow and controlled rewarming (< 0.5°C/hr)
- Avoid rebound hyperthermia and ICP
- Keep normothermia at least 48 hours
- Avoid hyperkalemia
  - Potassium shifts extra cellular
  - Potassium supplements should be stopped prior to rewarming
- Avoid hypotension and hypovolemia due to vasodilation

**72 hour re-evaluation**
- Extubate
- Continue supportive care
- Withdrawal of life support
Indications beyond Cardiac Arrest: Primary injury to the brain

- Contusion
- Blunt or Penetrating Trauma
- Diffuse Axonal Injury (DIA)
- Subarachnoid Hemorrhage (SAH)
- Stroke: ischemic vs. Hemorrhagic
- Intracranial Hemorrhage
- Subdural or Epidural Hematoma

Secondary Brain Injury Matters
Major cause of death and disability for patients who have survived primary injury

<table>
<thead>
<tr>
<th>FEVER</th>
<th>Why temperature matters?</th>
<th>HYPOTHERMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>41°</td>
<td>Accelerates Injury</td>
<td>37°</td>
</tr>
<tr>
<td>40°</td>
<td></td>
<td>38°</td>
</tr>
<tr>
<td>39°</td>
<td></td>
<td>39°</td>
</tr>
<tr>
<td>38°</td>
<td></td>
<td>40°</td>
</tr>
<tr>
<td>37°</td>
<td></td>
<td>41°</td>
</tr>
</tbody>
</table>

North American Brain Injury Study: Hypothermia
- Multicenter study of post-TBI hypothermia sponsored by the National Institutes of Health
- Hypothermia was induced to 33 degrees C buy 8 hours after insult and maintained to 48 hours
- Mortality was 28% with hypothermia and 27% with normothermia; poor outcomes equal at 57%
TH in traumatic brain injury

- Studies not as positive as those with cardiac arrest
- Why?
  - Time course of neuronal death is different
  - Peak levels of neuron-specific enolase (serum biomarker of neuronal death) occurs days after cardiac arrest, whereas they peak hours after traumatic brain injury


NABIS:Hypothermia IIR

- The primary hypothesis of NABIS:H IIR is as follows: Induction of hypothermia after severe traumatic brain injury to reach 33.0°C within 4h of injury and maintained for 48h in patients aged 16–45 years will result in an increased number of patients with good outcomes at 6 months after injury compared to patients randomized to management at normothermia.
- This trial did not confirm the utility of hypothermia as a primary neuroprotective strategy in patients with severe traumatic brain injury.


Clinical trials assessing the effects of hypothermia on neurological outcome in patients with traumatic brain injury and intracranial hypertension.

Fever control in brain injury

Neuro ICU Fever Is Common:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Fever Above &gt;38°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subarachnoid Hemorrhage</td>
<td>73%</td>
</tr>
<tr>
<td>Intracerebral Hemorrhage</td>
<td>91%</td>
</tr>
<tr>
<td>Traumatic Brain Injury</td>
<td>68%</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>61%</td>
</tr>
</tbody>
</table>

Fever Is Harmful

- Temperature elevations after brain ischemia worsen the resulting degree of injury
- Fever associated with increased mortality and worse outcome
- 1 degree increase raises risk of poor outcome by 2.2 times
- Mortality rate of stroke patients studied at 3 months was 1% in normothermic versus 16% in hyperthermic group

Fever's Role in LOS in the Neuro ICU

Fever powerful contributor to excessive length of stay in the hospital and in the Neuro ICU.

<table>
<thead>
<tr>
<th>Fever Level</th>
<th>Increased # days in ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt;39.6°C)</td>
<td>10 days</td>
</tr>
<tr>
<td>Medium (38.5-39.5°C)</td>
<td>5.5 days</td>
</tr>
<tr>
<td>Low (to 38.5°C)</td>
<td>1.7 days</td>
</tr>
</tbody>
</table>


IVTM for fever in ICU

- Prospective, randomized, controlled study of 296 Neuro ICU patients(TBI, SAH, CI, ICH)
- Compared intravascular cooling to existing best fever management methods
- Result: 64% reduction in the incidence of fever with IVTM
- 25% reduction in use of antipyretics
- No safety issue!
Hypothermia in Acute Spinal Cord Injury

Hypothermia in multisystem trauma

- 30%-50% of trauma mortality occurs before hospital
- Of those who die after arriving at the hospital, 70%-80% die within 24-48 hours
- Exsanguination is the most common cause of death in the first 48 hours after admission
- Once controlled, usually significant ischemic insult
- Some clinical trials underway, but by extrapolation, would hope this would improve outcomes

Clinical Applications Where Intravascular Temperature Management Has Been Used for Cooling

- Therapeutic hypothermia after cardiac arrest
- Fever control in Neuro/Surgical ICU
- ICP (intracranial pressure) management
- Therapeutic hypothermia for brain trauma and stroke
- Acute liver failure
- Adjunct with interventional procedure
- Malignant hyperthermia
- Heat stroke
- Spinal cord injury
- Spinal surgery
- Adjunct with hemi-craniectomy
- Status epilepticus
Clinical Applications Where Intravascular Temperature Management Has Been Used for Warming

Trauma victims
Accidental hypothermia
Burn surgery and intensive care
Cardiac surgery
OPCAB (off-pump coronary artery bypass)
Post-bypass pump (prevention of after-drop)
LVAD (left ventricular assist device)
Transplant
Thoracic aneurysm surgery
Maintain viable donor organs for transplantation

Figure 3. Options for sedation during therapeutic normothermia. NMB, neuromuscular blockade; SAS, Sedation and Agitation Scale (137); RASS, Richmond Agitation and Sedation Scale (138); T, temperature; BIS, bispectral index; EEG, electroencephalography.
<table>
<thead>
<tr>
<th>Body System</th>
<th>Physiologic Effect</th>
<th>Nursing Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral</td>
<td>Decreased metabolic demands</td>
<td>Monitor pulse, respirations, and O2 saturation.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased intracranial pressure</td>
<td>Increase fluid restriction.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased level of consciousness</td>
<td>Observe for signs of increased ICP.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tension headaches (e.g., migraine)</td>
<td>Monitor for signs of increased ICP.</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Decreased appetite</td>
<td>Monitor for signs of decreased ICP.</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Decreased bowel sounds</td>
<td>Monitor for signs of decreased ICP.</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Insulin resistance</td>
<td>Administer insulin to maintain glucose levels.</td>
</tr>
<tr>
<td>Immune</td>
<td>Suppression of white blood cells</td>
<td>Monitor for signs of increased ICP.</td>
</tr>
</tbody>
</table>

*Table 1: Common physiologic effects of hypotension*