Post-Cardiac Arrest Therapeutic Hypothermia
(Targeted Temperature Management)

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Following this session, the participant will be able to:

1) Identify indications and contraindications for post-cardiac arrest therapeutic hypothermia.

2) Discuss post cardiac arrest reperfusion pathophysiology and the neuroprotective intent of mild hypothermia.

3) List key protocol and monitoring needs for safe and effective implementation of post-cardiac arrest hypothermia therapy.

4) Appreciate the outcomes of post-cardiac arrest hypothermia therapy.
Therapy Evolution

• 1940 – 1960
  – Attempts made with deep, prolonged hypothermia
  – Outcomes were improved, but results were variable and management issues were abundant
  – Assumption: primary protective mechanism was decrease in metabolic rate
Two Landmark Studies

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

STEPHEN A. BERNARD, M.B., B.S., TIMOTHY W. GRAY, M.B., B.S., MICHAEL D. BUIST, M.B., B.S.,
BRUCE M. JONES, M.B., B.S., WILLIAM SILVESTER, M.B., B.S., GEOFF GUTTERIDGE, M.B., B.S., AND KAREN SMITH, B.SC.

NEJM, February 21, 2002
International Liaison Committee on Resuscitation (IL-COR) issued a statement supporting the use of post-cardiac arrest hypothermia therapy.

“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.”

• 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 VF (Class IIa).
• Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (Class IIb.)

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

IIa: Weight of evidence/opinion is in favor of usefulness/efficacy
IIb: Usefulness/efficacy is less well established by evidence/opinion.

Circulation 2005: 112: IV-84-IV-88; originally published online Nov 28, 2005.
Part 7.5: Post resuscitation Support
2008: Outcomes Remain Poor

**JAMA** (2008; 300:1423)
Review of 20,520 arrests by resuscitation outcomes consortium
Survival to hospital discharge:
- Overall: 4.6%
- EMS treated: 8% (3-16%)

**Circulation** (2008; 118:2452)
- Of the 25% of patients who survive to the hospital, in-hospital mortality is 70%
In-Hospital Mortality

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

POST-ARREST BRAIN INJURY IMPLICATED IN 30-50% OF HOSPITAL DEATHS.

Circulation 2008;118:2452
doi:10.1161/CIRCOUCOMES.109.889576
Acute Immediate Post-Cardiac Arrest Care (AHA 2010)
Brain loses its $O_2$ stores within 20 seconds of cardiac arrest.

A cellular change cascade begins within minutes to hours after ischemic brain injury.

*These changes are called post resuscitation disease, reperfusion injury, or secondary brain injury.*
The processes last for hours to days after the initial injury and can be retrigged by new ischemic events.

Brain cells can recover, become necrotic, or enter an apoptosis pathway.

Apoptosis is driven by mitochondrial dysfunction, disorders in cellular energy metabolism (ATP), and enzyme release.

The processes are temperature dependent. Moderate to mild hypothermia can decrease or block them.
O₂ deprivation $\Rightarrow$ anerobic glycolysis and $\downarrow$ ATP

$\uparrow$ intracellular phosphate, lactate, and H⁺ $\Rightarrow$ acidosis & Ca⁺ influx into the cells

Failure of ATP-dependent cellular pumps that normally rebalance intracellular Ca⁺, Na⁺, and K⁺

Excess intracellular Ca⁺ $\Rightarrow$ mitochondrial dysfunction, enzyme system activation, and release of glutamate into extracellular space.
Glutamate

- Excitatory neurotransmitter that stimulates calcium influx into the cell
- Prolonged glutamate exposure causes neuro hyperexcitability ⇒ injury and cell death.

- **Mild** hypothermia can improve calcium balance and interrupt the hyperexcitability / cell death cycle.
- **Early** initiation of cooling is likely critical to impact this!
Immune & inflammatory response begins within 1 hour.

- TNF-α and interleukin-1 release ⇒ leukocyte production
- Complement system activated ⇒ Neutrophil, monocyte, and macrophage movement
- Free radical production ⇒ Mechanisms that normally balance free radicals are overwhelmed ⇒ Further tissue injury

Hypothermia

-Suppresses ischemia induced inflammatory reactions, cytokine release, and nitric oxide production.
- Impairs neutrophil and macrophage function.
- Mediates, but does not stop, free radical processes (low temperatures are most effective for free radical processes)
• Injured brain generates temperature & local edema prevents heat dissipation ⇒ furthers injury
• Arrest and CPR cause coagulation cascade activation ⇒ increases thrombosis risk
• Vasoactive mediator release ⇒ causes vasoconstriction and hypoperfusion

Hypothermia
• Has some anticoagulatory effects: platelet dysfunction and inhibition of coagulation cascade
• Decreases mediator imbalance
• Probably increases ischemia tolerance
Therapeutic Hypothermia
VHVI Inclusion Criteria

1. Cardiac arrest with primary cardiac etiology
2. Ability to initiate protocol within 6-12 hours of return of spontaneous circulation
3. Age 18 or older
4. Unresponsive patient not following commands after ROSC
   Brain stem reflexes (cough, gag, corneal) and pathological/posturing movements are permissible.
5. Estimated time from arrest to ROSC less than 60 minutes.
Therapeutic Hypothermia
VHVI Exclusion Criteria

1. Awakes spontaneously with purposeful movement
2. Known pregnancy
3. Initial temperature less than 93.2°F (34°C)
4. Known terminal illness
5. Recent major head trauma or traumatic arrest
6. Other causes of coma (drug intoxication, pre-existing coma prior to arrest)
7. Patients with known bleeding diathesis or ongoing bleeding.
Non-Cardiac Etiologies
Non-Shockable Rhythms

Seder, CC Neurology, 2008

“Although data are strongest for TH in patients who experience VT or VF arrest, it is unreasonable to assume that the neuro-protective benefits of hypothermia are limited to a specific heart rhythm or location. TH should be considered after any cardiac or respiratory arrest, whether inside or outside the hospital.”
LESSONS LEARNED:
THE “CAN’T HURT” PHILOSOPHY CAN HURT

• Cooling patients with cardiac arrest and probable brain anoxia where the initial etiology of the arrest was not the heart.

• Examples:
  – Drowning
  – Electrocution
  – Choking
  – Hanging
  – Drug Overdose
  – Pulmonary Embolus

OUTCOMES MUCH POORER

Emotional Costs to Families and Healthcare System Costs Must be Considered
Implementing the Protocol
Hypothermia should be initiated within 6 hours of the event!
(Shorter times to target temperature have not yet demonstrated benefit)
All unwitnessed or witnessed with fall ⇒ to ED first for head/neck traumagram

(STEMIs may be excepted by attending)
Temperature Management

- Hypothermia target = 32° – 34° C
- Get to target temperature **ASAP**
- Prevent temperature decreases below 30° due to increased risk for spontaneous fibrillation
- Assess for/prevent shivering
- **Keep at target temperature until 24 hours after the time of the initial event.**
  - There are program-specific variations related to maintenance time
- **Rewarm slowly at .25 degrees/hour (16-18 hours)**
  (Cooling device programs help to control this rate!)
Temperature Management Systems
Surface, Convection, IV Catheter, Traditional

**Surface**
Example: Bard Arctic Sun / Philips Innercool

**IV Catheter**
Examples: Zoll Alsius / Philips Accutrol
Temperature Management Systems
Surface, Convection, IV Catheter, Traditional

**Traditional**
Example: Cincinatti Subzero, Gaymar

**Convection**
Example: Life Recovery Systems ThermoSuit
Supplemental Cooling Measures

Ice Packs

No longer recommended for pre-hospital cooling!!

Up to 2 L NSS
Room temperature or chilled
If chilled – peripheral only
PRE-HOSPITAL COOLING WITH 2 LITERS OF 4°C IV NSS – NO LONGER RECOMMENDED

- Decreased patient temp about 1.2° by time of hospital arrival
- Reduced time to target temp by about 1 hour
- **Had no effect of rate of survival to hospital discharge or to neurologic outcome among surviving patients (VF & non-VF)**
- Associated with more in-route re-arrest (26 vs 21%)
- Associated with increased pulmonary edema
- Reasons not clear – possibly related to decreased coronary artery perfusion pressure (IV versus surface cooling) and/or reduction of arterial pH & pO₂.

Temperature Management

• For safety, two core temperature sources are monitored:
  – PA (will not attach to Arctic Sun) - gold standard
  – Bladder (OK if no urine)
  – Esophageal
  – Rectal (delayed response)
Rewarming (Decooling)

- 0.25 degrees per hour
- When temperature reaches 36°C, paralytic infusions are stopped. Paralytics are not reversed.
- When 3 – 4 twitches (TOF) are present or the patient is breathing over the ventilator, sedation weaning begins.
Prevention of Fever After Rewarming

- Maintain temperature less than 37.5°C for 72 hours from the time of arrest.
- Keep pads on after normothermia is achieved.
- If temperature increases, use temperature control system as tolerated.
- Tylenol Q6hrs X 4 - when rewarming is started.
- Prevent shivering.
Protocol Implementation

Family Support

Traumatic Event And Then “The Wait”

- Palliative Care Consult on all Therapeutic Hypothermia Patients
Shivering Control
Sedation, NMBs, Other

- Paralyzed to prevent shivering and increased metabolic demands
  - Sustained can ↑ metabolic rate as much as 100%
  - Shivering may augment reperfusion injury and free radical formation

- Shivering temperatures are unpredictable (not just 1° below set-point)

- Shivering may decrease during maintenance phase and increase again during rewarming phase
• Vecuronium bolus (availability), then Cisatracurium infusion
  • 2 mcg/kg/min - titrate to Train of Four (TOF)
  • May require NMB increases despite 0/4 twitches if other evidence of shivering is present
• Counter-warming
• Alternatives to paralytics include:
  • Sedation (fentanyl, midazolam, propofol)
  • High dose magnesium (limited in renal failure)
  • Demerol
  • Buspirone
  • Combinations
Monitoring the adequacy of paralysis

Train of Four Monitoring

• Target: 1 to 2 twitches unless otherwise ordered
• May take more than baseline MAs to elicit twitches
• Spontaneous respiratory effort
• The Arctic Sun’s heat generation arrows
• The Arctic Sun’s water temperatures are also used to assess paralysis adequacy (shivering creates heat)
• May require NBM despite 0 / 4 twitches
Shivering and BIS

- BIS reflects both EEG and EMG. When shivering is present, the EMG affects the numerical value and it can no longer be used as a marker of sedation.
- A normal EMG is flat and 0.
SEDATION:
Propofol – unless not hemodynamically tolerated
Midazolam if propofol not tolerated

COMFORT:
Fentanyl infusion - if indicated
BIS Monitoring

- Usual sedation target range: 40 – 60 or as ordered
- Use usual BIS target ranges, but numbers may drop below target due to hypothermia or possible neuro event
- BIS SR (Suppression Ratio)
Electrolytes

Potassium

- $K^+$ closely monitored, but not aggressively treated
- Levels drop while cold (intracellular movement), but go back up while warming
- While hypothermic, potassium is usually only treated if less than 2.8 or if symptomatic
- Standard potassium replacement protocol is not utilized

SLOW, CONTROLLED REWARMING HELPS TO PREVENT RAPID ELECTROLYTE AND GLUCOSE SWINGS
Magnesium

• Increased renal excretion
• If arrhythmias are present – may give magnesium and/or an antiarrhythmic
• Target Magnesium = 2.0 meq/L or greater
• If less than 2.0 ⇒ magnesium sulfate 4 gms IV
Hypothermia causes:

- Decreased insulin secretion
- Mild to moderate insulin resistance
- ↓ renal glucose clearance
- ↓ liver glycogen stores

Interventions:

- Insulin Drips with Q1 hour glucose checks
- Target glucose: 120-180 (avoid hypoglycemia)
- High requirements while cold
- Can drop quickly during rewarming
- Proactive drip titration – standard insulin protocol may not work
- No SQ insulin

Controlled rewarming helps to prevent rapid shifts.
Nutrition Support

- Not started until rewarmed
- Combined NMB, narcotics, vasopressors, hypothermia, and hypoperfusion
- Real Estate Competition
Medications

- Clopidogrel (Plavix) given NG/OG (no alternate form)
- No other PO meds
- Cardiac ASA Rectal / Acetaminophen Rectal
- No subcutaneous or IM medications
- “Do not refrigerate” medications like mannitol avoided
• Cerebral metabolism decreases by 6 – 10% for each 1° C decrease in body temp.

• At 32°C, metabolic rate, O₂ consumption and CO₂ production decrease to 50 – 65% of normal.

• ↓ CO₂ production ⇒ **respiratory alkalosis** ⇒ cerebral vasoconstriction

• ↑ fat metabolism ⇒ ↑ glycerol, free fatty acids, ketonic acids, and lactate ⇒ mild **metabolic acidosis**

• The oxyhemoglobin dissociation curve **shifts to left** ⇒ less tissue oxygen extraction
In hypothermia, changes in gas partial pressures result in over-estimation of PaO₂ and PaCO₂ and underestimation of pH.

• ABGs could be “temp-corrected”
• Alternate approach: adjust targets!!
  – Target pCO₂: 32 - 48
  – Target pH: 7.35 - 7.40
• ABGs on admission and Q 6 hours X 4
• High PaO$_2$s in early therapy correlate with poorer outcomes (published retrospective case review)
  — Target PaO$_2$: 80-150

• Ventilator adjustments to avoid hyperventilation (↑ cerebral vasoconstriction) and hyperoxygenation (↑ reperfusion injury)

• Mild metabolic acidosis in hypothermia is extracellular and is usually not treated.
Hemodynamic Monitoring

- Arterial Line
- PA Catheter
- Surface ECHOs or Serial TEEs with Imacor

Complexity may be augmented by underlying pathologies:
- Post STEMI / PCI
- Cardiogenic Shock
Hemodynamics

**BLOOD PRESSURE / PERFUSION**

- **MAP target:** 80-90 mmHg (until normothermic)
  
  Neuro protection – prevention of secondary insult
  – Norephinephrine
  – Vasopressin

- **SVR and BP increases from cold** ⇒ may require vasodilator infusion
  
  - Nicardipine infusion for SBP > 180
  - If BP is “auto” high, may be compensatory to perfuse injured brain – don’t bring SBP below 150
**Hemodynamics**

**Fluid Status**
- Cold diuresis common
- If volume depleted, BP ↓ during rewarming
- Fluid status monitoring: PA catheter pressures don’t always match TEE findings in these patients

**Heart Rate / Arrhythmias**
- Heart rate decreases
  - Increase target temperature from 33° to 34° (with order)
  - Pacing
- Reperfusion arrhythmias if post PCI
- Recurrent ventricular arrhythmias from unresolved pathology
Hemodynamics

- Below 33°, ECG can show Osborn waves – no treatment
• **Initial Head CTs**
  - R/O head bleed as cause of arrest!
  - ED traumagram
  - Portable CT scanner

• **Transcranial Doppler Studies**

• **BIS Monitor**
  - Sedation
  - “Burst” Activity (Suppression Ratio Monitoring)
  - Score Correlation with Prognosis
• EEG Monitoring
  • Seizures suggest poor prognosis, but early treatment is needed
  • Continuous bedside EEGs ⇒ Internet connection with neuro to primary team calls if seizure activity noted ⇒ Then Neuro consult
  • Important during hypothermia initiation and during rewarming / Duration of monitoring is determined by EEG findings / If no seizures, usually stopped when normothermic
• C-Spine Injuries
  – Traumagrams in ED
  – C-Collars for unwitnessed & witnessed arrest with fall
  – Collar clearance by Spinal Service is required.
Neuro recovery time varies

Changing paradigms for Neuro Assessment / Recovery

Immediate post-therapy deficits:
  – Short-term memory loss
  – Impaired judgment and decision-making skills

Still needed: Improved assessment of deficits and better patient support plans through full recovery.

(Ancedotal reports: 6 – 9 month recovery period)

CPC (Cerebral Performance Category) scores utilized for outcome assignment
Glasgow-Pittsburgh Cerebral Performance Categories (CPC)

- **CPC1** = Good cerebral performance
  - conscious, alert, able to work, might have mild neurologic or psychological deficit.
- **CPC2** = Moderate cerebral disability
  - conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
- **CPC3** = Severe cerebral disability
  - conscious, dependent on others of daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
- **CPC4** = Coma or vegetative state
  - any degree of coma not fulfilling brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
- **CPC5** = Brain death
Respiratory

• Aspiration risk from arrest or CPR
• Impaired WBC function
• Ventilator associated pneumonia risk / interventions
• Ventilator Management: Don’t over-oxygenate or over-ventilate

Skin

• Persistent low water temperatures on surface cooling devices = potential problem
Other Support

- Coronary Artery Disease
- Cardiogenic Shock
- Aspiration
- Underlying Pathologies

CRRT  VDR  Ventilation  Pacemaker
VAD   ECMO  Bed  Prone  Roto
IABp
Impact of Early Cath

- Retrospective review of 269 patients from 6 hospitals treated with therapeutic hypothermia after (1) VF arrest and (2) no evidence of STEMI.
- Findings:
  - Coronary occlusions are common even in the absence of EKG changes
  - Early catheterization performed before or during cooling was associated with a significantly decreased risk of mortality when compared with patients in whom cath was deferred until after of therapeutic hypothermia completion.

Care Withdrawal Concerns With In-Progress Hypothermia

- “Permission” to stop hypothermia even if in progress on transfer
- Risks Inherent in Rapid Rewarming
- TDS Consults
  - Traditionally - did not call until rewarmed
  - Brain Death versus Organ Donation after Cardiac Death (DCD)
Post Cardiac Arrest Therapeutic Hypothermia

Withdrawal Guidelines When Discontinuation Determinations Are Made After Therapy Initiation

Approved by the Therapeutic Hypothermia Committee: January 2013

**PATH ONE**

Additional clinical information is obtained and it is determined that therapeutic hypothermia is contraindicated or not appropriate.

**PATH TWO**

Additional information is obtained identifying care **futility**

**OR**

Family communicates patient or family wishes with request for therapy cessation and **care withdrawal or comfort care only**.

**AND**

It has been determined that the patient is a **candidate for organ donation or the TDS evaluation or TDS/family conversations are still in progress**.

**PATH THREE**

Additional information is obtained identifying care **futility**

**OR**

Family communicates patient or family wishes with request for therapy cessation and **care withdrawal or comfort care only**.

**AND**

It has been determined that the patient is not a **candidate for organ donation**.
**PATH ONE**
Regardless of current temperature and therapy time, rewarming is begun at protocol rate of 0.25°/hour.

Therapeutic Hypothermia protocol interventions are applied until normothermic.

**PATH TWO**
Regardless of current temperature and therapy time, rewarming is begun at protocol rate of 0.25°/hour.

Therapeutic Hypothermia protocol interventions are applied until normothermic.

Once normothermia is achieved, TDS evaluations are completed and donor protocols are begun or care withdrawal is performed per usual protocols.

If, at any time in the rewarming process, the determination is made that the patient is not a candidate for organ donation, switch to Path 3.

**PATH THREE**
Neuromuscular blockers and Temperature Management system (Arctic Sun) are discontinued (i.e. passive rewarming). If the patient is not already on Fentanyl, Fentanyl infusion is considered for comfort.

Prior to ventilator support withdrawal, neuromuscular blockade must be gone.

- The Intensivist or Critical Care Fellow on the CVICU Service is consulted to determine if reversal of the paralytic agent is indicated when the patient has at least 1/4 twitches (paralytic reversal cannot be done at 0/4 twitches). The Intensivist or CC Fellow can administer reversal agents AND provide direction for the possible need for subsequent, timed doses of Glycopyrollate and Neostigmine.

- When TOF assessment nets 4/4 twitches (through elimination or reversal), care withdrawal is performed or comfort care is initiated per usual protocols — regardless of temperature.
“In unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac cause, hypothermia at a targeted temperature of 33°C did not confer a benefit as compared with a targeted temperature of 36°C.”

• **ILCOR UPDATE: December 2013**
  - No greater risk of adverse events at 33°C
  - “Pending formal consensus on the optimal temperature, we suggest that clinicians provide post-resuscitation care based on the current treatment recommendations”

• **CONSIDERATIONS:**
  - Study excluded unwitnessed asystolic arrests
  - Some exclusions from inability to consent
  - Survival rates were extremely high (50%)
  - 40% received cardiac cath
  - Median time from arrest to ROSC was 25 minutes
  - In the 33°C group, the time from randomization to goal temperature was nearly 8 hours
• No greater risk / Potential Benefit to Patient Subsets

• At this time, VUMC protocols remain the same – target 33°C.

• Change = Greater emphasis on avoidance of temperatures of greater than 37.5°C for 72 hours from the time of arrest.
VUMC: January 2014

- 300 patients in database / 270 with full data
- Survival: 42%
- Witnessed Arrest: 80%
- Bystander CPR: 60%
- Shockable Rhythm: 150
- STEMI: 24%
- Poor prognosis: Non-cardiac etiology and unwitnessed arrest with PEA
She was taken by ambulance to Vanderbilt’s emergency department, where doctors began to cool her body temperature to about 89 degrees to reduce the risk of brain injury.
Summary

- Post cardiac arrest therapeutic hypothermia therapy is decreasing mortality and morbidity
- Hypothermia changes metabolic and hemodynamic "normals". Successful use of this therapy requires a modified, multi-system, multi-specialty plan of care.
- Successful implementation demands:
  1) A committed and knowledgeable multidisciplinary team
  2) Early identification of patients who are eligible for this therapy
  3) Streamlined processes that facilitate early initiation and smooth handovers.
  4) Processes that allow for other diagnostic and therapeutic interventions to occur concurrent with hypothermia therapy.
  5) Flexibility and fluid protocol modification as more is learned about this therapy.
Select References


