Hypothermia in NeuroCritical Care: Past, Present and Future

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Henry Ford Hospital
Objectives/Outline

- Briefly review the history of targeted temperature management (TTM) in the ICU.
- Review the physiology of thermoregulation.
- Review the evidence for TH in the ICU:
  - Cardiac arrest
  - TBI/SCI
  - ICH/SAH
  - Stroke
- Future Direction
Past

Edwin Smith Papyrus - Oldest medical text and first description of HT.
A Brief History of Therapeutic Hypothermia

In 1937, Dr. Temple Fay began cooling patients to 32°C for 24 hours in an attempt to relieve symptoms of metastatic cancer.

Fay later reported use of hypothermia in patients with head trauma.

In 1950s, Bigelow introduced hypothermia for neurologic protection during cardiac surgeries.

A Brief History of Therapeutic Hypothermia

Late 1950s – Dr. Peter Safar, CPR and Hypothermia

CPCR – cardiopulmonary cerebral resuscitation
What is fever?

- A response to an infectious, lesional, toxic, or inflammatory exposure representing an elevated set point of body temperature. Often in toxic or lesional injury, the set point will be lost.
Fever in the NICU, Cause or Effect?

- After controlling for illness severity, diagnosis (stroke, ICH, SAH), age, complications and fever are independently associated with longer ICU stay, higher mortality, and worse outcome. Fever associated with increased levels of excitotoxins, oxygen radicals, destabilization of cell membranes, and increased number of abnormal electrical depolarizations.
  
  Diringer, MN. *Crit. Care Med.* ’04.

- Induced NT via intravascular cooling (Alsius CoolLine) is effective in reducing fever burden (1.6 vs 10.6% time in fever range) attenuates ICP by approximately 3.63 mmHg, and reduces intracranial HTN burden (% of time >25mmHg ICP) by 2.3± 2.8% vs 9.4± 11.4%. All findings significant.

  Puccio AM et al. *Neurocritical Care*. 11(1) ’09.
Why Hypothermia?

- Major benefit: prevention and treatment of ischemia-related syndromes by **slowing spread of ischemic damage** and **reducing reperfusion damage**

- **Animal data overwhelmingly support benefit of mild hypothermia** for prevention and treatment of ischemic conditions in the brain and spinal cord
Moderate Hypothermia - Neurological Effects

Induced hypothermia:

- decreases cerebral metabolic rate of oxygen (CMR0₂)
  - CMR0₂ decreases 6-7% for each 1°C decrease in core temperature
  - decreases cerebral blood volume via autoregulation (vasoconstriction)
- lowers intracranial pressure (ICP)
- has anticonvulsant properties
- abort activated programmed cell death pathways

Complications:

- the CNS is remarkably tolerant to even profound hypothermia
  animal models of exsanguination cardiac arrest and “suspended animation”

Moderate Hypothermia - Cardiovascular Effects

Accidental (i.e. uncontrolled) hypothermia:

- shivering increases global metabolic rate and $O_2$ demand
- can exacerbate underlying hypoxia, especially cardiac

Induced (i.e. therapeutic) hypothermia with Shivering Ablated!

- lowers cardiac metabolic demand
- decreases heart rate
- increases systemic vascular resistance
- stroke volume is unchanged to slightly increased
- MAP remains constant and CO is lowered

Complications?

- ventricular arrhythmias
  - risk increases with severe hypothermia ($<30^\circ C$)

Hyperthermia– Neurological Effects
Moderate Hypothermia - Lung, Kidney, Gut

Pulmonary:

- few direct effects on the respiratory system
- given decrease in global metabolic rate, requires lower minute ventilation

Renal:

- decreases reabsorption of solute in the ascending limb of the loop of Henle
  increases urine output (“cold diuresis”)  

FEN/GI:

- decreases gut motility
- decreases insulin secretion from the pancreas
  increased serum glucose levels
- intracellular potassium shifts - hypokalemia
Moderate Hypothermia - Hematological Effects

White Blood Cells

- lowers number of circulating WBCs
- suppresses neutrophil release from bone marrow in response to infection
- reduces production of pro-inflammatory cytokines
- impairs PMN chemotaxis and oxidative killing

Platelets

- decreases platelet aggregation, increasing bleeding time
- downregulates GPIb-IX complex, decreases thromboxane
- overall number unchanged

Coagulation

- increases clotting times

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Explanation</th>
<th>Time from Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent/Reduce Apoptosis</td>
<td>Ischaemia can induce apoptosis and calpain-mediated proteolysis. Hypothermia can prevent or reduce this process</td>
<td>Hours to weeks.</td>
</tr>
<tr>
<td>Reduce mitochondria dysfunction/improve energy production.</td>
<td>Mitochondrial dysfunction occurs in the hours-days following ischemia, possibly triggering apoptosis. Hypothermia reduces metabolic demands, thus decreasing production of free radicals. Mild-to-moderate hypothermia (30–35°C) is able to reduce this event cascade following reperfusion.</td>
<td>Hours to days.</td>
</tr>
<tr>
<td>Decreased BBB permeability, thus less edema</td>
<td>Mitigation of BBB permeability and improved energy reserve for membrane pumps via lower metabolism, intracellular alkalosis, and decreased DNA damage.</td>
<td>Hours to days.</td>
</tr>
<tr>
<td>Less excitotoxicity</td>
<td>Decreased release of glutamate and less accumulation of intracellular Ca++. Decreased activation of kinases and excitotoxic cascades.</td>
<td>Minutes to 72 h</td>
</tr>
<tr>
<td>Metabolic reduction</td>
<td>CMR_{O2} and CMR_{glu} decrease 5-8% for each 1°C.</td>
<td>Hours to days</td>
</tr>
<tr>
<td>Decreased inflammation</td>
<td>Inflammatory cytokine cascade limited by hypothermia.</td>
<td>First hour to 5 days</td>
</tr>
<tr>
<td>Reduced cerebral thermopooling</td>
<td>Some areas in the brain have significantly higher temperatures than the surrounding areas and measured core temperature. These differences can increase during injury, with up to 2–3°C higher temperatures in injured areas of the brain. Hyperthermia can increase the damage to injured brain cells; this is mitigated by hypothermia.</td>
<td>Minutes to days</td>
</tr>
</tbody>
</table>

Adapted from Polderman '08 *Lancet.*
Present

Yesterday is history
Tomorrow is mystery
But today is a gift, that is why it is called the “Present”
Techniques for Inducing Hypothermia

External/Surface Cooling:
- ice packs, cooling blankets
- max decrease 0.5°C per hour
- requires intubation, paralysis

Internal Cooling
- NG/bladder lavage with ice-cold fluids
- IV boluses of ice-cold saline
- helpful at initiation of external cooling
Surface Techniques

**Methods**
- Blankets
- Ice packing
- Alcohol bathing
- Fans

**Problems**
- Slow temperature change (<1 C/hr)
- Obese patients
- Poor control - overshoot
- Difficult to administer
- Inability to cool conscious patients
Surface Temperature Management

Mallinckrodt

Gaymar

CSZ

Cincinnati Sub-Zero

Arizant Healthcare Inc.

Bair Hugger® Temperature Management

Augustine Medical

Medivance™

INNERCOOL Therapies
Arizant Healthcare, Inc.
Bair Hugger®

Temperature Management System

Currently manufactures only warming units:
• Acute Care
• OR

Polar Air® no longer manufactured
• Provides cooling and warming in the OR
• Still in use in many hospitals
Cincinnati Sub-Zero
Medivance Arctic Sun™
Temperature Management System

Conductive warming and cooling

Water filled “pads” form-fitted to patient
Endovascular Temperature Management Systems:
ALSIOUS

Cool Line™ Catheter Placement

\[ T_1 = 37°C \quad T_2 = 36.5°C \]

Blood Flow

Cool Saline flows through catheter and balloons

Heat exchange with the blood

Blood Flow

Triple Microtherm™ Balloons

Saline flow within the balloons creates a proprietary vortex flow pattern which maximizes heat exchange with blood as it passes by.

Icy™ Catheter Placement
Radiant Medical
SetPoint® Temperature Management System
Innercool therapies
Celsius Control™ System (CCS)

- Flexible gold-alloy heat exchanger with covalently bonded heparin coating
- Place via introducer sheath (left or right femoral vein)
- Place blindly with guidewire or under fluoro
- Distal tip should be positioned in IVC just below diaphragm
- Confirm tip placement with KUB if not placed under fluoro
Average size of human IVC = 11mm – 23mm*

- Innercool Celsius Control Catheter™
  - 10.7F = 3.5mm

- Alsius Fortius™ Catheter
  - 47F = 15.5mm
    (size relative to Innercool - 348%)

- Alsius ICY™ Catheter
  - 24F = 8mm
    (size relative to Innercool - 124%)

- Radiant Reprieve™ Catheter
  - 28F = 9.3mm
    (size relative to Innercool - 162%)

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The Neurologist and Cardiac Arrest

“Out with the old”
- Wait 3-7 days and prognosticate
- “Levy criteria”  
  *JAMA*, 1985

“...In with the new”
- Acute neuroprotection with therapeutic hypothermia
MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

The Hypothermia After Cardiac Arrest (HACA) Study Group


“In patients who have been successfully resuscitated after cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia increased the rate of a favorable neurologic outcome and reduced mortality”
TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

Bernard, SA et al
Melbourne, Australia


“We conclude that induced hypothermia improves outcomes in patients who are comatose after resuscitation from out-of-hospital cardiac arrest.”
HACA study group assigned 275 patients who had spontaneous circulation restored within 60 minutes of the arrest to therapeutic hypothermia or conventional therapy and normothermia. At six months, patients treated with hypothermia were significantly more likely to have a favorable neurologic outcome with a good recovery or only moderate disability (55 versus 39 percent for normothermia, risk ratio 1.4) and a lower mortality (41 versus 56 percent, risk ratio 0.74).
Bernard et al evaluated a selected group of 77 patients who remained unconscious after resuscitation. Those randomly assigned to treatment with hypothermia were significantly more likely to have a good outcome and be discharged to home or a rehabilitation facility (49 versus 26 percent for normothermia). After adjusting for age and time from arrest to return of spontaneous circulation, hypothermia was associated with a significantly better outcome compared with normothermia (odds ratio 5.25).
Meta-analyses concluded that induced hypothermia improves short-term neurologic recovery and survival in patients resuscitated from out of hospital cardiac arrest, cardiac arrest of presumed cardiac origin, and cardiac arrest with VF/VT as the presenting rhythm.
Only 13 to 19 percent of patients with out-of-hospital cardiac arrest fulfill both major inclusion criteria for these trials: VF as the initial cardiac rhythm and restoration of spontaneous circulation.
Hypothermia Not beneficial in Nonshockable Cardiac Arrest Patients

- Retrospective review of 1145 consecutive out-of-hospital cardiac arrest patients in whom ROSC was obtained demonstrated:
  - Treatment with HT = 65% VT/VF, 60% PEA/AS
  - Increased time to ROSC in PEA group.
  - Good Outcome:
    - VT/VF: w/ HT 44%, w/o HT 29%
    - PEA/AS: w/ HT 15%, w/o HT 17%

Schulman ’11
Circulation.
Can Adjusting the Timing of HT Improve Outcomes?

- Functional outcome was shown to be improved in both the Berbard ‘02 *NEJM* and CA Study Group ‘02 *NEJM* studies, with the former also demonstrating improved survival.

- Limited animal or clinical data on the effect of initiation of HT after ROSC or duration on outcome.

- Available data mixed.
Impact of HT on Survival, Neurologic Function, and Neurodegeneration after cardiac arrest

- **Question:** Is the efficacy of post-CA HT dependent on the onset and duration of therapy?
- **Prospective, randomized study of 268 male rats treated to NT or HT after 10min CA.**

<table>
<thead>
<tr>
<th>Time from ROSC to HT (hours)</th>
<th>7 Day Survival % for NT (37°C)</th>
<th>7 Day Survival % for HT for 24 or 48 hours (33°C)</th>
<th>% Good Recovery-NT</th>
<th>% Good Recovery-HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>17</td>
<td>45*</td>
<td>2</td>
<td>24*</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>36*</td>
<td>2</td>
<td>24*</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>36*</td>
<td>2</td>
<td>19*</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>14</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*p<0.05
Predictors of Outcome after Out-of-Hospital CA

- Hypothesis: Admission clinical criteria (i.e. rhythm, duration of CA, shock) may identify which patients may most benefit from HT.
- 74 patients with OHCA (VT/VF, AS, PES) receiving HT (surface cooling) at a single center were prospectively review.
- Conclusion: Time from collapse to ROSC strongly associated with outcome. If ROSC ≤ 25 minutes, 65.7% survival; if ROSC ≥ 25 minutes, then 3.1% survival.

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<tr>
<th>Variable</th>
<th>Survival</th>
<th>Good neurologic outcome</th>
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<tr>
<td>Time from collapse to ROSC</td>
<td>≤25 mins</td>
<td>25/38 (65.7%)</td>
</tr>
<tr>
<td></td>
<td>&gt;25 mins</td>
<td>1/12 (8.3%)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial arrest rhythm</td>
<td>VF</td>
<td>23/38 (60.5%)</td>
</tr>
<tr>
<td></td>
<td>Non-VF</td>
<td>6/12 (50%)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Circulatory shock</td>
<td>No</td>
<td>17/40 (42.5%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>12/34 (35.3%)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>0.53</td>
</tr>
</tbody>
</table>

Oddo ‘08 Crit Care Med.

- Initial rhythm
  - Unknown n=17
    - ICU discharge
      - 8 survivors (47%)
      - 8 good outcome (47%)
    - VT/VF n=686
      - 534 survivors (78%)
      - 338 good outcome (49%)
    - Asystole n=217
      - 103 survivors (47%)
      - 41 good outcome (19%)
    - PEA n=66
      - 31 survivors (47%)
      - 14 good outcome (21%)

- Hospital discharge
  - 8 survivors (47%)
  - 8 good outcome (47%)
  - 463 survivors (67%)
  - 364 good outcome (53%)
  - 65 survivors (30%)
  - 47 good outcome (22%)
  - 19 survivors (29%)
  - 14 good outcome (21%)

- Follow-up
  - 8 survivors (47%)
  - 8 good outcome (47%)
  - 412 survivors (61%)
  - 380 good outcome (56%)
  - 54 survivors (25%)
  - 46 good outcome (21%)
  - 18 survivors (27%)
  - 15 good outcome (23%)
...so the jury is still out on if varying the duration of HT may change outcome. Are there predictors we can use to improve selection of CA patients (i.e. which PEA/AS patients to cool?)
Prediction of Recovery

- Prospective study of 95 patients with ROSC treated with HT for ABI and monitored with cEEG. Burst suppression or SE pattern predicted poor outcome (0% survival both.) A continuous EEG pattern, before/during/after HT predicted recovery (91% PPV at initiation, 87% PPV at NT.)
  

- Prospective study of 34 CA patients given HT and monitored with EEG. Presence of non-reactive, prolonged discontinuous, or seizure/epileptic d/c predicted non-survival w/ PPV 100%.
  
EEG Patterns as Predictors of Outcome

- “Alpha coma” pattern is typically considered a poor prognostic sign, especially in setting of CA. Iragui ‘83 *J Neuro, NS, Psych.*

- How this may be changed by HT is an ongoing area of research.
HFHS Therapeutic Hypothermia Protocol for VF/Vtach Arrest with ROSC
TBI
Clinical Evidence - TBI

“Effects of therapeutic hypothermia on intracranial pressure and outcome in patients with severe head injury”

Kees H. Polderman, et al
VU University Medical Center
Amsterdam,
The Netherlands

TBI Results Mixed

- 48hrs of HT in *National Acute Brain Injury Study: Hypothermia* (NABISH) not effective (Clifton ’01 *New England Journal of Medicine*)
- Outcomes in TBI studies best in centers with experience using hypothermia (Polderman ’08 *Lancet*, Clifton ’01 *Journal of Neurosurgery*.).
National Acute Brain Injury Study: Hypothermia II (NABIS II)- A randomized, multicenter trial of patients with TBI (BP>110/60, GCS 3-8, non penetrating trauma, ≤3 other injured organ systems) enrolled w/in 2.5 hours of injury cooled to 33°C HT, or 37°C for NT, for 48 hours. Primary outcome was Glasgow Outcome Scale score @ 6mo. 52 pts received HT, 56 received NT.
Larger number of episodes of ICP elevation (>20 mmHg for >2hr), and total complications in the HT group.

NT group older.

No 6 mo GOS difference.

Subgroup analysis of patients w/ evacuated hematomas treated w/ HT had fewer poor outcomes c/w NT (n=28, 15 HT/13NT.)

Stopped after interim analysis of 97 patients for futility.
Spinal Cord Injury
BACKGROUND: Although a number of neuroprotective strategies have been tested after spinal cord injury (SCI), no treatments have been established as a standard of care.

OBJECTIVE: We report the clinical outcomes at 1-year median follow-up, using endovascular hypothermia after SCI and a detailed analysis of the complications.

METHODS: We performed a retrospective analysis of American Spinal Injury Association and International Medical Society of Paraplegia Impairment Scale (AIS) scores and complications in 14 patients with SCI presenting with a complete cervical SCI (AIS A). All patients were treated with 48 hours of modest (33°C) intravascular hypothermia. The comparison group was composed of 14 age- and injury-matched subjects treated at the same institution.

RESULTS: Six of the 14 cooled patients (42.8%) were incomplete at final follow-up (50.2 [9.7] weeks). Three patients improved to AIS B, 2 patients improved to AIS C, and 1 patient improved to AIS D. Complications were predominantly respiratory and infectious in nature. However, in the control group, a similar number of complications was observed. Adverse events such as coagulopathy, deep venous thrombosis, and pulmonary embolism were not seen in the patients undergoing hypothermia.

CONCLUSION: This study is the first phase 1 clinical trial on the safety and outcome with the use of endovascular hypothermia in the treatment of acute cervical SCI. In this small cohort of patients with SCI, complication rates were similar to those of normothermic patients with an associated AIS A conversion rate of 42.8%.

KEY WORDS: Cooling catheter, Hypothermia, Neuroprotection, Quadriplegia, Spinal cord injury, Trauma
Levi AD ’10 Neurosurgery

- Methods (phase I safety trial)
  - Hypothermia arm no steroids
  - MAP > 90mmHg
  - 48hr @ 33°C, warm @0.1°C/hour
  - OG/NG feeding
  - Historical controls

<table>
<thead>
<tr>
<th></th>
<th>Age, Mean (range), y</th>
<th>Mechanism of Injury, MVA/MCC</th>
<th>Solumedrol Protocol</th>
<th>Timing of Surgery, % &lt;24 h</th>
<th>Estimated Blood Loss, Mean (SEM), mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>34.5 (17-73)</td>
<td>10/14</td>
<td>3</td>
<td>50</td>
<td>392 (95)</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>39.4 (16-62)</td>
<td>10/14</td>
<td>0</td>
<td>85</td>
<td>186 (41)</td>
</tr>
</tbody>
</table>
SAH
Hypothermia for >72 hours in poor grade SAH patients, combined with barbiturate coma, demonstrated no effect on outcome compared to standard care. Gasser S ‘03 *J Neurosurg. Anest.*

Intraoperative hypothermia to 33°C demonstrated no significant difference in outcome, ICU LOS, or morbidity. However, the majority of the patients were of a good clinical grade with little to gain from such a therapy. Todd MM ‘05 *NEJM.*
A prospective, randomized, control trial of endovascular cooling for SAH (50%), ICH (40%), and ischemia (10%) to a goal temp of 36.6°C. N=102

Equivalent LOS, outcome, mortality, and complications. Increased r/o infection in cooling group, this did not effect outcome.

Safe. Not weighted for outcome.
Clinical Evidence – Fever in SAH

“Achieving Normothermia in Patients With Febrile Subarachnoid Hemorrhage”

N. Badjatia, MD; J. O’Donnell, R.N.; J.R. Baker, MD, PhD; D. Huang, MD, PhD; C. Ayata, MD; D.M. Greer, M.D.; B.S. Carter, M.D., Ph.D.; C.S. Ogilvy, M.D.; C.T. McDonald, MD

Critical Care 2009
The febrile response has been implicated in the development of cerebral vasospasm/DCI. Badjatia N ‘09 Crit Care Med.
Hypothermia in Neurosurgery
“Planned Ischemia”

- Blood supply to lesion cut-off
- Focal ischemia for 5-45 min
- Neuroprotection desired
Benefits of Hypothermia in Neurosurgery
Supported by...

- Clinical expert opinion
- Surgical textbooks
- Literature
  - Case reports
  - Uncontrolled patient series

Few rigorous randomized, controlled trials
IHAST - Intraoperative Hypothermia during Aneurysm Surgery Trial

Mild hypothermia as a protective therapy during intracranial aneurysm surgery

Hindman BJ, Todd MM, Gelb AW, et al. University of Iowa, Iowa City, IA

Neurosurgery 1999;44:23-32
IHAST 1

114 patients
neurosurgery for cerebral aneurysm clipping

Normothermic Group
$T_{eso} = 36.5 \text{ @ clipping}$
- 29 Unruptured
- 28 SAH

Hypothermic Group
$T_{eso} = 33.5 \text{ @ clipping}$
- 33 Unruptured
- 24 SAH

IHAST-1
No Difference in Other Safety Outcomes

No Adverse Effect of Hypothermia on:
- Need for ICU at 24, 72 hrs
- Post-op complications:
  - Bleeding
  - Pneumonia / respiratory complications
  - Cardiovascular
  - Brain swelling
- Duration of hospitalization
- Mortality
IHAST-1
Conclusions: Hypothermia in Neurosurgery

- Suggests benefit of hypothermia (in SAH)
  - Acute neuro status (24-72 hrs)
  - Long term outcomes (3-6 months)

- No significant safety issues
  - Trend to longer intubation (<2 hrs)

- Surface temperature management suboptimal
  - Slow
  - Not reliable
IHAST 2 - Mild Intraoperative Hypothermia during Surgery for Intracranial Aneurysm – Part 2

Michael M. Todd, M.D. et al
University of Iowa,
Iowa City, IA

IHAST-2

- Essentially same DOE as IHAST-1
- 1001 SAH patients with preoperative World Federation of Neurological Surgeons score of I, II, or III ("good-grade patients") randomized to:
  - Hypothermia (33°C) induced by surface cooling, or
  - Normothermia (36.5°C)

- Endpoint:
  - Neuro status (NIHSS) at 3 months
IHAST 2 – Conclusion

“Intraoperative hypothermia did not improve the neurologic outcome after craniotomy among good-grade patients with aneurysmal subarachnoid hemorrhage.”
ICH
ICH

- Induced hypothermia to 30-32°C in 8 patients with spontaneous ICH improved symptoms of elevated ICP, but 6 died of systemic complications. Howell DA ‘58 Canad. Med Asso J.

- 40 patients receiving mild, localized head cooling for 48 hours, in addition to osmotic therapy, displayed significantly reduced cerebral edema compared to controls. This effect remained 2 weeks after cooling. Feng H ‘02 Zhonghua Yi Za Zhi.
Methods

12 pt w/ supratentorial ICH 25 mL were treated by hypothermia of 35°C for 10 days. Evolution of hematoma volume and perifocal edema was measured by cranial CT. Functional outcome was assessed after 90 days.

Conclusions

Hypothermia prevented the increase of peri-hemorrhagic edema in patients with large sICH. Although no patient in the hypothermia group died until day 90, 7 patients in the control group died.

Kollmar R ‘11 Stroke.
Ischemic Stroke
Hypothermia Trials in Stroke

- COOL AID Pilot Cooling for Acute Ischemic Brain Damage - Pilot
- Hemicraniectomy and Moderate Hypothermia in Patients With Severe Ischemic Stroke: No Efficacy.
- NOT-HOT Normothermia (w. Acetaminophen) and Stroke Outcome (n=16) - ? Effect
- CHILI (Controlled hypothermia in large infarction) within 72 hours, surface cooling - stopped
- Combined Cytoprotection tPA Study – 20 patients, caffeine, ethanol and t-PA plus intravascular hypothermia to 35°C – No Efficacy.
- ICTuS-L (Intravenous Thrombolysis plus Hypothermia for Treatment of Ischemic Stroke) – 130 patients, endovascular to 33°C, t-PA within 6 hours – No Effect on Mortality
HT for Malignant CNS Edema

- Animal models demonstrate smaller infarct volumes with slower rewarming.
  
  Kollmar R J NT ’09

- Prospective, observational analysis of the Copenhagen Stroke Study Registry determined for each 1°C increase in body temperature at admission following stroke, relative risk of poor outcome increased by 2.2.
  
  Kammersgaard LP ’00 Stroke
  Reith J ’96 Lancet

- Mortality of malignant MCA stroke as high as 80%.
  
  Kollmar R J. NT ’09

- Clinical data demonstrates increasing ICP as patients with large ischemic strokes are rewarmed.
  
  Steiner R Stroke ’01
HT for Malignant CNS Edema

- HT in 25 pts w/ malignant MCA stroke an average of 14hr from symptom onset were reviewed. Goal temp of 33°C was maintained for 48-72hrs.
- Mortality 44%
- Increased ICP w/ rewarming and was associated w/ death.

Schwab S Stroke ‘98
European society of intensive care medicine study of therapeutic hypothermia (32-35°C) for intracranial pressure reduction after traumatic brain injury (the Eurotherm3235Trial)

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For all author emails, please log on. 

The electronic version of this article is the complete one and can be found online at:
http://www.trialsjournal.com/content/12/1/8

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Stages of therapeutic management of raised intracranial pressure after traumatic brain injury [37,43].

**STAGE 1**
Admission to the ICU
Ventilation PaO2 ≥11kpa
PaCO2 4.5-5.0kpa
Sedation
Analgesia ± paralysis
30° head of bed elevation
Intravenous fluids ± inotropes to maintain mean arterial pressure ≥80mmHg

Ventriculostomy ± cerebrospinal fluid drainage
Surgical removal of space occupying lesions ± prophylactic anticonvulsants

**STAGE 2**
Mannitol (maintain serum osmolarity <315 mOsm/kg)
Hypertonic saline (avoid in hyponatraemic patients, caution in patients with cardiac or pulmonary problems)
Inotropes to maintain CPP ≥60mmHg
Monitor blood magnesium levels and replace as required

Barbiturates not permitted
± therapeutic hypothermia

**STAGE 3**
Barbiturate therapy
Decompressive craniectomy

Methods/design

- This is a pragmatic, multi-centre randomised controlled trial examining the effects of hypothermia 32-35°C, titrated to reduce intracranial pressure <20 mmHg, on morbidity and mortality 6 months after traumatic brain injury. The study aims to recruit 1800 patients over 41 months. Enrolment started in April 2010.

- Participants are randomised to either standard care or standard care with titrated therapeutic hypothermia. Hypothermia is initiated with 20-30 ml/kg of intravenous, refrigerated 0.9% saline and maintained using each center's usual cooling technique. There is a guideline for detection and treatment of shivering in the intervention group. Hypothermia is maintained for at least 48 hours in the treatment group and continued for as long as is necessary to maintain intracranial pressure <20 mmHg.
<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Witnessed VT/VF arrest with ROSC &lt;60min</td>
<td>NNT 5</td>
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<tr>
<td></td>
<td>Reduction in ICP</td>
<td>Decreased ICP does not equate better outcomes.</td>
</tr>
<tr>
<td>III</td>
<td>Witnessed PEA/asystolic arrest</td>
<td>COOL AID and hypothermia in IV tPA</td>
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<tr>
<td></td>
<td>Stroke</td>
<td>Cardiac surgery and thoracoabdominal aortic aneurysm repair (brain and spinal cord protection)</td>
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<tr>
<td></td>
<td></td>
<td>Control of ICP in hepatic encephalopathy/failure</td>
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<tr>
<td></td>
<td></td>
<td>Improved oxygenation in ARDS</td>
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<tr>
<td>IV</td>
<td>Reducing MI size</td>
<td>Status epilepticus</td>
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<td></td>
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<td>SAH</td>
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<td></td>
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<td>Contrast nephropathy</td>
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</tbody>
</table>

Adapted from Polderman '08 Lancet.
Consensus statement of American Thoracic Society, European Respiratory Society, European Society of Intensive Care Medicine, Society of Critical Care Medicine, Societe de Reanimation de Langue Francaise: 

...Regarding fever, it is a generic response to so many pathologic processes that no recommendation can currently be made for or against targeted temperature management.
Future
Future

- Better Targets and outcome measures as animal studies do not always translate to humans.
- ? Animal Data on hibernation with profound hypothermia - ?????suspended animation
- Experimental Conductive cooling devices with faster cooling time and better control – NASA space program/DoD.
Thank You
Questions??????

Two Stupid Chickens:

How do I get to the other side?!!

You are on the other side!