TOO COOL OR NOT TOO COOL-
THERAPEUTIC HYPOTHERMIA IN THE ICU
SCCM TX 2017
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DISCLOSURE

• I have no relationships with commercial companies to disclose.
OBJECTIVES

• Review the basic science of hypothermia and its applications in hypoxic-ischemic neuronal injury
• Summarize current clinical evidence for use of therapeutic hypothermia
  • Use in neonatal asphyxia and cardiac arrest (Adults and Pediatrics)
  • Limitations of available evidence
HISTORY OF HYPOTHERMIA

- Concept developed in the 1950s
  - Hypothermic dogs survived 20min of cardiac arrest
- 1960s Neurosurgery for large aneurysms under cardiac arrest
- 1970s Ascending aortic arch surgery
Simplified scheme of the mechanism after ischemia
Effects of mild hypothermia

Ca++ cycling, delayed neuronal death, swelling, vascular compression, no-reflow

Inflammation, axonal transport, adhesion molecules, cytoskeleton, receptors/channels, inhibition protein synth., lactate, acidosis, ATP hydrolysis, inhibition Na/K+

Depolarization, immediate cell death

Energy depletion, mitochondrial overload, NO, iNOS, glutamate, NMDA, non-NMDA

Calcium influx

Apoptosis, heat stress, killer proteins, genomic responses, lipolysis, polyamines, cytokines

IEGs, free radicals, arachidonate, BBB, NMDA receptors, metabotropic receptors

Calcium mobilisation, VSCC, stretch

Clotting, BBB permeability, edema, vasodilation, altered gene response, Ca++ influx, Ca++ influx
Multiple Processes Contribute to Brain Injury

- Hypothermia Window
- Protein Synthesis Inhibition
- Endothelial injury -> platelet & fibrin activation -> small vessel obstruction & inflammation
- Cerebral Hypoperfusion
- Oxidative Stress
- Excitatory Amino Acid Release
- Energy Failure / Acidosis
- Cell Death – Proteases, apoptosis, necrosis

2 Hours
24 Hours
48 Hours

Guy Clifton, MD, PhD
NEUROPROTECTIVE EFFECTS OF HYPOTHERMIA

• Multi-focal damage from generation of free radicals- "post-resuscitation syndrome"

• Intra-ischemic hypothermia for brain protection used in surgery and circulatory arrest states

• In rat models: ↓ cerebral edema, ↓ blood brain barrier permeability, ↓ cerebral atrophy

• Lowers CBF and ICP

Marion et al. 1997
Negovsky 1988
NEUROPROTECTIVE EFFECTS OF HYPOTHERMIA

• ↓ Cerebral metabolic rate by 6-7% per ↓ 1°C body core temp; increase O₂ supply to ischemic areas
• ↓ lactate and excitatory amino acids such as glutamate and dopamine
• ↓ ICAM-1 expression
• ↓ neutrophil migration to ischemic tissue

Ilievich UM Anesth Analg. 1994
Berger C Stroke. 2002
Inamasu J Neurol Res. 2001
HYPOThERMIA FOR CLINICAL APPLICATIONS?

• Can the laboratory data from be applied clinically hypoxic-ischemic brain injury?
COOL CAP PERINATAL ASPHYXIA STUDY

• 25 Center study in term newborns with HI-encephalopathy
• Evaluated use of selective head cooling using dedicated device
• Random assignment w/in 6h of birth to head cooling for 72h or conventional care

COOL CAP PERINATAL ASPHYXIA STUDY

• Inclusion: term infant w/clinical evidence of mod to severe encephalopathy or seizures and evidence of perinatal HI
  • (Apgar ≤ 5 at 10 min or severe acidosis w/in 1 hr of birth) and abnormal aEEG w/in 6 h
• Rectal temp maintained at 34-35°C for 72 hr
• Primary outcome: death or severe disability at 18 mo

Perinatal Hypothermia

Groups well matched at baseline

Randomized 234 with mod-severe HIE + abnormal amplitude-integrated EEG
1° outcome: death or severe disability

< 6 hrs; 34.5±0.5°C

Control-118
66% poor outcome

Hypo-116
55% poor outcome

OR for primary outcome: 0.61, 95% CI, 0.34 to 1.09.

Bradycardia more common in HT group and scalp edema resolved without intervention.
HYPOTHERMIA- PERINATAL ASPHYXIA

- Logistic regression analysis controlling for pre-randomization severity of encephalopathy suggested protective effect (p=0.05; OR 0.57; 0.32, 1.01)
- No effect in infants with most abnormal aEEG changes
- Adverse outcome reduced from 65.9% in controls (n=88) to 47.6% in cooled (n=84), p=0.01
  - ARR = 18.3%; NNT = 6 (95% CI:3 to 27)

WHOLE BODY HYPOTHERMIA FOR NEONATAL HIE

- 15 center NICHD Neonatal Network trial of systemic hypothermia (72 h) in neonates with HIE
  - 1º outcome: reduction of death or severe disability at 18-22 mo
  - Cooled with servo-controlled blanket; monitored rectal temp to target of 33.5ºC
    - Controls at 36.5-37ºC skin temp
  - Randomized block design at each center; 798 screened, 239 eligible and 208 enrolled

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothermia Group (N=102)</th>
<th>Control Group (N=106)</th>
<th>Relative Risk (95% CI)††</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
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<tr>
<td>Death or moderate or severe disability;‡</td>
<td>45 (44)</td>
<td>64 (62)</td>
<td>0.72 (0.54–0.95)</td>
<td>0.01</td>
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<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
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<tr>
<td>Death</td>
<td>24 (24)</td>
<td>38 (37)</td>
<td>0.68 (0.44–1.05)</td>
<td>0.08</td>
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<tr>
<td>Death or disability‡</td>
<td></td>
<td></td>
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<tr>
<td>Among infants with moderate encephalopathy</td>
<td>22 (32)</td>
<td>30 (48)</td>
<td>0.69 (0.44–1.07)</td>
<td>0.09</td>
</tr>
<tr>
<td>Among infants with severe encephalopathy</td>
<td>23 (72)</td>
<td>34 (85)</td>
<td>0.85 (0.64–1.13)</td>
<td>0.24</td>
</tr>
<tr>
<td>Survival</td>
<td>78 (76)</td>
<td>68 (66)</td>
<td></td>
<td></td>
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<tr>
<td>Bayley Mental Development Index score‡§</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥85</td>
<td>39 (52)</td>
<td>25 (40)</td>
<td>1.24 (0.83–1.83)</td>
<td>0.27</td>
</tr>
<tr>
<td>70–84</td>
<td>17 (23)</td>
<td>13 (21)</td>
<td>1.08 (0.57–2.05)</td>
<td>0.81</td>
</tr>
<tr>
<td>&lt;70</td>
<td>19 (25)</td>
<td>24 (39)</td>
<td>0.71 (0.43–1.17)</td>
<td>0.18</td>
</tr>
<tr>
<td>Bayley Psychomotor Developmental Index score¶§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥85</td>
<td>46 (62)</td>
<td>34 (55)</td>
<td>1.10 (0.82–1.48)</td>
<td>0.53</td>
</tr>
<tr>
<td>70–84</td>
<td>8 (11)</td>
<td>6 (10)</td>
<td>1.19 (0.38–3.76)</td>
<td>0.77</td>
</tr>
<tr>
<td>&lt;70</td>
<td>20 (27)</td>
<td>22 (35)</td>
<td>0.80 (0.48–1.33)</td>
<td>0.39</td>
</tr>
<tr>
<td>Disabling cerebral palsy**</td>
<td>15 (19)</td>
<td>19 (30)</td>
<td>0.68 (0.38–1.22)</td>
<td>0.20</td>
</tr>
<tr>
<td>Blindness††</td>
<td>5 (7)</td>
<td>9 (14)</td>
<td>0.50 (0.17–1.44)</td>
<td>0.20</td>
</tr>
<tr>
<td>Severe hearing impairment **</td>
<td>3 (4)</td>
<td>4 (6)</td>
<td>0.54 (0.10–3.02)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

*NNT = 6 (95% CI, 3 to 22) for HT therapy to prevent one death or severe disability.*

* Percentages are based on the number of infants for whom data were available.
† Relative risks shown are adjusted according to center. CI denotes confidence interval.
‡ Data were unobtainable for three patients in the control group. Severe disability was defined as any of the following: Mental Development Index score below 70, Gross Motor Function Classification System (GMFCS) grade level 3 to 5, hearing impairment requiring hearing aids, or blindness. Moderate disability was defined as a Mental Development Index score of 70 to 84 and one or more of the following: GMFCS grade of level 2, hearing impairment with no amplification, or a persistent seizure disorder.
§ Sixty-nine infants in the hypothermia group and 63 in the control group had moderate encephalopathy, and 32 infants in the hypothermia group and 36 in the control group had severe encephalopathy.
¶ Sixty-nine infants in the hypothermia group and 63 in the control group had moderate encephalopathy, and 32 infants in the hypothermia group and 36 in the control group had severe encephalopathy.
TOBY STUDY

• Prospective, multi-center, randomized neonatal trial in UK (325 pts recruited)
• Infants less than 6 hrs old, 36 weeks and perinatal encephalopathy
• Cooling 33.5°C for 72 hrs or 37°C
• Rewarming no more than 0.5°C/hr
• Primary outcome: death or severe disability (18 months)

Azzopardi NEJM 2009
TOBY RESULTS

• Cooled group
  • 42 deaths, 32 survival with severe disability
• Noncooled group
  • 44 deaths, 42 survival with severe disability
• Either outcome: RR 0.86, P 0.17
  • Increased survival rate without neuro disability
    (RR 1.57; p=0.003)

Azzopardi NEJM 2009
RESULTS

• Cooled infants increased survival rate w/o neuro abnormality (RR 0.67, P 0.003)

• Cooling had reduced risk for cerebral palsy (RR 0.67 P 0.03)
  • Improved developmental scores

• Adverse events similar in two groups
  • Hypotension, ↓ Plts, ICH, ↑ Coag time

Azzopardi NEJM 2009
Eleven randomized trials reviewed

- 1505 term and late preterm infants with moderate-severe encephalopathy and intrapartum asphyxia

Therapeutic Hypothermia Resulted

- Statistically significant reduction in combined outcome of mortality or major neuro disability to 18 mo
- RR 0.75; RD -0.15, 95% CI -0.20 to -0.10
- Mortality reduced- RR 0.75 (95% CI 0.64 to 0.88)
- Adverse events: Bradycardia, thrombocytopenia
COCHRANE CONCLUSIONS

- Therapeutic hypothermia is **beneficial** to term and preterm newborns with HIE
- Reduces mortality without increasing major disability in survivors
- Both large neonatal HI trials showed benefit in moderate HI encephalopathy group
  - Suggests that HT may not be effective if neuro injury severe
  - Ability to stratify by aEEG 24h/day is likely limited

Cochrane Reviews, 2013
'LITTLE ADULTS' VS. 'BIG CHILDREN'?
INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

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. BIUST, M.B., B.S.,

Comatose adults resuscitated from VF

33° X 12 h
N = 43

Normothermia
N = 34

49%
Good Neuro Outcome*

26%
Good Neuro Outcome

*D/C to Home or Rehab
Adj OR=5.25;
95% CI, 1.47-18.76 **P=.046
NNT = 5 (2.3 – 81)

HYPOTHERMIA IN ADULT ARREST – EUROPEAN TRIAL

• Randomized survivors OOH witnessed VF/VT with coma after ROSC
  • Goal was to cool to temp 32-34 °C within 4 hours of ROSC but median was 8 hours
  • Sedated and Intermittent NMB for shivering
  • Blinded assessment of outcome at 6 months
• 3551 patients screened and 275 studied (only 7.7% of total arrest population)

HACA Study Group. NEJM 2002; 346: 549-56
HACA: Multicenter European Trial

Adults resuscitated from out-of-hospital CA
N = 3551; 275 witnessed VF

32-34° X 24 h
N = 137
55% Good Neuro Outcome*
41% Died**

Normothermia
N = 138
39% Good Neuro Outcome
55% Died

*6 month CPC 1-2; RR=1.4; 95% CI, 1.08-1.81**P=.02
ARI=16%; NNT=6 (4 to 25) to prevent one adverse neuro outcome
NNT=7 to prevent one death

NEJM 2002;346:549-556
International trial 939 unconscious adults after out-of-hospital cardiac arrest of presumed cardiac cause to targeted temperature management at either 33°C or 36°C. The primary outcome was all-cause mortality through the end of the trial.

- 50% of hypothermia died vs 48% of normothermia died (hazard ratio with a temperature of 33°C, 1.06; 95% confidence interval [CI], 0.89 to 1.28; P=0.51)
- No difference of poor neurologic function (risk ratio, 1.02; 95% CI, 0.88 to 1.16; P=0.78)
- 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
COCHRANE REVIEW - 2017

• 6 randomized and quasi-randomized controlled trials (1412 patients)
• Trials comparing conventional cooling methods versus no cooling
  • Cooling group- Pts more likely for favorable neurological outcome (RR 1.94, CI 1.18-3.21)
  • Increased incidence of PNA and Hypo K+ in hypothermia group
• Mild therapeutic hypothermia improve neurological outcome after cardiac arrest
  • specifically with better outcomes than with no temperature management
COCHRANE REVIEW

- Slightly increased incidence of pneumonia (RR 1.15, 95% CI 1.02 to 1.30; two trials; 1205 participants) and hypokalemia (RR 1.38, 95% CI 1.03 to 1.84; two trials; 975 participants) among participants receiving therapeutic hypothermia.

- No significant differences in reported adverse events between hypothermia and control groups. Overall the quality of the evidence was moderate (pneumonia) to low (hypokalemia).
COCHRANE CONCLUSIONS

• Mild therapeutic hypothermia improve neurological outcome after cardiac arrest, specifically with better outcomes than occur with no temperature management (moderate quality evidence)

• Target temperature (34°C or lower)- consistent with current best medical practice

• Insufficient evidence therapeutic hypothermia benefits for in-hospital cardiac arrest, asystole or non-cardiac causes of arrest
An amazing save

16-month-old revived after an hour without a pulse

By Neil Nisperos, Staff Writer

Article Created: 02/20/2008 10:10:22 PM PST
MONTCLAIR - Michael’s heart wasn’t beating and he wasn’t breathing for the first hour he was in the emergency room. Tests performed hours later showed the 15-month-old baby boy found floating in a backyard pool had no sign of brain activity. Photo Gallery: Miracle baby survives after drowning

That was little more than a month ago.