WA-ACEP Journal Club

Value of Therapeutic Hypothermia as a Treatment Modality
(May 18, 2011)

Today’s Outline

- Review History and Objectives of JC
- Summary of November JC
- Therapeutic Hypothermia
  - Current status as treatment modality
  - Literature on TH in cardiac arrest
  - “Cutting Edge” uses
  - Sample Protocols in current use
- Open Forum

Background on WA-ACEP Journal Club

- Proposed by WA-ACEP Board in 2009
- Funded by National ACEP Grant in 2010
- Coordinated by WA-ACEP Board Education Subcommittee
- This is our second session

Strategic Goals for JC

- Bi-annual Webinars
- Open to all WA-ACEP members
- CME
- Active participation of WA EM Residents

Review of WA-ACEP Journal Club Objectives

- To the extent possible, standardize medical care on controversial topics
- Improve communication amongst state providers
- Stimulate literature discussion
- Promote skills in the critical evaluation of the literature.

Today’s Topic – Therapeutic Hypothermia

- Current status as treatment modality
- Literature on TH in cardiac arrest
  - Should we expand beyond post V-fib arrest?
  - Pro/Con argument
- “Cutting Edge” uses
- Sample Protocols in current use
### Common Template for article presentations

- Title
- Objective of Study
- Methodology/Study Design
- Results
  - Statistical Analysis
  - Variables Involved
- Panel Discussion
  - Was the Objective of the study met?
  - Biases/Flaws/Extrapolations
- Key References
- Short Open Discussion on each paper

### Therapeutic Hypothermia

- **Where are we today?**
  - **Consensus Paper**
    - Circulation 2008: 118; 2452-2483
    - International Liaison Committee on Resuscitation
      - American Heart Association
      - Australian & New Zealand Council on Resuscitation
      - European Resuscitation Council
      - Heart & Stroke Foundation of Canada
      - InterAmerican Heart Foundation
      - Resuscitation Council of Asia
      - Resuscitation Council of Southern Africa

### ILCOR Objective

- Review all literature pertaining to the unique pathophysiologic state of Post Cardiac Arrest Syndrome
  - Post-arrest Brain Injury
  - Post-arrest Myocardial Dysfunction
  - Systemic Ischemia/ Reperfusion Response
  - All complicated by the unresolved process that caused the initial arrest.

### ILCOR Methodology

- Epidemiology
- Pathophysiology
- Therapeutic Strategies
- Post Cardiac Arrest Prognostication
- Pediatric Considerations
- Challenges to Implementation
- Bibliography (374 key references)

### Epidemiology

- Early Post arrest Phase: 20 minutes to 6-12 hours
- Intermediate Phase: 12 to 72 hours
- Recovery Phase: Beyond 3 days
- Cerebral Performance Categories: 1 & 2 good - 5 dead
- One Canadian Study; 71% ICU admits after ROSC still died before discharge.

### Pathophysiology

- Post Arrest Brain Injury: Increased with pyrexia, hyperglycemia, & seizures. 68% of in house deaths attributable to brain death.
- Post Arrest Myocardial Dysfunction: EF decreases from 55% to 20% even with normal coronary perfusion. “Stunning”. Peaks at 8 hours, resolved by 72 hours.
- Systemic Ischemia/ Reperfusion: Similar to Sepsis.
- Precipitating Pathology: OOH Arrest, 50% due to MI. InH Arrest, 11% due to MI.
Therapeutic Strategies

- Monitoring: Hemodynamically is EGDT. MAP 65-100. CVP 8-12.
- Oxygenation: O2 sats 94-96%, avoid free radicals/ hyperoxia.
- Circulatory Support: Preload first, Inotropes second, IABP third.
- Management ACS: PCI!
- Sedation & Neuromuscular Blockade: Control Seizures & myoclonus. Up to 15% after ROSC have seizures, and up to 40% of those remain comatose.
- Glucose Control: Target 80-144.

Therapeutic Strategies: Mild Hypothermia

- ONLY therapy post-arrest to be proven to increase both survival & Cerebral Performance Category!
- Pyrexia MUST be avoided!
- 3 Phases: Induction, Maintenance & Rewarming

Complications Associated with Therapeutic Mild Hypothermia

- Shivering
- Increases SVR & reduces CO
- Induces Arrhythmia
- Diuresis: Associated hypophosphatemia, hypokalemia, hypomagnesemia, hypocalcemia.
- Impair Immune Response
- Hyperglycemia
- Delays Drug Metabolism

Think Magnesium

Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest AND Treatment of Comatose Survivors of Out of Hospital Cardiac Arrest with Induced Hypothermia

- Multifactoral. Best remains bedside neurological exam with focus on cranial nerves at day 3 to predict poor outcome.
- Hypothermia protocol may delay this.

Prognostication Post Arrest
Implementation Challenges

Pro Article

Pertinent References


Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: a prospective study.

Mauro Oddo, et al.
Department of Critical Care Medicine
Lausanne University Medical Center and Faculty of Biology and Medicine, Lausanne, Switzerland
Crit Care Med 2008; 36:2296 - 2301

Study Objectives

- Better define the role of therapeutic hypothermia in the general clinical setting
- Identify early predictors of good outcome.

Study Parameters

- Design
  - Prospective Cohort
  - Inclusion Criteria
    - Consecutive subjects, aged < 80 yrs admitted for persistent coma following out-of-hospital cardiac arrest.
    - Single center (tertiary, academic)
**Study Parameters**

- **Variables**
  - Predictors: Predefined clinical variables obtained at admission
    - Duration of CA (defined as the time from collapse to ROSC)
    - Initial arrest rhythm (VF or non-VF)
    - Hemodynamic status (presence or absence of postresuscitation circulatory shock)
  - Outcomes:
    - Survival
    - Neurologic status at discharge (Good = CPC 1-2)

- **Study Parameters (con’t)**
  - **Statistical Analysis**
    - Multivariable logistic regression
    - Time from collapse to ROSC was not linear
    - Covariates
      - Age
      - Sex
      - Initial arrest rhythm (VF or non-VF)
      - Arterial lactate on admission to the emergency room
      - Presence of circulatory shock on admission to the ICU.

**Results**

- 88 Eligible patients
  - 11 excluded for Age > 80
  - 3 excluded for underlying terminal disease
- 74 patients included in study
  - 46% had post arrest circulatory shock
  - 51% VF initial rhythm
  - 39% survival
  - Of survivors, 32% good neurologic outcome.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival</th>
<th>Good neurologic outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from collapse to ROSC</td>
<td>≤25 min</td>
<td>≥25 min</td>
</tr>
<tr>
<td>p value</td>
<td>0.99</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 3. Outcome based on the time from collapse to ROSC, initial arrest rhythm, and postresuscitation circulatory shock.

**Results**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from collapse to ROSC ≤25 min</td>
<td>0.10</td>
<td>0.01-0.63</td>
<td>0.01</td>
</tr>
<tr>
<td>Lactate level at hospital admission</td>
<td>0.70</td>
<td>0.36-1.41</td>
<td>0.32</td>
</tr>
<tr>
<td>Initial arrest rhythm (VF or non-VF)</td>
<td>1.40</td>
<td>0.83-2.32</td>
<td>0.20</td>
</tr>
</tbody>
</table>

| ROC: Area Under Curve | 0.93 |

Table 4. Multivariable analysis of early independent predictors of survival in patients with non-aortic ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with mild hypothermia.
Results

Previous retrospective study reassessed using collapse→ROSC interval.

<table>
<thead>
<tr>
<th>Time from Collapse to ROSC</th>
<th>Numben of Patients</th>
<th>Hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤24 hours</td>
<td>350 (2.2%)</td>
<td>104 (5.6%)</td>
</tr>
<tr>
<td>&gt;24 hours</td>
<td>527 (1.8%)</td>
<td>241 (13.5%)</td>
</tr>
</tbody>
</table>

Data represent number of patients with indicated outcome or categories, with permission from [1].

ROSC: return of spontaneous circulation

Conclusions

- Were the objectives met?
  - Two strong predictors of good outcome with therapeutic hypothermia were identified (Time to ROSC and Lactate)
  - Initial Rhythm failed to predict survival in multivariable analysis.

Pros/Cons

Pros
- Directly compares predictors using multivariable logistic regression.
- Strong predictors identified

Cons
- No interactions or higher order models examined.
- Selection Bias?
  - Single Tertiary Academic Center
  - Small #’s
  - Doubtful power
- Generalizable?
  - Physician-led EMS resuscitation team
  - Multifaceted post-arrest care provided.

Take Home Points

- All cardiac arrest rhythms eventually lead to asystole.
- "Absence of evidence is not evidence of absence". - D Altman BMJ
- Identification of initial rhythm is not exact (Pokorna et al, Resuscitation 2011)
- Initial rhythm is not an adequate predictive marker on which to base the decision to cool.

Late Breaker

  - 80% Survival, 55% with favorable neurologic outcome.


  - 75% of Cardiac etiology of arrest were witnessed vs. 58% of non-cardiac etiology (p<0.0001).

References


Con Article

Is Hypothermia After Cardiac Arrest Effective in Both Shockable and Nonshockable Patients?


Background

- Origin for the use of TMH for post-ventricular fibrillation (VF)/ventricular tachycardia (VT) cardiac arrest (CA)
  - Improved neurologic and survival outcomes for post-VF/VT CA patients (“Works for some patients”)
- Extension of concept to non-VF/VT CA patients (Post-Cardiac Arrest Syndrome)
  - Several small studies with equivocal results (“May not help much, but does not appear to ‘harm’ either”)
- In 2011, the American Heart Association now recommends TMH for PEA/asystole CA patients

Study Objective

Assess the influence of therapeutic hypothermia on hospital outcome in out-of-hospital cardiac arrest (OHCA) patients, separately in those with VF/VT and in those with PEA/asystole as initial presenting rhythm

Study Parameters

- Overall Study Design
  - Type: Observational prospective registry of 1145 patients
- Setting: Tertiary care center, Paris, France
- Time: January 2000 - June 2009
- Inclusion Criteria: Nontraumatic OHCA patients admitted consecutively after successful return of spontaneous circulation (ROSC)
- Exclusion Criteria: None specified

Pretty convincing, right?
Methods

Data Collection – Primary Data Point
- Neurologic outcome upon hospital discharge as defined by the Cerebral Performance Category (CPC) Scale

<table>
<thead>
<tr>
<th>Table 1. Cerebral Performance Category Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good outcome:</td>
</tr>
<tr>
<td>1 Conscious and alert with normal function or only slight disability.</td>
</tr>
<tr>
<td>2 Conscious and alert with moderate disability.</td>
</tr>
<tr>
<td>Bad outcome:</td>
</tr>
<tr>
<td>3 Conscious with severe disability.</td>
</tr>
<tr>
<td>4 Comatose or persistent vegetative state.</td>
</tr>
<tr>
<td>5 Brain dead or death from other causes.</td>
</tr>
</tbody>
</table>

Study Groups

- 2000-2003 ("Pre-TMH")
  - VF/VT without TMH
  - VF/VT with TMH

- 2004-2006 (Adoption)
  - VF/VT without TMH
  - VF/VT with TMH

- 2007-2009 (Routine)
  - VF/VT without TMH
  - VF/VT with TMH

Methods

- Statistical Analyses
  - Chi Square
  - Student t Test
  - Single Multivariable Logistic Regression Analysis
  - Odds Ratio with 95% Confidence Intervals (CI)
  - Wald Test

Results

Main Points of Interest

Nonadjusted Odds Ratio for Use of TMH
- VF/VT: 1.91 (95% CI, 1.38-2.66)
- Non-VF/VT: 0.83 (95% CI, 0.49-1.40)*

Adjusted Odds Ratio for Use of TMH
- VF/VT: 1.90 (95% CI, 1.18-3.06)
- Non-VF/VT: 0.71 (95% CI, 0.37-1.36)*

*Did not achieve statistical significance

Interlude

Odds Ratio (OR)
- A method of comparing whether the probability of a certain event is the same for two groups
- An OR of 1 = the event is equally likely in both groups
- OR > 1 = the event is more likely in the first group
- OR < 1 = the event is less likely in the first group

Several caveats:
- OR can exaggerate the size of effect
- Assumes disease is uncommon
- Assumes study population was randomly selected

Results

Main Points of Interest

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Results

1105 patients admitted survivors of OHCA

- 708 Pts (64%) VF/pulseless VT
- 437 Pts (38%) Asystole/PEA

Hypothermia Group: 457 Pts (65%)
No Hypothermia Group: 251 Pts (35%)

Good Outcome
201 Pts (44%)
73 Pts (29%)
38 Pts (15%)

Limitations

- Applicability? Are populations & times comparable to U.S.?
- Patients admitted directly to ICU
- Patients not randomized
- Use of specific cooling technique
- Multiple statistical tools
- Suggestion that TMH for non-VF/VT is “harmful” did not achieve statistical significance

Strengths

- Large sample size, one of the largest studies evaluating the use of TMH for non-VF/VT cardiac arrest patients
- Used patients before, during, & after routine use of TMH
- Used resuscitation guidelines, TMH protocols, and CPC scale similar to other referenced studies
- Collected and analyzed numerous other data points
- Findings for VF/VT group correlates with other studies

Summary

- Pertinent Outcome
  - Longer delays to resuscitation were inversely associated with a better neurologic outcome
- Primary Outcomes
  - TMH nearly doubled the probability of being discharged with a favorable neurologic outcome in patients resuscitated from VT/VT cardiac arrest
  - TMH tended to decrease the probability of being discharged with a favorable neurologic outcome in patients resuscitated from non-VF/VT cardiac arrest
**Discussion Points**

- Do the results pass the “sniff test”?
- Are the results applicable to your practice?
- Will the results affect your practice?
  - If not, why not? “Will not hurt”?
  - If yes, how? Can application be “selective”? In-hospital cardiac arrest? Known short delay before ROSC?

**Cutting Edge Uses**

- Very early hypothermia induced in patients with severe brain injury (the National Acute Brain Injury Study: Hyperthermia II)

**Conclusion**

**Why Do the Study?**

- Previous study, NABIS I, looked at hypothermia induce within first 10 hours.
- Hypothermic group had increased mortality
- BUT subgroup analysis indicated that very early hypothermia might improve mortality

**Study overview**

- Randomized multicenter trial
- 2 treatment groups: normothermia and hypothermia to 33°C for 48 hours.
- Hypothermia treatment was induced within 2-1/2 hours from trauma
- Hypothermia was induced immediately upon arrival by either EMS or the emergency department
- Inclusion criteria: 16-45 years, none penetrating brain injury, not responsive to instructions

**Hypothermia Induced By**

- Using Artic Sun surface cooling mat
- Room temperature ventilated air
- Chilled IV crystalloid
- Gastric lavage with cold H2O
**Exclusion Criteria:**

- 2 sets of exclusion criteria.
- At randomization
  - hypotensive (SBP <110; DBP<60)
  - HR>120
- Injury was greater than 2.5 hrs ago
- After complete assessment & resuscitation:
  - GCS 3 and NR pupils
  - Abrev Injury score 4 or more (excluding brain)
  - Hypoxia (O2 sat <94%)

**Results**

- Large number patients screened to get reasonable sample size
- Groups were reasonably matched
  - Normothermic slightly older 31 vs 26
  - Normothermic slightly sicker

**Table 1** — Demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia</th>
<th>Normothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26 (9)</td>
<td>31 (11)</td>
</tr>
<tr>
<td>GCS score 5-8</td>
<td>33 (63%)</td>
<td>22 (49%)</td>
</tr>
<tr>
<td>GCS score 3-4</td>
<td>19 (37%)</td>
<td>23 (51%)</td>
</tr>
<tr>
<td>Non-reactive pupils</td>
<td>6 (12%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Surgical lesion removed in first 24 h after injury</td>
<td>15 (29%)</td>
<td>15 (33%)</td>
</tr>
<tr>
<td>Prehospital hypotension</td>
<td>7 (15%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Prehospital hypoxia</td>
<td>11 (23%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Injury severity score</td>
<td>30 (6)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Abbreviated injury severity score for head</td>
<td>4.56 (0.61)</td>
<td>4.47 (0.63)</td>
</tr>
<tr>
<td>Positive blood alcohol</td>
<td>17 (59%)</td>
<td>17 (59%)</td>
</tr>
<tr>
<td>First temperature (°C)</td>
<td>36.1 (0.8)</td>
<td>36.0 (0.9)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (%). GCS=Glasgow coma scale.

**Hypothermia Did Not Improve Mortality or Neuro Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Poor outcome</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>p valu e</td>
</tr>
<tr>
<td>Primary analysis</td>
<td>RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>All patients (n=97)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypothermia (n=52)</td>
<td>31 (60%)</td>
<td>1-08  (0.08-2.1)</td>
</tr>
<tr>
<td>Normothermia</td>
<td>25</td>
<td>-</td>
</tr>
</tbody>
</table>

**Subgroup Analysis:**

Hypothermia Didn’t Help In Any Subgroup
Subgroup analysis

<table>
<thead>
<tr>
<th></th>
<th>Poor outcome</th>
<th></th>
<th>Died</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (% )</td>
<td>RR (95% CI)</td>
<td>p value</td>
<td>n (% )</td>
</tr>
<tr>
<td>Diffuse brain injury (n=69)</td>
<td>42 (61%)</td>
<td>1-44 (0.95-2.17)</td>
<td>0.09</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>Hypothermia (n=37)</td>
<td>26 (70%)</td>
<td>1-44 (0.95-2.17)</td>
<td>0.09</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Normothermia (n=32)</td>
<td>16 (50%)</td>
<td>1-44 (0.95-2.17)</td>
<td>0.09</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Surgically removed haematomas (n=28)</td>
<td>14 (50%)</td>
<td>1-44 (0.95-2.17)</td>
<td>0.09</td>
<td>7 (25%)</td>
</tr>
<tr>
<td>Hypothermia (n=15)</td>
<td>5 (33%)</td>
<td>1-44 (0.95-2.17)</td>
<td>0.09</td>
<td>1 (67%)</td>
</tr>
<tr>
<td>Normothermia (n=13)</td>
<td>9 (69%)</td>
<td>1-44 (0.95-2.17)</td>
<td>0.09</td>
<td>5 (39%)</td>
</tr>
</tbody>
</table>

**Bottom line**
- Hypothermia does not help in blunt trauma to the brain
- Hypothermia does not improve outcome wither due to diffuse brain injury or hemorrhage

**Cooling Methods for Inducing Hypothermia**

What is the best way?

**Many Ways to Be Cool**
- **Simplest:** 30 ml/ kg cold (4 C) lactated Ringer's over 30 minutes
- **Simple:** pack head, neck, torso and limbs and ice packs
  - Used in seminal Australian study on hypothermia and V. fib arrest (NEJM 346:557, 2002)
- **Low tech:** Cooling mattress that covers the body
  - Used in seminal European study on hypothermia and V. Fib arrest (NEJM 236:549, 2002)
- **Hi Tech:** Intravascular cooling systems

**Two Recent Studies in ICU Patients**
- **Crit Care 11 R91, 2007**
  - Water circulating blankets/gel pads/intravascular cooling cool faster than IV cold saline and ice packs or air blanket cooling.
  - With Intravascular cooling temperature more constant
  - But do these cooling methods give a better clinical outcome? Study did not answer
- **Crit Care 39: 443, 2011**
  - Surface cooling with blanket (Artic Sun) vs Intravascular cooling (Coolgard)
  - No difference in survival to D/C, neurological outcomes at D/C and at 6 mos
### Bottom Line

- Most likely any cooling methods will do in ED.
- Cooling blanket makes most sense in a patient who will be in ED for awhile and/or no significant money issues
  - Needs less nursing involvement
  - Keeps temperature constant
  - Less messy

### PRMCE Protocol

- **Indications**
  - V-fib/Pulseless VTach
  - Spontaneous Return of Circulation
  - Comatose
- **Goals**
  - Temp 33 C for 24 hours after SROC
  - Passive re-warming if pt awakens
  - Diazepam/Meperidine for shivering (q30 min)
- Cinncinatti Sub Zero cooling machine

### HMC Protocol

- **Indications**
  - V-fib, Pulseless V Tach, PEA, Asystole
  - SROC w/in 1 hour
  - Unresponsive
  - > 18 y/o
- **Goals**
  - Temp of 33 C w/in 4 hours
  - Continue for 24 hour after SROC
    - After 24 hours passive re-war to 37 C over 4 hours
  - Fentanyl/Midazolan/Vecuronium
- Artic Sun Temperature Management System

### Open Forum

- Who else has protocols currently in place?
  - Do they differ significantly

### Moving forward

- Monkey Survey for input coming out soon.
- Suggestions on future JC's
  - Topics
  - Format changes