Therapeutic hypothermia after cardiac arrest and in critical care

Benjamin S. Abella, MD, MPhil

Center for Resuscitation Science
Department of Emergency Medicine
University of Pennsylvania

Cardiac arrest: introduction

300,000 arrests/year in U.S.A.

3/4 Out-of-hospital
1/4 In-hospital

Survival to hospital discharge
1-5%
10-20%

Becker et al, 1993
Peberdy et al, 2003

The post-arrest problem

Reperfusion injury

Damage observed after restoration of blood flow to ischemic tissues
**Hypothermia mechanisms**

- ischemia → reperfusion → reactive oxygen species (ROS) → inflammatory cascades → mitochondrial dysfunction
- vascular dysfunction/hypotension → apoptosis – organ dysfunction → cerebral edema
- hypothermia

**Modern era of hypothermia use**

<table>
<thead>
<tr>
<th>Method</th>
<th>Duration (hours)</th>
<th>Target temp (°C)</th>
<th>ROSC (min)</th>
<th>VF (%)</th>
<th>Female sex (%)</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HACA</td>
<td>24</td>
<td>22 (16-30)</td>
<td>33</td>
<td>22</td>
<td>(27-37)</td>
<td>65 (53-69)</td>
</tr>
<tr>
<td>Bernard</td>
<td>24</td>
<td>24 (17-32)</td>
<td>77</td>
<td>77</td>
<td>(30%)</td>
<td>68 (57-75)</td>
</tr>
<tr>
<td>Idrissi</td>
<td>Up to 4</td>
<td>33 (27-37)</td>
<td>12</td>
<td>12</td>
<td>(39%)</td>
<td>74 (66-79)</td>
</tr>
</tbody>
</table>

**Modern era of hypothermia use**

<table>
<thead>
<tr>
<th>Method</th>
<th>Duration (hours)</th>
<th>Target temp (°C)</th>
<th>ROSC (min)</th>
<th>VF (%)</th>
<th>Female sex (%)</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HACA</td>
<td>24</td>
<td>22 (16-30)</td>
<td>33</td>
<td>22</td>
<td>(27-37)</td>
<td>65 (53-69)</td>
</tr>
<tr>
<td>Bernard</td>
<td>24</td>
<td>24 (17-32)</td>
<td>77</td>
<td>77</td>
<td>(30%)</td>
<td>68 (57-75)</td>
</tr>
<tr>
<td>Idrissi</td>
<td>Up to 4</td>
<td>33 (27-37)</td>
<td>12</td>
<td>12</td>
<td>(39%)</td>
<td>74 (66-79)</td>
</tr>
</tbody>
</table>

**Adverse events: HACA trial**

<table>
<thead>
<tr>
<th></th>
<th>Normothermia n = 138</th>
<th>Hypothermia n = 137</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>19%</td>
<td>26%</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>32%</td>
<td>36%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>29%</td>
<td>37%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Renal failure</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Pressure sores</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Differences not statistically significant

**Hypothermia trials: outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia (%)</th>
<th>Normothermia (%)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive at hospital discharge with favourable neurological recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HACA</td>
<td>72/136 (53%)</td>
<td>50/137 (36%)</td>
<td>1.51 (1.14-1.89)</td>
<td>0.006</td>
</tr>
<tr>
<td>Bernard</td>
<td>21/43 (48%)</td>
<td>9/34 (26%)</td>
<td>1.79 (0.99-2.43)</td>
<td>0.052</td>
</tr>
<tr>
<td>Idrissi</td>
<td>4/16 (25%)</td>
<td>1/17 (6%)</td>
<td>4.25 (0.70-23.83)</td>
<td>0.16</td>
</tr>
<tr>
<td>Alive at 6 months with favourable neurological recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HACA</td>
<td>71/136 (52%)</td>
<td>50/137 (36%)</td>
<td>1.44 (1.12-1.76)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Hypothermia in the guidelines

AHA Guidelines 2005 conference
Dallas, January 22-29, 2005
Several hundred cardiac arrest experts
Closed meeting, rigorous process

CPR/BLS/ACLS guidelines underwent revision
New guidelines released supporting hypothermia, published 11/2005

Are we using hypothermia?

Two internet survey studies of U.S. physicians
Critical care, cardiology, emergency medicine

Abella BS et al, 2005
Ever used hypothermia: 13% (n=263)

Merchant RM et al, 2006
Ever used hypothermia: 26% (n=1839)

Utilization of hypothermia

Practical issues of cooling

1. How to cool?
2. When to start cooling?
3. How deep to cool?
4. How long to keep cool?
How to cool?

- Ice packs, cooling blankets, catheters...

University of Chicago Hospitals (UCH) initial experience (2003-4): cooling blanket and/or ice packing

Advantages: cheap, non-invasive, ‘off the shelf’

Disadvantages: slow cooling, can be messy, lack of thermostatic control

Difficulties with ice bag cooling

Merchant RM et al. 2006

Retrospective chart review of cooling cases
From three hospitals (2 in U.S., 1 in U.K.)

Found 20/32 cases (62.5%) were overcooled

Trends towards better outcome in non-overcooled pts

Suggests need for thermostatic feedback control

Surface cooling in the real world

Example A

Merchant RM et al. 2006

Simple cooling methods

Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report

Bernard S et al. 2003

Study in 22 post-arrest patients

Infused 30 ml/kg ice cold saline

Average temperature drop of 1.5°C

Remember: 1. No maintenance or rewarming
2. Large fluid load (safety unproven)
**Is cold saline enough?**

Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. 2007

Andrew Kühler, Andreas Danner, Claudia Warnziller, Thomas Urey, Alexander Sprung, Heidrun Linert, Matthias Kühler, Michael Holzer, Heinz G Muth, Fritz Steier, Antonio Legnani

Cooling was fast … But maintenance was hard

65% cooled to target within 60 minutes 77% failed to stay cool during course

**Real world usage: Switzerland**

Outcome at discharge for out-of-hospital VF arrest

<table>
<thead>
<tr>
<th>Baseline</th>
<th>CPC 5</th>
<th>CPC 4</th>
<th>CPC 3</th>
<th>CPC 2</th>
<th>CPC 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Real world usage: Switzerland**

Outcome at discharge for out-of-hospital asystole arrest

<table>
<thead>
<tr>
<th>Baseline</th>
<th>CPC 5</th>
<th>CPC 4</th>
<th>CPC 3</th>
<th>CPC 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Real world usage: Switzerland**

Outcome at discharge for all rhythms with post-arrest hypotension and shock

<table>
<thead>
<tr>
<th>Baseline</th>
<th>CPC 5</th>
<th>CPC 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooling</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Real world usage: Philadelphia**

Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. 2009


Combined hypothermia and early goal-directed therapy

Cooling intervention with historical controls

Cooled any rhythm, both in and out of hospital arrest

Target temperature 33°C, maintained for 24 hrs

**CPC 1-2 survivors**

Before protocol 22% 44% After protocol
**Real world usage: Oklahoma**

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non-Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to target temp (min)</td>
<td>194</td>
<td>188</td>
</tr>
<tr>
<td>Coronary intervention</td>
<td>7/19 (37%)</td>
<td>4/30 (13%)</td>
</tr>
<tr>
<td>Admission G.C.S.</td>
<td>4.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>19/49 (39%)</td>
<td></td>
</tr>
<tr>
<td>Survival with G.C.S. 14-15</td>
<td>16/19 (84.2%)</td>
<td></td>
</tr>
</tbody>
</table>

**HACA registry data**

- Large multinational registry of post-arrest patients
- Started by Alsius Corporation; now via European Resuscitation Council
- Collects data from any cooling method

**HACA registry data**

- Clinical application of mild therapeutic hypothermia after cardiac arrest
- Hypothermia patients: n=462
  - Endovascular device: n=347
  - Ice packs, fluids: n=114
- Most with witnessed O-O-H, most "cardiac cause"

**HACA registry data**

- Technique
  - Average cool duration: 24 hours
  - Cooling rate: 1.1/1.3 °C per hr
  - Rewarming time: 8-9 hours
- Outcomes
  - CPC 1,2 at discharge: 45% (32% b.l.)
  - Bleeding rate: 3%
  - Bleeding requiring Rx: 1.2%

**A second hypothermia registry**

Nielsen et al, 2009

- Infection and seizures are common
- Bradycardia (13%)
- Significant bleed (4%)

**Cooling and PCI**

- Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention

**Bottom line:** cooling and immediate cardiac cath are safe and compatible
Hypothermia resource website

Hypothermia in pediatrics

Post-resuscitation trials being initiated currently
external cooling (ice bags and cooling blanket)
Use of ECMO as cooling circuit?
VF more common in pediatrics than thought
Nadkami V et al, 2004
Nadkami V et al, 2006

Cooling and MI

COOL MI trial (2003):
Failed to show benefit
In human randomized trial
Using catheter-based cooling
-- however...
Rapid cooling preserves the ischaemic myocardium against mitochondrial damage and left ventricular dysfunction 2009

Other hypothermia applications

General concept:
cooling as “brain protection”
- traumatic brain injury
- subarachnoid hemorrhage
- cerebrovascular accident
- fever control in all of the above

Cerebrovascular accident

Plentiful animal data:
Cooling shrinks penumbra, lowers ICP

Clinical experience: CVA

Cooling lowers ICP – and ICP matters!

Schwab et al, 1998
Hypothermia in the news

July 23, 2007
Cover story on Hypothermia
Human angle: Profiled survivors

Buffalo Bills player Kevin Everett treated with hypothermia

“I was trying to pull out all the stops to help this young man,” Cappuccino said Wednesday at a news conference.
He had heard of the therapy, called moderate hypothermia, at a conference attended by doctors from the Miami Project to Cure Paralysis who have been experimenting with it for more than a decade.

September 14, 2007

Hypothermia in the news

Popular Science
January, 2009

“Freezing the Heart to Save the Life”
Good graphics showing effects of cooling

The future: regionalized care?

The feasibility of a regional cardiac arrest receiving system

Daniel P. Davis
Roger Fisher
Steven Aquar
Marcilyn Mate
Binger Och
Luka McClain-Young
Monath Kanany
Colleen Drapke
Gayle N. Yike
Theodore C. Chan
James E. Donahue

2007

Hypothermia and post-arrest care – Not for everyone?
Idea being implemented:
Minnesota
North Carolina
Arizona

The future: cooling during arrest?

Mild hypothermia during advanced life support: a preliminary study in out-of-hospital cardiac arrest
Cedric Bhat
Jose Jacques Poirier
William More
Xavier Amo
Codric Dox
Basil O'Chayos
Massimo Sivori
Pierre Quasicoeur

Supported by animal data
Problem: how to cool rapidly enough?
How to make it feasible?

Training for hypothermia

Hypothermia Training Institute at Penn

Intensive two day CME course in hypothermia methods, protocols, and applications

Designed for critical care, cardiology or emergency medicine physicians and nurse managers – i.e., local champions
Will offer “hypothermia certification”
Workshop design – small course size – will hold quarterly
Acknowledgements

Lance Becker
Mation Leary
Bob Neumar
Dave Galeski
Roger Band
Brenden Carr
Bary Fuchs
Dan Kolansky
Vinay Nadkarni
Raina Merchant
Daniel Herzberg
David Fried
Emily Esposito
Raghu Seethela

CRS Center for Resuscitation Science