The clinical evidence: Hypothermia for cardiac arrest.

Fritz Sterz, Vienna, Austria
YEARS AGO ...

- 150 000  homo sapiens
- 5000  1st human cultures
- 691  1st human autopsy
  (1315, Mondino di Luzzi, Bologna)
- 378  1st description of human circulation
- 160  ether anesthesia (1846)
- 110  bloodpressure (1896)
- 63  penicillin
- 50  modern CPR
YEARS AGO ...

- **3500 B.C. Edwin Smith Papyrus**
  - with numerous references to the use of cold as therapy

- **Napoleon's Russian campaign** (Baron de Larrey, French army surgeon)
  - packed the limbs in ice prior to amputations to render the procedures painless

- **early twentieth century** (Temple Fay neurosurgeon)
  - pioneered "human refrigeration" as a treatment for malignancies and head injuries

- **1961 Irving Cooper**
  - developed the first closed cryoprobe system
  - ushered in the modern era of cryogenic surgery

- **World War II**
  - Nazis confiscated Fay’s data (3rd Int Cancer Congress 1939)
  - brutally applied his refrigeration techniques (Dachau)

- **late 80s**
  - interest was rekindled

- **currently under way**
  - several large multi-center clinical studies

Simplified Scheme of Proposed Mechanisms of Cerebral Ischemia.
K.-A. Hossmann
Do You Cool - 2005?

Internet based survey in UK, US, Finland and Australia (2248 of 13272 email surveys completed), emergency and critical care physicians and cardiologists

2003

YES 13%  NO 87%

2005

YES 26%  NO 74%

YES 36%  NO 64%

Merchant Crit Care Med 2006;34:7
Why not?

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not enough data</td>
<td>49%</td>
</tr>
<tr>
<td>Too technically difficult</td>
<td>35%</td>
</tr>
<tr>
<td>Have not considered it</td>
<td>34%</td>
</tr>
<tr>
<td>Not part of ACLS</td>
<td>23%</td>
</tr>
<tr>
<td>Cooling methods slow</td>
<td>13%</td>
</tr>
<tr>
<td>Initial attempts unsatisfactory</td>
<td>3%</td>
</tr>
<tr>
<td>Concern about consent</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>16%</td>
</tr>
</tbody>
</table>

Merchant *Crit Care Med* 2006;34:7

Neue Reanimations Guidelines 2005
Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was VF.

Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.
Unconscious adult patients with 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).
HYPOTHERMIA AND CEREBRAL VASCULAR LESIONS

I. EXPERIMENTAL INTERRUPTION OF THE MIDDLE CEREBRAL ARTERY DURING HYPOTHERMIA*

LIEUT. HUBERT L. ROSOMOFF, M.C., U.S.N.R.
Naval Medical Research Institute, National Naval Medical Center.
Bethesda, Maryland

Journal of Neurosurgery

13 (4); 244-255 (1956)
Fig. 1.—Decrease of cerebral blood flow and oxygen consumption with lowered temperature.
Peter Safar (1924-2003)

- known as the father of cardiopulmonary resuscitation (CPR)
Peter Safar emphasised that saving the heart and lungs would have little value if the brain were not similarly protected.

He promoted CPCR (Cardio Pulmonary Cerebral Resuscitation), which relied on mild hypothermia to preserve cerebral function.
“Second” Steps

Peter Safar, Pittsburgh, USA

Dog outcome studies:

- Leonov, JCBFM 1990
- Sterz, Crit Care Med 1991
- Weinrauch, Stroke 1992
- Kuboyama, Crit Care Med 1993
- Safar, Stroke 1996

Mild hypothermia after CA improved neurologic outcome and brain histology
First clinical experiences with therapeutic Hypothermia after CA already 1958 through Williams and Spencer:

- 2 children and 2 adults
- watercooled matress
- 24 – 72 hours at 30 – 34 Celsius (until awake)
- one patient hat a neurologic defect

Williams GR Jr, Spencer FC.
The clinical use of hypothermia following cardiac arrest.  
Benson DW, Williams GR Jr, Spencer FC, Yates AJ. Pioneer Publication with a case series of 12 cooled patients and 7 controls

- Comatose survivors
- Asystole or VF
- 31-32°C
- Cooling until neurologic recovery (3 h to 8 days)
- water-filled blanket

Clinical pilot trials of therapeutic hypothermia after cardiac arrest

Favorable Neurologic Recovery

![Graph showing favorable neurologic recovery](image-url)
Randomized clinical trials of therapeutic hypothermia after cardiac arrest

The New England Journal of Medicine

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA


Resuscitation 51 (2001) 275–281

Mild hypothermia induced by a helmet device: a clinical feasibility study

Said Hachimi-Idrissi *, Luc Corne, Guy Ebinger, Yvette Michotte, Luc Huyghens

Department of Critical Care Medicine and Cerebral Resuscitation Research Group, AZ-VUB, Free University of Brussels, Laarbeeklaan, 101, B-1090, Brussels, Belgium
Randomized Clinical Trials
Favorable Neurologic Recovery

HACA Bernard H.-Idrissi

Hypothermia
Normothermia
## Randomized Clinical Trials
### Favorable Neurologic Recovery

**Review:** Hypothermia for neuroprotection after cardiopulmonary resuscitation

**Comparison:** C1 Survival with good neurological recovery

**Outcome:** C1 Up to hospital discharge

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Normothermia</th>
<th>Hypothermia</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernard</td>
<td>21/42</td>
<td>9/34</td>
<td></td>
<td>15.31</td>
<td>1.89 [1.00, 3.57]</td>
</tr>
<tr>
<td>HACA</td>
<td>52/136</td>
<td>50/137</td>
<td></td>
<td>63.95</td>
<td>1.45 [1.11, 1.90]</td>
</tr>
<tr>
<td>Idrissi</td>
<td>3/16</td>
<td>0/17</td>
<td></td>
<td>0.74</td>
<td>7.41 [0.41, 138.11]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>194</strong></td>
<td><strong>139</strong></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>1.53 [1.19, 1.96]</strong></td>
</tr>
</tbody>
</table>

**Total events:** 36 (Normothermia), 59 (Hypothermia)

**Test for heterogeneity:** $\chi^2 = 1.76$, df = 2 ($P = 0.41$), $I^2 = 0$

**Test for overall effect:** $Z = 3.34$ ($P = 0.0008$)

---

0.1 0.2 0.5 1 2 5 10

Favours normothermia  Favours hypothermia
Randomized clinical trials of therapeutic hypothermia after cardiac arrest
Individual Patient Data Meta-Analysis

\( N = 384 \)

**Short term effects of hypothermia**
- survive until discharge -> risk ratio 1.36 (95% CI 1.11 to 1.59)
- good neurological -> risk ratio 1.61 (95% CI 1.24 to 1.99)
- 6 patients needed to be treated -> 6 (95% CI 4 to 17)

**Long term effects of hypothermia (6 months)**
- good neurological within -> risk ratio 1.40 (95% CI 1.10 to 1.69)
- alive & good at -> risk ratio 1.47 (95% CI 1.13 to 1.80)
- 6 patients needed to be treated (95% CI 4 to 21)
Helsingborg, Lund and Malmö

- 86 patients
  - female 29
  - age 64 years
- NaCl 4°C
  - 30 ml/kg
  - 100ml/min
  - initiated in the ER
- Thermowrap®
  - admission to the ICU
  - 33°C for 24 hours

Northern Hypothermia Network
www.scctg.org

T Karlsson et al, Resuscitation 2004
- no adverse effects
- time to reach target temperature
  - 134 min

<table>
<thead>
<tr>
<th></th>
<th>At hospital discharge</th>
<th>Good outcome</th>
<th>Bad outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF (VT) (55 pat)</td>
<td></td>
<td>35 (64%)</td>
<td>20 (36%)</td>
</tr>
<tr>
<td>Asyst/PEA (31 pat)</td>
<td></td>
<td>6 (19%)</td>
<td>25 (81%)</td>
</tr>
</tbody>
</table>

T Karlsson et al, Resuscitation 2004
Among reasons cited for non-use:

- and 28% felt that cooling methods were technically too difficult or too slow

33.8 °C on admission

MJ Foedisch, M Fischer - Bonn / FRG
Good Neurological Outcome
OPC 1&2

13

2

MJ Foedisch, M Fischer - Bonn / FRG, Resuscitation 2004
Cool-Shock I Study:
Mild Hypothermia as positive Intervention in Cardiogenic Shock

S Schmidt-Schweda, et al - Univ of Goettingen, Goettingen, Germany
The American Heart Association Scientific Sessions 2004

### Table

<table>
<thead>
<tr>
<th></th>
<th>CI</th>
<th>SVI</th>
<th>HR</th>
<th>MAP</th>
<th>RA</th>
<th>PCWP</th>
<th>SVR</th>
<th>PVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>2.9±0.4</td>
<td>31±4</td>
<td>93±9</td>
<td>69±5</td>
<td>11±2</td>
<td>17±3</td>
<td>1123±157</td>
<td>209±82</td>
</tr>
<tr>
<td>Hypo</td>
<td>3.5±0.5**</td>
<td>42±5***</td>
<td>84±7</td>
<td>81±7*</td>
<td>11±4</td>
<td>18±2</td>
<td>993±119</td>
<td>227±99</td>
</tr>
</tbody>
</table>

* *, **, *** = p<0.05, 0.01, 0.001

- Cooling (1 hour, n=6) significantly improved HD
  - increase in cardiac index (CI, l/min/m²)
  - increase in stroke volume index (SVI, ml/m²)
  - increase in mean arterial pressure (MAP, mmHg)

- no severe adverse events

- 2 pat. developed intermittent atrial fibrillation at 33°C

- similar results were observed in patients, cooled for 24 hours (n=6)
From evidence to clinical practice: Effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. Oddo M et al. Crit Care Med 2006 - Lausanne University Hospital, Switzerland

- Retrospective - historical controls
- 109 patients
- Pulmonary artery temperature
- External cooling
  - ice bags
  - cooling mattress (Cincinnati SubZero, Cincinnati, OH)
- 24 hrs
- Sedation, analgesia and paralysis

Ventricular Fibrillation

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>CPC 1 Total Recovery</th>
<th>CPC 2 Moderate Disability</th>
<th>CPC 3 Severe Disability</th>
<th>CPC 4 Vegetative State</th>
<th>CPC 5 Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic hypothermia</td>
<td>18/43 (41.9)</td>
<td>6/43 (13.9)</td>
<td>2/43 (4.7)</td>
<td>0/43 (0)</td>
<td>17/43 (39.5)</td>
</tr>
<tr>
<td>Standard resuscitation</td>
<td>6/43 (14.0)</td>
<td>5/43 (11.6)</td>
<td>8/43 (18.6)</td>
<td>0/43 (0)</td>
<td>24/43 (55.8)</td>
</tr>
</tbody>
</table>

**Asystole or Pulsless Electrical Activity**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPC 1 Total Recovery</td>
</tr>
<tr>
<td>Therapeutic hypothermia</td>
<td>2/12</td>
</tr>
<tr>
<td>Standard resuscitation</td>
<td>0/11</td>
</tr>
</tbody>
</table>
From evidence to clinical practice: Effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest.
Intravasale Kühlung
Eine Methode zur Erzielung steuerbarer Hypothermie
Behmann F.W. und Bontke E.
Pflügers Archiv, Bd. 263, S 145-165 (1956)
Survival and Neurological Recovery

Survival 30 days: CoolGard (n=97) 69% vs Control (n=941) 50%, p<0.001

Good Survival 30 days: CoolGard (n=97) 53% vs Control (n=941) 34%, p<0.001

M Holzer et al, Stroke 2006
Odds ratio (log-scale) for discounted observational data combined with an empirical prior based on three randomised controlled trials

- combining the discounted observational data with data from the randomised trials
- empirical Bayes estimate for the odds ratio of the three trials was
  - 1.87 (95% CI 1.19 to 2.94) (prior odds ratio)
- the posterior odds ratio was
  - 1.72 (95% CI 1.27 to 2.34)
Cold infusions alone are effective for induction of therapeutic hypothermia but don’t keep patients cool after cardiac arrest. A. Kliegel et al. Resuscitation 2006
1 patient died
- 5 hours after inclusion
- from cardiogenic shock

8 (40%) survived to discharge
- 7 of those had ventricular fibrillation
- 7 (35%) favourable neurological outcome
## Levels of Therapeutic Hypothermia

<table>
<thead>
<tr>
<th>Levels of Hypothermia</th>
<th>$T_{core}$ (° C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>33 - 36</td>
</tr>
<tr>
<td>Moderate</td>
<td>28 - 32</td>
</tr>
<tr>
<td>Deep</td>
<td>18 - 28</td>
</tr>
<tr>
<td>Profound</td>
<td>5 - 18</td>
</tr>
<tr>
<td>Ultra-Profound</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

Chain of Survival
"The Norwegian Style"

The fifth ring:
- early and optimal inhospital treatment
- a standardised treatment protocol
- therapeutic hypothermia
Among reasons cited for non-use:

- 49% felt that there were not enough data
  - When?
  - How fast?
  - How long?
  - How deep?

OUR SOLUTION TO FIND IT OUT

www.erchacar.org
HACA REGISTRY
www.erchacar.org
Descriptive Analysis of Collected Data

- all patients: 587
  - Hypothermia: 462
  - Normothermia: 123
20 active sites

Klinik für Anästhesiologie und Intensivmedizin
Klinikum Schwerin
Catharina Hospital Eindhoven
KH Wiener Neustadt
Regionaal Ziekenhuis Jan Yperman
Gornoslaskie Centrum Medyczne
Reanimation Medicale CHU Rouen
Royal United Hospital
Turku University Hospital
KH Barmh. Schwestern Linz
ICU / Kuopio University Hospital
University Hospital Maastricht
HUS / Jorvi Hospital
Hôpital Lariboisière
KH Barmh. Brüder Linz
Kinderklinik, Helios-Klinikum Wuppertal
Evangel. Krankenhaus Bonn
Ullevaal University Hospital
University of Helsinki - Acute Stroke Unit
Dep of Emergency Medicine - Univ of Vienna
The European Consortium of Resuscitative Hypothermia Research
Study Protocol

Draft-Version 2006_10_05

Submission

http://ec.europa.eu/research/future/index_en.cfm

The European Hypothermia Network

Friberg H & Sterz F
Future European Union research policy

On 5 April the European Commission adopted a proposal for a new EU programme for research. The proposal provides new incentives to increase Europe's growth and competitiveness, recognising that knowledge is Europe's greatest resource, and its role as a world leader in certain sectors. The programme will also for the first time provide support for the best in European research and innovation. A new feature of the programme is the requirement that it will seek to support research excellence and innovation, a requirement that will play an important role in Europe's future competitiveness. The proposal prioritises the desirability of participation in the programme, and in this context, through various initiatives. In this context, there are many elements of continuity: in practice, for the majority of participants, the programme itself will not change, but participation will become simpler.

For a full overview on FP 7 Proposal, see "FP 6 - Building Knowledge Europe - The EU's New Research Framework Programme 2007-2013".

Further information

For the latest press releases visit the research press centre.

Related sites

- Towards FP - the EU's new framework programme
- European Research Policy
- Research Themes in FP7
- Technology Platforms.info
- European Research Area
- EuropeAID
- Investing in Research: Action plan for Europe (towards 3% of GDP)

Key documents for FP 7

- Proposals for the Seventh Framework Programme
- Proposals for the FP7 Specific Programmes
- Proposal for the Rules for Participation

Guidance documents

- FP7 rules for participation (24 kb)
- Comparison between FP6 provisions under FP6 and FP7 proposal (83 kb)

Compare with FP6

- FP6 and its specific programmes
- Rules for Participation for FP6

Background information

- Communication: "Building the EU's knowledge for growth" (213 kb)
- Commission staff working paper: "Simplification in the 7th Framework Programme, SEC(2005)284 (244 kb)
- Results of the general consultation for views on the Commission Proposal "Science and Technology, the Key to Europe's Future - Guidelines for Future European Union Policy to Support Research" in 2004 (Statistical overview of results (58 kb), Report on the results of the consultation (73 kb), Perspectives to the consultation on research themes in FP7 (42 kb)
“Out-of-hospital Cooling”
“Fluids and Temperature Control”
“In-hospital Cooling”
“Temperature Control”

- 24, 48 & 72 hours
“Out-of-hospital Cooling”

- out-of-hospital (cold fluids)
- in-hospital cooling
EC-RHR

“Fluids and Temperature Control”

- out-of-hospital (tepid fluids)
- in-hospital temperature control
EC-RHR

“In-hospital Cooling”

- out-of-hospital standard medical care
- in-hospital cooling
“Temperature Control”

- out-of-hospital standard medical care
- in-hospital temperature control
24, 48 & 72 hours
EC-RHR

fritz.sterz@meduniwien.ac.at
...nothing works without a good team!!

ER - General Hospital of Vienna:

- 65 Nurses
- 35 Doctors
- 8 Ward clerks
- 4 Nurse Aides
- 4 Orderlies
- 4 Secretaries
On the 8th day god created hypothermia...