Hypothermia for the treatment of Myocardial infarction and Cardiogenic shock

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Randomised trials for hypothermia for the treatment of cardiac arrest

- HACA-trial: 285 patients
- Bernard-trial: 77 patients
- Hachimi-Idrissi trial (feasibility): 30 patients
- Mori-trial (abstract): 55 patients
- Laurent-trial (stopped early): 42 patients
- Total: 478 patients
- Guidelines based on: 362 patients
Background hypothermia for the heart

Hypothermia is used successfully protect the heart during:

CABG

Heart transplantations
Treatment of Myocardial infarction:

Revascularisation

- Thrombolysis
- Direct-PCI
Treatment of Myocardial infarction: Cardioprotection

• The next challenge
• Successfull animal experiments (usually short series)
• Failure in man
• Intensive research area (cyclosporin, postconditioning, adenosine)
• Hypothermia is the most powerful treatment in animal models
Mechanism of Cardioprotection

- Cyclosporin: Mitocondria
- C5a inhib: Complement
- Adenosine: Inflammation
- Postcond: Myocyte(?)
- PKCdelta-: Myocyte apoptosis
- ?: Metabolism
- ?: Reactive hyperemia
- ?: Endothelium
- ?: Systemic effects

Hypothermia
Hypothermia in the prevention of MI – Animal studies

**Duncker et al. 1996** *(Am J Physiol 270, H1189)*

Open chest swine. Ligation of LAD. External cooling.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Infarct size (%) of area at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>0%</td>
</tr>
<tr>
<td>36</td>
<td>20%</td>
</tr>
<tr>
<td>37</td>
<td>40%</td>
</tr>
<tr>
<td>38</td>
<td>60%</td>
</tr>
<tr>
<td>39</td>
<td>80%</td>
</tr>
</tbody>
</table>

**Hale, Dave & Kloner 1997** *(Basic Res Cardiol 92, 351)*

Open chest rabbit. Ligation of LAD. Topical cooling on the myocardium. Temp lowered locally by 6°C within 5 min. To examine if hypothermia instituted after onset of ischemia is effective.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Infarct size (%) of area at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early local hypothermia</td>
<td>23%</td>
</tr>
<tr>
<td>Late local hypothermia</td>
<td>43%</td>
</tr>
<tr>
<td>Normothermia</td>
<td>44%</td>
</tr>
</tbody>
</table>

**Conclusion:**

Hypothermia after onset of ischemia can protect the heart!
Hypothermia in the prevention of MI
Animal studies

Open surgery ligation of LAD in pigs.
34 C during 40 out of 60 min ischemia (Radiant).

80% relative reduction in infarct size (P < 0.001)

Based on this study on 22 animals two major clinical trials were conducted

Hypothermia for MI

- Two failed larger clinical studies
- "Bad timing"
Hypothermia in the prevention of MI – COOL-MI

COOL-MI Trial (Radiant)
325 patients

No difference in Day 30 SPECT infarct size (1° endpoint)
Cooling deemed safe and well-tolerated (94% tolerated hypothermia).

Anterior MI
<35 C before reperfusion
49% reduction in infarction size

![Image of cardiac equipment and SPECT scan]

![Chart showing reduction in infarction size]

- All Test (N=61): 17.9%
- <35 C (N=16): 9.3%
- ≥35 C (N=38): 21.9%
- Control (N=59): 18.2%

P-values:
- All Test vs. <35 C: P = 0.0129
- All Test vs. ≥35 C: P = 0.0496
- All Test vs. Control: P = 0.9229
- <35 C vs. Control: P = 0.3033
ICE-IT

(228 patients)

Mean SPECT Infarct Size (% of LV)

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Evaluable Patients</td>
<td>13.5</td>
<td>14.2</td>
</tr>
<tr>
<td>Measured* SPECT</td>
<td>10.2</td>
<td>13.2</td>
</tr>
</tbody>
</table>

N = 108      N = 109
N = 99      N = 105

23% Relative Reduction

P = 0.14

*No imputed values
ICE-IT

ICE-IT
(228 patients)

Anterior MI

P = 0.09 (43% reduction)

Control (N = 38)
All Hypo (N = 36)
Tpci <35 (N = 10)
Tpci >35 (N = 26)
COOL MI II (Radiant Medical)

- Started Spring 2006
- 225 patients
- Anterior MI
- Symptoms < 6 hrs
- Primary endpoint: Reduction in infarct size (SPECT)

No Mandatory target temperature <35°C prior to PCI

Terminated 2008 after Zoll acquisition of Radiant Medical
Ongoing clinical trials: Life Recovery System

The trial will explore the feasibility of cooling heart attack (STEMI) patients with the ThermoSuit System before blood flow is restored to the heart.

Patients will be sedated and cooled after entry into the emergency room and prior to percutaneous coronary intervention in the catheterization laboratory.

It is expected that the ThermoSuit System will enable cooling of the patient to 34 degrees C after a treatment of 30 minutes or less and within the 90-minute door to balloon time requirement for treating ST-elevation acute myocardial infarction patients.

Twenty patients will be enrolled in the study.
CAMARO-trial (Velomedix)

Infusion of cold fluid into the abdomen.

Risk of bleeding in STEMI patients receiving aspirin, clopidogrel/prasugrel, Gp-blockers/bivalirudin and heparin?
Timeline STEMI

30 min → hours

15 min

15 min

15 min

Ambulance

Arrival Cathlab

Angiography

PCI

Reperfusion
Hypothermia for MI

- Is target temp <35C the key?
- How can that be achieved?
- How can we cool the awake patient?

More basic animal research needed
Endovascular cooling (Celsius Control system) gives a more rapid induction of hypothermia compared to surface cooling.
Endovascular cooling alone

~ 20-25 min to reach < 35°C

Dae et al, Am J Physiol, 2002
Hypothermia protocol for rapid cooling

Combination hypothermia: Cold saline (4°C), 1000 ml iv infusion in 5 min as a ”kick start” for quick initiation of hypothermia together with an endovascular cooling catheter.

- 1000 ml cold saline (4°C)
- Quick initiation of hypothermia

Celsius Control System™
Endovascular cooling catheter (14 F)
Initiation and maintaining hypothermia
Endovascular alone: ~ 20-25 min to reach < 35°C

Combination hypothermia: ~ 5 min to reach < 35°C (Cold saline and endovascular cooling)
Methods

Experimental closed chest porcine model
Catheter based occlusion of the LAD by inflation of a PCI-balloon
In vivo Spect and finally MRI
Ex Vivo Spect and MRI
Infarct assessment – Ex Vivo

Ex-vivo SPECT

A typical bull’s eye image of the area at risk after occlusion of the LAD

Ex-vivo MRI

A long axis and a short axis ex-vivo MRI image of an anterior MI
Ex-vivo MRI: 0,5mm slice, (~200 images/heart)
Infarction size measured with *ex vivo* MRI

MRI validated against TTC
(Kim et al. Circulation 1999)
TTC compared with ex vivo MRI

Approx 7
1-1.2 cm slices

200, 0.5 mm slices
Reperfusion injury

Infarction size

Reperfusion

Ischemia

Time
Infarct development in different species

Infarct development is 7.8 times slower in man
40 min in pig = approx 5 hours in man

Hedström et al. J Cardiovasc Imaging, 2009
Cooling before or after reperfusion – Cool pig-study 1

Pre-reperfusion hypothermia

- Ischemia (40 min)

Normothermia (38°C) Hypothermia (33°C)

Induction of hypothermia

Post-reperfusion hypothermia

- Ischemia (40 min)

Normothermia (38°C) Hypothermia (33°C)

Normothermia

- Ischemia (40 min)

Normothermia (38°C)
~ 5 min to reach < 35°C with cold saline and endovascular cooling
Infarct size/area at risk

Gotberg et al., BMC Cardiovascular Disorders, 2008
Microvascular obstruction

Microvascular obstruction (%)

- Pre-reperfusion hypothermia: n=7, 0%
- Post-reperfusion hypothermia: n=7, 10%
- Normothermia: n=5, 30%

Jaffe 2008 Circulation
Speckled infarction

Pre-reperfusion hypothermia

Region of infarction by *ex vivo* MRI

Area at risk from SPECT 45%

Post-reperfusion hypothermia

Region of infarction by *ex vivo* MRI

Area at risk from SPECT 50%

Normothermia

Region of infarction by *ex vivo* MRI

Area at risk from SPECT 46%
Speckled infarction in pig

Hypothermia causes disruption of the wavefront phenomenon (first described by Jennings)
Also seen in hypothermia by Dae et al., Am J Physiol, 2002, with SPECT
Conclusion

• Hypothermia before reperfusion reduces infarct size by 40%

• Protection against microvascular obstruction

• A combination of cold saline and catheter based cooling provides rapid cooling to target temperature in 5 min

• A clinically applicable protocol
Hypothermia for MI

• Prolonging ischemi to induce hypothermia?
• Proof of effect of hypothermia on reperfusion injury alone?
• Cold saline alone? (poor mans hypothermia)
Reperfusion injury?

- **Normothermia**
  - Ischemia (40 min)
  - Normothermia (38°C)

- **Hypothermia (NaCl)**
  - Ischemia (45 min)
  - Normothermia (38°C)

- **Combination hypothermia**
  - Ischemia (45 min)
  - Normothermia (38°C)
  - Hypothermia (33°C)

Induction of hypothermia
Temperature at the time of reperfusion:

**Combination hypothermia:** $34.5 \pm 0.1^\circ C$

**Cold saline:** $35.2 \pm 0.3^\circ C$
Infarct size

Combination hypothermia: 18% reduction in infarct size (p=0.03)
Despite 5 min prolonged ischemia
Mikrovascular obstruction

Combination hypothermia: 95% reduction of MO (p<0.01)
Cold saline: 74% reduction of MO (p<0.01)
Conclusions

• Combination hypothermia just before reperfusion reduces infarct size by 18% and microvascular obstruction with 95% despite prolonged ischemic time.

• An infusion of cold saline alone does not reduce infarct size but reduces microvascular obstruction with 74%.

• Hypothermia reduce reperfusion injury.
Prolonged hypothermia after reperfusion?

**Extended hypothermia**
- Ischemia (40 min)
- Normothermia (38°C) → 75 min active hypothermia (33°C)

**Shorter active hypothermia**
- Ischemia (40 min)
- Normothermia (38°C) → 30 min active hypothermia (33°C)

**Normothermia**
- Ischemia (40 min)
- Normothermia (38°C)

Induction of hypothermia
Prolonged hypothermia after reperfusion?

Increase from 15 min to 60 min postreperfusion hypothermia did not improve infarct size
Window of opportunity for cooling

Ischemia | Post-ischemia
---|---

Ischemia | Post-ischemia

D.Erlinge
RAPID MI-ICE pilot
(Safety and Feasibility study in man)

• 20 Patients (10 cooled vs 10 non-cooled).
• STEMI
• <6 hrs from onset of symptoms
• <35°C Temperature before attempt to cross lesion with guidewire
• Receive 1-2 liters of cold saline before PCI, followed by cooling with the intravascular Celsius catheter system for 2.5 hours.

- Primary outcome: Safety & Feasibility
- Secondary outcome: Reduction in infarct size (MR)
Big questions before RAPID MI-ICE

- Volume overload
- Heart failure
- Reaching target temp
- Shivering
- Safety
- Feasibility
Infarct size with Cardiac MRI at day 4

Area at risk with Cardiac MRI (T2-stir)

Validated against SPECT

M Carlsson et al, JACC Cardiovasc Imaging 2009
Timeline STEMI

- Ambulance
- Arrival Cathlab
- Angiography
- Buspirone
- Meperidine iv
- Cold saline 1-2 l
- PCI
- Endovascular catheter placement
- Temp
- Reperfusion
<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothermia (n=9)</th>
<th>Control (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 ± 10</td>
<td>58 ± 7</td>
</tr>
<tr>
<td>Women</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Infarct related artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>RCA</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Onset of symptoms to reperfusion (min)</td>
<td>174 ± 51</td>
<td>174 ± 62</td>
</tr>
<tr>
<td>Door-to-balloon time (min)</td>
<td>43 ± 7</td>
<td>40 ± 6</td>
</tr>
<tr>
<td>Initial TIMI flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>2/3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Successful revascularisation</td>
<td>9</td>
<td>9</td>
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<tr>
<td>TIMI 3 flow post PCI</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Procedural time (min)</td>
<td>55 ± 24</td>
<td>40 ± 18</td>
</tr>
<tr>
<td>Abciximab</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
Feasibility

3 min prolonged procedure before reperfusion

Temp: $34.7 \pm 0.3^\circ\text{C}$ at reperfusion

All patients reached target temp
### Safety

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothermia (n=9)</th>
<th>Control (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day mortality</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Re-infarction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30 day MACE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>VT/VF</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hematoma</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Data are presented as means ± SD for all comparisons.
CHILL-MI
Rapid Endovascular Catheter Core Cooling combined with cold saline as an Adjunct to Percutaneous Coronary Intervention For the Treatment of Acute Myocardial Infarction

A Randomized, Controlled Study of the Use of Central Venous Catheter Core Cooling combined with cold saline as an Adjunct to Percutaneous Coronary Intervention For the Treatment of Acute Myocardial Infarction
Protocol

In the Hypothermia Arm, intravascular cooling (to a target of 33 °C) will begin prior to diagnostic angiography and PCI.

Patients will receive 1-2 liters of cold (4° C) saline solution as needed to achieve target temperature < 35 °C prior to PCI.

After first reperfusion cooling will be maintained for 1 hour. Then the cooling catheter will be removed and the patient will spontaneously rewarm to 37 °C at CCU.

Hypothermia Arm patients will also be treated with meperidine, buspirone and warming blankets to suppress shivering.
FOR ALL PATIENTS

At Baseline:
- CK-MB
- CBC and Chem-7
- Record temperature

During 24-hr peri-PCI Period:
- CK-MB @ 4-, 16-, 24-hrs
- CBC and Chem-7 @ 24-hrs
- Record temperature @ 24-hrs

Also:
- CBC and Chem-7 on Day 2 or Hospital Discharge
- MRI @ day 4+2 days

HYPOTHERMIA ARM

Prior to Dx Angiogram
- Start anti-shivering meds
- Infuse cold saline
- Place cooling catheter
- Initiate cooling to 33C

PCI + Hypothermia
- Record temp at 1st reperfusion

Hypothermia
- 60 min after 1st reperfusion
- Remove cooling cath.

Transfer to CCU
- Spontaneous rewarming

TRANSFER TO CCU

CONTROL ARM

Standard PCI
- Record temp at 1st balloon

TRANSFER TO CCU

Hospital Discharge
- Physical Exam

30 Days Post-PCI
( Window: Day 25 to 45)
- Eval MACE, SAE, revascularization

3 Months Post-PCI
- Eval MACE, SAE, revascularization

6 Months Post-PCI
- Eval MR, MACE, SAE, revasc.
- Subject completes study
Primary Efficacy Endpoint: Cardiac MRI infarct size as a percentage of area at risk at 4±2 days.
Secondary Efficacy Endpoints:

- MRI infarct size (as a percentage of left ventricle size) 4±2 days after PCI.
- The composite of cardiovascular death, heart failure or serious ventricular arrhythmias at hospital discharge.
- Ejection fraction at 6 months (MRI) at 6 month.
- MACE: Death, MI, hospitalization at 6 months.
- NYHA/AHA Cardiac Functional Class at 6 months.
- Angiographic outcomes (TIMI flow grade, TIMI myocardial perfusion grade)
How to succeed with hypothermia for MI

• Rapid cooling early during ischemia and reach target temp before reperfusion
• Combine cold saline with catheter cooling
• Short post-reperfusion cooling (avoiding the need for intensive care unit, avoiding complications in immobilised patient)
• Do everything in the cathlab.
Hypothermia for Cardiogenic shock

- **Normothermia**
  - Ischemia (40 min)
  - Normothermia (38°C)

- **Hypothermia**
  - Induction of hypothermia
  - Ischemia (40 min)
  - Normothermia (38°C) to Hypothermia (33°C)

- **Duration**
  - 4 h
~ 45 min hypothermia to reach < 34°C

No saline to avoid beneficial effects of volume
Survival

Induction of hypothermia

Normothermia: 3/8 survivors

Hypothermia: 8/8 survivors
Hemodynamic parameters

Heart rate (bpm)

Mean arterial pressure (mmHg)

* 3/8 survivors in the normothermia group
Hemodynamic parameters

**Stroke volume (ml)**

- **CO**

**Cardiac output L/min**

- *3/8 survivors in the normothermia group*
Blood gas parameters

Arterial pH

Arterial base excess (mmol/L)

* 3/8 survivors in the normothermia group
Blood gas parameters

Mixed venous saturation (%)

* 3/8 survivors in the normothermia group
Conclusions Cardiogenic shock

Performance of endovascular cooling: ~ 45 min to reach < 34ºC

Mild hypothermia: 1. Reduced acute mortality: 0/8 vs 5/8
   2. Improved hemodynamics
   3. Improved metabolic balance (blood gas)

Results suggest that hypothermia may be an important adjunctive therapy in cardiogenic shock
Conclusion

Hypothermia as an adjunct to PCI for STEMI can:

1. Reduce infarct size
2. Reduce Microvascular obstruction
3. Improve Cardiogenic chock