Monitoring and predicting outcome in cooled patients

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50 years old male
Primary rhythm VF, 45 minutes until ROSC
MCI with LAD occlusion, PTCA
Therapeutic Hypothermia, 33°C at 7 hours
Sepsis at day 3
Epileptic status at day 5

Determination of prognosis after cardiac arrest may be more difficult after introduction of therapeutic hypothermia

Kjetil Sunde, Oona Dunlop, Morten Rostrup, Märten Sandberg, Hans Sjøholm, Dag Jacobsen
Determination of prognosis after cardiac arrest may be more difficult after introduction of therapeutic hypothermia

Kjetil Sunde\textsuperscript{a,*}, Oona Dunlop\textsuperscript{b}, Morten Rostrup\textsuperscript{b}, Märten Sandberg\textsuperscript{c}, Hans Sjøholm\textsuperscript{d}, Dag Jacobsen\textsuperscript{b}

Will this patient survive with good outcome?

Is this worth the effort?

How long should I carry on treatment?
Outcome prediction by emergency physicians

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Predictive Accuracy %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>70</td>
<td>65</td>
<td>69</td>
</tr>
<tr>
<td>1h</td>
<td>80</td>
<td>48</td>
<td>73</td>
</tr>
<tr>
<td>24h</td>
<td>81</td>
<td>58</td>
<td>76</td>
</tr>
</tbody>
</table>

Sensitivity: patients with poor outcome, classified correctly
Specificity: patients with good outcome, classified correctly

Prognostic evaluation of cerebral hypoxia after CPR
Austrian Interdisciplinary Consensus Conference

- 105 different parameters were critically evaluated

- The consensus meeting identified 26 parameters, which allow the prognostic evaluation of cerebral hypoxia

Wien Klin Wochenschr 2002; 114:422-427
Demographic parameters

• Age:
  > 70 years: unfavorable

• Co-morbidity:
  CMP, renal failure: unfavorable
  AP: favorable
Preclinical parameters I

- **Etiology** (non-cardial = unfavorable)
- **ECG** (VF = favorable)
- **Witnessed** = favorable
- **Basic life support** (no BLS = unfavorable)
- **Time intervals**
  - no-flow < 6 min & low-flow < 30 min = in 50% favorable
  - no-flow < 6 min & low-flow > 30 min = in 3% favorable
- **Cumulative epinephrine dose**
  - (independent predictor of poor outcome)

Wien Klin Wochenschr 2002; 114:422-427
Preclinical parameters II

- Pupillary light reflex immediately after ROSC (missing = unfavorable)
- Coughing-swallowing after ROSC (missing = unfavorable)
- GCS after ROSC (GCS < 9 = unfavorable)
- Spontaneous gasping during CPR (favorable)
- Spontaneous gasping after ROSC (favorable)
Clinical parameters

- Glucose levels (high levels unfavorable)
- Serum S-100/NSE (independent predictor of poor outcome)
- Body temperature (> 38° unfavorable)
- GCS (< 5 after 3 d = unfavorable)
- APACHE II (> 20 unfavorable)
- Pupillary light reflex at admission (missing = unfavorable)
- Corneal reflex at day 3 (missing = unfavorable)
- Convulsions and/or myoclonus (= unfavorable)
Electrophysiological parameters

- **EEG 48h after CA**, cave: sedation unfavorable: triphasis potentials, theta coma, alpha coma, low voltage delta, isoelectric EEG

- **Sensory evoked potentials**: with sedation early (N-20) and late (N-70) SEP
  24h: N-70 more predictive than N-20
  48h: absent N-20 potentials = unfavorable


Wien Klin Wochenschr 2002; 114:422-427
Neuroradiology

• CT
edema 3d: unfavorable
ratio gray/white substance basal ganglia < 1.18: unfavorable
• MRI
hyper-intensity in basal ganglia-cerebellum-cortex
 = unfavorable
• SPECT
global cortical hypoperfusion = unfavorable

Prognostic parameters for evaluation of brain function after CPR

Prediction of unfavorable Outcome with **Sensitivity > 90 %**

- Duration of cardiac arrest > 15 min immediately
- Absent pupillary responses > 3 days
- Absent corneal reflexes > 3 days
- Absent motor responses to pain > 3 days
- Glasgow Coma Score < 5 points > 3 days
- Status epilepticus/myoclonus > 3 days
- EEG: isoelectric/burst suppression > 48 h
- Bilateral absent SEP N20 peaks > 24 h

Wien Klin Wochenschr 2002; 114:422-427
**Duration of Cardiac Arrest and Therapeutic Hypothermia**

NoFlow 10 min, CPR 5 min
Hypothermia 34°C 2 hours

<table>
<thead>
<tr>
<th>Best OPC</th>
<th>Control</th>
<th>After ROSC (34°C)</th>
<th>During CPR (34°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Normal</td>
<td></td>
<td>● ● ● ● ● ● ● ●</td>
<td></td>
</tr>
<tr>
<td>2 Moderate Disability</td>
<td>●</td>
<td>● ● ● ●</td>
<td>● ● ● ● ● ● ● ●</td>
</tr>
<tr>
<td>3 Severe Disability</td>
<td>● ● ● ● ● ● ● ●</td>
<td>● ● ● ● ● ● ● ●</td>
<td></td>
</tr>
<tr>
<td>4 Coma</td>
<td>● ● ● ●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Brain Death</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NoFlow 13-17 min, CPR 20 min
Hypothermia 34.5°C 20 hours

<table>
<thead>
<tr>
<th>Outcome</th>
<th>13 min</th>
<th>15 min</th>
<th>17 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPC 1</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPC 2</td>
<td></td>
<td>●●●</td>
<td></td>
</tr>
<tr>
<td>OPC 3</td>
<td></td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>OPC 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPC 5</td>
<td>●</td>
<td>●●●</td>
<td>●</td>
</tr>
<tr>
<td>NO ROSC</td>
<td>●</td>
<td>●●●</td>
<td>●●●</td>
</tr>
</tbody>
</table>

NDS 15 (6; 21) % 45% 58%

 Janata et al. 8th Congress of the ERC
Time Course of Recovery after Cardiac Arrest

Table 2
Times to appearance of consciousness and post-awakening faculties in patients remaining disabled and in patients recovering completely

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients remaining disabled</th>
<th>Patients recovering completely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median time (h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consciousness</td>
<td>I</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>24</td>
</tr>
<tr>
<td>Speech</td>
<td>I</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>13</td>
</tr>
<tr>
<td>Personal necessities</td>
<td>I</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>12</td>
</tr>
</tbody>
</table>

* *P<0.05; **P<0.01; ***P<0.001 (Mann-Whitney) I, Group I, II, Group II.
I, immediate EEG activity
II, no immediate EEG activity

Jorgensen Resuscitation 1999;41:145
Therapeutic Hypothermia Therapy might Interfere with Clinical Neurologic Examination

Duration of Therapy > 35 hours

- Fentanyl
- Midazolam
- Rocuronium
It Might be Rather the „Concomitant“ Medication than the Temperature …

• Isoflurane, but not mild hypothermia, depresses the human pupillary light reflex
  Volunteers, ±35°C, ±isoflorane anesthesia

• Latency of pupillary reflex dilation during general anesthesia
  Volunteers, propofol anesthesia
Change of Midazolam Serum Concentration during Hypothermia

15 brain-injured patients

Fukuoka Resuscitation 2004;60:225
Serum Neuron-Specific Enolase and S-100B Protein in Cardiac Arrest Patients Treated With Hypothermia

Tiainen et al. Stroke 2003;34:2881
Serum Neuron-Specific Enolase and S-100B Protein in Cardiac Arrest Patients Treated With Hypothermia

Tiainen et al. Stroke 2003;34:2881
Serum Neuron-Specific Enolase and S-100B Protein in Cardiac Arrest Patients Treated With Hypothermia

Cut-off with Specificity > 95% was higher in the hypothermia group
Hypothermia might protect brain despite initial neuronal damage

Tiainen et al. Stroke 2003;34:2881
Systematic review of early prediction of poor outcome in anoxic-ischaemic coma

33 studies (n = 4386); 14 parameters (clinical data, EEG, SEP)
Aim: Identification of patients with unfavourable outcome (CPC 4 – 5)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pooled positive-likelihood ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burst-suppr./isoelectric EEG &lt; 7d</td>
<td>9.0</td>
<td>2.5–33.1</td>
</tr>
<tr>
<td>Absent pupillary reactions on day 3</td>
<td>10.5</td>
<td>2.1–52.4</td>
</tr>
<tr>
<td>Bilat. absence SEP N20 peak &lt; 7d</td>
<td>12.0</td>
<td>5.3–27.6</td>
</tr>
<tr>
<td>Absent motor responses to pain, day 3</td>
<td>16.8</td>
<td>3.4 – 84</td>
</tr>
</tbody>
</table>

Conclusion: „SEP most useful method to predict poor outcome“

Zandbergen et al. Lancet 1998; 352:1808
Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia

Rundgren et al. Intensive Care Med. 2006; Epub
Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia

<table>
<thead>
<tr>
<th>aEEG pattern</th>
<th>All patients</th>
<th>CPC 1</th>
<th>CPC 2</th>
<th>CPC 3</th>
<th>CPC 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Suppression-burst</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Alpha-coma</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Flat</td>
<td>24</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td><strong>At normothermia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>20</td>
<td>12</td>
<td>6</td>
<td>2(^a)</td>
<td>–</td>
</tr>
<tr>
<td>Generalised</td>
<td>5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5(^b)</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laterised</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2(^b)</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppression-burst</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2(^b)</td>
</tr>
<tr>
<td>Flat</td>
<td>5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5(^b)</td>
</tr>
</tbody>
</table>

\(^a\) One of two patients died of cardiac failure before leaving hospital.

\(^b\) All patients died in hospital.

Rundgren et al. Intensive Care Med. 2006; Epub
Sensory evoked potentials (SEP)
Elektrophysiological assessment of the afferent sensory pathway in CA survivors

305 comatose patients within 72h after CPR

<table>
<thead>
<tr>
<th>SEP peak</th>
<th>no brain damage</th>
<th>ischemic brain damage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 73</td>
<td>n = 232</td>
</tr>
<tr>
<td>N9 (plexus brachialis)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>N13 (cervical cord)</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>P15 (thalamus)</td>
<td>100%</td>
<td>63%</td>
</tr>
<tr>
<td>N20 (sensory cortex)</td>
<td>100%</td>
<td>59%</td>
</tr>
<tr>
<td>P25 (sensory cortex)</td>
<td>100%</td>
<td>55%</td>
</tr>
<tr>
<td>N35 (cortico-cortical interact.)</td>
<td>98%</td>
<td>45%</td>
</tr>
<tr>
<td>N70 (cortico-cortical interact.)</td>
<td>98%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Sensory evoked potentials (SEP)

Long – latency sensory evoked potentials following cardiac arrest

N70 peak latency cut off: 130ms  
(n = 160)

Sensitivity: 97%  
(correct prediction of unfavorable outcome)

Specificity: 94%  
(correct prediction of favorable outcome)

Time-dependency of sensory evoked potentials in comatose CA survivors

Allow a period of at least 24 hours after CPR for obtaining a reliable prognosis based on SEP

Gendo et al. Intensive Care Med 2001
Hypothermia Does not Alter SEP Amplitude

Surgery for intraocular melanoma with hypothermia + hypotension

Kottenberg et al. Anesthesiology 2003; 98:1112
Hypothermia Does not Alter SEP Amplitude

Kottenberg et al. Anesthesiology 2003; 98:1112
Somatosensory and brainstem auditory evoked potentials in cardiac arrest patients treated with hypothermia

Somatosensory and brainstem auditory evoked potentials in cardiac arrest patients treated with hypothermia

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia (N=30)</th>
<th>Normothermia (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical N13</td>
<td>30 (100%)</td>
<td>30 (100%)</td>
</tr>
<tr>
<td>Cortical N20</td>
<td>27 (90%)</td>
<td>19 (70%)</td>
</tr>
<tr>
<td>CPC 1 and 2</td>
<td>23 (76%)</td>
<td>13 (48%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>75%</td>
<td>80%</td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

SEP 24-28 hours after ROSC

Summary

• Immediately after ROSC outcome prediction is virtually impossible

• Temporal sequence of recovery of brain functions may be delayed by hypothermia

• „All“ comatose patients after CA should be treated by therapeutic hypothermia and appropriate intensive care

• SEP are valuable tool in prognosis of unfavorable outcome