Postanoxic coma: prognosis after therapeutic hypothermia
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Chapter 6

Hypothermia after cardiopulmonary resuscitation prolongs peripheral and central conduction times of somatosensory evoked potentials

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Submitted
Abstract

Objective
To investigate the effect of mild hypothermia on conduction times and amplitudes of median nerve somatosensory evoked potentials (SEP) in patients after cardiopulmonary resuscitation (CPR).

Methods
Patients treated with hypothermia after CPR, who underwent SEP recording during hypothermia and after rewarming, were selected from a prospectively collected database. Latencies and amplitudes of N9 (peripheral conduction time, PCT), N13 and N20 were measured. The central conduction time (CCT) was defined as peak-peak latency N13- N20. Recordings of 25 patients were assessed by a second observer to determine the intraclass correlation coefficient (ICC).

Results
A total of 115 patients were included. Mean body temperature at SEP during hypothermia was 33.1°C (SD 0.8) and after rewarming 37.1°C (SD 0.8). Mean latencies of N9, N13 and N20 and mean CCT were significantly longer during hypothermia. There were no consistent differences in amplitudes. There was an almost perfect ICC for assessment of latencies and amplitudes.

Conclusion
This study shows that PCT and CCT of median nerve SEP are significantly prolonged during treatment with hypothermia after CPR compared with after rewarming. Amplitudes do not differ consistently.
Hypothermia prolongs conduction times of SEP

Introduction

In the last decade, the high reliability of median nerve somatosensory evoked potentials (SEP) in predicting poor outcome in comatose patients after cardiopulmonary resuscitation (CPR) has led to an increased use of this test in the Intensive Care Unit (ICU)\(^1,2\).

An important advantage of SEP is the diminished susceptibility to metabolic changes or sedative drugs compared to other prognosticators, such as neurologic examination or electroencephalography\(^3-5\). Muscle activity and interference of electric devices are known for their negative influence on the noise levels of SEP recording and increase the chance of misinterpretation. Administration of muscle relaxants and turning electric equipment off in order to reduce noise levels < 0.25 μV will improve the interobserver reliability\(^6\).

Another possible pitfall is the effect of deep hypothermia on the SEP responses, which is predominantly investigated in patients during cardiothoracic surgery\(^7-11\). Nowadays, treatment with mild hypothermia (32-34°C) in patients admitted after CPR is part of international guidelines and it is widely implemented in the Netherlands\(^2,12,13\).

Therefore, the aim of this study was to investigate the effect of mild hypothermia on peripheral and central conduction times and amplitudes of median nerve SEP recorded during and after hypothermia treatment in patients after CPR.

Methods

Patients were selected from the prospectively collected data of the “SEP during mild hypothermia after CPR”- and the “Prognosis of postanoxic coma after hypothermia” database\(^14,15\). The research protocol and consent procedures of these prospective multicenter cohort studies were approved by the ethics committees of all collaborating hospitals. Adult patients treated with hypothermia (32-34°C) after a non-traumatic CPR were included. Exclusion criteria were pre-existing diseases with a life expectancy of less than six months, severe disability before CPR, and no obtained informed consent. Informed consent was obtained from a legal representative shortly after the patient’s hospital admission. When the patient regained consciousness and was able to judge the situation properly, informed consent was also obtained from the patient. The present study included patients if a SEP was recorded during hypothermia and after rewarming.
The following data were collected from the databases: age, gender, duration of CPR, time to return of spontaneous circulation (ROSC), presenting rhythm (ventricular fibrillation/ventricular tachycardia versus pulseless electric activity/asystole), hypoxemia as cause of CPR, time from collapse to SEP recording, temperature during SEP recording, use of sedative drugs and neuromuscular blocking agents during SEP recording, and Glasgow Outcome Scale (GOS) after 30 days. Poor outcome was defined as death or vegetative state (GOS 1-2)\(^\text{16}\). Cortical N20 responses of median nerve SEP were recorded with standard procedures. In the study protocol, right and left median nerves were stimulated at the wrist by a bipolar surface electrode with a frequency of 3 to 5 Hz and a stimulus duration of 0.2 ms to produce a thumb twitch. Two sets of at least 512 responses were averaged. Filter band pass was from 3 Hz to 2 kHz or 20 Hz to 2kHz. Electrodes (Ag/AgCl) were placed at Erb’s point (N9), the cervical spine (C5-C7, N13), and CP3 and CP4 respectively, according to the international 10-20 system (N20). Fz or “linked ears” were used as reference. The electrode resistance was kept below 5 kOhm. The SEP after rewarming was performed in patients who remained in a coma after regaining normal body temperature and who were thought to have cleared all sedative drugs and metabolites.

Printed copies from the SEP recordings (left and right; hypothermia and after rewarming) were requested from the hospitals. The recordings were blinded for date and temperature. The curves were assessed by the first author (AB), in case of doubt, curves were discussed with JK. Patients were excluded if the printed copies could not be retrieved. To calculate the intraclass correlation coefficient of assessment of latencies and amplitudes, SEP recordings of 25 randomly selected patients were independently assessed by a second observer (DL).

Latencies (milliseconds, ms) and amplitudes (microvolt, μV) of N9 (peripheral conduction time), N13 and N20 were measured. The central conduction time (CCT) was defined as peak-peak latency N13-N20. The amplitudes of N9 and N13 were measured from baseline to peak. The amplitude of N20 was measured from peak P14 to peak N20. Due to the fact that the recordings were only available on printouts and enlargement of scales was impossible, “invisible” peaks could not reliably be assessed and were therefore scored as undeterminable. In case of too many artifacts, the recording was assessed as undeterminable. The undeterminable results were coded as missing values in the analyses.

Primary outcome was defined as differences in latencies and amplitudes of the different SEP components between hypothermia and after rewarming in the same patient.
Statistical analysis

Patient characteristics were described according to their distribution. Variables were expressed as mean and standard deviation (when normally distributed) or as medians and interquartile ranges (IQR, when not normally distributed). Categorical variables were expressed as percentages (n). Statistical significance was considered to be at $p < 0.05$. When appropriate, statistical uncertainty was expressed by 95% confidence intervals (CIs). Differences of SEP latencies and amplitudes between hypothermia and after rewarming for right-sided and left-sided stimulation were calculated with the dependent t-test or the Wilcoxon signed rank test. Furthermore, the correlation of time to SEP during hypothermia and latencies of N20 was calculated with the Pearson’s correlation coefficient. The intraclass correlation coefficient (ICC) was calculated to determine the interobserver agreement in measurement of latencies and amplitudes, and expressed as the kappa$^{17}$.

Results

A total of 121 patients were included. Six patients were excluded because printed copies of SEP recordings during hypothermia and after rewarming could not be retrieved. Baseline characteristics are presented in Table 1. Ninety-six out of the remaining 115 patients (83%) had a poor outcome at 30 days after CPR. Median time from CPR until recording of SEP during hypothermia was 21 hours (IQR 15-24) and 62 hours (IQR 49-77) until SEP after rewarming. The mean body temperature during SEP recording in the period of hypothermia was 33.1°C (SD 0.8) and after rewarming, 37.1°C (SD 0.8). There was no effect of the time from collapse to SEP during hypothermia on latency of N20 after right-sided ($r\ -0.05$, $p = 0.66$) or after left-sided stimulation ($r\ -0.17$, $p = 0.17$).

SEP latencies were normally distributed and are summarized in Table 2. Mean latencies of N9, N13 and N20 on both sides were significantly longer during hypothermia compared to those measured after rewarming. The mean CCT was significantly longer during hypothermia.

The amplitudes were not normally distributed and are presented in Table 3. Significantly higher amplitudes were measured for the N9 after right-sided stimulation and the N13s on both sides during hypothermia compared to the amplitudes after rewarming. The amplitudes of the N20s did not differ. An example of SEP recordings during hypothermia and after rewarming in the same patient is shown in Figure 1.
### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total, n = 115</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>88 (77)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>65 (13)</td>
</tr>
<tr>
<td>Presenting rhythm, n (%)</td>
<td></td>
</tr>
<tr>
<td>VF/VT</td>
<td>75 (65)</td>
</tr>
<tr>
<td>Non-VF/VT</td>
<td>38 (33)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Duration CPR (min.), median (IQR)</td>
<td>20 (12-30)</td>
</tr>
<tr>
<td>Time to ROSC (min.), median (IQR)</td>
<td>25 (16-40)</td>
</tr>
<tr>
<td>GOS, n (%)</td>
<td></td>
</tr>
<tr>
<td>1 Death</td>
<td>94 (82)</td>
</tr>
<tr>
<td>2 Vegetative state</td>
<td>2 (2)</td>
</tr>
<tr>
<td>3 Severe disability</td>
<td>10 (9)</td>
</tr>
<tr>
<td>4 Moderate disability</td>
<td>6 (5)</td>
</tr>
<tr>
<td>5 Good recovery</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

CPR = cardiopulmonary resuscitation; GOS = Glasgow Outcome Scale; IQR = interquartile range; ROSC = return of spontaneous circulation; SD = standard deviation; VF = ventricular fibrillation; VT = ventricular tachycardia

### Table 2 Latencies of N9, N13, N20 and the central conduction time of the median nerve somatosensory evoked potentials measured during hypothermia and after rewarming in the same patients.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Hypothermia (ms)</th>
<th>Normothermia (ms)</th>
<th>Difference (ms)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N9</td>
<td>RS stimulation</td>
<td>64</td>
<td>13.5 (1.4)</td>
<td>11.6 (1.3)</td>
<td>1.9 (1.7-2.1)</td>
</tr>
<tr>
<td>N9</td>
<td>LS stimulation</td>
<td>64</td>
<td>13.1 (1.6)</td>
<td>11.4 (1.4)</td>
<td>1.8 (1.5-2.0)</td>
</tr>
<tr>
<td>N13</td>
<td>RS stimulation</td>
<td>75</td>
<td>17.8 (1.7)</td>
<td>15.3 (1.5)</td>
<td>2.5 (2.2-2.8)</td>
</tr>
<tr>
<td>N13</td>
<td>LS stimulation</td>
<td>75</td>
<td>17.2 (1.6)</td>
<td>15.1 (1.5)</td>
<td>2.2 (1.9-2.4)</td>
</tr>
<tr>
<td>N20</td>
<td>RS stimulation</td>
<td>57</td>
<td>25.4 (1.9)</td>
<td>22.1 (1.7)</td>
<td>3.3 (2.9-3.7)</td>
</tr>
<tr>
<td>N20</td>
<td>LS stimulation</td>
<td>54</td>
<td>25.3 (2.2)</td>
<td>22.1 (1.9)</td>
<td>3.2 (2.8-3.6)</td>
</tr>
<tr>
<td>CCT</td>
<td>RS stimulation</td>
<td>46</td>
<td>7.5 (0.9)</td>
<td>6.5 (1.0)</td>
<td>1.0 (0.7-1.3)</td>
</tr>
<tr>
<td>CCT</td>
<td>LS stimulation</td>
<td>44</td>
<td>7.9 (1.0)</td>
<td>6.9 (1.0)</td>
<td>1.0 (0.6-1.3)</td>
</tr>
</tbody>
</table>

All values are expressed pairwised as mean values (standard deviation or 95% confidence intervals); p values were calculated with the dependent t-test.

RS = right-sided; LS = left-sided; ms = milliseconds; CCT = central conduction time (latency N20 - N13)
Hypothermia prolongs conduction times of SEP

**Table 3** Amplitudes of N9, N13 and N20 of the median nerve somatosensory evoked potentials measured during hypothermia and after rewarming in the same patient group.

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia (µV)</th>
<th>Normothermia (µV)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N9 RS stimulation</td>
<td>1.3 (0.6-2.1)</td>
<td>1.0 (0.5-1.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>N9 LS stimulation</td>
<td>1.2 (0.6-1.9)</td>
<td>1.1 (0.5-1.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>N13 RS stimulation</td>
<td>1.1 (0.4-1.6)</td>
<td>0.9 (0.3-1.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>N13 LS stimulation</td>
<td>1.1 (0.5-1.8)</td>
<td>0.9 (0.4-1.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>N20 RS stimulation</td>
<td>0.6 (0.4-1.3)</td>
<td>0.8 (0.4-1.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>N20 LS stimulation</td>
<td>0.8 (0.4-1.3)</td>
<td>0.8 (0.4-1.4)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

RS = right-sided; LS = left-sided; µV = microvolt
*number of patients included in the analysis with the Wilcoxon signed rank test
All values are expressed as median values (interquartile range); p values were calculated with the Wilcoxon signed rank test.

The SEPs of 25 patients were assessed independently by two observers. The two observers disagreed in 11% of the latency and 12% of the amplitude components if the component was determinable or not. Overall, there was an almost perfect agreement for assessment of latencies, ICC 0.998 (95%CI 0.997-0.999), as well as for amplitudes, 0.94 (95%CI 0.90-0.96)\(^1\).\(^7\)

**Discussion**

This study showed that peripheral and central conduction times of median nerve SEP were prolonged during treatment with hypothermia after CPR compared with recordings after rewarming in the same patient. Furthermore, the amplitudes of N13 were significantly higher during hypothermia. Other amplitudes did not differ consistently between hypothermia and after rewarming.

Median nerve SEP is used for prognostication in comatose patients after CPR\(^1\),\(^2\). Bilaterally absent N20 cortical responses after treatment with hypothermia were found to have a specificity of 100% and therefore an FPR of 0\(^15\),\(^18\)-\(^20\). However, Leithner et al. reported one patient, treated with hypothermia after CPR, who recovered despite absent cortical N20 responses after rewarming\(^21\). Therefore, it is important to elucidate the influence of treatment with hypothermia after CPR on SEP recordings.
Figure 1 Example of somatosensory evoked potentials recordings of the median nerve in the same patient during treatment with hypothermia after cardiopulmonary resuscitation and after rewarming.

Somatosensory evoked potentials recordings of the median nerve after right-sided stimulation during hypothermia (left) and after rewarming (right). From top to bottom: N9 (Erb’s point), N13 (cervical spine), ipsilateral somatosensory cortex (CP4), contralateral somatosensory cortex (CP3), CP3-CP4. Latencies during hypothermia: N9 15.6 ms, N13 20.9 ms, N20 28.7 ms; Latencies after rewarming: N9 12.4 ms, N13 16.8 ms, N20 22.4 ms.

In the original prospective cohort studies “SEP during mild hypothermia after CPR” and “Prognosis of postanoxic coma after hypothermia”, poor outcome after 30 days was found in 66% and 49%, respectively, which is similar to other studies in patients treated with hypothermia after CPR. In the patients selected for this study, 83% had a poor outcome after 30 days. This difference is caused by selection of the patients, as a SEP after rewarming was only performed in patients who, after regaining normal body temperature and clearing of sedative drugs and metabolites, remained in a coma.

Hypothermia is known to prolong the latency of SEP, due to slowing of nerve conduction along axons and synaptic delay, caused by decreased membrane potential. At lower temperatures conduction velocity in the median nerve has been reported to decrease about 2 m/s/°C. Most literature available describes the influence of deep hypothermia (11.4-30.1°C) on median nerve SEP when performed during hypothermic cardiopulmonary resuscitation.
Hypothermia prolongs conduction times of SEP bypass\textsuperscript{7-11,25}. The cortical N20 response disappears with temperatures between 14.5 and 29.6°C and latencies of peripheral and central components are prolonged\textsuperscript{7-11,25,26}. There is one previous study on the influence of treatment with hypothermia after CPR on SEP latencies and amplitudes. Tiainen et al. found significant longer latencies of the N13 and N20 in the patient group treated with hypothermia (33.0°C) after CPR, compared to a patient group not treated with hypothermia (37.5°C) after CPR\textsuperscript{27}. Also the CCT was significantly longer during hypothermia and the nerve conduction velocity was significantly lower in the hypothermia group (46.2 m/s vs. 53.5 m/s). This study confirmed these results in a larger group of patients. Furthermore, in this study latencies during hypothermia and after rewarming were compared within the same patient, which excluded influences of patient’s height or comorbidity, such as diabetes mellitus. Gendo et al. have shown that latencies of the cortical N20 response decreased about 2 ms within 24 hours after CPR\textsuperscript{28}. In our study, the median time to SEP during hypothermia was 21 hours and there was no influence of time from collapse to SEP on N20 latencies.

Normal values of median nerve SEP latencies have been established in 50 subjects and were: 9.7 ms (SD 0.8) for N9, 13.5 ms for N13 (SD 0.9), and 19.0 ms (SD 1.0) for N20\textsuperscript{29}. Tiainen et al. found N20 latencies of 20.5-21.0 ms in the patient group not treated with hypothermia after CPR, which is within the range of normal values\textsuperscript{27}. However, in our study, N20 latencies after rewarming were at 3 SD above the normal values during normothermia. A possible explanation for this prolongation could be the ongoing influence of sedative drugs. In the Netherlands, an opioid in combination with midazolam or propofol are often administered during hypothermia and their metabolism is diminished due to lower temperatures\textsuperscript{2,30}. However, the effects of these drugs on SEP recordings are considered to be minimal and are related to drug concentrations and maximal during peak concentrations after bolus delivery\textsuperscript{3,5,31,32}. Another explanation could be that the selected patients in this study had more extensive brain damage leading to prolongation of latencies, as they were still in a coma after hypothermia treatment and subsequent rewarming.

Studies on the influence of hypothermia on the amplitudes of SEP components have presented conflicting results, but most pointed towards an increase of the N9 amplitude, and a decrease in amplitude of the N13 and N20 amplitude with decreasing temperatures\textsuperscript{7,8,11,26}. Tiainen et al. did not find differences in amplitudes of the N20 responses between patients treated with hypothermia after CPR and patients not treated with hypothermia\textsuperscript{27}. In the present study, higher amplitudes were measured for N13 during hypothermia on both sides and for N9 only after right-sided stimulation. A possible
explanation could be that the hypothermia was not deep enough to cause consistent results.

There is only one study on interobserver variation in interpretation of SEPs as absent or present, which showed a substantial interobserver agreement ($k = 0.74$), when noise levels were low (< 0.25 μV)\textsuperscript{6}. We found an almost perfect agreement between two observers for measurement of latencies and amplitudes.

An important limitation of this study is that available printed copies of the SEP curves were used for the assessment. This applies especially to the assessment of amplitudes. As different scales were used between the hospitals, these values might be less reliable. The assessment should ideally have been done on the monitor of the system used for recording, but this was not possible.

In conclusion, this study showed that peripheral and central conduction times of median nerve SEP were prolonged during treatment with hypothermia after CPR compared with recordings after rewarming in the same patient. Furthermore, N20 latencies after rewarming remained longer in this patient group compared to the normal population. This is an important pitfall in assessing median nerve SEP in patients after CPR.

**Acknowledgments**

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**References**

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