Postanoxic coma: prognosis after therapeutic hypothermia
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Chapter 5

Prognosis of coma after therapeutic hypothermia: a prospective cohort study

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Abstract

Objective
This study was designed to establish the reliability of neurologic examination, neuron-specific enolase (NSE), and median nerve somatosensory-evoked potentials (SEPs) to predict poor outcome in patients treated with mild hypothermia after cardiopulmonary resuscitation (CPR).

Methods
This multicenter prospective cohort study included adult comatose patients admitted to the intensive care unit (ICU) after CPR and treated with hypothermia (32–34°C). False-positive rates (FPRs 1 - specificity) with their 95% confidence intervals (CIs) were calculated for pupillary light responses, corneal reflexes, and motor scores 72 hours after CPR; NSE levels at admission, 12 hours after reaching target temperature, and 36 hours and 48 hours after collapse; and SEPs during hypothermia and after rewarming. The primary outcome was poor outcome, defined as death, vegetative state, or severe disability (Glasgow Outcome Scale 1–3) after 6 months.

Results
Of 391 patients included, 53% had a poor outcome. Absent pupillary light responses (FPR 1; 95% Cl, 0–7) or absent corneal reflexes (FPR 4; 95% Cl, 1–13) 72 hours after CPR, and absent SEPs during hypothermia (FPR 3; 95% Cl, 1–7) and after rewarming (FPR 0; 95% Cl, 0–18) were reliable predictors. Motor scores 72 hours after CPR (FPR 10; 95% Cl, 6–16) and NSE levels were not.

Interpretation
In patients with persisting coma after CPR and therapeutic hypothermia, use of motor score or NSE, as recommended in current guidelines, could possibly lead to inappropriate withdrawal of treatment. Poor outcomes can reliably be predicted by testing brainstem reflexes 72 hours after CPR and performing SEP.
Introduction

The prediction of neurologic outcome in patients who remained in a coma after cardiopulmonary resuscitation (CPR) has been investigated extensively. The findings were summarized in a practice parameter of the American Academy of Neurology (AAN), published in 20061-4. The algorithm for the prediction of poor outcome presented in this practice parameter had to be based on data collected in patients who were not treated with mild hypothermia after admission. However, this treatment has become standard care in many countries and is part of all guidelines5,6. Therefore, new data are needed to predict the outcome in patients who remain in a coma after hypothermia treatment. The predictive value of the standard diagnostic methods might well be different in these patients because of the modified natural history of the condition or the use of sedative drugs administered during cooling7,8. Several single-center series have been published, suggesting that the 2006 algorithm, indeed, cannot be used anymore9-13. The aim of our multicenter prospective cohort study was to investigate the reliability of diagnostic methods such as neurologic examination, serum concentrations of neuron-specific enolase (NSE), and median nerve somatosensory-evoked potentials (SEPs) to predict poor outcome in patients treated with mild hypothermia after in- and out-of-hospital CPR.

Patients and Methods

Patient Cohort and Procedures

This multicenter prospective cohort study was performed in 10 Dutch mixed medical-surgical intensive care units (ICUs) of 1 university-affiliated and 9 non–university-affiliated hospitals. The cohort included adult patients, admitted to the ICU, who remained in a coma after CPR, and who were treated with mild hypothermia. Exclusion criteria were preexisting diseases with a life expectancy of less than 6 months, severe disability before CPR, CPR due to hypovolemic shock, and absence of informed consent. The cooperating hospitals were not obligated to keep records of patients admitted after CPR who were not eligible for the study. Included patients were treated with hypothermia (32°C–34°C) in combination with sedative drugs in accordance with the local hospital’s protocol. Sedative drugs used were midazolam, propofol, and opiates. Patients who died during hypothermia treatment were not excluded from analyses.

The research protocol and consent procedures were approved by the ethics committees of all collaborating hospitals. 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.

Neurologic examination, consisting of the Glasgow Coma Scale (GCS) score and brainstem reflexes, was performed 48 and 72 hours after CPR by the attending ICU physician or a neurologist.

Serum samples for determination of NSE levels were drawn on ICU admission, 12 hours after reaching the target temperature of 32°C to 34°C, and 36 and 48 hours after collapse. Samples were stored at -20°C for later analysis in a central laboratory (Radboud University Nijmegen Medical Center), using monoclonal 2-sided single-incubation immunoluminometric assay with a Liaison automated analyzer (DiaSorin, Saluggia, Italy). Results of serum NSE levels were not available to the treating physicians.

Cortical N20 responses of median nerve SEPs were recorded with standard procedures during hypothermia\(^\text{14}\). A second SEP 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. Recordings were assessed by the local clinical neurophysiologists and documented as “absent” (bilaterally absent cortical N20 responses after left and right median nerve stimulation, in the presence of a cervical potential), “present” (cortical N20 response present on at least 1 side), or “undeterminable” (technically insufficient recording). Undeterminable SEP results were considered as present. The results of the SEPs recorded during hypothermia were not disclosed to the treating physicians to avoid any influence of the test results on treatment decisions. If a second SEP was performed after the patient had regained a normal body temperature, the results were disclosed to the treating physicians and treatment decisions were recorded.

Neurologic outcome was assessed with the Glasgow Outcome Scale (GOS), 1 week, 1 month, and 6 months after admission via a telephone interview with the patient or a legal representative\(^\text{15}\). The primary outcome of the study was poor outcome, defined as death, vegetative state, or severe disability after 6 months (GOS 1–3). Secondary outcomes were death or vegetative state (GOS 1–2) 1 month after CPR and mortality after 1 week, 1 month, and 6 months. The study protocol contained no guidelines for withholding or withdrawing treatment. These decisions were at the discretion of the treating physician. In the Netherlands the results of SEP in normothermic patients are used in most hospitals to predict prognosis and absent cortical responses are a reason to withdraw treatment\(^\text{8}\).
Additional data collected were gender, age, in- or out-of-hospital cardiac arrest, presenting rhythm (ventricular fibrillation [VF] or ventricular tachycardia [VT] vs asystole or pulseless electrical activity [PEA]), time from collapse to bystander basic life support, time from collapse to return of spontaneous circulation, previous medical history as described in the patient’s chart, duration of hypothermia, time of discontinuation of sedative drugs, use of sedative drugs or neuromuscular blocking agents during SEP, use of sedative drugs during neurologic examination, and reasons for limiting or withdrawing care. Scored reasons for treatment restrictions were divided into neurologic (options: neurologic examination, SEP result, or other neurologic reasons) and non-neurologic (options: cardiac/hemodynamic complications or other reasons).

Statistical Analyses
Patient characteristics were described according to their distribution. Variables were expressed as mean and standard deviation (continuous and normally distributed) or as medians and interquartile ranges (not normally distributed). Categorical variables were expressed as percentages (n). Differences between categorical variables were calculated by the χ² test. The GOS was used as the reference variable for a patient’s outcome. The percentages of correct identification of patients with a poor outcome were expressed as sensitivity and specificity. The false-positive rate (FPR) was calculated as 1 minus specificity. The FPR is considered a single proportion. Due to the low observed proportions, 95% confidence intervals (CIs) were calculated using the recommended method of the Confidence Interval Analysis software. Sensitivity, specificity, and FPR were calculated for all predictors of neurologic outcome (72 hours: motor score, pupillary light responses, corneal reflexes; NSE at admission, during hypothermia, and 36 and 48 hours after collapse; SEP during hypothermia and normothermia). Area under the receiver operating characteristic (ROC) curve was calculated for the NSE in relation to the GOS after 6 months. Statistical significance was considered to be at p < 0.05. When appropriate, statistical uncertainty was expressed by their 95% CIs. All analyses were performed with SPSS 18.1.

Results
Between December 2007 and August 2009, 391 patients were included. Characteristics of included patients are presented in Table 1. Outcome data after 1 and 6 months are presented in Table 2. After 6 months, 199 patients (51%) had died, 149 (75%) of whom died in the first week after admission. For these 149 patients, treatment was withdrawn in 62% and restricted in 26% (“do not resuscitate” orders and more extended limitations).
### Table 1 Characteristics of the 391 patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>64 (13.4)</td>
</tr>
<tr>
<td>Gender, male % (n)</td>
<td>73.1 (286)</td>
</tr>
<tr>
<td>Presenting rhythm, % (n)</td>
<td></td>
</tr>
<tr>
<td>VF or VT</td>
<td>76.5 (299)</td>
</tr>
<tr>
<td>Asystole or PEA</td>
<td>21.5 (84)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Location of CPR, % (n)</td>
<td></td>
</tr>
<tr>
<td>OHCA</td>
<td>86.7 (339)</td>
</tr>
<tr>
<td>IHCA</td>
<td>12.3 (48)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Time collapse to bystander BLS, median (IQR)</td>
<td>2 min (0-5)</td>
</tr>
<tr>
<td>Time collapse to ROSC, median (IQR)</td>
<td>20 min (11-30)</td>
</tr>
<tr>
<td>Time from CPR to ≤ 34°C, median (IQR)</td>
<td>315 min (218-450)</td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21.5</td>
</tr>
<tr>
<td>Heart failure</td>
<td>16.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13.6</td>
</tr>
<tr>
<td>COPD</td>
<td>10.5</td>
</tr>
</tbody>
</table>

BLS = basic life support; COPD = chronic obstructive pulmonary disease; CPR = cardiopulmonary resuscitation; IHCA = in-hospital cardiac arrest; IQR = interquartile range; OHCA = out-of-hospital cardiac arrest; PEA = pulseless electrical activity; ROSC = return of spontaneous circulation; SD = standard deviation; VF = ventricular fibrillation; VT = ventricular tachycardia.

Poor outcome was found in 208 patients (53%) of the complete group after 6 months. Seventy-two percent of the patients who recovered had a good recovery. In patients who were admitted after out-of-hospital cardiac arrest, the percentage of patients with poor outcome was lower (52%) compared to admittance after in-hospital cardiac arrest (75%), a difference of -23% (p < 0.003). Patients with asystole or PEA as the presenting heart rhythm had a higher rate of poor outcome (83%) when compared with patients with VF/VT (47%, difference of -37%, p < 0.001).
Table 2 Outcomes

<table>
<thead>
<tr>
<th>Glasgow Outcome Scale, n (%)</th>
<th>1 month</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>187 (48)</td>
<td>199 (51)</td>
</tr>
<tr>
<td>Vegetative state</td>
<td>3 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Severe disability</td>
<td>40 (10)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>121 (31)</td>
<td>49 (12)</td>
</tr>
<tr>
<td>Good recovery</td>
<td>35 (9)</td>
<td>124 (32)</td>
</tr>
<tr>
<td>Missing values</td>
<td>5 (1)</td>
<td>10 (3)</td>
</tr>
</tbody>
</table>

Table 3 presents the results of the different diagnostic tools to predict poor outcome after 6 months. For several reasons not all diagnostic methods were performed at all time points in all patients. Some patients died early after admission, so neurologic examination was not done at 72 hours and NSE samples were not taken after 48 hours. SEPs during hypothermia were not obtained outside office hours and many patients awoke after sedative drugs wore off, which made a second SEP unnecessary. Absent pupillary light responses and corneal reflexes were found in a small percentage of patients, 11% and 18%, respectively, but were actually a reliable test for outcome prediction (FPR 1 and FPR 4). Absent SEPs during hypothermia were found in 16% (43/263) of the recordings. Three patients of this group recovered to a good outcome. For a post hoc assessment, the original recordings were obtained and the traces were mixed with 10 other arbitrarily chosen SEP traces from patients after CPR. All 13 recordings were assessed by 2 blinded experienced neurophysiologists. They concluded that the 3 SEP recordings were undeterminable because there was too much noise in the registration. Correction of the results after this reassessment led to a FPR of 0 (95% CI, 0–3) for the SEP during hypothermia.

In 100 patients, SEPs were performed both during hypothermia and normothermia. In 85 patients, the results on both occasions were identical (20 absent, 65 not absent). In 2 patients SEPs were absent during hypothermia, but not absent during normothermia. In 13 patients SEPs were not absent during hypothermia, but absent during normothermia.
Table 3  Prediction of poor outcome after 6 months

<table>
<thead>
<tr>
<th>Test</th>
<th>Patients tested, n</th>
<th>Positive test result, n (%)</th>
<th>Positive test result and good outcome, n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 h motor score 1 or 2</td>
<td>284</td>
<td>112 (39)</td>
<td>16</td>
<td>74 (66-81)</td>
<td>90 (84-94)</td>
<td>10 (6-16)</td>
</tr>
<tr>
<td>72 h absent pupillary light responses</td>
<td>196</td>
<td>22 (11)</td>
<td>1</td>
<td>18 (12-26)</td>
<td>99 (93-100)</td>
<td>1 (0-7)</td>
</tr>
<tr>
<td>72 h absent corneal reflexes</td>
<td>130</td>
<td>23 (18)</td>
<td>2</td>
<td>26 (18-37)</td>
<td>96 (87-99)</td>
<td>4 (1-13)</td>
</tr>
<tr>
<td>Admission NSE &gt;33 μg/L</td>
<td>361</td>
<td>57 (16)</td>
<td>16</td>
<td>21 (15-27)</td>
<td>90 (84-94)</td>
<td>10 (6-16)</td>
</tr>
<tr>
<td>12 h hypothermia NSE &gt;33 μg/L</td>
<td>358</td>
<td>77 (22)</td>
<td>16</td>
<td>32 (26-39)</td>
<td>90 (85-94)</td>
<td>10 (6-15)</td>
</tr>
<tr>
<td>36 h NSE &gt;33 μg/L</td>
<td>334</td>
<td>100 (30)</td>
<td>14</td>
<td>50 (43-58)</td>
<td>91 (86-95)</td>
<td>9 (5-14)</td>
</tr>
<tr>
<td>48 h NSE &gt;33 μg/L</td>
<td>310</td>
<td>99 (32)</td>
<td>10</td>
<td>56 (49-64)</td>
<td>93 (88-96)</td>
<td>7 (4-12)</td>
</tr>
<tr>
<td>Absent N20s SEP hypothermia</td>
<td>263</td>
<td>43 (16)</td>
<td>3</td>
<td>28 (21-36)</td>
<td>98 (93-99)</td>
<td>3 (1-7)</td>
</tr>
<tr>
<td>Absent N20s SEP normothermia</td>
<td>128</td>
<td>42 (33)</td>
<td>0</td>
<td>38 (30-48)</td>
<td>100 (82-100)</td>
<td>0 (0-18)</td>
</tr>
</tbody>
</table>

All values are expressed as percentages with their 95% CIs.
CI = confidence interval; CPR = cardiopulmonary resuscitation; FPR = false-positive rate; NSE = neuron-specific enolase; SEP = somatosensory-evoked potential.
Information about treatment limitations was available from 42 patients in whom an absent SEP was found after rewarming. In 33 patients (79%) treatment was withdrawn and in 7 patients treatment was limited (“do not resuscitate”). All patients died, including the 2 patients in whom no treatment limitations were implemented.

The figure presents the ROC curves of the NSE results at the different time points. The NSE levels taken 48 hours after collapse showed the largest area under the curve of 0.82 (95% CI, 0.77–0.86), which is considered a “good” diagnostic accuracy. The optimal cutoff value of NSE after 48 hours was 58.3 µg/liter with a specificity of 93% (sensitivity 27%); levels >81.8 µg/liter yielded a specificity of 100% (sensitivity 18%).

![ROC curve of NSE levels. X-axis: 1-Specificity; Y-axis: Sensitivity. NSE-curve AUC (95% CI). Curve A, NSE I, 0.59 (0.52–0.65). Curve B, NSE II, 0.65 (0.58–0.71). Curve C, NSE III, 0.77 (0.72–0.83). Curve D, NSE IV, 0.82 (0.77–0.86). AUC = area under the ROC curve; CI = confidence interval; NSE = neuron-specific enolase; NSE I = admission NSE; NSE II = 12-hour hypothermia NSE; NSE III = 36-hour NSE; NSE IV = 48-hour NSE; ROC = receiver operating characteristic.](image)

**Discussion**

The results of this study show that absent pupillary light responses or absent corneal reflexes 72 hours after CPR or bilaterally absent cortical N20 responses in SEPs are reliable to predict a poor outcome in patients who are treated with mild hypothermia after CPR.
Study Population
Fifty-three percent of the patients in this study had a poor outcome, which is comparable to other reports on patients treated with hypothermia after CPR. In recent single-center studies by Rossetti and colleagues (n = 111) and Samaniego and colleagues (n = 53), 77% and 60% of patients, respectively, treated with hypothermia after CPR had a poor outcome\textsuperscript{11,12}. From 975 patients in the Hypothermia Registry, 54% showed a poor outcome (death, vegetative state, or severe disability) and in the 2 original studies on the effect of hypothermia poor outcome was found in 45% and 49%, respectively\textsuperscript{20-22}. These different outcome figures may be explained by different inclusion criteria for treatment with hypothermia. The original hypothermia studies used very strict inclusion criteria, whereas hypothermia treatment is currently used in a less restricted group of patients\textsuperscript{8,20}. In our study, inclusion bias may also have had a role. Physicians may have excluded patients who were regarded, for whatever reason, to have a very poor prognosis. Because we did not collect data on excluded patients, we cannot corroborate this assumption.

Neurologic Examination
Neurologic examination can be regarded as the foundation of clinical assessment and is always done as a first test in ICU patients who are expected to wake up after CPR. Absent pupillary light responses or corneal reflexes are found in a small number of patients 72 hours after CPR, but they have been known to be reliable predictors of poor outcome\textsuperscript{4}. This study confirms these findings in patients after hypothermia. Recently published single-center studies of patients treated with hypothermia after CPR and examined on day 3 to day 5 reported a 100% mortality in 34 of 222 patients with absent pupillary light responses\textsuperscript{10,12,13,23}. In 44 of 224 patients with absent corneal reflexes, 1 patient survived with a good neurologic outcome after 3 months. Furthermore, Rossetti and colleagues described data on 47 of 111 patients with at least 1 absent brainstem reflex (pupillary light responses, corneal reflexes, or oculocephalic reflex), of whom 2 had a good neurologic outcome\textsuperscript{11}. However, these patients were examined between 36 and 72 hours after CPR. Studies in patients not treated with hypothermia showed that a motor score no better than extension 72 hours after CPR was a good predictor of poor outcome and this diagnostic test was incorporated into the AAN practice parameter\textsuperscript{1,3,4}. Recent findings raised doubts about the reliability of the motor score in patients treated with hypothermia\textsuperscript{10-12}. In 357 patients examined at 36 hours up to day 5 after CPR and treated with hypothermia, 146 had a motor response no better than extension\textsuperscript{10-13,23}. The follow-up period varied between the studies. One of the surviving patients died during admission, 4 patients survived to hospital discharge, and 7 patients had a good neurologic outcome after at least 3 months. Based on these findings, combined with the FPR of 10 (95% CI, 6–16) we have found, we conclude that the motor score at 72 hours should no longer be
used as a predictor in daily clinical practice. A possible explanation for this decrease in reliability of the motor score is the use of sedative drugs during hypothermia and the accompanying decrease in metabolism. Poor motor scores after longer time intervals might still be predictive of poor outcome, but studies so far have not collected test results after 72 to 120 hours.

NSE
Although a systematic review suggested that an NSE serum level of >33 μg/liter is a reliable predictor in patients after CPR, data on several patients with good outcomes despite much higher NSE levels have since been reported. This can probably be explained by different laboratory methods used to determine NSE levels and other clinical factors such as hemolysis, which can lead to high NSE levels unrelated to brain damage. Data on NSE levels after hypothermia are again conflicting. Rundgren and colleagues reported NSE levels >28 μg/liter to be a reliable predictor, but Steffen and colleagues found that only NSE levels as high as 79 μg/liter had a 100% specificity. Samaniego and colleagues and Fugate and colleagues reported that 53 of 118 patients had NSE levels >33 μg/liter on days 1 to 3; 12 survived up to hospital discharge and 4 more patients had a good neurologic outcome (GOS 3–5) after 3 months. The results of our study show that an NSE level >33 μg/liter does not reliably predict poor outcome after treatment with hypothermia and substantiates the much higher level of approximately 80 μg/liter to be a better choice.

SEPs
Bilaterally absent cortical N20 responses after treatment with hypothermia were found in this and other studies to have a specificity of 100% and therefore an FPR of 0. These encouraging results could easily lead to the impression that SEP is a perfect test, but Leithner and colleagues published a case report of a patient who recovered despite absent cortical N20 responses after treatment with hypothermia. Zandbergen and colleagues already pointed out the dangers of interobserver variability. Reducing the noise caused by technical equipment (eg, cooling devices, ventilator, electrical bed) in the ICU environment or muscle activity (by administration of neuromuscular junction blocking agents) is important. In case of uncertainty about the recordings, the clinician should assess the results as “undeterminable.” Our results suggest that SEP during hypothermia is a reliable predictor. This supports the results of previous studies, which described a poor outcome in 16 patients (of a total group of 107) with an absent SEP during hypothermia after CPR. Whether SEP during hypothermia will be used in daily clinical practice remains questionable because treatment consequences during hypothermia will be limited. However, it could be used in a subset of patients to be informed about the
prognosis early during the ICU admission and prepare family members for the likely poor outcome.

Our findings and those of other investigators should lead to changes in guidelines, especially because methods currently recommended are based on studies performed before the implementation of hypothermia. Some of these recommended methods are no longer reliable and could lead to incorrect treatment withdrawal. Although the FPRs of absent pupillary light responses, absent corneal reflexes, and absent SEPs suggest a robust reliability, physicians should realize that the CIs are wide, which leads to uncertainty. In daily clinical practice, decisions about prognostication in the individual patient should not be based on 1 test but rather on the full clinical condition.

**Self-Fulfilling Prophecy**

A well-known problem with studies investigating the reliability of diagnostic methods to predict a poor prognosis is the so-called self-fulfilling prophecy. The tendency to restrict treatment selectively in patients with characteristics presumed to predict poor outcome may lead to the false conclusion that such characteristics are indeed good predictors of poor outcome. Symptoms and signs “known” to be related to a poor outcome will lead to treatment restrictions and therefore will prove to be good predictors, as the treatment restriction in itself will lead to the poor outcome. In the ideal study, treatment should not be limited or withdrawn in any patient included in the study, but for ethical and financial reasons such a study is impossible to conduct in daily clinical practice. In our study, results of NSE levels and SEPs during hypothermia were not disclosed to the treating physicians. However, results of neurologic examination and SEPs after rewarming were disclosed and especially the SEP results led to limitation or withdrawal of treatment in a large percentage of patients with absent SEPs. Given the 79% withdrawal after absent SEPs after patients regained normal body temperature, we cannot conclude with complete certainty that this test is absolutely reliable to predict a poor outcome.

In conclusion, in patients with persisting coma after CPR and treatment with hypothermia, motor scores 72 hours after CPR, and serum NSE levels are too unreliable for outcome prediction. Poor outcome can reliably be predicted with: (1) absent pupillary light responses or absent corneal reflexes 72 hours after CPR, or (2) bilateral absence of cortical N20 responses of the median nerve SEP. Based on the results of the SEP after rewarming, decisions about treatment limitations were made, which potentially have led to a self-fulfilling prophecy. Physicians assessing SEP results should be aware of the major consequences of inaccurate decisions when recordings are hampered by ICU noise.
Acknowledgments

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References