Continuous Amplitude-Integrated Electroencephalographic Monitoring is a Useful Prognostic Tool for Hypothermia-Treated Cardiac Arrest Patients

Running title: Oh et al.; aEEG monitoring in cardiac arrest patients receiving TH

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Abstract

Background—Modern treatments have improved the survival rate following cardiac arrest, but prognostication remains a challenge. We examined the prognostic value of continuous electroencephalography according to time by performing amplitude-integrated electroencephalography on cardiac arrest patients receiving therapeutic hypothermia.

Methods and Results—We prospectively studied 130 comatose patients treated with hypothermia from September 2010 to April 2013. We evaluated the time to normal trace (TTNT) as a neurological outcome predictor and determined the prognostic value of burst suppression (BS) and status epilepticus (SE), with a particular focus on their time of occurrence. Fifty-five patients exhibited a cerebral performance category score of 1-2. The area under the curve for TTNT was 0.97 (95% CI=0.92–0.99), and the sensitivity and specificity of TTNT<24 h after resuscitation as a threshold for predicting good neurological outcome were 94.6% (95% CI=84.9%–98.9%) and 90.7% (95% CI=81.7%–96.2%), respectively. The threshold displaying 100% specificity for predicting poor neurological outcome was TTNT>36 h. BS and SE predicted poor neurological outcome (positive predictive value of 98.3% and 96.4%, respectively). The combination of these factors predicted a negative outcome at a median of 6.2 h after resuscitation (sensitivity and specificity of 92.0% and 96.4%, respectively).

Conclusions—A TTNT<24 h was associated with good neurological outcome. The lack of normal trace development within 36 h, SE and BS were predictors of poor outcome. The combination of these negative predictors may improve their prognostic performance at an earlier stage.

Key words: heart arrest, hypothermia, EEG, prognosis
Since therapeutic hypothermia (TH) was shown to effectively improve the neurological outcome of comatose cardiac arrest survivors,\textsuperscript{1,2} TH has become the standard of care for a subset of these patients.\textsuperscript{3} However, the range of neurological outcomes remains wide, and prognostication has become more complex.\textsuperscript{4} Currently, neurological outcome prediction in these patients has primarily focused on end-of-life decisions, such as the withdrawal of life-sustaining therapies (LST),\textsuperscript{5} and such prognostication should be delayed beyond the previously recommended 72 h after cardiac arrest.\textsuperscript{6} However, early positive prognostication during the first few hours after the return of spontaneous circulation (ROSC) is important for treating physicians when counseling families and making appropriate treatment decisions, although not when deciding whether to withhold or withdraw LST because of a perceived poor neurological prognosis. The importance of the timing of the neurological assessment for prognostication is related to the earliest time at which the brain structures can recover function to enable reliable clinical assessment.\textsuperscript{7} Therefore, a good predictor should be based on a test that continuously reflects the status of the brain.

Following transient cerebral ischemia, a complex series of pathophysiological events associated with neuronal recovery can be observed via continuous electroencephalographic (EEG; cEEG) monitoring over time.\textsuperscript{8,9} The evolution of EEG patterns may provide clinically relevant information regarding the recovery from post-anoxic coma. In 2010, the American Heart Association published guidelines for the care of these survivors and recommended that EEG should be performed, promptly interpreted, and monitored frequently or continuously in comatose patients after ROSC.\textsuperscript{3} cEEG is a non-invasive technique that can be used to monitor the post-ischemic brain after cardiac arrest. However, early cEEG monitoring in these patients has remained challenging because it requires serial surveillance by experienced specialists, who are often unavailable or expensive. Amplitude-integrated electroencephalography (aEEG)
provides a simplified and, therefore, more readily available brain function monitoring tool for perinatal hypoxic-ischemic encephalopathy in neonates and cardiac arrest in adults. In neonates, the time required after birth for the aEEG to recover to a normal background pattern was the best predictor of poor neurological outcome, and all infants who did not recover a normal background pattern by 36–48 h either died or survived with severe disability. Regarding aEEG in adult patients undergoing TH, a continuous pattern at registration and at normothermia was associated with good neurological outcome, and burst suppression (BS) or status epilepticus (SE) during the normothermia period indicated poor neurological outcome.

The present study aimed to assess whether the time from ROSC to a normal trace (TTNT), as measured via continuous aEEG monitoring, represents a neurological outcome predictor for TH-treated adult cardiac arrest patients. The second aim was to determine the association between malignant aEEG patterns and poor neurological outcome, with a particular focus on the time of the occurrence of these patterns.

Methods

Study design and patients

This was a prospective observational study of TH-treated adult cardiac arrest patients at a single tertiary hospital from September 2010 to April 2013. During this period, all unconscious adult (age >19 years) patients receiving successful resuscitation were considered eligible for TH, and all TH-treated patients were monitored via aEEG. This study included consecutive patients with TH, but the patients were excluded if (1) they died within 72 h after cardiac arrest, (2) their cardiac arrest occurred as a result of spontaneous or traumatic brain injury, or (3) they had a known history of neurological diseases, such as epilepsy.
This study was approved by the Institutional Review Board of Seoul St. Mary’s Hospital. Informed consent from each patient’s next of kin was obtained; subsequently, if the patient recovered consciousness, consent was re-obtained from the patient.

**Therapeutic hypothermia protocol**

All patients who were resuscitated were considered eligible for TH at 33°C for 24 h according to the current recommendations. Prior to the induction of TH, sedation (midazolam, 0.08 mg/kg intravenously) and paralysis (rocuronium, 0.8 mg/kg intravenously) for shivering control were immediately administered, followed by continuous infusion of midazolam (0.04-0.2 mg/kg/h) and rocuronium (0.3-0.6 mg/kg/h). The target temperature of 33°C was maintained for 24 h.

After the completion of the TH maintenance period, controlled rewarming at a rate of 0.25°C/hour was performed until the patient’s temperature reached 36.5°C. Sedation and paralysis were reduced during rewarming and were discontinued as soon as the central temperature reached 35°C.

**aEEG monitoring and analysis**

As performed in our previous study, all patients were monitored via aEEG using a combined single-channel aEEG/EEG digital device (Olympic Medical CFM 6000, Natus, Inc., Seattle, WA, USA) as soon as possible by attending emergency physicians in the emergency department (ED); subdermal needle electrodes were applied across the forehead to record EEG channels Fp3-Fp4. Recording continued until the patient regained consciousness, the patient died, or at least 72 h had passed since ROSC. Clinically concerning or seizure-like activity on the aEEG or raw EEG scan resulted in the treatment of the patient according to the local protocol, and cEEG was initiated instead of aEEG if there were no limitations related to technician support for EEG. The patients experiencing SE were initially treated with boluses of valproic acid, levetiracetam and clonazepam,
followed by maintenance dosing. Pentobarbital was administered to refractory SE cases.

After clinical interpretation during treatment, all aEEG/EEG recordings were reinterpreted by an experienced neurologist (YMS) who was blinded to the neurological outcome and the clinical data. The aEEG background patterns were classified into the following categories using the voltage method\textsuperscript{11-13} (Figure 1): continuous normal voltage (CNV), discontinuous normal voltage (DNV), low voltage (LV), flat trace (FT), BS, and SE. CNV was defined as continuous cortical activity on the raw EEG scan; in addition, the upper margin of the aEEG scan, referred to as the aEEG maximum, was \(>10\,\mu\text{V}\), and the lower margin of the aEEG scan, referred to as the aEEG minimum, was \(>5\,\mu\text{V}\). DNV was defined as cortical activity except for discontinuous intermittent periods displaying a low amplitude on the EEG scan with an aEEG maximum \(>10\,\mu\text{V}\) and an aEEG minimum \(\leq 5\,\mu\text{V}\). The LV pattern was defined as an aEEG maximum \(\leq 10\,\mu\text{V}\), and FT was defined as isoelectric activity. We defined BS as the virtual absence of activity (<2 \(\mu\text{V}\)) between bursts of high voltage (>25 \(\mu\text{V}\)). SE was defined as repetitive epileptiform discharges with amplitudes >50 \(\mu\text{V}\) and a median frequency \(\geq 1\,\text{Hz}\) for >30 min, producing an aEEG trace exhibiting a sawtooth-like appearance with continuously narrowing bandwidths and increasing peak-to-peak amplitudes or with an abrupt elevation in the aEEG levels from the continuous background pattern. According to our definition, periodic epileptiform discharges (PEDs) were classified as SE. The aEEG background patterns from the beginning to the end of monitoring were analyzed according to their time of occurrence. To evaluate TTNT as a predictor of good neurological outcome for TH-treated adult cardiac arrest patients, we considered only CNV as a normal trace.\textsuperscript{11-13}

**Neurological outcomes**

In all patients, the prognosis after cardiac arrest treated with TH was determined based on a
combination of predictors of poor neurological outcome. However, in no patient was care withdrawn based on the results of these predictors prior to hospital discharge; the treatment team provided sufficiently prolonged life support to patients who did not recover consciousness after rewarming. Neurological outcome at 6 months after resuscitation was evaluated by the authors (KNP, SHK, and SHO) via a telephone interview. The neurological outcome measure was the score on the five-point Glasgow-Pittsburgh Cerebral Performance Category (CPC) scale at 6 months after ROSC. Neurological outcome was dichotomized as “good” or “poor.” Good neurological outcome was defined as a CPC score of 1 or 2, and poor neurological outcome was defined as a CPC score of 3, 4, or 5. If the patients who presented as CPC 1 or 2 ultimately died due to re-arrest within 6 months, we used the highest CPC score for classification.

**Statistical analysis**

The categorical variables were expressed as the numbers and percentages, and the continuous variables were expressed as the means and standard deviations or the medians and the 25th (Q1) and 75th (Q3) quartiles according to a normal distribution. Univariate comparisons of neurological outcome were performed using Chi-squared tests for categorical variables or using t-tests for continuous variables as required. The performance of the neurological outcome predictors was evaluated based on their sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) using an exact binomial 95% confidence interval (CI). To evaluate the prognostic value of the TTNT, receiver operating characteristic (ROC) analysis was performed; we determined the best TTNT threshold for the prediction of good neurological outcome, and 100% was used as the threshold of specificity for poor neurological outcome. The 95% CI was calculated for the area under the curve (AUC). Evolution-specific aEEG patterns and their time points were analyzed to evaluate the prognostic value of these factors for poor
neurological outcome. All statistical analyses were performed using SPSS version 16.0 (SPSS, Chicago, IL, USA) and the Medcalc program (Medcalc Software, Mariakerke, Belgium). All reported $P$ values are two-sided. A $P$ value $<0.05$ was considered to be significant.

**Results**

**Characteristics of the study population**

During the study period, 166 TH-treated adult cardiac arrest patients were monitored via aEEG; 36 patients were excluded from this study because of death within 72 h after ROSC. Ultimately, 130 patients were included in this study; a portion of this study cohort (55 patients) overlapped with that of our previous study. Of the included patients, 83 (63.8%) were male, and the mean patient age was 51.5±16.6 years. A majority of the patients (86.9%) experienced an out-of-hospital cardiac arrest; 45 patients (34.6%) exhibited an initial shockable rhythm, and the mean time from cardiac arrest to ROSC was 30.9±18.4 min. The median interval from ROSC to the initial aEEG reading was 134.5 min (Q1-Q3, 71.8–239.8 min). At 6 months after ROSC, 55 (42.3%) patients exhibited a good neurological outcome, and 77 patients (57.7%) exhibited a poor neurological outcome. The baseline characteristics of the included patients and the comparison between those exhibiting good and poor neurological outcome are shown in Table 1. Significant differences in the presence of a witness, the initial rhythm, the cardiac arrest etiology, and the time from arrest to ROSC were observed between the good and poor neurological outcome groups.

**EEG evolution in both neurological outcome groups**

**Figure 2** presents the EEG evolution in all patients over time between the good and poor neurological outcome groups. In most patients (98, 75.4%), the background pattern changed
during monitoring. In only 32 patients, the initial background pattern persisted without any evolution, and among these patients, most (24, 75.0%) initially exhibited a CNV trace and had a good neurological outcome. Eight patients who initially exhibited an LV pattern ultimately had a poor neurologic outcome without any evolution. A CNV trace was initially observed in 25 of the 130 patients (19.2%), most of whom exhibited a good neurological outcome. The initial observation of a CNV trace resulted in a PPV of 96.0% (sensitivity and specificity of 43.6% and 98.7%, respectively). One patient initially exhibiting a CNV trace developed circulatory shock without recovering consciousness and ultimately died.

Of the 105 patients not initially exhibiting a CNV trace, 51 patients exhibited a CNV trace within 72 h. Among these patients, 31 patients exhibited a good neurological outcome, and 20 patients exhibited a poor neurological outcome. A difference in TTNT was observed between the good and poor neurological outcome groups (Figure 3). All patients experiencing a good neurological outcome developed a CNV trace within 36 h.

**TTNT as a neurological outcome predictor**

A short TTNT predicted good neurological outcome. ROC analysis revealed that the diagnostic performance of the TTNT for neurological outcome was good, displaying an AUC of 0.97 (95% CI=0.92 to 0.99) (Figure 4). The achievement of TTNT within specific time windows in both neurological outcome groups is shown in Table 2. Using TTNT <24 h after ROSC as the threshold, the sensitivity, the specificity, the PPV, and the NPV for predicting good neurological outcome were 94.6% (95% CI=84.9% to 98.9%), 90.7% (95% CI=81.7% to 96.2%), 88.1% (95% CI=77.1% to 95.1%), and 95.8% (95% CI=88.1% to 99.1%), respectively. Alternatively, the threshold displaying 100% specificity (95% CI=93.5% to 100.0%) for predicting poor neurological outcome was TTNT >36 h after ROSC (sensitivity 78.7%, 95% CI=67.7% to
87.3% (Table 3). When we categorized patients into the mild or deep coma group according to
the results of each initial neurological examination, TTNT in the initially deep coma group
showed better prognostic performance than that in the mild coma group (Supplemental Table 1
and Supplemental Figure 1).

Other predictors of poor neurological outcome
The occurrence of BS and SE in both neurological outcome groups is shown in Table 2. In 57
patients (43.8%), BS was observed during monitoring, and the median time from ROSC to BS
was 4.3 h (Q1-Q3, 1.9–7.4 h). All of these patients except for one exhibited a poor neurological
outcome. The detection of a BS pattern predicted poor neurological outcome with a PPV of
98.3% (sensitivity and specificity of 74.7 and 98.2%, respectively) (Table 3). SE was observed
in 28 patients (21.5%), and the occurrence of SE within 72 h after ROSC (at a median of 16.6 h
after ROSC (Q1-Q3, 11.3–36.4 h)) predicted poor neurological outcome with a PPV of 96.4%
(sensitivity and specificity of 36.0 and 98.2%, respectively) (Table 3). In most of these cases (23,
82.1%), SE initially developed from a BS pattern. In these cases, the initiation of SE occurred at
a median of 11.3 h after ROSC (Q1-Q3, 7.2–32.7 h), and all of these patients exhibited a poor
neurological outcome. However, in 5 patients (17.9%), SE developed from a CNV. Although
these patients exhibited a CNV trace via the sequential evolution of the EEG pattern, SE abruptly
developed from the CNV trace at a median of 33.0 h after ROSC (Q1-Q3, 18.0–36.2 h). Among
these patients, one patient treated with anti-epileptic drugs regained consciousness 2 weeks after
ROSC.

The combination of negative predictors, consisting of no CNV development within 36 h
or the occurrence of BS or SE, in which poor neurological outcome was predicted if at least one
of these three criteria were met, improved prognostic performance. These negative predictors
were observed in 92.0% (69/75) of the patients who exhibited a poor neurological outcome at a median of 6.2 h after ROSC (Q1-Q3, 2.5–18.7 h). These combined aEEG-based negative indicators predicted poor neurological outcome with a specificity, PPV, and NPV of 96.4%, 97.2%, and 89.8%, respectively (Table 3).

Discussion

We evaluated the prognostic value of aEEG using a single-channel frontal montage for TH-treated cardiac arrest survivors during the initial 72 h after ROSC without withholding or withdrawing LST. Our study demonstrated that the application of aEEG was capable of the early prediction of neurological outcome in these patients. First, when the aEEG displayed a normal CNV trace within 24 h, the physicians were able to predict a good neurological outcome with a PPV of 88.1%. Second, the occurrence of SE or BS at any time and the lack of the development of a normal CNV trace within 36 h were associated with a poor neurological outcome at a high sensitivity. The combination of these negative predictors may improve their prognostic performance at an earlier stage.

Our findings were consistent with those published in a previous study. A cEEG background pattern was strongly associated with the recovery of consciousness. Cloosterman et al reported that cEEG monitoring during the first 24 h after resuscitation contributes to the prediction of both good and poor neurological outcome. In that study, continuous activity patterns within 12 h predicted good neurological outcome, and isoelectric or low voltage activity after 24 h predicted poor neurological outcome. Rundgren et al evaluated aEEG at a median of 8 h after cardiac arrest and after the patients achieved a normal temperature. In that study, an initial continuous pattern and the return of a continuous pattern at normothermia served as good
predictors of the recovery of consciousness. In our previous study based on a small number of cases, all of the patients exhibiting a good neurological outcome displayed a CNV trace within 26 h. However, the threshold TTNT for the prognosis of good neurological outcome was unknown when the normalization of the background pattern was delayed. In term infants exhibiting perinatal asphyxia at hypothermia, some investigators found that the recovery time to a normal background pattern was the best predictor of poor neurological outcome at a suggested threshold for aEEG normalization of 36-48 h of age. These findings were similar to our results, in which all patients experiencing a good neurological outcome developed a normal trace within 36 h. We used a continuous sedation protocol during hypothermia. Of the 55 patients exhibiting good outcome, 53 patients achieved a normal trace within the mean time of the initiation of sedative reduction (within 28.5 h after ROSC), and 2 patients exhibited a TTNT before sedative withdrawal (34.4 h and 35.1 h, respectively). Therefore, we believe that the effect of sedation on the TTNT threshold is minimal.

Most investigators agree that in patients treated with TH, the time to prognostication should be delayed beyond 72 h after rewarming. Early prognostication during TH should focus on good rather than poor neurological outcome. However, in some reports, LST was withdrawn prior to the resumption of normothermia by family request, or treatment was even suspended for some patients who were given a poor prognosis during TH. Our study showed that the presence of a normal aEEG pattern within 24 h after ROSC was a predictor of a good neurological outcome. This finding can impact treatment decisions even in cases in which the withdrawal of LST is considered to be consistent with the caregiver’s wishes without delayed prognostication.

The definition of BS was inconsistent between many studies, potentially influencing the
relevance of the observed predictive value of BS.\textsuperscript{13, 14, 16, 24} According to the definition of BS in “American Clinical Neurophysiology Society’s Standardized Critical Care EEG Terminology: 2012 version”, suppression was defined as a period in which the voltage was <10 $\mu$V.\textsuperscript{25} Alternatively, we defined BS as the virtual absence of activity (<2 $\mu$V) between bursts of high voltage (>25 $\mu$V) on aEEG. Using our revised definition, the occurrence of a BS pattern accurately predicted poor neurological outcome in all but one case.

Recent studies have demonstrated that SE is common in these patients and is associated with poor neurological outcome,\textsuperscript{14, 26-28} despite exceptional reports of recovery.\textsuperscript{29, 30} It is unknown whether prolonged SE contributes to secondary brain injury after cardiac arrest or whether SE is simply an epiphenomenon of severe brain injury. Our results suggest an answer to this question. Rossetti et al described benign post-anoxic SE in cases involving a reactive background.\textsuperscript{30, 31} Rundgren et al identified SE evolving from a continuous pattern in 10 patients and suggested that this type of SE reflects a less injured and potentially salvageable brain.\textsuperscript{14} In our study, 5 patients developed SE from a CNV trace via the sequential evolution of the EEG pattern. Although these patients exhibited a similar evolution pattern to that of other patients with good neurological outcome, inconsistent with our expectations, only one patient exhibited a good neurological outcome. We propose that in these cases, SE serves as a contributor to poor neurological outcome rather than as a simple epiphenomenon of severe brain injury and that appropriate treatment is necessary to recover consciousness. To distinguish this pattern of SE from more malignant SE patterns, cEEG monitoring may be an essential component of post-cardiac arrest care.

The introduction of mild hypothermia and standardized treatment protocols in the last decade has improved neurological outcomes in survivors of cardiac arrest.\textsuperscript{1, 3} In 2013, new strategies based on a near-normal temperature (36°C) not displaying differences compared to mild
hypothermia (33°C) were introduced. However, in both intervention groups, a significant number of patients did not regain consciousness after treatment. To improve neurological outcome in these patients, it is quite clear that tailored therapies according to the extent of brain injury are needed. Some investigators have attempted to categorize patients according to brain injury severity based on EEG. According to our results, based on early aEEG monitoring, these patients can be categorized early. The initial or early restoration of CNV predicts good neurological outcome in circumstances involving the maintenance of active care. Additionally, the development of CNV between 24 and 36 h after ROSC and SE originating from CNV render prognostication difficult. However, for cooled patients exhibiting an abnormal voltage trace during TH, a good neurological outcome remains possible even if normalization of the background patterns is delayed beyond 24 h. Alternatively, the lack of the development of a normal trace within 36 h and the occurrence of BS or SE originating from BS indicated a poor neurological outcome using the present cooling strategies. However, good neurological recovery in these patients may remain possible with advancements in the existing cooling strategies that have been associated with poor neurological outcome. Because the risk of extensive hypoxic brain injury increases over time, to spare these patients, it is important to identify those expected to exhibit a poor prognosis very early.

Interestingly, using the combination of negative predictors via continuous aEEG monitoring, prognostication was possible at a median 6.2 h after ROSC. To the best of our knowledge, our study represents the first attempt to address the issues of the time at which physicians determine the severity of brain injury using EEG and the time of prognostication. Future studies should continue to define patient subgroups and evaluate the benefit of tailored therapies for each patient's injury.

Several features of our study deserve further mention. First, withdrawal of LST based on
prognostication was not applied to our patients. Currently, the practice of withdrawal of LST is widespread based on recommendations and guidelines.\textsuperscript{5, 36} However, most prognostication studies were performed in Western countries, which have a social consensus regarding the withdrawal of LST, and these studies did not adequately address certain important limitations concerning the risk of bias. A `self-fulfilling prophecy` is present in most prognostication studies of cardiac arrest, in which the treating physicians are not blinded to the results of the neurological outcome prediction and use this prediction to make decisions regarding the withdrawal of LST.\textsuperscript{7, 37, 38} In South Korea, the withdrawal of LST for patients suffering from terminal illness remains under debate, and the social consensus and legislative processes are developing; the withdrawal of LST for post-cardiac arrest patients based on prognostication is not currently permitted.\textsuperscript{39} Our clinical and ethical situation resulted in the natural neurological outcome for these patients. Second, this study included consecutive patients with TH during the study period, but patients who died within 72 h after cardiac arrest were excluded. The aim of this study was to evaluate the prognostic value of continuous aEEG (from immediately after ROSC to 72 h later) according to time. Early death after ROSC is often caused by persistent hemodynamic instability leading to multiple organ failure.\textsuperscript{40, 41} If patients with good brain function but poor cardiorespiratory function were included in the study, the prognostic value of aEEG in the early phase would be confounded. However, our analysis did not include additional potential variables affecting neurological outcome, such as initial organ system dysfunction in 72 h survivors. For these reasons, our results should be interpreted cautiously.

**Limitations**

This study contained several limitations. First, we only performed frontal EEG monitoring via single-channel aEEG. Although SE was detected in 21.5\% of our patients, a result similar to that of
other reports using multichannel cEEG monitoring, our rate of good outcome was slightly lower than that of other studies. Our technique using single-channel monitoring may disturb the detection of focal epileptic activity, and this may influence the rate of good outcome in SE patients. However, reducing the number of channels used for bedside aEEG monitoring is crucial for facilitating the monitoring of the cerebral cortex and for its immediate application after ROSC. Because the frontal cortices are better protected than the parietal and occipital cortices and because continuous activity appeared first in the frontal leads after ROSC, the frontal cortices may represent neural recovery during the early stage. Second, this study used a single-center design in a country with a unique health care environment. This study design raises important questions regarding the generalizability of these results. A large, multi-center study including Western countries may provide more precise prognostic values and may help determine the utility of aEEG in this population. Third, although physicians are not permitted to withdraw LST in South Korea, there was an inevitable risk of bias because the treating team was not blinded to the aEEG data during treatment. Finally, especially regarding SE, our study could not differentiate PEDs from SE and did not evaluate clinical manifestations (such as myoclonus) that were examined in previous studies using cEEG.

Conclusions

Early aEEG monitoring of adult cardiac arrest patients receiving TH enabled the early prediction of neurological outcome. Based on these results, a TTNT within 24 h after ROSC was associated with good neurological outcome. The lack of CNV development within 36 h and the occurrence of SE or BS within 72 h after ROSC contributed to the prediction of poor neurological outcome. The combination of these negative predictors via aEEG monitoring may improve their prognostic performance at an earlier stage.
Conflict of Interest Disclosures: None.

References:


Table 1. Baseline demographic and clinical characteristics of the overall cohort and comparison between the good and poor neurological outcome groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall cohort (n=130)</th>
<th>Good neurological outcome (n=55)</th>
<th>Poor neurological outcome (n=75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>83 (63.8)</td>
<td>38 (69.1)</td>
<td>45 (60.0)</td>
<td>0.286</td>
</tr>
<tr>
<td>Age, years, mean±SD</td>
<td>51.5±16.6</td>
<td>49.2±16.6</td>
<td>53.3±16.5</td>
<td>0.166</td>
</tr>
<tr>
<td>Witnessed, n (%)</td>
<td>99 (76.2)</td>
<td>60 (57.7)</td>
<td>50 (66.7)</td>
<td>0.033</td>
</tr>
<tr>
<td>Shockable rhythm, n (%)</td>
<td>45 (34.6)</td>
<td>31 (56.4)</td>
<td>14 (21.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bystander CPR, n (%)</td>
<td>77 (59.2)</td>
<td>38 (69.1)</td>
<td>39 (52.0)</td>
<td>0.050</td>
</tr>
<tr>
<td>Cardiac cause, n (%)</td>
<td>89 (68.5)</td>
<td>47 (85.5)</td>
<td>42 (56.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OHCA, n (%)</td>
<td>113 (86.9%)</td>
<td>45 (81.8)</td>
<td>68 (90.7)</td>
<td>0.139</td>
</tr>
<tr>
<td>Time from arrest to ROSC, min, mean±SD</td>
<td>30.9±18.4</td>
<td>22.3±14.9</td>
<td>37.2±18.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from ROSC to aEEG application, min, median (Q1-Q3)</td>
<td>107.0 (48.8–189.8)</td>
<td>80.0 (39.0–189.0)</td>
<td>123.0 (61.0–192.0)</td>
<td>0.197</td>
</tr>
<tr>
<td>Time from ROSC to initial aEEG interpretation, min, median (Q1-Q3)</td>
<td>134.5 (71.8–239.8)</td>
<td>104.0 (61.0–236.0)</td>
<td>161.0 (81.0–245.0)</td>
<td>0.038</td>
</tr>
<tr>
<td>Total time of aEEG monitoring, h, mean±SD</td>
<td>56.7±14.7</td>
<td>45.7±12.5</td>
<td>64.7±10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from ROSC to target temperature, h, median (Q1-Q3)</td>
<td>2.5 (1.5–4.0)</td>
<td>2.9 (1.7–5.0)</td>
<td>2.0 (1.5–3.5)</td>
<td>0.232</td>
</tr>
<tr>
<td>Length of stay, days, median (Q1-Q3)</td>
<td>12.0 (6.0–22.0)</td>
<td>16.0 (12.0–35.0)</td>
<td>7.0 (5.0–18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival to discharge, n (%)</td>
<td>85 (65.4)</td>
<td>54 (98.2)</td>
<td>31 (41.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Neurological outcome at 6 months after ROSC

| CPC 1, n (%)                     | 50 (38.5) | 50 (90.9) | 0 (0.0) |
| CPC 2, n (%)                     | 5 (3.8)   | 5 (9.1)   | 0 (0.0) |
| CPC 3, n (%)                     | 7 (5.4)   | 0 (0.0)   | 7 (9.3) |
| CPC 4, n (%)                     | 6 (4.6)   | 0 (0.0)   | 6 (8.0) |
| CPC 5, n (%)                     | 62 (47.7) | 0 (0.0)   | 62 (82.7) |

SD, standard deviation; CPR, cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; aEEG, amplitude-integrated electroencephalography; CPC, cerebral performance category.

*: One patient who presented as CPC 1 and ultimately died due to re-arrest within 6 months was categorized as CPC 1.
Table 2. The achievement of time to normal trace within specific time windows and the occurrence of burst suppression and status epilepticus in both neurological outcome groups.

<table>
<thead>
<tr>
<th></th>
<th>Good neurological outcome (n=55)</th>
<th>Poor neurological outcome (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Time to normal trace &lt;24 h</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNV development within 24 h, n (%)</td>
<td>52 (94.5)</td>
<td>7 (9.3)</td>
</tr>
<tr>
<td>No CNV development within 24 h, n (%)</td>
<td>3 (5.5)</td>
<td>68 (90.7)</td>
</tr>
<tr>
<td><strong>B. Time to normal trace &gt;36 h</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNV development within 36 h, n (%)</td>
<td>55 (100.0)</td>
<td>16 (21.3)</td>
</tr>
<tr>
<td>No CNV development within 36 h, n (%)</td>
<td>0 (0.0)</td>
<td>59 (78.7)</td>
</tr>
<tr>
<td><strong>C. BS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BS development, n (%)</td>
<td>1 (1.8)</td>
<td>56 (74.7)</td>
</tr>
<tr>
<td>No BS development, n (%)</td>
<td>54 (98.2)</td>
<td>19 (25.3)</td>
</tr>
<tr>
<td><strong>D. SE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE development, n (%)</td>
<td>1 (1.8)</td>
<td>27 (36.0)</td>
</tr>
<tr>
<td>No SE development, n (%)</td>
<td>54 (98.2)</td>
<td>48 (64.0)</td>
</tr>
<tr>
<td><strong>E. Combination of the negative predictors of neurological outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occurrence of any negative predictor, n (%)</td>
<td>2 (3.6)</td>
<td>69 (92.0)</td>
</tr>
<tr>
<td>No occurrence of any negative predictor, n (%)</td>
<td>53 (96.4)</td>
<td>6 (8.0)</td>
</tr>
</tbody>
</table>

CNV, continuous normal voltage; BS, burst suppression; SE, status epilepticus.

*: The negative predictors of neurological outcome included no CNV development within 36 h and BS and SE occurring at any time.
Table 3. Sensitivity, specificity and positive and negative predictive values for the early prediction of good and poor neurological outcome.

<table>
<thead>
<tr>
<th>Time after ROSC, h</th>
<th>Prediction of neurological outcome</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive predictive value (95% CI)</th>
<th>Negative predictive value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNV development within 24 h</td>
<td>Good</td>
<td>94.6 (84.9–98.9)</td>
<td>90.7 (81.7–96.2)</td>
<td>88.1 (77.1–95.1)</td>
<td>95.8 (88.1–99.1)</td>
</tr>
<tr>
<td>No CNV development within 36 h</td>
<td>Poor</td>
<td>78.7 (67.7–87.3)</td>
<td>100.0 (93.5–100.0)</td>
<td>100.0 (93.9–100.0)</td>
<td>77.5 (66.0–86.5)</td>
</tr>
<tr>
<td>BS</td>
<td>Poor</td>
<td>74.7 (63.3–84.0)</td>
<td>98.2 (90.3–100.0)</td>
<td>98.3 (90.6–100.0)</td>
<td>74.0 (62.4–83.6)</td>
</tr>
<tr>
<td>SE</td>
<td>Poor</td>
<td>36.0 (25.2–47.9)</td>
<td>98.2 (90.3–100.0)</td>
<td>96.4 (81.7–99.9)</td>
<td>52.9 (42.8–62.9)</td>
</tr>
<tr>
<td>Combination of the negative predictors**</td>
<td>Poor</td>
<td>92.0 (83.4–97.0)</td>
<td>96.4 (87.5–99.6)</td>
<td>97.2 (90.2–99.7)</td>
<td>89.8 (79.2–96.2)</td>
</tr>
</tbody>
</table>

CNV, continuous normal voltage; BS, burst suppression; SE, status epilepticus; CI, confidence interval.

*: Median (interquartile range).

**: The negative predictors included no CNV development within 36 h and BS and SE occurrence at any time.
Figure Legends:

Figure 1. Classification of amplitude-integrated electroencephalograms using the voltage method.

Figure 2. Occurrence of background evolution and status epilepticus in all subjects. The x axis indicates the time point after resuscitation (h).

Figure 3. Time to normal trace for the patients in both groups.

Figure 4. Receiver operating characteristic curve for the prediction of good neurological outcome according to the time to normal trace. AUC, area under the curve; CI, confidence interval.
<table>
<thead>
<tr>
<th>Normal trace</th>
<th>Continuous normal voltage (CNV)</th>
<th>lower margin &gt; 5 µV and upper margin &lt; 10 µV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal trace</td>
<td>Discontinuous normal voltage (DNV)</td>
<td>lower margin = 5 µV and upper margin &gt; 10 µV</td>
</tr>
<tr>
<td></td>
<td>Low voltage (LV)</td>
<td>low amplitude (upper margin ≤ 10 µV)</td>
</tr>
<tr>
<td></td>
<td>Flat trace (FT)</td>
<td>isoelectric activity</td>
</tr>
<tr>
<td></td>
<td>Burst suppression (BS)</td>
<td>absent activity (&lt;2 µV) between bursts of high voltage (&gt;25 µV)</td>
</tr>
<tr>
<td></td>
<td>Status epilepticus (SE)</td>
<td>repetitive epileptiform discharges &gt;50 µV and a medium frequency ≥ 1 Hz for &gt; 30 min</td>
</tr>
</tbody>
</table>

**Figure 1**
Figure 3

Never regained normal trace during 72 h

- Good outcome
- Poor outcome

Time to normal trace (h)

- Good outcome
- Poor outcome

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Continuous Amplitude-Integrated Electroencephalographic Monitoring is a Useful Prognostic Tool for Hypothermia-Treated Cardiac Arrest Patients
Sang Hoon Oh, Kyu Nam Park, Young-Min Shon, Young-Min Kim, Han Joon Kim, Chun Song Youn, Soo Hyun Kim, Seung Pill Choi and Seok Chan Kim

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**Supplemental Table 1.** Area under the TTNT curve for good neurological outcome according to the results of each neurological examination

<table>
<thead>
<tr>
<th>Neurological examination</th>
<th>Test result</th>
<th>Area (95% CI) under the TTNT curve for neurological outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pupil light reflex</td>
<td>Positive (n=44)</td>
<td>0.943 (0.829-0.990)</td>
</tr>
<tr>
<td>(n=111)</td>
<td>Negative (n=67)</td>
<td>0.994 (0.934-1.000)</td>
</tr>
<tr>
<td>Corneal reflex</td>
<td>Positive (n=32)</td>
<td>0.919 (0.766-0.985)</td>
</tr>
<tr>
<td>(n=110)</td>
<td>Negative (n=78)</td>
<td>0.984 (0.925-0.999)</td>
</tr>
<tr>
<td>Spontaneous breathing</td>
<td>Positive (n=66)</td>
<td>0.967 (0.891-0.996)</td>
</tr>
<tr>
<td>(n=93)</td>
<td>Negative (n=27)</td>
<td>1.000 (0.872-1.000)</td>
</tr>
<tr>
<td>Motor response*</td>
<td>Positive (n=23)</td>
<td>1.000 (0.852-1.000)</td>
</tr>
<tr>
<td>(n=111)</td>
<td>Negative (n=88)</td>
<td>0.979 (0.923-0.998)</td>
</tr>
</tbody>
</table>

TTNT, time to normal trace; CI, confidence interval.

*: Positive motor response was defined as Glasgow Coma Scale-motor grade > 2
Supplemental Figure 1. Receiver operating characteristic curve for the prediction of neurological outcome according to the time to normal trace for each category of the initial degree of coma. PLR, pupillary light reflex; CR, corneal reflex; SB, spontaneous breathing; MR, motor response.
뇌파검사가 심정지 환자의 신경학적 회복을 조기예측할 수 있다

강 현 재 교수 서울대학교병원 순환기내과

초록

배경
최근 의료의 발전으로 심정지 후 생존율은 개선되었으나, 예후 예측은 여전히 어려운 과제로 남아 있다. 연구자들은 전복-통합 (amplitude-integrated) 뇌파검사를 시행함으로써, 저정한 치료를 받은 심정지 환자에서 시간에 따른 지속적 뇌파검사의 예후 평가에서의 가치를 검토하였다.

방법 및 결과
연구자들은 2010년 9월부터 2013년 4월 사이에 저정한 치료를 받은 130명의 흔수상태 환자를 전향적으로 연구하였다. 연구자들은 '정상적인 뇌파 소견을 보이는 시간(time to normal trace, TTNT)'을 신경학적인 결과의 예측인자로서 평가하였고, 발생 시간을 중심으로 하여 burst suppression과 status epilepticus의 예후 예측력을 확인하였다. 55명의 환자에서 대뇌 기능도 등급 지수(cerebral performance category score) 1-2의 소견을 보였다. TTNT의 곡선하 면적(area under the curve)은 0.97(95% CI, 0.92~0.99), 소생술 후 TTNT<24시간인 경우 좋은 신경학적 결과를 예측하는 민감도와 특이도는 각각 94.6%(95% CI, 84.9~98.9%)와 90.7%(95% CI, 81.7~96.2%)였다. 나쁜 신경학적 결과를 100% 특이도로 예측하는 임계치는 TTNT>36시간이었다. Burst suppression과 status epilepticus는 나쁜 신경학적 결과를 예측하는 지표이다(양성 예측도는 각각 98.3%와 96.4%). 이들 지표를 함께 고려하면 중양값으로 소생술 6.2시간 후 불량한 결과를 예측할 수 있었다(민감도, 92.0%; 특히도, 96.4%).

결론
TTNT<24시간은 좋은 신경학적 결과와 연관성을 보였다. 36시간 이내에 정상적인 뇌파 소견을 보여주지 못하거나, status epilepticus와 burst suppression을 보이는 경우 예후가 불량하였다. 이러한 불량한 결과의 예측인자들을 함께 고려함으로써, 좀 더 이론적 시점에 이들의 예후 예측력을 개선할 수 있을 것이다.