Hypothermia-treated cardiac arrest patients with good neurological outcome differ early in quantitative variables of EEG suppression and epileptiform activity*

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Objective: **To evaluate electroencephalogram-derived quantitative variables after out-of-hospital cardiac arrest.**

Design: **Prospective study.**

Setting: **University hospital intensive care unit.**

Patients: **Thirty comatose adult patients resuscitated from a witnessed out-of-hospital ventricular fibrillation cardiac arrest and treated with induced hypothermia (33°C) for 24 hrs.**

Interventions: **None.**

Measurements and Main Results: **Electroencephalography was registered from the arrival at the intensive care unit until the patient was extubated or transferred to the ward, or 5 days had elapsed from cardiac arrest. Burst-suppression ratio, response entropy, state entropy, and wavelet subband entropy were derived. Serum neuron-specific enolase and protein 100B were measured. The Pulsatility Index of Transcranial Doppler Ultrasonography was used to estimate cerebral blood flow velocity. The Glasgow-Pittsburgh Cerebral Performance Categories was used to assess the neurologic outcome during 6 mos after cardiac arrest. Twenty patients had Cerebral Performance Categories of 1 to 2, one patient had a Cerebral Performance Categories of 3, and nine patients had died (Cerebral Performance Categories of 5). Burst-suppression ratio, response entropy, and state entropy already differed between good (Cerebral Performance Categories 1–2) and poor (Cerebral Performance Categories 3–5) outcome groups ($p = .011$, $p = .011$, $p = .008$) during the first 24 hrs after cardiac arrest. Wavelet subband entropy was higher in the good outcome group between 24 and 48 hrs after cardiac arrest ($p = .050$). All patients with status epilepticus died, and their wavelet subband entropy values were lower ($p = .022$). Protein 100B was lower in the good outcome group on arrival at ICU ($p = .010$). After hypothermia treatment, neuron-specific enolase and protein 100B values were lower ($p = .002$ for both) in the good outcome group. The Pulsatility Index was also lower in the good outcome group ($p = .004$).**

Conclusions: **Quantitative electroencephalographic variables may be used to differentiate patients with good neurologic outcomes from those with poor outcomes after out-of-hospital cardiac arrest. The predictive values need to be determined in a larger, separate group of patients. (Crit Care Med 2009; 37: 2427–2435)**

Key Words: cardiac arrest; electroencephalography; recovery; hypothermia

Survival rate after out-of-hospital cardiac arrest is poor (1), although induced mild hypothermia treatment has been shown to improve it (2, 3). Neurologic recovery is determined primarily by the extent of hypoxic-ischemic encephalopathy that develops during and after circulatory arrest. Clinical, electrophysiological (4, 5), radiologic (6, 7), and biochemical methods (8, 9) have been used to evaluate early neurologic prognosis.

Suppression of electroencephalography (EEG) (10), lack of EEG reactivity (11), reduced α variability (12), and generalized epileptiform activity (13) have been related to poor neurologic recovery. However, the behavior of individual EEG characteristics is unclear, as in many studies they have been considered only as combined groups of malign or benign phenomena (14). EEG suppression and generalized epileptiform activity (14) seem to be associated with poor neurologic outcome, but it is not clear how soon after resuscitation these characteristics indicate poor outcome.

We used burst-suppression ratio (BSR) (15–17) for the quantification of suppressed EEG, and wavelet subband entropy (WSE)

*See also p. 2485.

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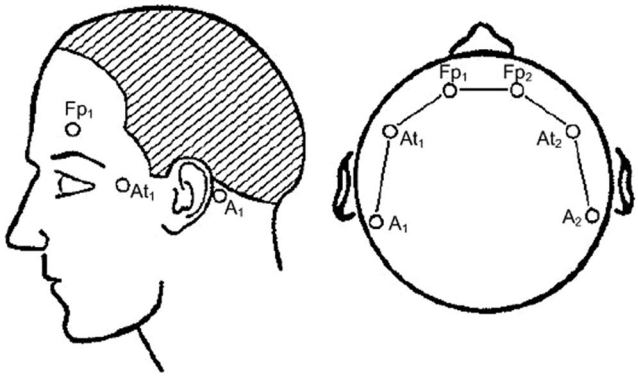

Figure 1. Placement of electroencephalographic electrodes used in the study. In addition, an entropy sensor was located above the Fp1 and Fp2 electrodes. At1/At2, electrode placement on both temporal bones laterally to the eyes. Modified (19) and reproduced with permission from *Neurology*.

Table 1. Baseline demographics and clinical characteristics of study population

	Good Outcome (n = 21)	Poor Outcome (n = 9)	*p*
Age	55 (24–74)	60 (26–77)	.176
Sex, male/female	16/5	8/1	.426
BMI, kg/m^2	25 (19–35)	28 (21–39)	.209
GCS	3 (3–8)	3 (3–5)	.278
SOFA 24 hrs	8 (3–12)	9 (5–13)	.304
ROSC, min	16 (9–33)	22 (15–31)	.104
CPR, yes/no	14/7	6/3	.500
BCLS, min	7 (3–13)	7 (5–11)	.406
ACLS, min	14 (3–35)	16 (12–25)	.263
Time to target temperature, hr	3 (1–5)	2 (0–13)	.449
Time to normothermia, hr	32 (30–36)	31 (30–39)	.304
LOS ICU, day	3 (1–14)	4 (2–13)	.244
LOS hospital, day	18 (5–36)	13 (5–31)	.226

BMI, body mass index; GCS, Glasgow Coma Scale Score on admission; SOFA, Sequential Organ Failure Assessment; ROSC, return of spontaneous circulation; CPR, bystander cardiopulmonary resuscitation; BCLS, response interval to basic cardiac life support; ACLS, response interval to advanced cardiac life support; Time to target temperature on arrival to ICU, Time to normothermia after initiating hypothermia treatment; LOS ICU, length of stay at intensive care unit; LOS hospital, length of stay at Helsinki University Hospital.

Data are presented as median (range).

(17) to detect epileptiform activity. This is the first study of WSE in patients resuscitated from cardiac arrest. We hypothesized that the quantitative variables of EEG (BSR, response entropy (RE), state entropy (SE), and WSE) would correlate with neurologic outcome after cardiac arrest. We also evaluated the time schedule in which the quantitative EEG variables could differentiate patients with a poor neurologic outcome from those with a good one.

MATERIALS AND METHODS

Patients

After Institutional Review Board approval, this prospective observational study was performed in the intensive care unit (ICU) of Meilahti Hospital, Helsinki University Hospital, Helsinki, Finland. All comatose (Glasgow Coma Scale score of ≤8) adult patients, resuscitated from a witnessed out-of-hospital ventricular fibrillation within an interval of <35 mins from collapse to restoration of spontaneous circulation and admitted to the ICU for therapeutic hypothermia, were screened. Exclusion criteria included terminal illness, psychoactive or anticonvulsive medication, known history of a neurologic disease, or alcohol or drug abuse. Written informed consent from each patient's next-of-kin was obtained.

Clinical Treatment

Basic and advanced cardiac life support was provided according to the guidelines of the European Resuscitation Council (18). All patients were evaluated by a cardiologist in the Emergency Department, and then transferred to the ICU for therapeutic hypothermia. If cardiac catheterization was required, hypothermia was induced afterward. Hypothermia of 33°C was induced for 24 hrs, using an intravascular cooling device (CoolGard 3000, Alcius, Irvine, CA). Patients were then rewarmed at 0.5°C/hr to normothermia. Midazolam (0.125 mg/kg/hr) and fentanyl (2 μg/kg/hr) were used for sedation, and pancuronium was provided for muscle relaxation. Pancuronium was discontinued when patients were rewarmed to 35.5°C; fentanyl and midazolam were discontinued when the patients' body temperature reached 36°C. The body temperature was measured via the intravascular cooling catheter. Patients were kept in a 30° semirecumbent position and mechanically normoventilated. Normoventilation was controlled by repeated blood gas analysis. The mean arterial pressure was maintained >65 mm Hg, using norepinephrine when needed. Plasma glucose was maintained between 4.4 and 8.0 mmol/L (79–144 mg/dL) with infusion of short-acting insulin when indicated. Patients regaining consciousness were extubated when they were hemodynamically stable, awake, and obeying commands. Patients not regaining consciousness were treated in the ICU for at least 3 days after cardiac arrest. Multichannel-EEG, somatosensory-evoked potentials, and computed tomography of the brain were performed if patients remained unresponsive 2 to 3 days after cardiac arrest.

Table 2. Raw EEG features during hypo- and normothermia according to outcome; values are numbers and percentages

	Good Outcome (n = 21), %	Poor Outcome (n = 9), %
Hypothermia		
Continuous EEG	14 (67)	4 (44)
Discharges	1 (5)	3 (33)
Suppression/B-S	5 (24)	1 (11)
Status epilepticus	0 (0)	0 (0)
Spindles	1 (5)	0 (0)
Myoclonia	0 (0)	1 (11)
Normothermia		
Continuous EEG	20 (95)[b]	3 (33)[a,b]
Discharges	1 (5)	1 (11)
Suppression/B-S	0 (0)	1 (11)
Status epilepticus	0 (0)[c]	4 (44)[c]
Spindles	0 (0)	0 (0)
Myoclonia	0 (0)	0 (0)

EEG, electroencephalogram; B-S, burst suppression.

[a]θ coma; [b]$p < .001$; [c]$p = .001$.

Study Protocol

EEG

On arrival at the ICU, the patients received EEG electrodes (Zipprep, Aspect Medical Sys-

Table 3. Median and range of quantitative parameters associated with good and poor neurological outcome during first and second day after cardiac arrest

	Good Outcome (n = 21)	Poor Outcome (n = 9)	*p*
0–24 hrs			
WSE	0.84 (0.75–0.85)	0.83 (0.69–0.85)	.137
BSR, %	18 (0–81)	65 (4–74)	.011
RE	20 (3–51)	10 (4–22)	.011
SE	19 (3–50)	9 (4–22)	.008
24–48 hrs			
WSE	0.84 (0.80–0.86)	0.82 (0.65–0.85)	.050
BSR, %	0 (0–17)	2 (0–26)	.045
RE	67 (26–83)	55 (29–78)	.150
SE	58 (24–76)	46 (28–68)	.193

WSE, wavelet subband entropy; BSR, burst-suppression ratio; RE, response entropy; SE, state entropy.

tems, Norwood, MA) applied to locations below the hairline (19) (Fig. 1) to record EEG channels Fp1-At1, Fp2-At2, At1-A1, and At2-A2. EEG was recorded continuously with a sampling frequency of 500 Hz, using a dedicated module of the compact anesthesia monitor (Datex-Ohmeda S/5, GE Healthcare, Helsinki, Finland). In addition, an entropy module (GE Healthcare) connected to an S/5 Monitor was used. The entropy sensor (GE Healthcare) was positioned interhemispherically above the Fp1 and Fp2 electrodes. Data were recorded with the S/5 Collect program (GE Healthcare), using a medical-graded PC (Advantech, Taipei, Taiwan) interfaced with an S/5 monitor. The recordings ended either when the patient was extubated or transferred to another ward, or when 5 days had elapsed from the time of the cardiac arrest.

A senior neurophysiologist (T.K.S.), who was blinded to the clinical outcome, other electrophysiological tests, and radiologic findings, analyzed the raw EEG recordings off-line. The following characteristics were evaluated from the EEG: continuity, suppression, burst-suppression, discharges, spindles, and status epilepticus with and without myoclonia.

The following EEG-derived quantitative variables were obtained off-line: BSR, SE, RE, and WSE. BSR, RE, and SE were derived by the entropy module, which has been validated as a monitor of hypnotic component of anesthesia (20). BSR is a well-established and commercially available index for quantifying the amount of EEG suppression (15, 16, 21). SE and RE are spectral entropy-based variables calculated from the frequency ranges of 0.8 to 32 Hz for SE and 0.8 to 47 Hz for RE (21). During anesthesia, SE monitors cortical activity, whereas RE can be utilized for the fast detection of patient responsiveness, including electromyographic responses. Decreasing WSE values are associated with epileptiform EEG activity during sevoflurane anesthesia (17). In this study, WSE was calculated with mother wavelet Daubechies 3 from a scale corresponding to an EEG frequency range of 16 to 32 Hz. WSE was calculated off-line with Matlab (version 7.5, MathWorks, Natick, MA) and Matlab Wavelet Toolbox (version 2.2).

For all EEG-derived variables, the median values for the first 24 hrs and 24 to 48 hrs of EEG recordings were calculated for statistical analysis.

Transcranial Doppler Ultrasonography

Transcranial Doppler (TCD) ultrasonography is a noninvasive technique for measuring cerebral blood flow velocity (22). The Pulsatility Index (PI) of TCD (Pioneer TC 4040, Nicolet-EME, Überlingen, Germany) was measured for each patient after normothermia was reached within the first 48 hrs after cardiac arrest. The middle cerebral artery was insonated at a depth of 49 to 55 mm. The same investigator conducted all measurements. PI is derived from the difference between systolic and diastolic flow velocity divided by the mean flow velocity (23).

Laboratory Measurements

Neuron-specific enolase (NSE) and protein 100B (S100B), commonly used biomarkers of brain damage, increase after cardiac arrest (9, 24). Blood was sampled from the arterial catheter when EEG monitoring was initiated (NSE and S100B), 24 hrs after cardiac arrest (NSE), upon rewarming to 35.5°C (NSE and S100B), 48 hrs from cardiac arrest (NSE), and when EEG monitoring of patients was ended (NSE and S100B). Blood gas analysis (including hemoglobin, glucose, and lactate) was performed at least every 4 hours. NSE and S100B were quantified (Elecsys, Roche, Basel, Switzerland), with reference ranges of 0.05 to 16 μg/L for NSE and 0.005 to 0.11 μg/L for S100B.

Functional Outcomes

Neurologic status was examined daily during ICU stay and at discharge from the university hospital. A neurologist (S.M.T.) evaluated patients 6 mos after cardiac arrest. Neurologic outcomes were assessed, using the Glasgow-Pittsburgh Cerebral Performance Categories (CPC), dividing cerebral performance into five categories. A CPC of 1 refers to normal cerebral function; a CPC of 2 refers to moderate cerebral disability; a CPC of 3 refers to severe neurologic disability; a CPC of 4 refers to comatose or vegetative state; and a CPC of 5 refers to death (25). Neurologic outcome was defined as "good" if the best-achieved CPC score was between 1 and 2 at any point within a 6-mo follow-up period. CPC scores ranging from 3 to 5 reflected a poor neurologic outcome.

Statistical Analysis

Based on the outcome results, patients were divided into neurologic outcome groups of "good" (CPC of 1–2) and "poor" (CPC of 3–5). All data were considered to have a non-Gaussian distribution, and are given as medians and ranges unless otherwise indicated. The differences between the medians of good and poor outcome groups for scalar scale parameters were examined, using the Mann-Whitney *U* test. To test the dependency between nominal scale parameters and outcome or EEG groups, the chi-square test was used. A $p \leq .50$ was considered statistically significant. Significant differences are reported without correction for multiple comparisons (26). All statistical analyses were calculated, using SPSS 14.0 (SPSS Inc, Chicago, IL).

Preliminary prediction analysis was carried out with General Diagnostic Optimizer program (27, 28), which uses stepwise heuristic Bayesian process. The program is controlled by parameters that describe the possible variables to be included in the prediction model. Heuristic process means that the program starts by including the best explaining variable first, and then adds variable by variable until the best model is reached. Typically, use of only some variables results in the model with the smallest number of false predictions.

RESULTS

Thirty consecutive patients were included in the study. EEG monitoring was started 2.6 to 13.3 hrs after cardiac arrest in all patients. A total of 1754 hrs of EEG were registered. A total of 691 hrs (mean = 23.0 hrs/patient) were collected during the first 24 hrs after arrival at the ICU, and 599 hrs (mean 19.7

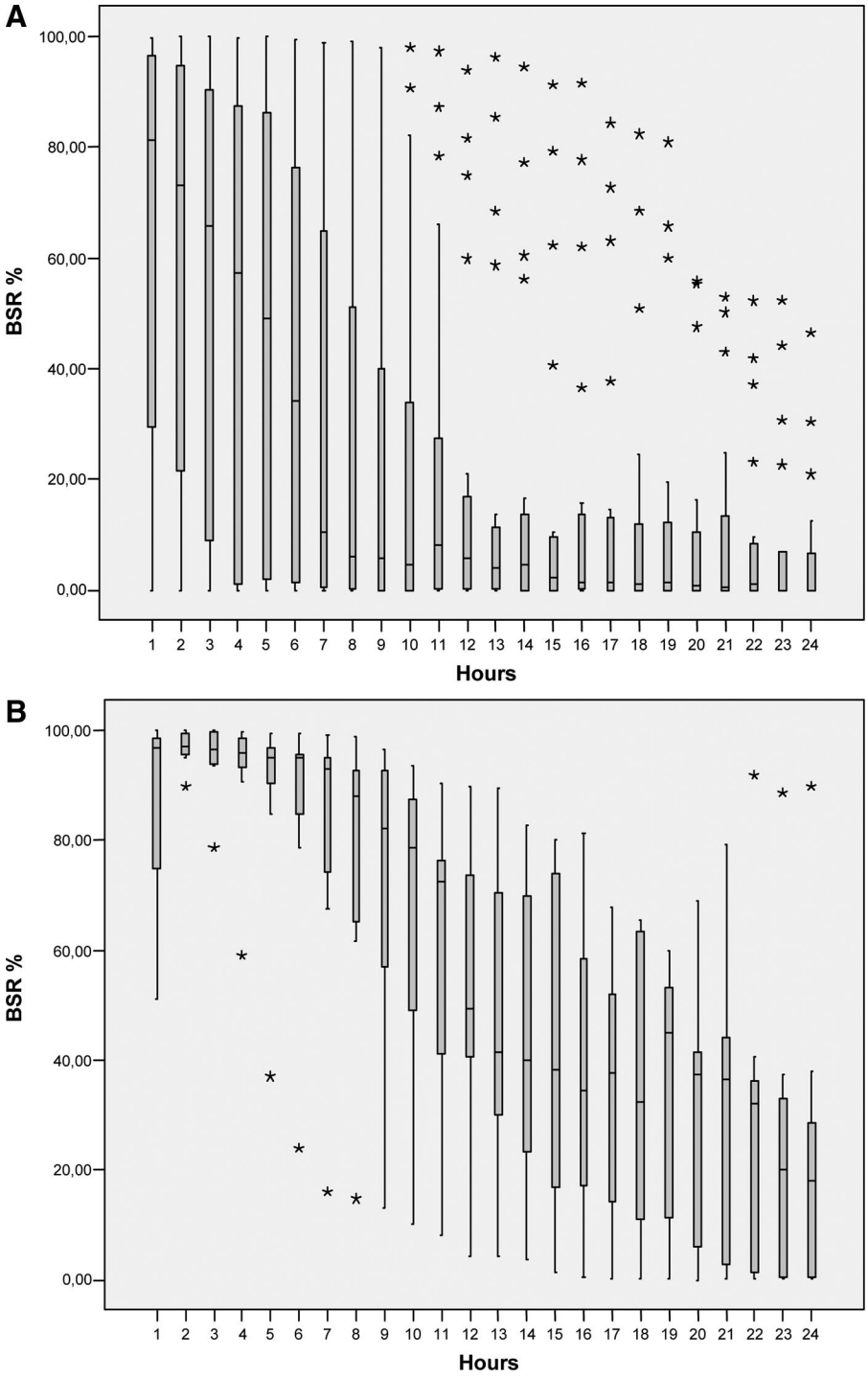

Figure 2. Evolution of burst-suppression ratio (*BSR*) between 1 and 24 hrs from the beginning of eletroencephalogram recording in the good outcome group (*A*), and in the poor outcome group (*B*). The *boxes* depict the distribution of hourly average values within the group. The *box* covers the distribution from 25th to 75th percentile. The *horizontal line within the box* represents the median value. The *whiskers* cover the distribution up to 1.5 times the box length further from the edges of the boxes. The values existing outside this range are shown as individual *asterisks* (*outliers*).

hrs/patient) were collected between 24 and 48 hrs. After rejection of the recordings with low-quality EEG signal or artifacts, 667 hrs (22.2 hrs/patient, 0–24 hrs) and 541 hrs (18.0 hrs/patient, 24–48 hrs) were subjected to further analysis. The preliminary analysis revealed that WSE values from channels Fp1-At1, Fp2-At2, At1-A1, and At2-A2 (Fig. 1) did not differ statistically, as evaluated by the p values of WSE for the discrimination of the outcome groups. WSE results are presented here for channel Fp1-At1.

Functional Outcomes

During the 6-mo follow-up, 21 patients had a best-achieved CPC of 1 or 2 (CPC 1: n = 13 patients; CPC 2: n = 8 patients); four patients had a best-achieved CPC of 3; and five patients had a best-achieved CPC of 4. At 6 mos after cardiac arrest, 21 patients were alive (CPC 1: n = 13; CPC 2: n = 7; CPC 3: n = 1) and nine patients had died. No patients remained in a persistent vegetative state. One patient with a primary CPC of 1 was discharged from the hospital, but died of recurrent cardiac arrest 92 days after initial cardiac arrest. Three others (CPC 3) died of collapse 13 to 22 days: two patients died of pneumonia, one patient died of an unknown cause. Five patients remained comatose until withdrawal of treatment. All patients with good outcomes returned home. The groups with good and poor neurologic outcomes were comparable in baseline demographic and clinical characteristics (Table 1).

EEG

All patients initially demonstrated a slow burst-suppression EEG pattern with long periods of suppression, which subsided gradually. Afterward, a low-amplitude rhythmic activity appeared. During hypothermia, EEG was continuous in 14 of 21 patients in the good outcome group (Table 2). After normothermia was reached, continuous EEG was detected in all except one patient in the good outcome group (Table 2). The EEG of that patient (with a final CPC of 2) revealed irregular discharge complexes without myoclonic status epilepticus. In the "good" outcome group, continuous EEG was found 22.0 hrs (range = 9.5–46.4 hrs) after hypothermia treatment had been started. Four of nine patients in the poor outcome group had continuous EEG 16.0 hrs (range = 6.9–24.8 hrs) after the start of hypothermia treatment. Three of those four patients had an abnormal ∈ coma-type pattern. Status epilepticus was diagnosed from the raw EEG in four patients; all four patients died in hospital without regaining consciousness. The difference in occurrence of continuous EEG between the outcome groups was not significant during hypothermia (p = .255), but was significant

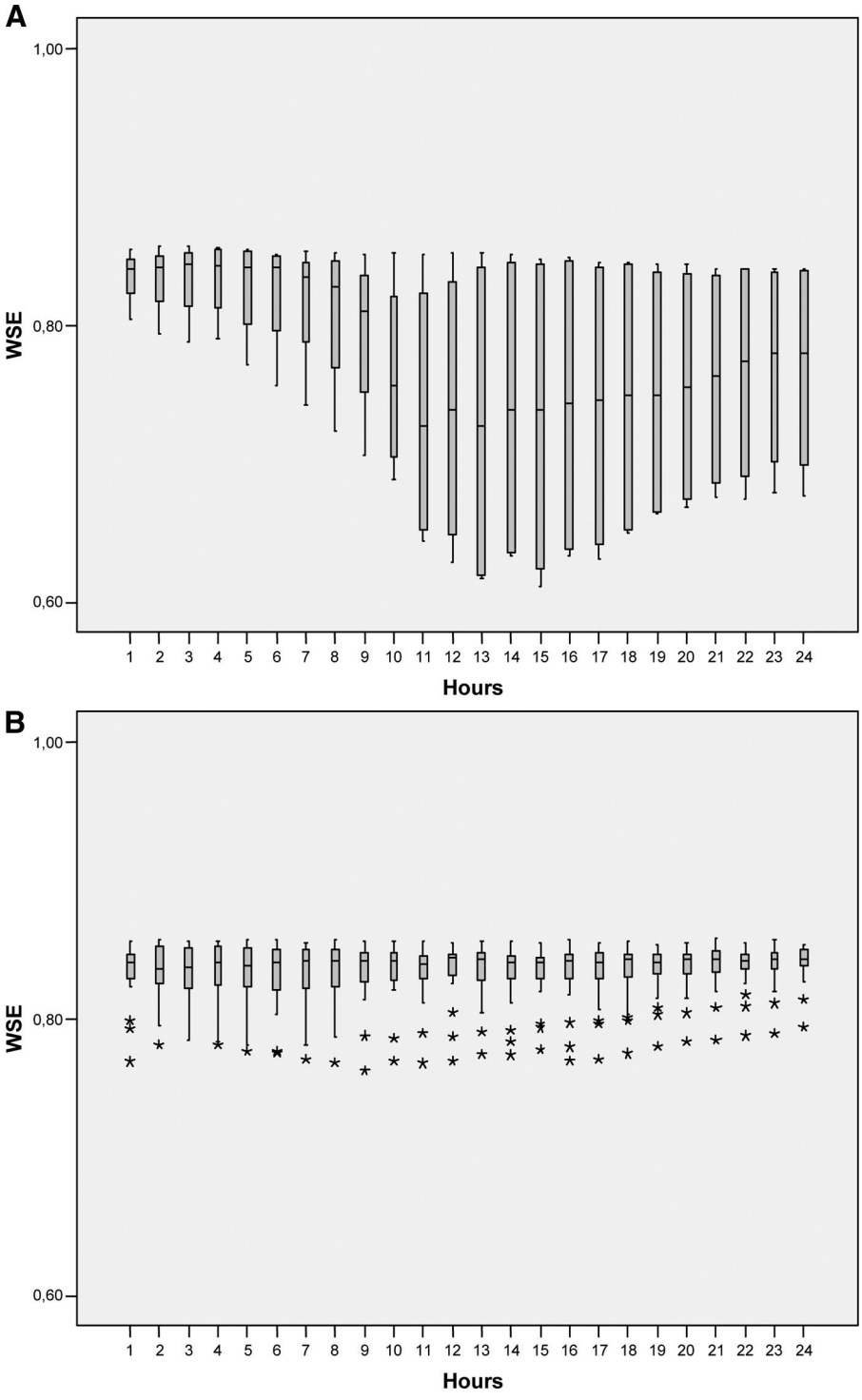

Figure 3. Evolution of wavelet subband entropy (*WSE*) between 1 and 24 hrs from the beginning of electroencephalogram recording in status epilepticus patients (*A*) and in nonstatus epilepticus patients (*B*). *C,* Evolution of WSE in status epilepticus patients. For each status epilepticus patient, 0 hr denotes the beginning of status epilepticus. The distribution of hourly WSE values between 12 hrs before and 24 hrs after onset of status epilepticus are shown. The *box* covers the distribution from 25th to 75th percentile. The *horizontal line within the box* represents the median value. The *whisker*s cover the distribution up to 1.5 times the box length further from the edges of the boxes. The values existing outside this range are shown as individual *asterisks* (*outliers*). The *boxes* depict the distribution of hourly average values within the group.

during normothermia ($p < .001$). Status epilepticus during normothermia was related to poor outcome ($p = .001$). Other EEG findings were not associated with outcome (Table 2).

Quantitative EEG Variables

BSR was significantly lower in patients with good outcomes during the first 24 hrs and 24 to 48 hrs after cardiac arrest (Table 3). The difference was more pronounced during hypothermia treatment (Fig. 2*A, B*). RE and SE were both significantly higher in the good outcome group during the first 24 hrs, but not during the second 24 hrs. WSE was slightly higher for patients in the good outcome group during the second 24 hrs (Table 3).

Between 24 and 48 hrs, WSE values were lower for status epilepticus patients compared with other patients ($p = .022$). In the first 24 hrs, the difference in WSE was nonsignificant ($p = .071$). The evolution of WSE in the first 24 hrs is illustrated in Figure 3*A* and *B* for patients with and without status epilepticus, respectively. The evolution of WSE for status epilepticus patients is presented in Figure 3*C*. The onset of status epilepticus for each patient (defined by the neurophysiologist as discharges over 50% of the time) was set to 0 hr, and hourly distributions of WSE from 12 hrs before onset to 24 hrs after onset are depicted.

Table 4 shows the sensitivities, specificities, positive prediction values, and negative prediction values for the prediction of poor outcome. The EEG variables WSE, BSR, SE, and RE are included in the table as well as the biochemical markers NSE and S100B. The thresholds of the variables are adjusted to maximize the number of correctly predicted outcomes. Table 5 presents the same information with thresholds of the variables adjusted for 100% specificity.

Biochemical Data and TCD

The biochemical results are summarized in Table 6. S100B values were lower in the good outcome group on arrival at the ICU ($p = .019$). After hypothermia treatment, NSE and S100B values were lower in the good outcome group ($p = .002$ for both outcome groups). NSE and S100B levels had a decreasing trend in the good outcome group, and an increasing trend in the poor outcome group, between the values measured on arrival at the ICU and at 35.5°C.

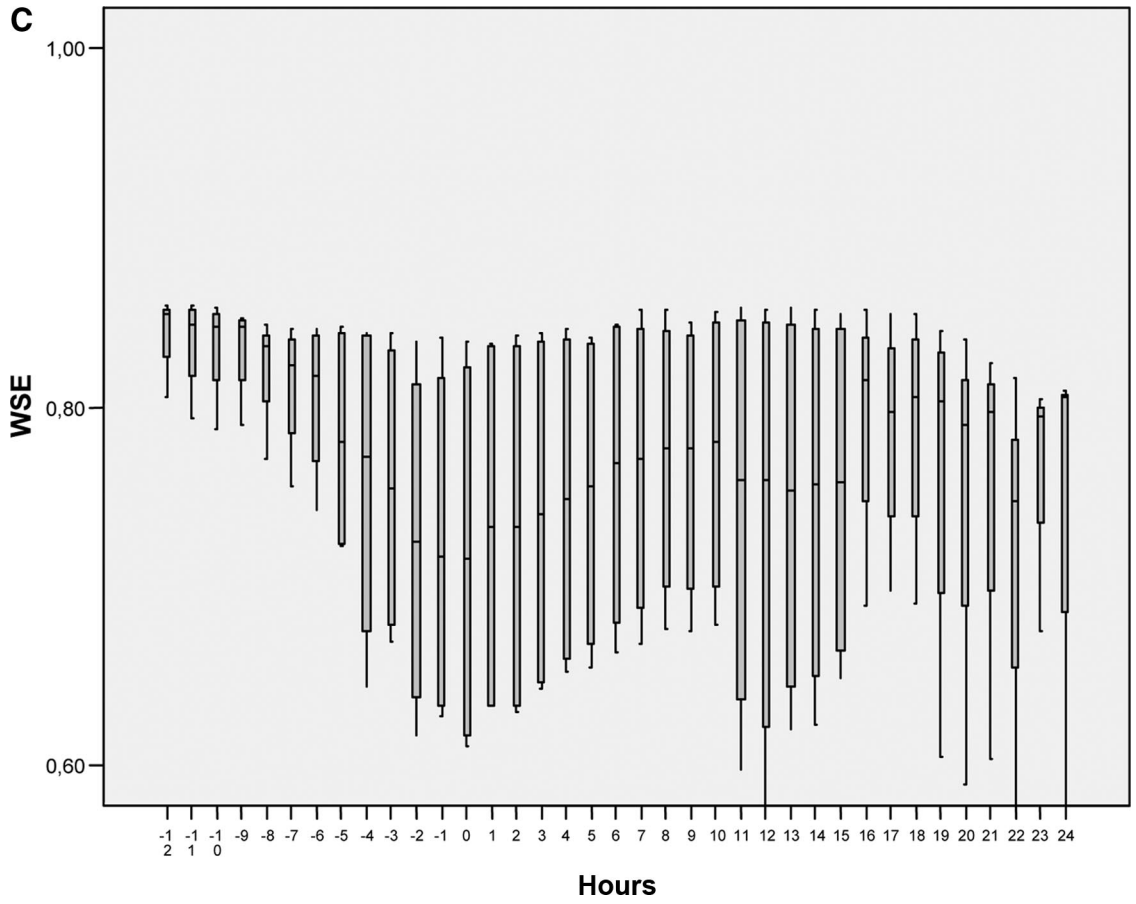

Figure 3. Continued.

Table 4. Sensitivities, specificities, positive prediction values, and negative prediction values for the prediction of poor outcome

Variable	Threshold	Sens	Spec	PPV	NPV
WSE 24 hrs	≤0.838	0.89	0.52	0.44	0.92
WSE 48 hrs	≤0.834	0.67	0.71	0.50	0.83
BSR 24 hrs	≥21.48	0.89	0.62	0.50	0.93
BSR 48 hrs	≥0.128	0.89	0.57	0.47	0.92
RE 24 hrs	≤12.53	0.78	0.81	0.64	0.89
RE 48 hrs	≤64.38	0.89	0.62	0.50	0.93
SE 24 hrs	≤11.84	0.78	0.81	0.64	0.89
SE 48 hrs	≤56.22	0.89	0.57	0.47	0.92
NSE 0 hr	≥18.90	0.44	0.48	0.27	0.67
NSE 24 hrs	≥21.40	0.56	0.62	0.38	0.76
NSE 35.5°C	≥20.20	0.78	0.71	0.54	0.88
NSE 48 hrs	≥19.50	0.78	0.80	0.63	0.89
NSE end	≥15.95	0.63	0.78	0.55	0.83
S100B 0 hr	≥0.355	0.78	0.81	0.64	0.89
S100B 35.5°C	≥0.095	0.89	0.76	0.62	0.94
S100B end	≥0.085	0.88	0.44	0.40	0.89

Sens, sensitivity; Spec, specificity; PPV, positive prediction value; NPV, negative prediction value; WSE, wavelet subband entropy; BSR, burst-suppression ratio; RE, response entropy; SE, state entropy; NSE, neuron specific enolase; S100B, protein 100B.

The thresholds of the variables are adjusted to maximize the number of correctly predicted outcomes.

The PI of TCD was lower in the good outcome group (0.85, range = 0.40–1.90) than in the poor outcome group (1.18, range = 0.90–1.90), $p = .004$.

DISCUSSION

The quantitative EEG variables BSR, RE, SE, and WSE were associated with the neurologic outcome after cardiac arrest in hypothermia-treated patients during the first 24 hrs (BSR, RE, and SE), and between 24 and 48 hrs (BSR and WSE). Status epilepticus after cardiac arrest is an ominous sign, with significantly lower WSE for status patients ($p = .022$), and was associated with death ($p = .001$).

Prediction of neurologic recovery after cardiac arrest requires several days (29, 30). Although we found an association with RE and SE, and discrimination between good and poor outcomes during the first 24 hrs, it should be noted that in burst-suppression EEG, SE and RE are calculated using burst-suppression information (21), and have a strong correlation with BSR (31, 32). BSR seems to maintain its association with poor outcome during the period of 24 to 48 hrs, unlike SE and RE. This suggests that the number of suppressed EEG periods is the relevant feature associated with outcomes. Although deep hypothermia may result in high BSR without an association with poor outcome, EEG is not significantly affected at a body temperature of 33°C (33, 34). The depressive effects of

Table 5. Sensitivities, specificities, positive prediction values, and negative prediction values for the prediction of poor outcome

Variable	Threshold	Sens	Spec	PPV	NPV
WSE 24 hrs	≤0.741	0.22	1.00	1.00	0.75
WSE 48 hrs	≤0.769	0.33	1.00	1.00	0.78
BSR 24 hrs	≥81.77	0.00	1.00	–	0.70
BSR 48 hrs	≥21.61	0.11	1.00	1.00	0.72
RE 24 hrs	≤1.89	0.00	1.00	–	0.70
RE 48 hrs	≤24.81	0.00	1.00	–	0.70
SE 24 hrs	≤1.80	0.00	1.00	–	0.70
SE 48 hrs	≤23.04	0.00	1.00	–	0.70
NSE 0 hr	≥33.30	0.00	1.00	–	0.70
NSE 24 hrs	≥52.35	0.11	1.00	1.00	0.72
NSE 35.5°C	≥40.30	0.11	1.00	1.00	0.72
NSE 48 hrs	≥59.25	0.11	1.00	1.00	0.72
NSE end	≥66.05	0.13	1.00	1.00	0.73
S100B 0 hr	≥0.815	0.33	1.00	1.00	0.78
S100B 35.5°C	≥0.195	0.33	1.00	1.00	0.78
S100B end	≥1.00	0.00	1.00	–	0.70

Sens, sensitivity; Spec, specificity; PPV, positive prediction value; NPV, negative prediction value; WSE, wavelet subband entropy; BSR, burst-suppression ratio; –, not applicable; RE, response entropy; SE, state entropy; NSE, neuron specific enolase; S100B, protein 100B.

The thresholds of the variables are adjusted for 100% specificity.

Table 6. Laboratory data in good and poor neurological outcome groups

	Good Outcome (n = 21)	Poor Outcome (n = 9)	*p*
NSE, μg/L			
0 hr	19.2 (7.9–32.3)	17.8 (12.8–28.2)	.449
24 hrs	19.8 (9.8–41.2)	22.0 (13.4–63.5)	.326
35.5°C	17.5 (9.8–33.7)	26.2 (18.0–43.1)	.002
48 hrs	15.3 (8.6–30.0)	26.8 (13.5–71.6)	.004
S-100B, μg/L			
0 hr	0.26 (0.06–0.64)	0.36 (0.15–3.90)	.019
35.5°C	0.08 (0.02–0.17)	0.14 (0.09–0.26)	.002
CK-MB, μg/L			
0 hr	8 (3–166)	10 (4–15)	.660
24 hrs	41 (5–959)	15 (7–90)	.187
48 hrs	112 (8–1000)	38.5 (9–158)	.084
TnT, μg/L			
0 hr	0.23 (0.03–5.17)	0.09 (0.03–0.75)	.275
24 hrs	0.76 (0.07–13.06)	0.42 (0.03–1.36)	.091
48 hrs	1.04 (0.03–12.78)	0.36 (0.03–3.74)	.205
Hb, g/L			
0 hr	130 (108–155)	128 (113–154)	.770
24 hrs	136 (104–164)	131 (100–151)	.533
48 hrs	120 (95–146)	129 (86–158)	.859
Gluc, mmol/L			
0 hr	10.1 (6.4–23.1)	13.2 (9.8–25.7)	.179
24 hrs	5.2 (3.9–8.0)	5.6 (4.3–7.2)	.372
48 hr	6.1 (4.0–6.9)	6.0 (3.5–7.4)	.891
Gluc, mg/dL			
0 hr	181.8 (115.2–415.8)	237.6 (176.4–462.6)	.179
24 hrs	93.6 (70.2–144.0)	100.8 (77.4–129.6)	.372
48 hrs	109.8 (72.0–124.2)	108.0 (63.0–133.2)	.891
Lact, mmol/L			
0 hr	4.2 (1.2–7.7)	4.1 (3.1–9.6)	.701
24 hrs	0.8 (0.4–1.2)	1.5 (0.5–5.0)	.134
48 hrs	1.0 (0.7–2.0)	1.0 (0.6–2.5)	.879
pH			
0 hr	7.24 (7.18–7.46)	7.24 (7.11–7.33)	.910
24 hrs	7.40 (7.23–7.46)	7.38 (7.28–7.46)	.563
48 hrs	7.39 (7.31–7.51)	7.36 (7.31–7.39)	.022

NSE, neuron specific enolase; S-100B, protein S-100B; CK-MB, creatinine kinase-MB; TnT, troponin T; Hb, hemoglobin; Gluc, glucose; Lact, lactate.

Median and range of laboratory tests measured on arrival (0 hr), after 24- and 48-hrs treatment S-100B and NSE were also measured after hypothermia treatment, when body temperature was 35.5°C.

hypnotics and analgesics on EEG readings during hypothermia treatment are obvious, but are equal in both groups. Benzodiazepines have been described to increase β frequency, but do not decrease EEG amplitude in frontal brain areas (35). Related to opioids, a slowing with an increase in the EEG amplitude has been demonstrated (36). In the study of Theilen et al (10), the use of midazolam and fentanyl as sedative agents did not increase the electroencephalogram silence ratio in healthy volunteers. However, barbiturates, propofol, etomidate, and γ-hydroxybuturate increased electroencephalogram silence ratio in a dose-dependent manner. In their study, electroencephalogram silence ratio was described as we describe BSR in the present study and the "critical range" 20% to 25% of electroencephalogram silence ratio measured 24 to 96 hrs after admission to the ICU correlated with poor outcome. In our study, a decision boundary at 20% BSR would have led to 89% sensitivity and 57% specificity in the detection of poor outcome from the mean BSR values of the first 24 hrs.

WSE has been previously used to quantify epileptiform activity during sevoflurane anesthesia (17). We demonstrated a gradual decrease in median WSE values 12 hrs before onset of status epilepticus (Fig. 3*C*). Status epilepticus in raw EEG was associated with poor outcome, as in previous studies (5, 13). All four patients with status epilepticus died. Status was visible only in EEG, as the patients received neuromuscular blockade, and was detected when data were analyzed off-line. Hence, no specific treatment to abolish status was undertaken. Our finding clearly showed that continuous EEG monitoring in patients with suspected ischemic encephalopathy should be adopted.

Decreasing WSE value might serve as an alert of status epilepticus for ICU careproviders unfamiliar with EEG. Only subhairline EEG channels were used in the present study, and therefore, possible localized epileptiform activity elsewhere was not detected.

Our study is in line with the study of Tiainen et al when considering NSE values (9). We also immediately found significant differences in S100B levels between the good and poor outcome groups on arrival at the ICU. Hachimi-Idrissi et al previously reported that serum S100B measured on patients' arrival at the hospital differed significantly between pa-

tients who recovered consciousness and those who did not, but their patients were not treated with hypothermia (37).

The limited number of patients in this study did not allow us to perform statistically reliable testing of the prediction properties of the measured indicators. Preliminary results of the prediction powers of selected indicators are presented in Tables 4 and 5. To examine the prediction power of a combination of EEG parameter and biochemical marker, an outcome prediction analysis with stepwise Bayesian approach was performed, which used WSE from the first 24 hrs and S100B when rewarmed (at 35.5°C) as inputs. The model predicted correctly the outcomes of 26 of 30 patients, resulting in sensitivity of 89%, specificity of 86%, positive prediction value of 73%, and negative prediction value of 95%. To validate these promising preliminary results, the classification model should be tested with a separate independent group of patients.

PI of TCD was significantly lower in the good outcome group. Our results are comparable with the study of Soehle et al, which indicated that PI >0.8 after subarachnoid hemorrhage was predictive of unfavorable outcome (38). Earlier PI >2.0 has been associated with increased intracranial pressure among comatose patients with liver failure (39).

Neuromonitoring of critically ill patients is still a challenge. Difficulties in interpreting raw EEG data and artifacts related to EEG data (40) have limited the use of EEG in critical care. Our results demonstrate that simple EEG variables of unstimulated hypothermic cardiac arrest patients could potentially differentiate good neurologic outcomes from poor ones. As a result, the ICU staff can interpret these variables without needing to consult a neurophysiologist. In the future, the use of quantitative EEG variables obtained from only a few registration electrodes applied below the hairline might lower the threshold to daily use of EEG monitoring.

CONCLUSIONS

Quantitative EEG variables may be used to differentiate patients with good neurologic outcomes from those with poor outcomes after out-of-hospital cardiac arrest. The predictive values need to be determined in a larger, separate group of patients.

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