FULL-LENGTH ORIGINAL RESEARCH

Generalized epileptiform discharges in postanoxic encephalopathy: Quantitative characterization in relation to outcome

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Summary

Objective: Electrographic status epilepticus is observed in 10–35% of patients with postanoxic encephalopathy. It remains unclear which electrographic seizure patterns indicate possible recovery, and which are a mere reflection of severe ischemic encephalopathy, where treatment would be futile. We aimed to identify quantitative electroencephalography (EEG) features with prognostic significance.

Methods: From continuous EEG recordings of 47 patients with generalized electrographic status epilepticus after cardiac arrest, 5-min epochs were selected every hour. Epochs were visually assessed and categorized into seven categories, including epileptiform discharges. Five quantitative measures were extracted, reflecting background continuity, discharge frequency, discharge periodicity, relative discharge power, and interdischarge waveform correlation. The best achieved outcome within 6 months after cardiac arrest was categorized as "good" (Cerebral Performance Category 1–2, i.e., no or moderate neurologic disability) or "poor" (CPC 3–5, i.e., severe disability, coma, or death).

Results: Ten patients (22%) had a good outcome. Status epilepticus in patients with good outcome started later (45 vs. 29 h after cardiac arrest, $p < 0.001$), more often ceased for at least 12 h (90% vs. 16%, $p = 0.02$), and was less often treated with antiepileptic drugs (30% vs. 73%, $p = 0.02$). Status epilepticus in patients with a good outcome always evolved from a continuous background pattern, as opposed to evolution from a discontinuous background pattern in 14 patients (38%) with a poor outcome. Epileptiform patterns of patients with good outcome had higher background continuity (1.00 vs. 0.83, $p < 0.001$), higher discharge frequency (1.63 vs. 0.90 Hz, $p = 0.002$), lower relative discharge power (0.29 vs. 0.40, $p = 0.01$), and lower discharge periodicity (0.32 vs. 0.45, $p = 0.04$).

Significance: Our results can be used to identify patients with possible recovery. We speculate that quantitative features associated with poor outcome reflect low neural network complexity, resulting from extensive ischemic damage.

KEY WORDS: Global cerebral ischemia, Continuous EEG monitoring, Critical care, Status epilepticus, Generalized periodic discharges, Quantitative EEG.

Electrographic status epilepticus occurs in 10–35% of comatose survivors of cardiac arrest[1–6] and has a strong association with poor outcome.[2,4,6–8] Due to the lack of widely accepted diagnostic criteria, several electrographic abnormalities may qualify as status epilepticus in postanoxic encephalopathy. It is unclear whether these various patterns reflect various grades of encephalopathy and prognosis, and for which of these patterns treatment with anticonvulsants may improve patients' outcome.[9,10] Although these have not been investigated systematically, certain

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Key Points

- Patients with postanoxic electrographic status epilepticus without preceding continuous background EEG always have a poor outcome
- A low epileptic discharge frequency and very regular interdischarge intervals are associated with poor outcome
- A continuous EEG background during status epilepticus and relatively low power of epileptic discharges are associated with good outcome
- Some electrographic seizure patterns may reflect severe ischemic encephalopathy, rather than a reversible epileptic phenomenon

differences between electrographic seizure patterns of patients with good and poor outcome have been observed. For example, generalized periodic discharges (GPDs) on a completely suppressed background are strongly associated with a poor outcome,[11] whereas patients with GPDs on a continuous, normal amplitude background may have a chance to survive.[12] Other possible determinants of poor outcome are based on case studies and include a very regular interdischarge interval, a constant discharge morphology, high spatial synchronization, and high relative power in the discharges.[8,11,13–15] In few small case series of survivors, opposite characteristics were observed.[3,16]

In addition to the seizure pattern itself, its temporal evolution may indicate possibility for recovery. Prolonged seizure duration is associated with a poor outcome in both convulsive and nonconvulsive status epilepticus.[17] Evolution of status epilepticus from a burst-suppression background, without preceding restoration of continuity, always resulted in a poor outcome in an observational study in 26 patients with postanoxic encephalopathy, whereas from patients with status epilepticus evolving from a continuous background, two survived.[6]

Seizure patterns that eventually lead to poor outcome appear to have a poor electrographic response to antiepileptic treatment.[4,15] Possible explanations are twofold. On one hand, electrographic seizures not responding to therapy tend to continue and may lead to secondary neuronal damage. On the other hand, not responding to medication may indicate severe encephalopathy instead of a true epileptic, reversible phenomenon.

Visual analysis of electroencephalography (EEG) in critical care suffers from poor interobserver agreement, despite efforts to introduce unified criteria.[18] Quantitative EEG overcomes this problem, and helps to save time in assessment of lengthy continuous EEG recordings. In addition, quantitative EEG allows for statistical analysis, which is an advantage for research purposes.

We aim to identify and quantify EEG characteristics of generalized postanoxic status epilepticus that help to select patients with or without possible recovery. We focus on seizure patterns and their temporal evolution, and use quantitative EEG features that reflect key features used in visual interpretation. We hypothesize that seizure onset before improvement to a continuous background, the absence of background continuity during seizures, a low discharge frequency, high periodicity, and high correlation between consecutive discharges indicate a poor prognosis.

Methods

Patients

Data were collected from two teaching hospitals in The Netherlands. Between July 2010 and September 2014, all subsequent comatose patients who were admitted to the intensive care unit (ICU) after cardiac arrest were included in a prospective cohort study on the predictive value of continuous EEG (cEEG) on outcome.[1] The Medical Ethics Committee Twente approved the protocol and waived the need for informed consent for EEG monitoring during the ICU stay and clinical follow-up. Patients were included in the current analysis if the EEG showed generalized electrographic seizures during the recording on visual analysis. We defined electrographic seizures as generalized spike-wave discharges at 3 Hz or faster, or clearly evolving discharges of any type at 4 Hz or faster, in accordance with standardized critical care EEG terminology.[18] Also included were generalized periodic discharges with a minimum frequency of 0.5 Hz. For continuous seizure activity, the minimum duration to qualify as status epilepticus was 30 min. Intermittent seizures of 5 min and longer, with maximum interseizure interval of 5 min were also included if the total seizure duration was >30 min. Rhythmic delta activity or burst-suppression patterns with epileptiform burst shapes were not included. Patients were excluded from the analysis if cEEG started later than 24 h after cardiac arrest or if they had any other concomitant severe brain injury (e.g., caused by trauma or stroke).

Outcome

The primary outcome measure was the best achieved cerebral performance category (CPC)[19] score in the first 6 months after cardiac arrest, assessed by telephone interviews at 3 and 6 months. This ordinal scale ranges from 1, indicating full recovery, to 5, indicating death. CPC scores were dichotomized into "good" (CPC 1–2, i.e., no or moderate neurologic disability) and "poor" (CPC 3–5, i.e., severe disability, coma, or death).

Other prospectively collected data were the following: gender, age, results of clinical neurologic evaluation (Glasgow Coma Scale scores, brainstem reflexes, and myoclonus), serum lactate levels, median nerve somatosensory

evoked potentials, all sedative medication, and medication for treatment of status epilepticus.

EEG recordings

EEG recordings were started as soon as possible within 24 h after patients' admission to the ICU, and continued until patients were awake or until the decision to withdraw treatment was made, with a maximum of 5 days. Twenty-one silver/silver chloride cup electrodes were placed on the scalp according to the international 10–20 system. Quantitative EEG analysis was performed offline. EEG data were not used for decisions regarding treatment withdrawal. However, treating physicians were not blinded to the EEG. Treatment of electrographic seizures was left to the discretion of the treating physician.

Selection of EEG epochs

Five minute EEG epochs were selected automatically every hour during the complete recordings. A computer algorithm, as used in a previous quantitative EEG study,[20] was applied to select only epochs that were free of artifacts. A movement artifact parameter was calculated as the relative fraction of high voltage signal (>200 μV), a muscle artifact parameter as the power ratio between high (25–40 Hz) and low (2–25 Hz) frequencies, and a loose electrode artifact parameter as the relative amount of zero signal (with standard deviation [SD] <1 μV for at least 1 s). A global artifact parameter was calculated from these three measures. Data from 10 min before and 10 min after a select time point were assessed and divided into segments of 30 s. The 10 consecutive segments with the lowest global artifact parameter were selected as final epoch. If the individual or global artifact parameters exceeded a predefined value, no epoch was selected for that hour. Before any further qualitative or quantitative analysis, all epochs were filtered by a zero-phase, sixth order Butterworth band-pass filter (0.5–30 Hz) and transformed to the longitudinal bipolar montage.

Qualitative categorization of EEG epochs

All epochs with raw EEG data were presented to a reviewer by the computer, in random order. The reviewer was blinded to the patients' clinical condition during the registration, the recording time of the epoch, and the patient's outcome. Epochs were visually inspected and placed in one the following categories: isoelectric, low voltage, burst-suppression, diffusely slowed, normal, or epileptiform. Isoelectric epochs were defined as epochs without visible EEG activity. Low voltage epochs were defined as epochs with visible EEG activity, but with all amplitudes below 20 μV. Burst-suppression was defined as the presence of clear increases in amplitude (bursts), followed by interburst intervals of at least 1 s with low-voltage activity (suppressions). Bursts were required to have EEG amplitudes >20 μV; otherwise the epoch was categorized as low voltage. Burst-suppression was further subdivided into "burst-suppression with identical bursts" and "burst-suppression without identical bursts." "Burst-suppression with identical bursts" was defined as burst-suppression in which shapes of subsequent bursts are identical.[21] Diffusely slowed epochs were defined as epochs with normal amplitude (>20 μV) for >90% of the time and dominant frequency in the delta or theta range (1–8 Hz). An epoch was categorized as normal if amplitudes were higher than 20 μV and the dominant frequency was 8 Hz or higher, irrespective of reactivity and anterior-posterior differentiation. Epileptiform epochs included electrographic seizures and GPDs. Electrographic seizures were defined as generalized spike-wave discharges or clearly evolving discharges of any type, without quantifiable interdischarge interval. GPDs were defined as a bilateral synchronous repetitions of a waveform with relatively uniform morphology and duration with a quantifiable interdischarge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals, with minimum frequency 0.5 Hz. We did not analyze electrographic seizures and GPDs separately, as the distinction between the two is often arbitrary in postanoxic encephalopathy. The visual analysis resulted in a time line of the temporal evolution of the EEG for every patient. The first epileptiform epoch on this time line defined the time of onset of status epilepticus. As a measure of the tendency of epileptic discharges to disappear, we determined whether epileptiform discharges ceased for at least 12 consecutive hours. We did not analyze the duration of status epilepticus, as we considered this problematic. First, epileptiform discharges might reappear after a seizure-free interval. Second, because of the decision to withdraw treatment, in many cases EEG recordings were terminated during ongoing status epilepticus. To indicate the reliability of the visual assessment, a random set consisting of 15% of all epochs was assessed by a second reviewer using the same protocol.

Quantitative EEG analysis

Quantitative EEG analysis and statistical analysis were performed with MATLAB (MATLAB and Statistics Toolbox Release R2013b, The MathWorks, Inc., Natick, MA, U.S.A.).

Assessment of background continuity

A background continuity parameter was extracted from all epochs to assess evolution of background continuity and to characterize epileptiform EEG patterns. The background continuity parameter C was defined as follows:

$$C = \frac{T_{norm}}{T_{norm} + T_{supp}}, \quad (1)$$

where T_{norm} is the amount of time for which the EEG has amplitude ≥10 μV, and T_{supp} is the amount of time for which the EEG is suppressed (<10 μV), with a minimum

suppression duration of 0.5 s. In fact, this continuity parameter is the inverse of the burst-suppression ratio.[22] This calculation was performed for all bipolar derivations individually and then averaged. The continuity index equals 0 for low-voltage or isoelectric EEG and 1 for continuous EEG activity. Burst-suppression patterns have values between 0 and 1. For the assessment of background continuity evolution in relation to the time of onset of status epilepticus, epochs were classified as continuous if the continuity index exceeded 0.9. This indicates that we accepted a maximum suppression time of 10% resulting from spontaneous fluctuations.

Quantitative analysis of epileptiform patterns

All EEG epochs that were marked as epileptiform during visual assessment were further analyzed with regard to four quantitative EEG measures, all closely related to visual observations: discharge frequency, discharge periodicity, relative discharge power, and discharge correlation. Calculations were performed per epoch and then averaged over all epileptiform epochs per patient.

All measures started with a detection algorithm for generalized epileptiform discharges. This algorithm is based on a method for detecting spike trains in neonatal seizures,[23] and is especially useful for detecting epileptiform discharges with a quantifiable interdischarge interval, as is the case for GPDs. It consists of a nonlinear energy operator to enhance signal with high amplitude and high frequency, defined as

$$\phi(n) = |(x_{n-1} \cdot x_{n-2}) - (x_n \cdot x_{n-3})|, \quad (2)$$

where $\phi(n)$ denotes the filtered signal, x_n the current sample of signal x, x_{n-1} the first sample before x_n, and so on. On the output of the nonlinear energy operator, we applied a moving average filter with a window size of 120 msec. Next, the signal was divided into epochs of 5 s, with overlap of 4 s. To each epoch, an adaptive threshold T was applied that was defined as

$$T = 0.6 \cdot [\sigma + q_3], \quad (3)$$

with σ and q_3 denoting the standard deviation and 75th percentile of the epoch, respectively. Unlike Deburchgraeve et al., we did not apply an additional "spikiness criterion" to further reduce the number the high-energetic segments. This was left out, because periodic discharges in postanoxic encephalopathy often have sharp instead of spiky waveforms,[18] and the "spikiness criterion" would exclude these types of discharges. If, after applying the adaptive threshold, the remaining high-energy segments were present in nine or more bipolar derivations at the same time, they were considered as "generalized discharges." Because most epileptiform discharges in postanoxic encephalopathy are generalized, we accepted lateralized periodic discharges not being detected. The minimum required duration of discharges was 60 msec and the minimum interval between subsequent discharges was 200 msec. The maximum duration of discharges was 0.5 s, because otherwise they would qualify as bursts, by definition.[18] A minimum amplitude for discharges of 20 μV was chosen to avoid electrocardiography (ECG) artifacts from being detected as epileptic discharges. The four features extracted are listed and explained in Table 1.

Statistical analysis

To test for differences in categorical variables between patients with good and poor outcome, we applied the chi-square test or Fisher's exact test, depending on the distribution. To test between-group differences for continuous variables, we applied Student's *t*-tests or Mann-Whitney *U* tests, where applicable. Agreement between the two observers in visual categorization of EEG epochs was tested with Cohen's kappa. All statistical testing was two-tailed, and p-values ≤ 0.05 were considered statistically significant.

Results

Patient characteristics

Of 288 patients who were monitored with cEEG after cardiac arrest, 47 had generalized electrographic status epilepticus and met the criteria for inclusion in this study. Patient characteristics are listed in Table 2, grouped by outcome. Patients with poor outcome did not differ from patients with good outcome in terms of age, gender, lactate level, timing and duration of cEEG recording, resuscitation characteristics, and sedation requirements. None of the patients with good outcome had a GCS score of 3 or absent pupillary light reflexes after 72 h. Myoclonus was observed in a majority (82%) of patients with poor outcome in the first 72 h after cardiac arrest, while only one patient with good outcome had myoclonus. A majority of patients was treated with antiepileptic drugs. More patients with poor outcome were treated (73 vs. 30%, p = 0.02), and if so, more different antiepileptic drugs were used, as compared with patients with a good outcome.

Qualitative assessment of EEG epochs

In total, 3,306 epochs were assessed by visual inspection. Of these epochs, 500 were assessed by a second reviewer. Cohen's kappa was 0.74 for the distinction between epileptiform and nonepileptiform epochs.

Temporal evolution of electrographic status epilepticus

Figures 1 and 2 show typical examples of the EEG evolution in patients with a poor and a good outcome, respectively. The patient in Figure 1 develops status epilepticus from a burst-suppression pattern, without preceding improvement to a continuous background. This is reflected by both the qualitative assessment and the quantitative

Table 1. Definitions of quantitative EEG features, extracted after applying the epileptiform discharge detection algorithm

Quantitative feature	Definition
Discharge frequency	1/(median interdischarge interval). The interdischarge interval is the difference in onset time between two consecutive generalized discharge segments.
Relative discharge power	The summed power in generalized discharge segments, divided by the total signal power. Calculated for each channel individually and then averaged over channels. Power was denoted as the square of the signal amplitude, averaged over time. Value [0–1]
Discharge periodicity	Fraction of all interdischarge intervals whose duration is no more than 25% shorter or longer than the median interdischarge interval. This feature was calculated only if the discharge frequency was >0.2 Hz. Value [0–1]
Discharge correlation	The average cross-correlation coefficient for each generalized discharge with its 10 preceding generalized discharges. Calculated for each channel individually and then averaged over channels. Value [0–1]. This feature was calculated only if the discharge frequency was >0.2 Hz

Table 2. Patient characteristics, grouped by outcome

	Poor outcome (CPC (3–5)	Good outcome (CPC 1–2)	p-Value
No. of patients	37	10	
Male	23 (62%)	7 (70%)	0.727
Age	68 (27–82)	68 (51–88)	0.848
Witnessed cardiac arrest	25 (68%)	7 (70%)	1.000
Resuscitation outside hospital	33 (89%)	9 (90%)	1.000
Initial rhythm VT/VF	19 (51%)	9 (90%)	0.083
No. of shocks	1 (0–16)	2 (0–5)	0.434
Cause of noncardiac origin	9 (24%)	1 (10%)	0.617
Lactate level (mmol/L)	2.5 (0.6–9.7)	1.5 (0.4–4.6)	0.177
Therapeutic hypothermia (33°C)	36 (97%)	9 (90%)	0.348
Sedation with propofol	34 (92%)	10 (100%)	1.000
Maximum dose (mg/kg/h)	2.7 (1.5–5.3)	3.6 (1.7–4.3)	0.130
Sedation with midazolam	16 (43%)	5 (50%)	0.734
Maximum dose (mg/kg/h)	0.14 (0.03–0.89)	0.14 (0.06–0.36)	0.924
Sedation with fentanyl	19 (51%)	7 (70%)	0.475
Maximum dose (μg/kg/h)	1.7 (1.0–2.9)	1.8 (1.3–2.6)	0.497
Sedation with remifentanil	7 (19%)	0 (0%)	0.318
Maximum dose (μg/kg/h)	6.3 (2.3–13)	–	–
Sedation with morphine	9 (24%)	2 (20%)	1.000
Maximum dose (mg/kg/h)	0.27 (0.20–0.65)	0.40 (0.22–0.58)	0.667
Treatment with antiepileptic drugs	27 (73%)	3 (30%)	0.023
Number of antiepileptic drugs	1 (0–3)	0 (0–2)	0.040
Treatment with phenytoin	17 (46%)	1 (10%)	0.065
Treatment with levetiracetam	8 (22%)	0 (0%)	0.147
Treatment with valproic acid	11 (30%)	3 (30%)	1.000
cEEG start time (h)	13 (3–24)	7 (2–17)	0.175
cEEG duration (h)	66 (20–217)	68 (59–166)	0.434
GCS ≥E1M2 at 72 h	7 (19%)	10 (100%)	<0.001
Present pupillary light reflexes at 72 h	33 (89%)	10 (100%)	0.113
Bilateral absent N20 response	16 (47%)	0 (0%)	0.066
Myoclonus observed within 72 h	32 (87%)	1 (10%)	<0.001

CPC, cerebral performance category; GCS, Glasgow Coma Scale score; VF, ventricular fibrillation; VT, ventricular tachycardia.
Numbers given as median (range) unless otherwise indicated.

continuity parameter. Note that background continuity improves with time, but never reaches values >0.9. Improvement of continuity is caused only by the increase in discharge frequency. Figure 2 shows the EEG evolution for a patient with good outcome. Note that, in contrast to Figure 1, the EEG readily improves to a continuous background, and remains continuous thereafter. Epileptiform discharges appear after background continuity has been reached. More clearly than for the patient in Fig. 1, discharges appear shortly after tapering sedative medication, and disappear quickly after the administration of an antiepileptic drug (phenytoin). The relative contribution of the discharges to the total signal power in this patient is low throughout time.

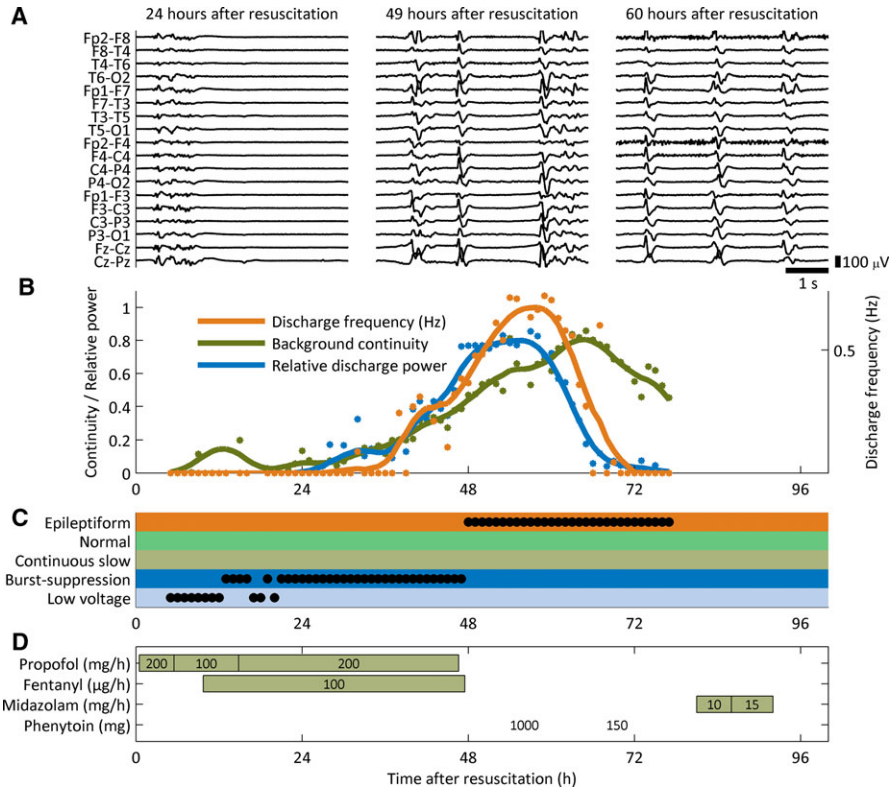

Figure 1.
Temporal EEG evolution of a patient with poor outcome. (**A**) Three samples of EEG at different time intervals. (**B**) Evolution of background continuity, discharge frequency, and relative discharge power over time. The dots represent the actual values, the line results from subsequently applying linear interpolation and a moving average filter with window length 5 h. (**C**) Results of categorization after visual interpretation. (**D**) Administered sedatives and antiepileptic drugs. Note: between 68 and 77 h, the detected discharge frequency drops suddenly. This occurred because during these hours the amplitude and spatial generalization of discharges had fallen below the detection threshold.
Epilepsia © ILAE

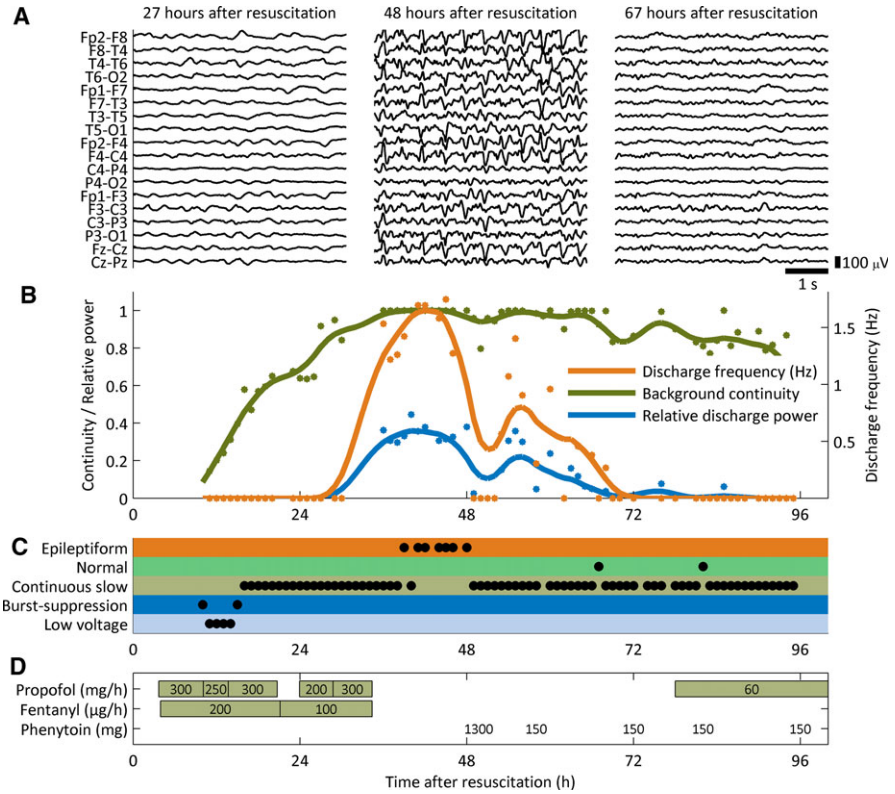

Figure 2.
Temporal EEG evolution of a patient with good outcome. (**A**) EEG samples at three instances of time. (**B**) Evolution of background continuity, discharge frequency, and relative discharge power over time. The dots represent the actual values, the line results from subsequently applying linear interpolation and a moving average filter with window length 5 h. (**C**) Results of categorization after visual interpretation. (**D**) Administered sedatives and antiepileptic drugs.
Epilepsia © ILAE

The upper part of Table 3 summarizes characteristics of the temporal evolution of electrographic status epilepticus for patients with poor and good outcome. All patients with good outcome improved toward a continuous EEG, defined as a background continuity parameter >0.9, before the onset of status epilepticus as compared with 62% of patients with

Table 3. Evolution of electrographic status epilepticus and quantitative EEG features of epileptiform epochs, grouped by outcome

	Poor outcome (CPC 3–5), n = 37	Good outcome (CPC 1–2), n = 10	p-Value
Evolution of status epilepticus			
Background continuity >0.9 before SE	23 (62%)	10 (100%)	0.02
Background continuity never >0.9	6 (16%)	0 (0%)	0.22
Time to onset of SE (h)	29 (13–56)	45 (39–62)	<0.001
Cessation of SE for at least 12 h	6 (16%)	9 (90%)	0.02
SE preceded by BS with identical bursts	26 (70%)	0 (0%)	<0.001
qEEG features of epileptiform epochs			
Background continuity	0.83 (0.43–1.00)	1.00 (0.92–1.00)	<0.001
Discharge frequency	0.90 (0.26–1.75)	1.63 (0.82–2.29)	0.002
Relative discharge power	0.40 (0.16–0.80)	0.29 (0.17–0.42)	0.01
Discharge periodicity	0.45 (0.08–0.85)	0.32 (0.20–0.57)	0.04
Discharge correlation	0.66 (0.30–0.87)	0.59 (0.30–0.64)	0.16

BS, burst-suppression; CPC, cerebral performance category; SE, status epilepticus; qEEG, quantitative electroencephalography.
Numbers given as median (range) unless otherwise indicated.

a poor outcome. Only 84% of patients with poor outcome ever improved to a continuous EEG. The median onset time of status epilepticus was 29 h after cardiac arrest for patients with poor outcome, and 45 h for patients with good outcome ($p < 0.001$). In patients with a good outcome, status epilepticus never started within 39 h after cardiac arrest. Epileptiform discharges were more likely to cease for at least 12 h in patients with good outcome (90% vs. 16%, $p = 0.02$). In 70% of patients with poor outcome, status epilepticus was preceded by burst-suppression with identical bursts as compared with none of the patients with a good outcome ($p < 0.001$).

Quantitative characterization of epileptiform epochs

Figure 3 shows two typical examples of observed EEG patterns, the result of the discharge detection algorithm, and the extracted quantitative EEG features. Figure 3A is a pattern that was observed in a patient with poor outcome. It shows generalized periodic discharges at regular intervals, with constant discharge morphology, high spatial synchronization, relative high power in the discharges, and a suppressed background, reflected by the extracted quantitative EEG features. The pattern in Figure 3B was observed in a patient with good outcome. It consists of periodic discharges that wax and wane, with evolving discharge morphology on a continuous, normal voltage background pattern. The interdischarge intervals are more variable, and spatial generalization is less obvious as compared with the pattern in Figure 3A. One can loosely state that pattern 3A is less "complex" and more "predictable" than pattern 3B.

In general, the discharge detection algorithm worked well, as illustrated in Figure 3. If we would define epochs as epileptiform if the detected discharge frequency was 0.5 Hz or higher, 78% of 3,306 epochs would be classified correctly, as compared with visual categorization. In the lower part of Table 3, comparisons of quantitative EEG features of epileptiform epochs of patients with poor and good outcomes are presented. Epileptiform epochs of patients with good outcome had higher background continuity (1.00 vs. 0.83, $p < 0.001$), higher discharge frequency (1.63 vs. 0.90 Hz, $p = 0.002$), lower relative discharge power (0.29 vs. 0.40, $p = 0.01$), and lower discharge periodicity (0.32 vs. 0.45, $p = 0.04$). Mean background continuity was never below 0.92 and mean discharge frequency was never below 0.82 Hz in patients with a good outcome. There was no statistically significant difference between patients with poor and good outcomes in correlation between subsequent discharge waveforms (0.59 vs. 0.66, $p = 0.16$).

Discussion

In this study, we present five quantitative EEG features of generalized status epilepticus in postanoxic encephalopathy in relation to possible recovery. Whereas previous studies relied on qualitative descriptions, we used quantitative EEG to overcome problems with interobserver agreement and to allow for statistical analysis. The selected quantitative EEG features are closely related to key aspects of visual assessment, which helps translating our results to clinical practice.

Unlike patients with a poor outcome, all patients with a good outcome improved toward a continuous EEG background pattern before the onset of status epilepticus. Outcome was always poor if status epilepticus developed during the first 36 h after cardiac arrest, the period with targeted temperature management and the associated sedative medication. Outcome was also invariably poor if electrographic status epilepticus was preceded by burst suppression with identical bursts. Seizure patterns of patients with good outcome showed higher background continuity, higher epileptic discharge frequency, lower relative discharge power, and lower discharge periodicity as compared with patients with poor outcome. Outcome was invariably poor when more than two antiepileptic drugs were needed to suppress seizure activity.

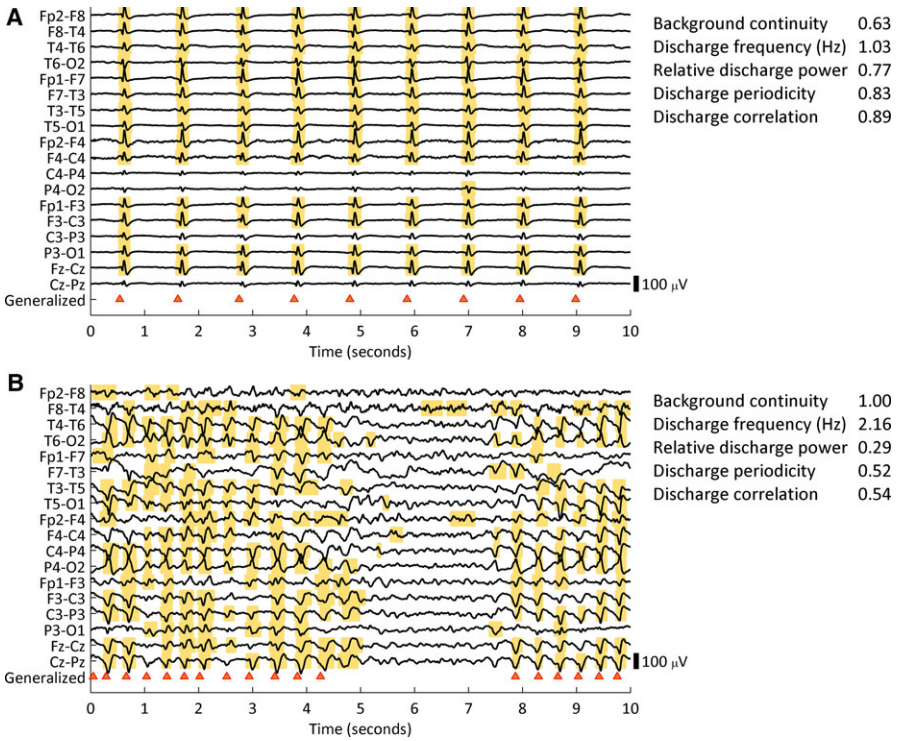

Figure 3.
Two examples of electrographic seizure patterns, as observed in study subjects. High-energetic segments selected by the detection algorithm are highlighted. Orange triangles at the bottom indicate when a generalized discharge is detected. (**A**) Typical example of electrographic seizure pattern as recorded from a patient with poor outcome. The pattern consists of generalized periodic discharges at regular intervals, with a constant morphology, high spatial synchronization, and relative high power in the discharges on a suppressed background. Note that all high-energetic segments are part of a generalized discharge. (**B**) Typical example of electrographic seizure pattern as recorded from a patient with good outcome. It consists of discharges that show evolving discharge morphology on a continuous, normal voltage background, where the interdischarge intervals are more variable, and spatial generalization is less obvious as compared with the pattern in **A**. Note that not all selected high-energy segments are discharges, and discharges with a low amplitude (below 20 μV) are not detected.

As compared with previous literature, the incidence of electrographic status epilepticus was high in our cohort. In addition, relatively many patients had a good outcome. In previous studies, the diagnosis of status epilepticus was often based on repetitive routine EEGs, typically applied later than 72 h after cardiac arrest, and the decision to perform EEG was often based on the presence of myoclonus.[2,3,8] In our study, electrographic seizure patterns leading to poor outcome had a longer duration and were more often accompanied by myoclonus, as compared with seizure patterns of patients with good outcome. Therefore, previous case series may have included a subsample of patients with a high probability of poor outcome. Early, self-limiting status epilepticus with a good outcome was probably not diagnosed. Another explanation for the relatively large fraction of patients with good outcome is the broad range of EEG patterns included in our study, as compared to previous work.

None of the 14 patients who developed status epilepticus before improvement to a continuous pattern survived. Moreover, 16% of patients with a poor outcome never improved toward a continuous background pattern. These results are in agreement with previous findings in a smaller case series of postanoxic status epilepticus[6] and with our own findings in an unselected population of postanoxic encephalopathy.[1] Apparently, early improvement toward a continuous background EEG is a key feature of recovery from postanoxic encephalopathy.

We chose to characterize electrographic seizure patterns by quantitative EEG features that closely resemble features assessed by visual analysis. Accordingly, the results can be used in clinical practice, where visual assessment is the gold standard and real-time quantitative EEG is often not available. However, for clinical decision making, differences between groups of patients with good and poor outcomes should ideally be translated into predictive values for individual patients. This would require a clear definition of threshold values, to be confirmed in a separate test set.

Seizure patterns of patients with a poor outcome differed from those with good outcome quantitatively, with more

background suppression, lower discharge frequency, and higher periodicity of discharges. These findings demonstrate that the damaged neural networks underlying electrographic seizures have a lower complexity in patients with poor outcome as compared with patients with good outcome. A lower network complexity reflects a greater extent of ischemic damage, indicating that, especially in patients with a poor outcome, "epileptiform" patterns are an expression of severe ischemic damage, rather than true epilepsy, which is potentially reversible by treatment with antiepileptic drugs. In a computer model, we have demonstrated that generalized periodic discharges may result from selective damage to excitatory synapses to inhibitory interneurons,[9] disrupting the essential balance between excitatory and inhibitory input in this microcircuit.[24] We speculate that in some patients this failure of excitatory input to inhibitory interneurons is irreversible; such persistent failure of synaptic transmission has indeed been suggested by Bolay and others.[25,26]

Patients with electrographic status epilepticus and poor outcome were more often treated with antiepileptic drugs and, if so, with more different drugs than patients with a good outcome. Still, seizures did not disappear in the majority of these patients. Many physicians treat electrographic status epilepticus after cardiac arrest, despite lack of evidence for a beneficial effect on patients' outcome. However, only one third of epilepsy experts treats these patients equally intensive as patients with overt status epilepticus.[27] Paradoxically, for most neurologists the threshold to treat patients with overt myoclonus is lower than for patients with nonconvulsive electroencephalographic seizures, whereas irreversible damage and a poor outcome are more likely in patients with myoclonus.[10] The effect of intensive antiepileptic treatment is currently under investigation in a randomized multicenter trial (NCT02056236).[28]

This study has limitations. First, all our findings are based on 5-min epochs that were automatically selected every hour during the first 72 h after cardiac arrest. Recurrent seizures lasting <60 min may therefore have been missed. However, epileptiform discharges in postanoxic encephalopathy usually do not disappear spontaneously within hours and will therefore most likely be detected, even using our limited temporal sampling. Second, the discharge detection algorithm was unable to classify 22% of all epochs correctly, as compared to visual analysis. However, our algorithm performed equally well as previously published seizure detection algorithms,[23,29,30] despite heterogeneity in discharge waveforms and background patterns. We considered the algorithm sufficiently reliable for adequate quantification and comparison of the studied parameters. Finally, our results may have been influenced by sedative agents. For example, propofol may induce discontinuities and—with high doses—burst-suppression patterns. However, in healthy brains, with the dosages that were used in our patients, the EEG remains continuous, with anteriorization of the alpha rhythm.[31] Moreover, maximum propofol doses were not significantly different in both outcome groups.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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