Value of electroencephalography for prognosis and treatment of comatose patients after circulatory arrest

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Abstract
All comatose patients after circulatory arrest initially have a severely abnormal disturbed electroencephalogram. The speed of normalisation is a robust contributor to prediction of outcome. Differences between patients with poor and good outcome are largest <24 hours after the arrest. Lasting suppression at ≥12 hours or synchronised patterns with >50% suppression at ≥24 hours are invariably associated with poor outcome. This includes burst suppression with identical bursts and generalised periodic discharges on a suppressed background. Recovery towards continuous patterns within 12 hours is strongly associated with a good outcome. Predictive values are highest at <24 hours despite the use of mild therapeutic hypothermia or sedative medication. Additional value of electroencephalography reactivity for the prediction of poor outcome is negligible. Computer-assisted analysis is equally reliable and may facilitate the use of the electroencephalogram at the bedside on intensive care units. Whether or not treatment of electrographic status epilepticus improves outcome is being studied in the Dutch multicentre randomised TELSTAR trial (NCT02056236).

Introduction
Comatose patients after circulatory arrest have an uncertain prognosis. Despite treatment on intensive care units, the outcome is poor in approximately half of all patients with out-of-hospital cardiac arrest as a result of severe postanoxic encephalopathy. Early recognition of patients without chances of recovery of brain function may prevent continuation of futile treatment and contribute to communication between doctors and patients.

The electroencephalogram (EEG) measures electrical potential differences between pairs of scalp electrodes. These primarily result from the sum of post-synaptic potentials, so EEG activity mainly reflects cortical synaptic activity. Since cortical synaptic activity is very sensitive to the effects of ischaemia, the EEG is sensitive to detection of ischaemia-induced cerebral malfunctioning. However, the specificity of pathological EEG activity for reliable prediction of poor or good outcome has long been uncertain. Over the past decade, various specific EEG patterns have been associated with poor or good outcome. It has become clear that the EEG can contribute to reliable outcome prediction if EEG patterns are classified in relation to the time since circulatory arrest. Here, we review the evidence of reliability of EEG-based outcome prediction, discuss treatment of epileptiform patterns and provide future perspectives.

Dynamics of brain activity after circulatory arrest
Within 10 to 40 seconds after circulatory arrest the EEG becomes iso-electric. Just as deep coma in the first hours after the arrest does not preclude full functional recovery, recovery of brain functioning is possible with iso-electricity on early EEG. In such cases improvement of EEG activity within 12 to 24 hours is vital. Absence of relevant improvement within that time window is invariably associated with a poor outcome. On the other hand, with recovery towards continuous, physiological rhythms within 12 hours, neurological prognosis is very good (figure 1).

EEG background pattern is at least as reliable as SSEP for prediction of outcome
Studies on the association between the EEG background pattern and outcome unrelated to timing of the EEG reported moderate predictive values. High predictive values have been found by EEG classification in relation to the time since circulatory arrest. Seven prospective cohort studies report on the value of ongoing suppression at 12 to 24 hours after circulatory arrest for prediction of poor outcome. Six studies partly overlap and together consist of 864 patients from five Dutch hospitals. The seventh included 100 patients from Yale University Hospital. In addition, there
is a retrospective cohort study in 211 patients from Italy. In all these studies, consecutive, unselected comatose patients after cardiac arrest were included. Continuous EEG measurements started within 12 to 24 hours and continued for at least three days, or until the patient died or recovered. Twenty-one electrodes were used according to the international 10-20 system. Patients were treated according to standard protocols for comatose patients after circulatory arrest. This indicated targeted temperature management [TTM] at 33°C with the necessary sedation [propofol, midazolam] in approximately three quarters, and TTM at 36°C in about one quarter of all included patients. Withdrawal of treatment was considered after ≥48-72 hours, during normothermia, and off sedation. Decisions were based on international guidelines including incomplete return of brainstem reflexes, treatment-resistant myoclonus, and bilateral absence of somatosensory evoked potentials [SSEPs]. The EEG in the first 2 hours was not taken into account. EEG analyses were performed offline, after registration. Evaluators were blinded to the time of the epoch since the arrest, treatment, and patient outcome. In the Dutch studies, outcome at six months was classified as good [cerebral performance category [CPC] 1 or 2 indicating no or moderate disability] or poor [CPC 3, 4 or 5, indicating severe disability, comatose or death]. In the American study, the best achieved score on the Glasgow Outcome Scale during admission was used [4 or 5 = good, 1, 2 or 3 = poor].

The eight studies together included 1175 patients. The proportion of patients with a poor outcome varied from 52-54% in the Dutch to 71% in the American studies. An iso-electric, suppressed (<10 μV) or low voltage (<20 μV) EEG at ≥24 hours after cardiac arrest was invariably associated with a poor outcome. Lasting suppression or synchronised patterns with >50% suppression at ≥12 hours after cardiac arrest were also invariably associated with a poor outcome. This included burst suppression with identical bursts. The sensitivity of these patterns together in identifying patients with a poor outcome varied between 28 and 84%. With no false positives in a total of 1175 patients, these EEG measures are at least as reliable as absent SSEP for prediction of poor outcome, since SEP guidelines are based on cohorts that included a total of 678 patients, and four false positives were reported. In addition, a continuous EEG pattern at 12 hours is strongly associated with a good neurological outcome. If patients with such a beneficial evolution of the EEG died, it was generally from failure of other organs than the brain, mostly the heart.

At least six other cohort studies, together including 1587 patients,

Figure 1. Upper panel: EEG pattern evolving from iso-electric to continuous, physiological activity within 12 hours. This evolution is favourable and the patient had a good outcome. Lower panel: EEG pattern evolving from nearly iso-electric to burst suppression and beyond 24 hours back to low voltage activity. This evolution is 100% unfavourable and the patient had a poor outcome
confirmed the reliability of EEG measures for prediction of poor outcome with false-positive rates of <2%,25-30 but terminology varies. Some researchers use the term ‘highly malignant’ EEG patterns. This is ill defined. However, suppressed patterns and synchronous patterns with >50% suppression were always included in definitions of ‘highly malignant’ patterns and invariably associated with a poor outcome. Reliability of burst suppression with identical bursts has been confirmed by visual EEG analysis in 522 patients with no false positives.25 A small cohort study suggests that repeated routine recordings are possibly as reliable as continuous EEG.32,33 In the group of patients with indeterminate outcome perspectives, EEG characteristics hold potential to predict the chance of permanent neurological deficits after late awakening, but this needs further research.34

**EEG background pattern contributes to multimodal prediction of poor outcome**

In at least four cohorts, EEG background pattern data were combined with clinical, biochemical, or SSEP data.11,21,25,35 The previously established high predictive values of absent pupillary light or SSEP responses at 48-72 hours for prediction of poor outcome were confirmed. Additionally, EEG parameters were found to be complementary to these conventional predictors. ‘Highly malignant’ EEG patterns are not always associated with absent SSEP,26 and in a substantial proportion of patients only one or two predictors of poor outcome were present. This indicates that with all tests together, more patients with a poor outcome could be identified reliably than with a single modality. Only in patients with a continuous EEG pattern with a dominant frequency of ≥8 Hz from 12 hours after cardiac arrest the SSEP was always present and this test therefore may be withheld.21,37

**Highest predictive value within 24 hours, despite medication**

Intuitively, analogous to the clinical course, the value of the EEG to predict patient outcome should increase with time elapsing since circulatory arrest.4 However, based on the data, the opposite turns out to be the case. Differences between patients with and without chances of recovery, as well as predictive values for good and poor outcome, are the largest within the first 24 hours after arrest.38 An important cause is the evolution towards aspecific EEG activity beyond 24 hours in many patients who eventually have a poor outcome.38 Whether or not such activity still includes qualitative or quantitative predictive characteristics warrants further study.26 Furthermore, it is generally considered that the EEG is not useful as a predictor during treatment with hypothermia or sedative medication.4 This is a misapprehension, not supported by data.10,11,39 Although ion channel kinetics and neurotransmitter release are temperature dependent, effects of few degrees are small and mild therapeutic hypothermia to 32ºC affects the EEG only mildly.40 Furthermore, propofol-induced EEG changes are well known. With the dosages that are mostly used during targeted temperature management, patterns remain continuous with anteriorisation of the ‘alpha’ rhythm, and iso-electricity will never be induced.41 If burst suppression is observed, bursts are heterogeneous and appear and disappear gradually.42 This is a physiological response of a relatively healthy brain to sedation and contrasts sharply with the observed pathological burst suppression patterns with identical bursts, with flat interburst intervals and abrupt transitions between suppression and burst activity (figure 2).24 Moreover, mean doses of sedative medication were lower in patients with unfavourable EEG patterns than in those with favourable patterns.9,10,20

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**Figure 2.** Two examples of burst suppression with identical bursts. The interval between the two epochs is approximately 24s in the left and 15s in the right panel. Note the similarity of shapes of subsequent bursts and the iso-electricity of interburst intervals. Burst suppression with identical bursts has only been observed after severe hypoxic or ischaemic brain damage and was invariably associated with a poor outcome.24
Burst suppression and status epilepticus

Burst suppression and status epilepticus are classically considered to be ‘unfavourable’ EEG patterns in patients with a postanoxic coma. However, specificity for predictions of poor outcome based on unselected groups of burst suppression or status epilepticus EEGs is moderate. This is because such patterns are also observed in a considerable proportion of patients who eventually have a good outcome. Only specific, well-defined subgroups of burst suppression or status epilepticus reliably predict a poor outcome.

Burst suppression

Burst suppression can be defined as an EEG with high amplitude activity of at least four phases and a duration of at least 500 ms [bursts], alternated by periods of low [<10 μV] or absent activity [suppressions] for more than 50% of the time. Such patterns can be physiological, for instance during early development, or pathological, for example in almost half of all comatose patients within the first 48 hours after cardiac arrest. Also, burst suppression can be induced by anaesthetics. The mechanisms involved in burst suppression are divergent, and range from reversible changes in synaptic functioning and Ca\(^{2+}\) homeostasis to selective neural death.

Characteristics to classify burst suppression patterns into subgroups with differences in clinical significance include the duration of the bursts and interburst intervals, maximum peak-to-peak voltage, area under the curve, the ratio of power in high versus low frequencies, and combinations with other pathological patterns, such as generalised periodic discharges. For example, longer suppressions are associated with poorer recovery in patients with postanoxic coma. Extreme similarity of burst shape is a distinct feature of some burst suppression patterns, which are classified as ‘burst suppression with identical bursts’ (figure 2): subsequent bursts in a particular channel are almost ‘photographic’ copies. Burst suppression with identical bursts was not observed in a series of 240 EEGs during anaesthesia or traumatic brain injury. Otherwise, this pathological EEG pattern may be seen in up to 20% of patients with postanoxic encephalopathy and a poor outcome, mostly on the first or second day. Burst suppression with identical bursts indicates severe encephalopathy and is invariably associated with a poor outcome.

Status epilepticus

The reported incidence of electrographic status epilepticus in comatose patients after cardiopulmonary resuscitation varies from 10 to 35% and depends on diagnostic criteria. Distinct epileptiform patterns, with evolving seizures, are rare. Other rhythmic activity, such as generalised periodic discharges or rhythmic delta activity, is more common. On the EEG, potential reversibility of status epilepticus in postanoxic coma is associated with evolution from patterns with continuous background activity, as opposed to evolution from a discontinuous background pattern. Furthermore, as compared with epileptiform patterns of patients with a poor outcome, in patients who eventually recovered, such patterns had a higher background continuity, higher discharge frequency [0.90 vs. 1.63 Hz], lower relative discharge power, and lower discharge periodicity (figure 3).
EEG after circulatory arrest

Apart from classification, the usefulness of treatment of electrographic status epilepticus after circulatory arrest is unclear. Ambivalence in this respect is reflected by the way these patterns are treated by Dutch and American epilepsy experts: approximately two thirds give antiepileptic drugs, but only one third treats as aggressively as in clinically overt status epilepticus. For most neurologists the threshold to treat patients with overt myoclonia is lower than for patients with non-convulsive electrographic seizures. However, irreversible damage is probably even more likely in patients with myoclonia, since the risk of a poor outcome is larger and neuronal necrosis more common.

In a retrospective cohort study of 139 patients, non-standardised, moderately intensive treatment with antiepileptic drugs did not improve outcome of electrographic status epilepticus after cardiac arrest. Effects of intensive treatment according to status epilepticus guidelines is currently being studied in the randomised, multicentre Treatment of Electroencephalographic STatus epilepticus After cardiopulmonary Resuscitation [TELSTAR] trial [NCT02056236; www.TELSTARtrial.nl].

**Figure 4.** Case 1 A-C: three EEG epochs at 5, 12 and 20 hours after cardiac arrest (CA), showing a favourable evolution towards a continuous EEG pattern within 24 hours. This is strongly associated with a good outcome. Case 2 A-C: Three EEG epochs showing an indeterminate evolution. At t=27 hours after arrest, the EEG still shows significant suppressions intermixed with delta and theta activity. Outcome is uncertain. Lower panels: quantitative analysis of the EEG patterns above with the Cerebral Recovery Index (CRI). Corresponding epochs are indicated with A-C. Case 1 shows an increase towards CRI >0.5 within 24 hours, with a final CRI=0.9. This is strongly associated with good outcome. For Case 2, CRI ≤0.5 at all points in time and CRI=0.2 at 24 hours. This is strongly associated with a poor outcome. Note that in both patients the EEG is nearly isoelectric in the first hours of the recording. In case 2, prognosis remains uncertain with visual analysis of the EEG, but can be classified as poor with use of the CRI.
EEG reactivity

EEG reactivity can be defined as any change in frequency or amplitude of the EEG background pattern resulting from application of an external stimulus.\textsuperscript{73,74} However, consensus about the characteristics of changes in a responsive EEG has long been lacking.\textsuperscript{77} External stimulation typically consists of auditory [shouting or clapping], somatosensory [painful pressure to the nail bed or supraorbital nerve], or visual [passive eye opening] input.\textsuperscript{78}

Absent reactivity to external stimulation of the EEG background pattern is much studied as a potential predictor of poor outcome of comatose patients after circulatory arrest. Two prospective and one retrospective cohort studies report strong associations between absent EEG reactivity and poor outcome.\textsuperscript{106} However, these results could not be replicated with a recent systematic multicentre study, and the additional predictive value of absent EEG reactivity testing, in addition to the EEG background pattern, was futile.\textsuperscript{79} Otherwise, adequate EEG reactivity to stimuli within the first 48 hours was strongly associated with good recovery.\textsuperscript{14,79,82}

Computer-assisted analysis

Application of the EEG on the intensive care unit is limited by the complexity of the signal, which typically cannot be interpreted by general intensive care nurses or staff. Computer-assisted analysis may help.\textsuperscript{83} Techniques to assist in the interpretation of continuous EEG background patterns include time frequency trend curves,\textsuperscript{84,85} quantification of hemispheric asymmetry,\textsuperscript{86} and an explicit classification of the EEG in common categories [e.g. iso-electricity, burst suppression or diffusely slowed patterns].\textsuperscript{27}

A few articles present techniques specifically aiming at outcome prediction in patients with a postanoxic encephalopathy. One of the earliest studies is on the use of amplitude-integrated EEG [aEEG].\textsuperscript{88} In a prospective cohort of 34 patients, all 20 patients with a continuous aEEG pattern at normothermia regained consciousness. All 14 patients with flat patterns, burst suppression, or status epilepticus aEEG patterns died in hospital.\textsuperscript{85,88} Other quantitative EEG features studied include the burst suppression ratio and entropy measures, with differences between patients with good and poor outcome on a group level, but limited predictive value for individual patients.\textsuperscript{12,89}

The Cerebral Recovery Index [CRI] was introduced in 2013 and is based on a combination of features, including amplitude and continuity, derived from an 18-channel EEG recording.\textsuperscript{90,91} The CRI is normalised in the range [0-1], with 0 indicating severe encephalopathy and 1 indicating normal brain functioning. In independent training and test sets using deep learning, CRI at 12 and 24 hours after cardiac arrest predicted poor outcome without false positives at 58% sensitivity and good outcome at a specificity of 95% and a sensitivity of 48% (figure 4).\textsuperscript{92} Note the importance of evolution in time: in both groups there is improvement of the mean EEG pattern. However, in patients with a good outcome, mean improvement is twice as fast as in patients with a poor outcome.

Conclusion

In comatose patients after circulatory arrest, the EEG background pattern in the first 24 hours provides reliable information on the severity of encephalopathy and enables reliable prediction of outcome in 40-50% of patients, despite treatment with hypothermia or sedative medication. For poor outcome prediction, the EEG is as reliable as and complementary to the SSEP. The EEG is the first modality to also allow prediction of a good outcome. Computer-assisted interpretation of the EEG may assist in outcome prediction and facilitate bedside use at intensive care units. Epileptiform patterns are of unknown significance and effects of treatment with antiepileptic drugs are uncertain. Whether or not treatment of electrographic status epilepticus improves outcome is being studied in the randomised multicentre Treatment of Electroencephalographic SThatus epilepticus After cardiopulmonary Resuscitation [TELSTAR] trial [NCT02056236].

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