Review

EEG in postanoxic coma: Prognostic and diagnostic value

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Article history:
Accepted 1 February 2016
Available online 11 February 2016

Keywords:
EEG
Postanoxic encephalopathy
Postanoxic coma
Outcome prediction
Electrographic status epilepticus

Abstract

Evolution of the EEG background pattern is a robust contributor to prediction of poor or good outcome of comatose patients after cardiac arrest. At 24 h, persistent isoelectricity, low voltage activity, or burst-suppression with identical bursts predicts a poor outcome without false positives. Rapid recovery toward continuous patterns within 12 h is strongly associated with a good neurological outcome. Predictive values are highest in the first 24 h, despite the use of mild therapeutic hypothermia and sedative medication. Studies on reactivity or mismatch negativity have not included the EEG background pattern. Therefore, the additional predictive value of reactivity parameters remains unclear. Whether or not treatment of electrographic status epilepticus improves outcome is studied in the randomized multicenter Treatment of Electroencephalographic Status epilepticus After cardiopulmonary Resuscitation (TELSTAR) trial (NCT02056236).

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1. Introduction

Comatose patients after cardiac arrest have an uncertain prognosis. Despite treatment on intensive care units, approximately half have a poor outcome as a result of severe postanoxic encephalopathy (Zandbergen et al., 1998). 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. Absent somatosensory evoked potential (SSEP) responses and absent pupillary or corneal reflexes at 72 h after cardiac arrest are included in current guidelines as reliable predictors of a poor outcome (Sandroni et al., 2014; Nolan et al., 2015). However, these measures have a low sensitivity for detection of an eventual poor outcome: only ~20% of patients without chances of recovery can be identified (Zandbergen et al., 2006; Cloostermans et al., 2012).

Electroencephalography (EEG) measures electrical potential differences between pairs of scalp electrodes. These potential differences primarily result from the sum of synchronous inhibitory and excitatory postsynaptic potentials, caused by dendritic currents of many aligned cortical pyramidal cells, in turn creating electrical dipoles between soma and apical dendrites. Thus, EEG activity mainly reflects cortical synaptic activity (van Putten, 2014). Since cortical synaptic activity is very sensitive to the effects of hypoxia, the EEG is sensitive to detection of hypoxia-induced cerebral damage (Hofmeijer and van Putten, 2012). However, the specificity of pathological EEG activity for reliable prediction of poor outcome has long been uncertain (Sandroni et al., 2014). With this review, we show that specific pathological or physiological EEG patterns allow an accurate prediction of either good or poor outcome of patients with postanoxic encephalopathy, if patterns are adjudicated in relation to time since cardiac arrest. Epileptiform patterns, including electrographic status epilepticus, are of unknown significance, and treatment effect are indistinct. Parts of this article have been published previously in a Dutch language journal (Hofmeijer et al., 2016).

2. Dynamics of brain activity after cardiac arrest

Within ten to forty seconds after circulatory arrest the EEG becomes isoelectric (van Dijk et al., 2014) reflecting massive cortical synaptic arrest (Hofmeijer and van Putten, 2012). Just as deep coma in the first hours after cardiac arrest does not necessarily preclude full functional recovery, recovery of brain function is possible, even if the EEG is isoelectric. However, timely improvement is vital. In case of unconsciousness after cardiac arrest, lack of improvement on timescales of several days is associated with a poor prognosis (Zandbergen et al., 1998). Analogous, EEG activity has to improve within 24 h. Absence of relevant improvement within that time window is invariably associated with a poor outcome (Tjepkema-Cloostermans et al., 2015; Hofmeijer et al., 2015a; Sivaraju et al., 2015). Otherwise, with recovery toward continuous, physiological rhythms within 12 h, neurological prognosis is very good. In that case, patients’ prognosis depend on damage to other organs than the brain (Tjepkema-Cloostermans et al., 2015; Hofmeijer et al., 2015a).

The relevance of ‘time-to-appearance’ of particular EEG activity has first been described in the 1980’s, before the use of mild therapeutic hypothermia (Jørgensen and Malchow-Møller, 1981; Jørgensen and Malchow-Møller, 1981a,b). In patients with a postanoxic encephalopathy and an isoelectric EEG immediately upon resuscitation, analysis of serial EEG recordings with a duration of 6–8 h, repeated at intervals of 4–24 h during the first week, showed that restoration of continuous EEG activity within 8 h predicted good outcome. Otherwise, patients with a poor neurological outcome showed slower or no recovery of physiological EEG rhythms.

3. Classification of the EEG background pattern in postanoxic encephalopathy

The EEG background pattern in postanoxic encephalopathy can be visually classified as one of six relatively easily recognizable categories: (i) iso-electric, (ii) low voltage (<20 μV), (iii) burst-suppression (including the subgroup of “burst-suppression with identical bursts”), (iv) epileptiform (status epilepticus and generalised periodic discharges), (v) continuous activity with frequencies lower than 8 Hz (diffusely slowed EEG), and (vi) continuous activity with frequencies ≥8 Hz (“normal” EEG) (Cloostermans et al., 2012; Hirsch et al., 2013; Hofmeijer et al., 2014b; Gaspard, 2015). Iso-electric, low voltage, and “burst-suppression with identical bursts” are unfavorable patterns. Patterns with continuous activity, either diffusely slowed or normal, are favorable. Other are uncertain or intermediate. Transitions are usually gradual, in hours (Fig. 1) (Cloostermans et al., 2012).

4. Evolution of the EEG background pattern is a reliable outcome predictor

Studies on the association between the EEG background pattern and outcome unrelated to timing of the EEG since cardiac arrest found moderate predictive values (Zandbergen et al., 2006; Wennervirta et al., 2009; Kawai et al., 2011; Rittenberger et al., 2012; Rossetti et al., 2012; Legriel et al., 2013). Four prospective cohort studies report on the value of evolution of the EEG background in time. Three studies partly overlap and together consist of 277 patients from two Dutch hospitals (Cloostermans et al., 2012; Tjepkema-Cloostermans et al., 2015; Hofmeijer et al., 2015a). The fourth counts 100 patients from Yale University Hospital (Sivaraju et al., 2015). In all studies, consecutive, unselected comatose patients after cardiac arrest were included. Continuous EEG measurements started within 12–24 h and continued for at least three days, or until a patient died or completely recovered. Twenty-one electrodes were used according to the international 10–20 system. Patients were treated according to standard protocols for comatose patients after cardiac arrest. This indicated targeted temperature management to 33 °C with the necessary sedation (propofol, midazolam) in the vast majority. Withdrawal of treatment was considered after ≥72, during normothermia, and off sedation. Decisions were based on international guidelines including incomplete return of brainstem reflexes, treatment resistant myoclonus, and bilateral absence of evoked SSEPs (Wijdicks et al., 2006). The EEG within 72 h was not taken into account. EEG analyses were done off-line, after the registrations. To this end, EEG epoch of five minutes at 12, 24, 48, and 72 h after cardiac arrest were selected by the computer and randomly presented to two of three evaluators. Evaluators were blinded to the time of
the epoch since cardiac arrest, treatment, and patient outcome. Patterns were classified as explained above. In the Dutch studies, outcome at six months was classified as the score on the Glasgow–Pittsburgh “Cerebral Performance Category” (CPC), dichotomized as good (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 proportion of patients with a poor outcome varied from 52% to 54% in the Dutch studies to 71% in the American. A lasting isoelectric or low voltage (<20 µV) pattern at 24 h after cardiac arrest was invariably associated with a poor outcome in all cohorts. In two studies, burst suppression with identical bursts was also invariably associated with a poor outcome (0 false positives, 100% specificity, narrow confidence intervals, Table 1) (Hofmeijer et al., 2015a; Sivaraju et al., 2015). The sensitivity of these patterns together to identify patients with a poor outcome varied between 28% and 84%. A continuous pattern with physiological rhythms at 12 h, either diffusely slowed or normal, was strongly associated with a good outcome. If patients with such a beneficial evolution of the EEG died, it was always from failure of other organs than the brain, mostly the heart.

Table 1

<table>
<thead>
<tr>
<th>Predictive outcome</th>
<th>Specitivity (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable EEG pattern at 12 h</td>
<td>Good</td>
<td>91%* (86–95)</td>
<td>55% (46–64)</td>
<td>84%* (75–91)</td>
</tr>
<tr>
<td>Unfavorable EEG pattern at 24 h</td>
<td>Poor</td>
<td>100% (98–100)</td>
<td>42% (36–49)</td>
<td>100% (96–100)</td>
</tr>
<tr>
<td>Absent pupillary light responses at 48 h</td>
<td>Poor</td>
<td>100% (97–100)</td>
<td>17% (12–25)</td>
<td>100% (86–100)</td>
</tr>
<tr>
<td>Absent SSEP at 72 h</td>
<td>Poor</td>
<td>100% (90–100)</td>
<td>100% (34–54)</td>
<td>100% (92–100)</td>
</tr>
<tr>
<td>Unfavorable EEG pattern at 24 h, absent pupillary light responses at 48 h, or absent SSEP at 72 h</td>
<td>Poor</td>
<td>100% (97–100)</td>
<td>100% (41–58)</td>
<td>100% (95–100)</td>
</tr>
</tbody>
</table>

The first cohort included 277 patients from two Dutch hospitals (Hofmeijer et al., 2015a), the second 100 patients from Yale University Hospital (Sivaraju et al., 2015); 220 patients had a poor outcome, 100 patients had a good outcome; favorable = continuous activity, either diffusely slowed or normal; unfavorable = isoelectric, low voltage (<20 µV), or burst suppression with identical bursts; EEG = electroencephalography; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

* Patients with a favorable EEG pattern and a poor outcome died as a result of failure of other organs than the brain.

** Predictive values based on the Dutch cohort, only.
the brain, mostly the heart. With regard to prognostication, a small cohort study suggests that repeated routine recordings are possibly as reliable as continuous EEG (Alvarez et al., 2013).

5. EEG background pattern contributes to multimodal outcome prediction

In two studies, EEG background patterns data were combined with clinical, biochemical, and other electrophysiological (SSEP) data (Hofmeijer et al., 2015a; Sivaraju et al., 2015). The previously established high predictive values of absent pupillary light responses at 48–72 h and absent SSEP response at 72 h were confirmed. Additionally, EEG parameters were found to be complementary to these conventional predictors: in a substantial proportion of patients only two or three predictors were present, so that all tests together could reliably identify more patients with a poor outcome (50–84%) than a single modality (Table 1).

6. Highest predictive value within 24 h, despite medication

Intuitively, analogs to the clinical course, the value of the EEG to predict patient outcome increases with time elapsing since cardiac arrest (Sandroni et al., 2014). However, based on the data, the opposite turns out. Differences between patients with and without chances of recovery, as well as predictive values for good and poor outcome, seem to be the largest within the first 24 h after cardiac arrest (Hofmeijer et al., 2015b). An important cause is the evolution toward aspecific EEG activity beyond 24 h in many patients who eventually have a poor outcome (Hofmeijer et al., 2015a). Whether or not such activity still includes qualitative or quantitative predictive characteristics remains to be elucidated.

Also, it is generally considered that the EEG is not useful as a predictor during treatment with hypothermia or sedative medication (Sandroni et al., 2014). This is a misapprehension, not supported by data (Rossetti et al., 2007; Hofmeijer et al., 2015a; Sivaraju et al., 2015). Although ion channel kinetics and neurotransmitter release are temperature dependent, effects of few degrees are small and mild therapeutic hypothermia to 32 °C hardly affects the EEG (Schomer and Lopes da Silva, 2011). Furthermore, propofol induced EEG changes are well known. In the dosages that were used, patterns remain continuous with anteriorization of the “alpha” rhythm and will not induce iso-electricity (Hindriks and van Putten, 2012). If burst-suppression is induced, bursts are heterogeneous and appear and disappear gradually (Reddy et al., 1992). This is a physiological response of a relatively healthy brain to sedation and contrasts with the observed patho- logical burst suppression patterns with identical bursts, with flat interburst intervals and abrupt transitions between suppression and burst activity (Fig. 2) (Hofmeijer et al., 2014b). Moreover, mean doses of sedative medication were lower in patients with unfavorable EEG patterns than in those with favorable patterns (Tjepkema-Cloostermans et al., 2015; Hofmeijer et al., 2015a).

7. Burst-suppression and status epilepticus

Burst-suppression and status epilepticus are classically considered as the ultimate ‘malignant’ EEG patterns in patients with a postanoxic coma (Zandbergen et al., 2006; Rundgren et al., 2010; Thenayan et al., 2010; Rittenberger et al., 2012; Legriel et al., 2013; Oh et al., 2013; Sadaka et al., 2015; Sivaraju et al., 2015). Various observational studies found associations with a poor outcome. However, specificity was mostly moderate (Westhall et al., 2013; Sandroni et al., 2014). This is, because such patterns are also observed in a considerable proportion of patients who eventually have a good outcome. In fact, burst suppression consists of heterogeneous EEG activity with diverse probabilities of recovery (Cloostermans et al., 2012).
7.1. 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 (Hirsch et al., 2005). Such patterns can be physiological, for instance during early development, or pathological, for example in almost half of comatose patients within the first 48 h after cardiac arrest (Cloostermans et al., 2012). Also, burst-suppression can be induced by anesthetics (Yoon et al., 2012). The mechanisms involved in burst-suppression are divergent, and range from reversible changes in synaptic functioning and Ca²⁺ homeostasis to selective neural death (van Putten and van Putten, 2010; Liley and Walsh, 2013; Brandon Westover et al., 2015).

Characteristics to classify burst-suppression patterns into subgroups with presumed 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 (Akrawi et al., 1996), and combinations with other pathological patterns, such as generalized periodic discharges (Fugate et al., 2010; Søholm et al., 2014). For example, longer suppressions were associated with poorer recovery in patients with postanoxic coma (Wennervirta et al., 2009). Extreme similarity of burst shape is a distinct feature of some burst-suppression patterns, which are classified as ‘burst-suppression with identical bursts’ (Fig. 2). Herewith, subsequent bursts in a particular channel are almost ‘photographic’ copies. Burst-suppression with identical bursts was never observed in a series of 9600 EEGs during anesthesia 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 (Hofmeijer et al., 2014b). Burst suppression with identical bursts indicates severe encephalopathy and is invariably associated with a poor outcome (Hofmeijer et al., 2014b, 2015a; Tjepkema-Cloostermans et al., 2015; Sivaraju et al., 2015).

7.2. 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 (Snyder et al., 1980; Rossetti et al., 2007; Mani et al., 2012; Rittenberger et al., 2012; Ruijter et al., 2014; Seder et al., 2015). Distinct epileptiform patterns, with evolving seizures, are rare (Hirsch et al., 2013; Knight et al., 2013). Other rhythmic activity, such as generalized periodic discharges or rhythmic delta activity, is more common (Rossetti et al., 2007; Hirsch et al., 2013; Hofmeijer et al., 2014a; Milani et al., 2014). It is unclear whether these various patterns all reflect true epileptiform activity, with possibility to return to normal, or rather are a direct expression of severe encephalopathy, in which treatment with antiepileptic drugs would be futile (Young and Claassen, 2010; Tjepkema-Cloostermans et al., 2013a). Three aspects are relevant in this consideration (van Putten and Hofmeijer, 2015). First, true epileptiform activity is associated with an increased energy demand. For instance, during repetitive seizures in rats, cerebral blood flow rose >200% to meet the enhanced metabolic requirements (Kreisman et al., 1991). Changes in energy demand in patients with generalized periodic discharges are unknown, but an increased metabolism has been demonstrated with PET or SPECT in some patients with lateralized periodic discharges (Hughes, 2010). Second, seizures may give rise to secondary neuronal damage. This may be direct neuronal death, if energy demands are larger than supplies (Gualtieri et al., 2013), or mediated by modulations of synaptic transmission (Naylor et al., 2005). Whether neuronal integrity or synaptic functioning is compromised during generalized periodic discharges is unknown. Third, with epileptiform activity, network architecture is, in principle, sufficiently preserved to return to normal synchronization. If network architecture is severely disrupted in patients with generalized periodic discharges, resulting from massive cell death or irreversible synaptic damage, recovery or restoration is probably not possible.

In 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 (Ruijter et al., 2015). 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 (Fig. 3) (Rossetti et al., 2009; Ruijter et al., 2015; Sivaraju et al., 2015).
7.3. Treatment of status epilepticus

Apart from classification, the usefulness of treatment of electrographic status epilepticus after cardiac arrest is unclear (Chong and Hirsch, 2005; Cronberg, 2015; Rossetti, 2015). Ambivalence thereon is reflected by the way these patterns are treated by Dutch and American epilepsy experts: approximately two thirds give anti-epileptic drugs, but only one third treats as aggressive as in clinically overt status epilepticus (Abend et al., 2010; Bouwes et al., 2010). 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 (Krumholz et al., 1988; Young et al., 1990; Sandbergen et al., 1998; Rossetti et al., 2009; Sandroni et al., 2014). In a retrospective cohort study of 139 patients, unstandardized, moderately intensive treatment with anti-epileptic drugs did not improve outcome of electrographic status epilepticus after cardiac arrest (Hofmeijer et al., 2014a). In an uncontrolled case series of 39 patients with ill-defined status epilepticus, 2 (6%) had a good outcome after aggressive anti-epileptic treatment (unpublished data). This proportion is essentially the same as those reported in the literature, regardless of any treatment. Effects of intensive treatment, if necessary up to barbiturates, is currently studied in the randomized, multicenter Treatment of Electroencephalographic Status Epilepticus After cardiopulmonary Resuscitation (TELSTAR) trial (NCT02056236; www.TELSTARtrial.nl) (Ruijter et al., 2014).

8. 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 (Young, 2000; Horn et al., 2014). However, consensus about the characteristics or timing or duration of changes in a responsive EEG are lacking. 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. Nipple pinching is probably more effective than pinprick at the nose base or finger-nail compression to cause detectable EEG changes (Tsotsou et al., 2015). Studies comparing somatosensory with sound or visual stimuli are lacking (Hermans et al., 2016).

Absent reactivity to external stimulation of the EEG background pattern is a measure that is much studied as a potential predictor of poor outcome of comatose patients after cardiac arrest. Two prospective cohort studies report on predictive values between 48 and 72 h after return of spontaneous circulation, during normothermia, in the absence of sedative medication. One cohort included 111 patients (Rossetti et al., 2010), the other 61 (Rossetti et al., 2012). Both are from the same research group and it is unclear whether these patient groups overlap. An additional research group reported on 54 patients, retrospectively (Crepeau et al., 2013). In these three studies, absence of reactivity of the EEG background pattern was invariably associated with a poor outcome. Otherwise, in a subgroup of 36 patients of whom EEG data were available from a total of 79 with postanoxic myoclonia, three recovered toward a good outcome, despite absent reactivity between 48 and 72 h (Bouwes et al., 2012). In the first 24 h, during hypothermia, absence of reactivity was associated with an unfavorable outcome with false positive rates of 1–7% and a sensitivity of up to 74% (Rossetti et al., 2012; Crepeau et al., 2013; Oddo and Rossetti, 2014). In one cohort the timing of testing was unclear and the false positive rate was 8% (Sivaraju et al., 2015). Otherwise, reactivity to stimuli within the first 48 h was strongly associated with good recovery (Rossetti et al., 2010; Thenayan et al., 2010; Crepeau et al., 2013; Tsotsou et al., 2013).

Important disadvantages of reactivity are lack of clear diagnostic criteria and an unclear effect of sedative medication (Gilmore et al., 2015). Reported inter-observer variability rates are moderate (Westall et al., 2015). In none of the foregoing studies, quality and quantity of the stimuli was sufficiently defined and standardized. Measurements of reactivity were often done visually, unblinded, with a large risk of bias.

Furthermore, all studies exploring the value of EEG reactivity for prognostication evaluated this feature as an “isolated characteristic”. None included additional analyses of the background EEG patterns. Since the EEG pattern may already contain sufficient information for reliable prognostication (Hofmeijer et al., 2015a; Sivaraju et al., 2015), the additional predictive value of reactivity is unclear. Indeed, a reactive EEG may be associated with a continuous background pattern with physiological rhythms, while a non-reactive EEG may rather represent a low-voltage background pattern (Tsotsou et al., 2015).

9. Computer assisted analysis

Application of the EEG for measurement of brain functioning and brain damage of comatose patients 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 (Friberg et al., 2013). Techniques to assist in the interpretation of continuous EEG background patterns include time frequency trend curves (Friedman et al., 2009; Oddo et al., 2012), quantification of hemispheric asymmetry (van Putten, 2006), and an explicit classification of the EEG in common categories (e.g. iso-electricity, burst-suppression, or diffusely slowed patterns) (Cloostermans et al., 2011).

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) (Rundgren et al., 2006). In this application, two channels were used (C3–P3 and C4–P4), displayed on a semilog scale (0–100 µV), after digital filtering between 2 and 15 Hz. In a prospective cohort of 34 patients, all 20 patients with a continuous aEEG pattern at normothermia (mean 37 h after arrest) regained consciousness. All fourteen patients with flat patterns, burst-suppression, or status epilepticus aEEG patterns died in the hospital (Rundgren et al., 2006, 2010). In a cohort of 30 patients, individual quantitative EEG features, such as the burst-suppression ratio, response entropy, and state entropy, predicted poor-outcome during the first 24 h after cardiac arrest, with a sensitivity of 78% and a specificity of 81% (Wennervirta et al., 2009). Another approach to quantify the EEG background pattern was based on two methods to monitor anesthesia depth: the burst suppression ratio and the approximate entropy. Additionally, reactivity was analyzed with a method based on frequency features of the signal. In 46 patients with a postanoxic encephalopathy these measures were associated with clinical outcome on a group level, but predictive values for individual patients were not reported (Noirhomme et al., 2014).

The Cerebral Recovery Index (CRI) was introduced in 2013 and is based on a combination of five features, including amplitude and continuity, derived from an 18-channel EEG recording (Tjeenkma-Cloostermans et al., 2013b). The CRI is normalized in the range [0–1], with 0 indicating severe encephalopathy and 1 normal brain functioning. In an independent training (n = 56) and test set (n = 53), CRI < 0.29 at t = 24 h invariably predicted poor outcome. CRI > 0.69 at t = 24 was invariably associated with a good outcome (Fig. 4). Note the importance of evolution in time: in both groups there is improvement of the mean EEG pattern. In most patients
there is at least some return of activity, even if the initial EEG showed no signs of electrocerebral activity. However, in patients with a good outcome, mean improvement is twice as fast as in patients with a poor outcome.

Few studies aimed to quantify reactivity to particular stimuli. For example, thirteen EEG parameters were compared to quantify changes in the spectral characteristics between 1-min epochs before and after stimulation. Of all single quantitative EEG features evaluated, those based on the temporal Brain Symmetry Index showed the highest diagnostic accuracy (Hermans et al., 2016), with similar performance as visual assessment, but moderate inter-rater agreement (Gwet, 2008).

Auditory evoked potentials include information on cortical functioning. Preservation of auditory evoked potentials as evaluated with mismatch negativity paradigms were associated with a good outcome in 30 comatose patients after cardiac arrest (Tzovara et al., 2013). A change of auditory discrimination between two recordings, the first within 24 h after cardiac arrest, during hypothermia, and the second during normothermia, was studied: deterioration was observed in all non-survivors, while improvement was seen in most survivors. A 19-channel EEG and multivariate decoding were used. Again, EEG background patterns were not reported and the additional predictive value of mismatch negativity remains unclear.

10. Conclusion

In comatose patients after cardiac arrest, the EEG background pattern in the first 24 h 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 prognostication. Given the high additional predictive values, future guidelines for outcome prediction after cardiac arrest should include early EEG background pattern measures.

Studies on reactivity or mismatch negativity should include the EEG background pattern to establish the additional predictive value of such parameters. Epileptiform patterns are of unknown significance and effects of treatment with anti-epileptic drugs are indistinct. Whether or not treatment of electrographic status epilepticus improves outcome is studied in the randomized multicenter Treatment of Electroencephalographic Status epilepticus After cardiopulmonary Resuscitation (TELSTAR) trial (NCT02056236).

Conflict of interest

Michel J.A.M. van Putten is co-founder of Clinical Science Systems, Leiden (www.clinicalscience.systems). Jeannette Hofmeijer has no conflicts of interest.

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