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Single electroencephalographic patterns as specific and time-dependent indicators of good and poor outcome after cardiac arrest

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HIGHLIGHTS

- Based on standardised definitions of continuity of background activity we identified single EEG patterns with 100% specificity for good or poor outcome.
- Good outcome was predicted by continuous pattern at 12 h.
- Poor outcome was predicted by isoelectric pattern since 12 h, by burst-suppression pattern since 24 h and by suppression pattern since 48 h.

ABSTRACT

Objective: To evaluate the prognostic value of single EEG patterns recorded at various time-frames in postanoxic comatose patients.
Methods: This retrospective study included 30-min EEGs, classified according to the definitions of continuity of background activity given by the American Clinical Neurophysiology Society. Isoelectric pattern was distinguished from other suppressed activities. Epileptiform patterns were considered separately. Outcome was dichotomised based on recovery of consciousness as good (Glasgow Outcome Scale [GOS] 3–5) or poor (GOS 1–2).
Results: We analysed 211 EEGs, categorised according to time since cardiac arrest (within 12 h and around 24, 48 and 72 h). In each time-frame we observed at least one EEG pattern which was 100% specific to poor or good outcome: at 12 h continuous and nearly continuous patterns predicted good outcome and isoelectric pattern poor outcome; at 24 h isoelectric and burst-suppression predicted poor outcome; at 48 and 72 h isoelectric, burst-suppression and suppression (2–10 μV) patterns predicted poor outcome.
Conclusions: The prognostic value of single EEG patterns, defined according to continuity and voltage of background activity, changes until 48–72 h after cardiac arrest and in each time-frame there is at least one pattern which accurately predicts good or poor outcome.
Significance: Standard EEG can provide time-dependent reliable indicators of good and poor outcome throughout the first 48–72 h after cardiac arrest.

1. Introduction

For many decades EEG has been used routinely for prognostication in postanoxic comatose patients, using various classifications before therapeutic hypothermia (TH) entered clinical practice (e.g. Hockaday et al., 1965; Synek, 1988; Young et al., 1997). Despite this widespread use of EEG in clinical practice, the

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guidelines for prognostication in postanoxic patients published by the American Academy of Neurology (Wijdicks et al., 2006) did not recommend the use of EEG as its prognostic accuracy was still considered insufficient on the basis of pre-TH evidence of EEG studies.

In the following years several new prospective (Cloostermans et al., 2012; Hofmeijer et al., 2015; Rundgren et al., 2010; Sivaraju et al., 2015; Tjepkema-Cloostermans et al., 2015) and retrospective (Crepeau et al., 2013) studies gave new evidence about the prognostic role of EEG. These studies indicated that the prognostic meaning of EEG patterns varied according to the timing of recording. They also showed that early EEG recordings can reliably predict good outcome, whereas previous research had only considered predictors of poor outcome. These findings derived from continuous EEG recordings in TH-treated patients analysed combining several EEG patterns into few easily recognisable categories.

Following this renewed interest and the need of prognostic guidelines for TH-treated patients, a European advisory statement (Sandroni et al., 2014) suggested that the presence of certain EEG patterns (absence of reactivity, burst-suppression) at 72 h after cardiac arrest (CA) predicted poor outcome. However the authors noted that definitions were inconsistent among the studies (especially for burst-suppression) and that the overall quality of evidence was low. No mention was made of prognostication in the first 24 h after CA because of insufficient evidence.

There was clearly a need for standardised definitions in this field and the recent guide to terminology for EEG in critical care (Hirsch et al., 2013) published by the American Clinical Neurophysiology Society (ACNS) represents an important advance in this respect.

Two studies have used this terminology for prognostic grading of EEGs in postanoxic patients (Sivaraju et al., 2015; Søholm et al., 2014) and have proposed EEG categories consisting of several patterns with unfavourable or favourable prognostic significance, finding a strong specificity for poor outcome and a somewhat lower specificity for good outcome.

In the present study we used the ACNS terminology to describe single EEG patterns in postanoxic patients in terms of the continuity parameter. Our aim was to evaluate retrospectively the prognostic significance of single EEG patterns defined according to ACNS terminology, and to analyse how their predictive value changed during the first 12–72 h after CA.

2. Materials and methods

2.1. Patients

From our EEG database we retrospectively identified all adult (>16 years old) comatose patients who underwent EEG study after CA of presumed cardiac origin, treated with TH and admitted to the Emergency Department of Careggi Teaching Hospital (Florence, Italy) between January 2007 and June 2014. EEGs were performed on request by ICU physicians. Exclusion criteria were: absence of EEG recordings taken within 72 h from CA; CA of non-cardiac origin; TH not performed or interrupted within 24 h from CA; intra-operative CA; presence of other severe neurological injury (such as intracranial haemorrhage, traumatic brain injury, intoxication due to drugs or carbon monoxide); presence of severe extra-neurological pathology implying a life expectancy of less than six months.

Approval for the study was obtained from the local Institutional Review Board with a waiver on the requirement for informed consent as EEG recordings were part of the current standard clinical management.

2.2. Treatment protocol

Mild endovascular TH was started as soon as possible and maintained for 24 h. The CoolGard Icy Catheter (Alsius Corp., Irvine, California, U.S.A.; 8.5fr) was positioned in the right femoral vein. Patients' core temperature was maintained at 32–34 °C (tympanic temperature). Strict glucose homeostasis was maintained in accordance with the post-resuscitation support protocol. Clinical parameters were monitored continuously and an arterial blood gas analysis was performed every 2 h. At the end of the cooling period patients were allowed to return passively to normothermia. The sedation protocol consisted of a bolus of IV midazolam at 0.03 mg/kg followed by an infusion of 1 mg/h, or propofol 1–2 mg/kg/h. Neuromuscular paralysis was induced with a bolus of 0.4 mg/kg atracurium, followed by an initial infusion of 4 μg/kg/min if was required to facilitate ventilation or to abolish shivering. Venous districts were monitored frequently using ultrasound to detect deep venous thrombosis. No complications occurred during or after the cooling procedure.

2.3. EEG recordings

Standard 30-min EEG recordings were initiated as soon as possible after patients arrived in the ICU using a portable digital machine (EBN GalNT, Florence, Italy). Ten needle to 21 silver-silver chloride electrodes were placed according to the international 10–20 system. When reduced montage was applied a bipolar longitudinal montage with Fp2, F4, C4, P4, O2, Fp3, F3, C3, P3, O1 was used. Recordings were acquired with a sampling rate of 128 Hz. During reviewing digital filters (low-pass filter = 30 to 70 Hz; time constant = 0.1 or 0.3 s; notch filter = 50 Hz) and sensitivity gain (2 to 10 μV/mm with a standard gain of 7 μV/mm) were adjusted according to interpretation needs. When more than one recording was available for a patient, we included the first EEG in the study. Recordings were retrospectively organised into four time-frames relative to the CA: 12 h (range: 6–13 h post-CA), 24 h (range: 14–30 h post-CA), 48 h (range: 33–62 h post-CA), 72 h (range: 67–96 h post-CA).

2.4. EEG classification

All EEGs were classified retrospectively according to the most recent terminology for EEGs recorded in ICU (Hirsch et al., 2013). The main parameter used to classify background activity was 'continuity', but 'voltage' and 'reactivity' were also considered. Reactivity was defined as a clear, reproducible change in background frequency and/or amplitude following auditory (clapping and calling patient's name loudly) and/or noxious stimulations (nail bed and supraorbital notch pressure). *Isoelectric* (voltage < 2 μV) recordings were also identified although the original classification did not distinguish them from suppressed activity (voltage < 10 μV).

All recordings with ictal or periodic epileptiform activity were assigned to a separate category (*Epileptiform discharges*) independent of background activity. EEGs showing sporadic (i.e. non-periodic) epileptiform activity were also included in this category if the epileptiform activity was classified as "abundant" according to above-mentioned ACNS terminology (Hirsch et al., 2013). Thus, the main patterns identified were: *continuous*; *nearly continuous*; *discontinuous*; *burst-suppression*; *burst-suppression with highly epileptiform bursts*; *suppression*; *isoelectric*; *epileptiform discharges*.

2.5. Burst-suppression with identical bursts

In addition to ACNS classification, the EEGs with *burst-suppression* (including those *with highly epileptiform bursts*) at 12

and 24 h were visually subdivided in those with *identical bursts* and those without, according to the original definition of Hofmeijer et al. (2014). The first five minutes of each recording were visually reviewed. Bursts were considered identical if the first 500 ms showed identical morphology, irrespective of amplitude or subsequent duration of bursts or interburst intervals.

2.6. Outcome assessment

Neurological outcome 6 months after CA was evaluated by telephone interview with the patient or the patient's caregiver, and graded according to the five-point Glasgow Outcome Scale (GOS) (Jennett and Bond, 1975) with 1 corresponding to death and 5 to good recovery with minimal or no disability. Outcome was dichotomised as "good" (GOS 3–5: recovery of consciousness) or "poor" (GOS 1–2: death or vegetative state). The interviewer was not aware of the EEG findings.

2.7. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) for normally distributed data and as median and interquartile ranges (IQR) for non-normally distributed data. Categorical variables are presented as number (n) and percent. We analysed the prognostic value of each EEG pattern in each time-frame.

For each pattern we calculated sensitivity (SEN), specificity (SPE), positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals (CIs) using the binomial distribution (Confidence Intervals Analysis software 2.0, ©Trevor Bryant, University of Southampton, USA). The false positive rate (FPR) and related CIs were also calculated (FPR = 1 − SPE).

3. Results

The sample consisted of 211 patients. Demographic data and outcomes are reported in Table 1. For each time-frame EEG recordings started respectively at a median time of 9.0 h after CA (IQR 5) for the 12 h group, 23 h after CA (IQR 6) for the 24 h group, 44.75 h after CA (IQR 13.6) for the 48 h group and 83 h (IQR 17) for the 72 h group.

The distribution of EEG patterns within each time-frame is shown in Fig. S1 in the Supplementary Data. Not all patterns are present in each time-frame: at 12 h no recordings showed *epileptiform discharges*; *burst-suppression with highly epileptiform bursts* was not observed after 24 h; *burst-suppression* and *discontinuous* patterns were absent after 48 h.

Table 1
Demographics and clinical outcomes of patients (n = 211).

Variable	*N* (%)
Age, mean ± SD [range]	57.1 ± 18.8 [16–90] years
Male:Female	133:78 (63.0:37.0)
Onset rhythm	
Shockable	89
VF/VT	89 (42.2)
Non-shockable	84
Asystole	50 (23.7)
PEA	34 (16.1)
Not assessed	38 (18.0)
Outcome	
Good	78
GOS 5	16 (7.6)
GOS 4	35 (16.6)
GOS 3	27 (12.8)
Poor	133
GOS 2	57 (27.0)
GOS 1	76 (36.0)

SD = standard deviation; VF/VT = ventricular fibrillation/ventricular tachycardia; PEA = pulseless electrical activity.

3.1. EEG patterns in patients with good outcome

The EEG patterns of patients who went on to have good outcome are shown in Fig. 1a (for more details see Tables S1–S4 in Supplementary Data).

At 12 h post-CA *continuous* and *nearly continuous* patterns were present only in patients who went on to have a good outcome. The voltage of *continuous* and *nearly continuous* patterns was typically >20 μV but sometimes in the 10–20 μV range. None of the patients who went on to have a good outcome showed *burst-suppression with highly epileptiform bursts* or *isoelectric* pattern. The two *discontinuous* EEGs were reactive (stimulus-induced suppressions).

At 24 h post-CA the notable finding was that none of the patients who went on to have a good outcome showed *burst-suppression* or *isoelectric* patterns, although one showed *epileptiform discharges* (status epilepticus).

At 48 h post-CA only three patterns were observed in patients who went on to have a good outcome: *continuous*, *nearly continuous* and *epileptiform discharges*. *Discontinuous*, *burst-suppression*, *suppression* and *isoelectric* patterns were absent in this group by this point.

The distribution of EEG patterns at 72 h post-CA was similar to that observed at 48 h post-CA.

Reactivity was only invariably associated with subsequent good outcome at 12 h. In every time-frame absence of reactivity was observed in several patients who went on to have a good outcome (Tables S1–S4 in Supplementary Data).

3.2. EEG patterns in patients with poor outcome

Fig. 1b represents the EEG patterns of patients who went on to have a poor outcome in all the time-frames (for more details see Tables S1–S4 in Supplementary Data).

Interestingly, at 12 h post-CA *burst-suppression with highly epileptiform discharges* and *isoelectric* patterns were only observed in patients who went on to have a poor outcome. None of the patients who subsequently had a poor outcome showed *continuous* or *nearly continuous* patterns at this point.

At 24 h post-CA a greater variety of patterns was present in this group: *continuous* (one patient: normal-voltage alpha, unreactive); *nearly continuous* (one patient: low-voltage theta, unreactive); *epileptiform discharges* (nine patients); *burst-suppression with highly epileptiform bursts*; *burst-suppression* and *isoelectric* patterns.

At 48 h post-CA *discontinuous*, *burst-suppression*, *suppression* and *isoelectric* EEGs were present only in patients who subsequently had a poor outcome. One patient's EEG showed *continuous* activity (normal-voltage, theta/delta, unreactive).

At 72 h post-CA *suppression* and *isoelectric* patterns were observed only in patients who subsequently had a poor outcome. *Continuous* or *nearly continuous* EEG activity was present in some patients in the poor outcome group at this point.

Most patients who went on to have a poor outcome failed to show reactivity in any of the time-frames (Tables S1–S4 in Supplementary Data).

3.3. Burst-suppression with identical bursts

At 12 h three patients had *burst-suppression with identical bursts*: two of the three patients with *highly epileptiform bursts* and one of the seven patients without.

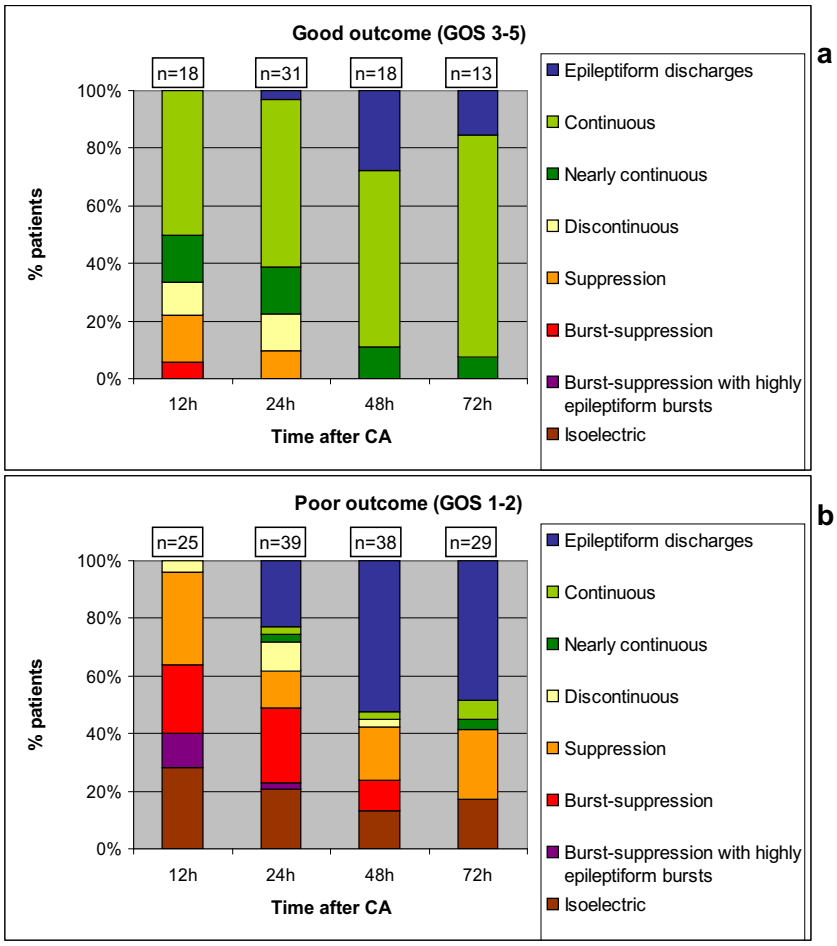

Fig. 1. Distribution of EEG patterns in patients with good (a) and poor (b) outcome over time.

At 24 h four patients had *burst-suppression with identical bursts*: the one with *highly epileptiform bursts* and three of the ten without.

All patients with *burst-suppression* (with or without *identical bursts* or *highly epileptiform bursts*) went on to have poor outcome except for one patient at 12 h, who subsequently had good outcome: the EEG of this patient did not show *identical bursts* or *highly epileptiform bursts*.

3.4. Prediction of good and poor outcome from EEGs in different time-frames

Table 2 shows the sensitivity, specificity, predictive values and false positive ratios for EEG patterns predictive of good and poor outcomes in each time-frame.

At 12 h post-CA *continuous* and *nearly continuous* patterns have a 100% positive predictive value (PPV) for good outcome. Later on the same patterns still have a high PPV for good outcome, but it is no longer 100%.

In each time-frame at least one EEG pattern had a PPV of 100% for poor outcome: *isoelectric* pattern at 12 h; *isoelectric* and *burst-suppression* patterns at 24 h; *isoelectric*, *burst-suppression* and *suppression* patterns at 48 h; *isoelectric* and *suppression* patterns at 72 h (*burst-suppression* was not observed in any patients at 72 h). This chronological progression in the specificity of the various patterns is shown in Fig. 2.

Statistics relating to the presence and absence of EEG reactivity are reported in Table S5 in Supplementary Data. As a predictor of poor outcome, absence of reactivity had the highest PPV at 48 h (85.7%); the PPV was similar at 72 h and lower at 12 and 24 h (72.7% and 67.9% respectively). As a predictor of good outcome presence of reactivity had maximum PPV (100%) at 12 h; values were below 90% in the later time-frames.

4. Discussion

In our retrospective analysis highly accurate outcome prediction (PPV = 100%) was possible in all time-frames, although the relevant EEG patterns varied: at 12 h *continuous* and *nearly continuous* patterns predicted a good outcome and *isoelectric* pattern predicted a poor outcome; at 24 h *isoelectric* and *burst-suppression* patterns predicted a poor outcome and at 48 h and 72 h *isoelectric*, *burst-suppression* and *suppression* patterns predicted a poor outcome (*burst-suppression* was not observed at 72 h).

These results are in line with previous prospective (Cloostermans et al., 2012; Hofmeijer et al., 2015; Rundgren et al., 2010; Sivaraju et al., 2015; Tjepkema-Cloostermans et al., 2015) and retrospective (Crepeau et al., 2013) studies, which reappraised the prognostic role of EEG in postanoxic coma. These studies were based on continuous EEG recordings (cEEG) and both simple (Cloostermans et al., 2012) and more detailed (Crepeau et al., 2013) EEG classifications have been used. One of the important contributions of the new wave of studies was that they emphasised the prognostic significance of EEG patterns as a function of time from CA, reporting not only predictors for poor outcome but also, and for the first time, for good outcome.

Table 2
Sensitivity, specificity, predictive values and false positive rate of EEG patterns for outcome prediction at different times after CA.

	Predicting	SEN (95% CI)	SPE (95% CI)	PPV (95% CI)	NPV (95% CI)	FPR (95% CI)
12 h (n = 43)						
Cont + NearlyC	Good outcome	66.7% (43.7–83.7%)	100% (86.7–100%)	100% (75.7–100%)	86.6% (63.7–90.8%)	0.0% (0.0–13.3%)
BS	Poor outcome	36.0% (20.2–55.5%)	94.4% (74.2–99.0%)	90.0% (59.6–98.2%)	51.5% (35.2–67.5%)	5.6% (1.0–25.8%)
Suppression	Poor outcome	32.0% (17.2–51.6%)	83.3% (60.8–94.2%)	72.7% (43.4–90.3%)	46.9% (30.9–63.6%)	16.7% (5.8–39.2%)
Isoelectric	Poor outcome	28.0% (14.3–47.6%)	100% (82.4–100%)	100% (64.6–100%)	50.0% (34.5–65.5%)	0.0% (0.0–17.6%)
ED	Poor outcome	–	–	–	–	–
24 h (n = 70)						
Cont + NearlyC	Good outcome	74.2% (56.8–86.3%)	94.9% (83.1–98.6%)	92.0% (75.0–97.8%)	82.2% (68.7–90.7%)	5.1% (1.4–16.9%)
BS	Poor outcome	28.1% (16.5–43.8%)	100% (89.0–100%)	100% (74.1–100%)	52.5% (40.0–64.7%)	0.0% (0.0–11.0%)
Suppression	Poor outcome	12.8% (5.6–26.7%)	90.3% (75.1–96.7%)	62.5% (30.6–86.3%)	45.2% (33.4–57.5%)	9.7% (3.3–24.9%)
Isoelectric	Poor outcome	20.5% (10.8–35.5%)	100% (89.0–100%)	100% (67.6–100%)	50.0% (37.9–62.1%)	0.0% (0.0–11.0%)
ED	Poor outcome	23.1% (12.6–38.3%)	96.8% (83.8–99.4%)	90.0% (59.6–98.2%)	50.0% (37.7–62.3%)	3.2% (0.6–16.2%)
48 h (n = 56)						
Cont + NearlyC	Good outcome	72.2% (49.1–87.5%)	97.4% (86.5–99.5%)	92.9% (68.5–98.7%)	88.1% (75.0–94.8%)	2.6% (0.5–13.5%)
BS	Poor outcome	10.5% (4.2–24.1%)	100% (82.4–100%)	100% (51.0–100%)	34.6% (23.2–48.2%)	0.0% (0.0–17.6%)
Suppression	Poor outcome	18.4% (9.2–33.4%)	100% (82.4–100%)	100% (64.6–100%)	36.7% (24.7–50.7)	0.0% (0.0–17.6%)
Isoelectric	Poor outcome	13.2% (5.8–27.3%)	100% (82.4–100%)	100% (56.6–100%)	35.3% (23.6–49.0%)	0.0% (0.0–17.6%)
ED	Poor outcome	52.6% (37.3–67.5%)	72.2% (49.1–87.5%)	80.0% (60.9–91.1%)	41.9% (26.4–59.2%)	27.8% (12.5–50.9%)
72 h (n = 42)						
Cont + NearlyC	Good outcome	84.6% (57.8–95.7%)	89.7% (73.6–96.4%)	78.6% (52.4–92.4%)	92.9% (77.4–98.0%)	10.3% (3.6–26.4%)
BS	Poor outcome	–	–	–	–	–
Suppression	Poor outcome	24.1% (12.2–42.1%)	100% (77.2–100%)	100% (64.6–100%)	37.1% (23.2–53.7%)	0.0% (0.0–22.8%)
Isoelectric	Poor outcome	17.2% (7.6–34.5%)	100% (77.2–100%)	100% (56.6–100%)	35.1% (28.8–51.2%)	0.0% (0.0–22.8%)
ED	Poor outcome	48.3% (31.4–65.6%)	84.6% (57.8–95.7%)	87.5% (64.0–96.5%)	42.3% (25.5–61.1%)	15.4% (4.3–42.2%)

SEN = sensitivity, SPE = specificity, PPV = positive predictive value, NPV = negative predictive value, FPR = false positive rate, CI = confidence interval, Cont = continuous, NearlyC = nearly continuous, BS = burst-suppression, ED = epileptiform discharges.

Previous guidelines (Wijdicks et al., 2006) did not include EEG among the prognostic indicators as its prognostic accuracy was considered insufficient on the basis of pre-TH evidence. A recent set of European guidelines (Sandroni et al., 2014) recognised EEG as a prognostic indicator, but with caveats owing to the lack of strong statistical evidence from pooled data of the available studies. It is also well-known that interpretation of EEGs requires more training than the evaluation of other prognostic indicators such as clinical examination and somatosensory evoked potentials (SEPs), and non-expert interpretation of EEG entails the risk of lowering its overall prognostic value. Recent studies (Cloostermans et al., 2012; Crepeau et al., 2013 Hofmeijer et al., 2015; Rundgren et al., 2010; Sivaraju et al., 2015; Tjepkema-Cloostermans et al., 2015) are less heterogeneous with respect to the classification and to the timing of recordings, however they still show some differences in definitions for what is nominally the same pattern.

We think that a classification scheme based on clear, strict and standardised definitions of patterns should be used to facilitate comparison among different studies. The terminology proposed by the ACNS (Hirsch et al., 2013) for the EEG in critically ill patients is the most recent attempt to provide such a classification scheme and has been shown to have high inter-rater agreement, at least with respect to periodic or rhythmic activity (Gaspard et al., 2014; Hirsch et al., 2013).

A recent retrospective study was the first to use a classification based on the ACNS terminology in comatose postanoxic patients (Søholm et al., 2014). The authors reported that EEGs showing alpha or theta frequencies were associated with lower mortality, whereas burst-suppression and suppression patterns proved a FPR = 0% for poor outcome. However the EEG analysis did not take into account the timing of the recording, which was highly variable (range: 0–9 days post-CA, median: 3 days). Evidence from several prospective (Cloostermans et al., 2012; Hofmeijer et al., 2015; Rundgren et al., 2010; Sivaraju et al., 2015; Tjepkema-Cloostermans et al., 2015) and one retrospective (Crepeau et al., 2013) studies showed that the prognostic value of patterns varies as a function of the time since CA. A recent prospective cEEG study (Sivaraju et al., 2015) also used ACNS terminology, classifying patterns primarily according to the voltage of background activity. This study reported that burst-suppression predicted poor outcome with PPV = 100% throughout the 6–72 h after CA, and suppression/low-voltage pattern did so from 24 h onwards, whereas normal voltage pattern had predicted good outcome throughout the observation period with a somewhat lower PPV.

In our study we retrospectively analysed each EEG pattern singularly, whereas most previous study grouped several patterns into few larger categories for statistical analysis. The high PPV that we found for *continuous* and *nearly continuous* patterns within the first 12 h after CA and the lower specificity in later time-frames are in line with previous prospective cEEG studies (Cloostermans et al., 2012; Hofmeijer et al., 2015; Tjepkema-Cloostermans et al., 2015), which found that continuous activity with voltage >20 μV had a high specificity for good outcome, especially at 12 h. Noteworthy our *continuous* and *nearly continuous* patterns had a 100% PPV at 12 h even if they also included activities with voltage in the range 10–20 μV, more similarly to another retrospective study (Crepeau et al., 2013).

One could argue that our *continuous* and *nearly continuous* categories may have included some patterns predictive of a poor outcome, such as alpha/theta-coma (ATC), but because all the patients in our sample who had *continuous* or *nearly continuous* EEG patterns within 12 h from CA went on to recover consciousness it is, in practice, unlikely that this happened. The same cannot be said of the group who displayed *continuous* or *nearly continuous* patterns in the later time-frames, and this probably explains why some patients showing *continuous* and *nearly continuous* EEGs in the later time-frames went on to have a poor outcome. ATC is unlikely to occur in the first 12 h (Berkhoff et al., 2000). The pathogenesis of ATC is thought to involve alternative generators and sub-cortical pathways including the caudate nucleus, amygdala, hypothalamus, brain stem and basal forebrain (Abusleme and Chen, 2009; Berkhoff et al., 2000; Fossi et al., 2004; Kaplan et al.,

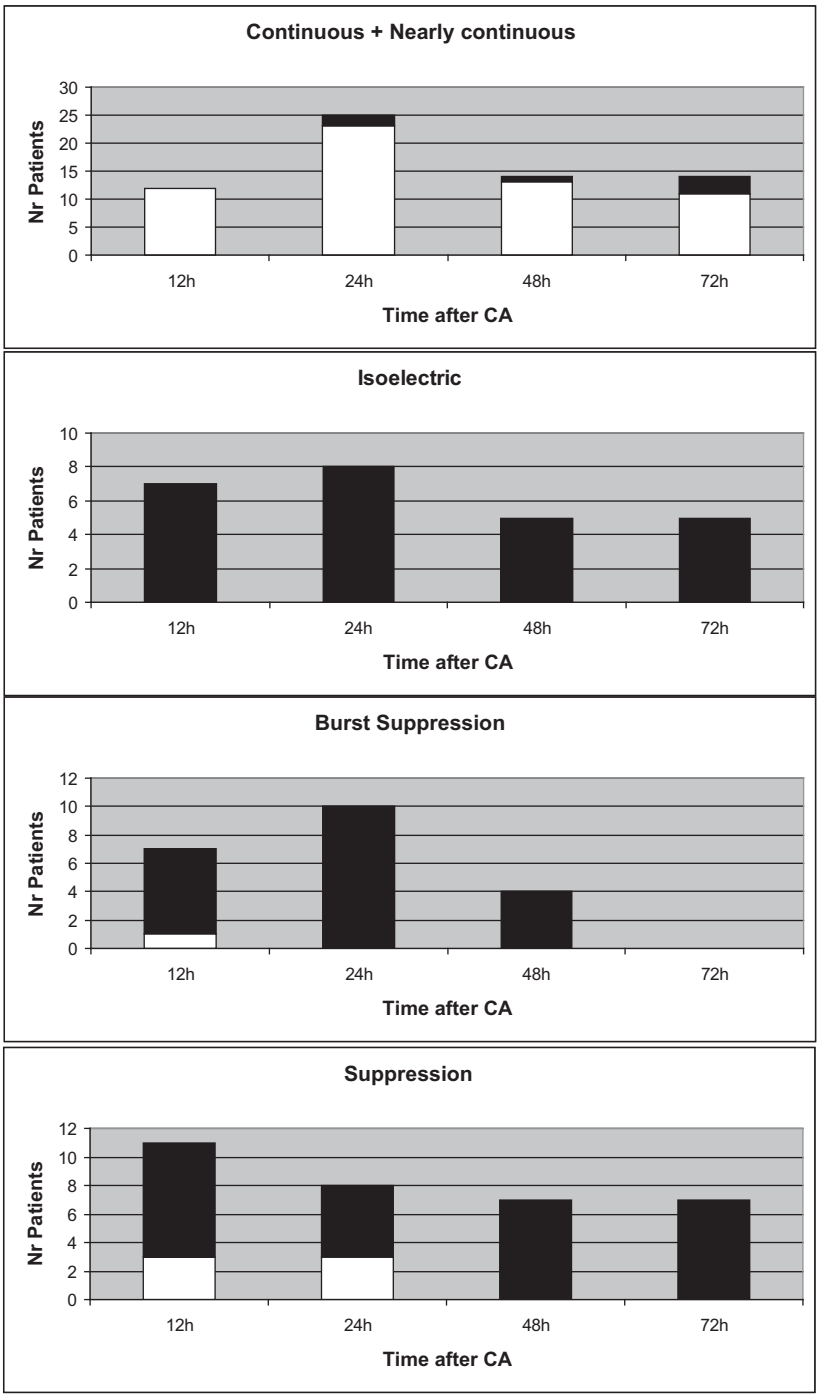

Fig. 2. Single EEG patterns predictive for good or poor outcome at different timings (white = good outcome; black = poor outcome).

1999). It is conceivable that the organisation of these sub-cortical circuits, which are responsible for the appearance of a *de novo* alpha rhythm, does not occur immediately after CA.

Similarly to other recent prospective (Cloostermans et al., 2012; Hofmeijer et al., 2015; Rundgren et al., 2010; Sivaraju et al., 2015; Tjepkema-Cloostermans et al., 2015) and retrospective (Crepeau et al., 2013) studies we also found several patterns with a 100% PPV for poor outcome, with a time-dependent specificity. In fact we observed that each *isoelectric*, *burst-suppression* and *suppression* patterns gained specificity = 100% over time one after another as soon as 12 h and until 48 h. This progressive, sequential and time-dependent acquisition of specificity of each different pattern at 12, 24 and 48 h is in line with the above-mentioned studies and it is of clinical interest to know that poor outcome is predictable even before 24 h when *isoelectric* pattern is found.

In comparing our results to other studies we also have to take into account the differences in outcome definitions: we classified regaining of consciousness as a "good" outcome regardless of disability, whereas other authors have classified severe disability as a "poor" outcome. Our choice was due to the necessity of appropriately plan the rehabilitation phase since, according to local protocols, intensive rehabilitation is indicated when prognostic tests do not exclude recovery of consciousness (even if minimal) irrespective of any grade of motor disability. For this purpose, GOS

was considered equivalent to Cerebral Performance Categories (CPC) and preferred to it for practical reasons (part of our data were originally collected for a comparison with previous SEP studies which employed GOS). However, despite some methodological differences, our data are comparable with most recent EEG studies (Cloostermans et al., 2012; Crepeau et al., 2013; Hofmeijer et al., 2015; Rundgren et al., 2010; Sivaraju et al., 2015; Tjepkema-Cloostermans et al., 2015) and confirm the high prognostic specificity for several EEG patterns if considered as a function of time.

With respect to *epileptiform discharges*, in our sample this pattern never reached 100% PPV for poor outcome at any interval during the observation period. This is consistent with several other prospective (Cloostermans et al., 2012; Hofmeijer et al., 2015; Rossetti et al., 2010; Sivaraju et al., 2015) and retrospective (Amorim et al., 2015; Ribeiro et al., 2015) studies which reported that this pattern was not invariably predictive of a poor outcome in TH-treated patients.

Recently a distinct burst-suppression subtype with identical bursts has been described with both visual and quantitative analysis in four prospective studies (Hofmeijer et al., 2014, 2015; Sivaraju et al., 2015; Tjepkema-Cloostermans et al., 2015). In our retrospective series *identical bursts* were visually identified. We found that *identical bursts* recur more often but not exclusively among EEGs with *highly epileptiform bursts*, suggesting that these two subtypes may partially overlap but not coincide. Burst-suppression with identical bursts has been found highly specific for poor outcome (Hofmeijer et al., 2014, 2015; Sivaraju et al., 2015; Tjepkema-Cloostermans et al., 2015). Analogously, all our patients with *burst-suppression with identical bursts* went on to have poor outcome; the same did all patients with *burst-suppression with highly epileptiform bursts*, suggesting a more severe anoxic encephalopathy underlies these two peculiar patterns.

However we found a high prognostic specificity also for *burst-suppression* as a whole (in our study only one patient with *burst-suppression*, without *identical* or *highly epileptiform bursts*, had good outcome): this finding, together with the small sample size, limits the possibility of analysing if the two subtypes have a higher specificity compared to conventional *burst-suppression*. The unfavourable prognostic value of *burst-suppression* in our study is similar to the other study which defined burst-suppression according to the ACNS terminology (Sivaraju et al., 2015), which requires at least 50% of suppression (it is conceivable that the amount of suppression is also a relevant prognostic factor).

In our retrospective study absence of reactivity was less specific to poor outcome than in a prospective study by Oddo and Rossetti (2014), in which all patients with unreactive EEG during TH went on to have a poor outcome, except for one. In our study absence of reactivity never reached PPV = 100% for poor outcome, although PPV and FPR values indicated greater specificity in the period 48–72 h post-CA than in the period 12–24 h post-CA. Reactivity can be affected by sedation and TH, which may limit its value as a prognostic indicator, especially in the early post-CA period.

There has been relatively little research into presence of reactivity in postanoxic coma, especially during TH. We found that presence of reactivity had high PPV for good outcome, but only a small subgroup of patients were reactive in the time-frames we investigated. Based on our findings, we suggest that presence of reactivity has greater prognostic value in the very early post-CA phase (within 12 h of CA), when it is evident in spite of sedation, whereas absence of reactivity becomes more predictive of poor outcome later on (48–72 h post-CA), when there is less interference from sedation effects.

An open issue is whether cEEG should be preferred to standard EEG for prognostication in postanoxic coma. Our study was based on standard EEG recordings, but many recent prospective (Cloostermans et al., 2012; Hofmeijer et al., 2015; Rundgren et al., 2010; Sivaraju et al., 2015; Tjepkema-Cloostermans et al., 2015) and retrospective (Crepeau et al., 2013) studies have used cEEG. cEEG studies have been instrumental in identifying the times at which various EEG patterns acquire significant prognostic value and in demonstrating that it is possible to predict good as well as poor outcomes at a very early stage. However, cEEG is not as widely available as standard EEG and it is also more expensive. A recent investigation (Crepeau et al., 2014) was unable to demonstrate that cEEG was a more cost effective prognostic tool than standard EEG in clinical practice. Swedish guidelines (Cronberg et al., 2013) recommend at least one standard EEG and consider cEEG as a secondary option. In our opinion standard EEG can be as informative as cEEG as a predictor of outcome, provided that the timing of the recording is considered, as the certain patterns only have the highest predictive value in certain time-frames.

Our study has several limitations. First, this study is a retrospective investigation with a potential selection bias since not all CA-patients were examined with an EEG.

Second, the small samples in each time-frame mean that the confidence intervals (CIs) are wide and so the results should be interpreted with caution; however other studies have reported similar CIs.

Third, sedation has a dose-dependent confounding effect on EEG activity which cannot be controlled for in a retrospective study. However the sedative doses specified in the TH protocol used at our institution are not usually sufficient to induce burst-suppression or suppression of EEG activity. Our results might not generalise to protocols in which higher doses of sedatives are used.

Fourth, because this was a retrospective study of standard EEGs, we categorised recordings into time-frames spanning several hours during which significant changes of EEG patterns could have occurred (especially in the range 14–30 h). cEEG best follows time-related evolution of EEG patterns, however many institutions do not have cEEG routinely available. On the other hand it is practically impossible to have recordings at pre-established time-points when standard EEG is employed, so it is necessary to have reference points at intermediate times for a correct prognostic interpretation. Therefore, the variability in the timing of EEGs in our study reflects actual clinical practice when standard EEG recordings are employed and provides an indication of the time-frames in which a reliable prognostic value is maintained for certain patterns when cEEG is not available. Moreover we find encouraging the fact that our results with standard EEG are basically in line with cEEG studies, meaning that maybe sufficient prognostic information can be obtained with a more easily available and cheaper EEG technology.

As a last point, the risk of self-fulfilling prophecy cannot be completely ruled out in this kind of studies. At our institution active withdrawal of life-sustaining therapies is not applied, however, since clinicians were not blind to the results of EEGs as they were part of clinical practice, we cannot completely rule out that it may have somehow influenced the intensity of treatment. On the other hand the higher proportion of patients with final outcome of vegetative state in our study (27.0%) compared to $\leqslant$5% of others (Cloostermans et al., 2012; Crepeau et al., 2013; Hofmeijer et al., 2015; Rundgren et al., 2010) indirectly confirms that EEG results scarcely influenced decisions about life-sustaining treatment.

5. Conclusions

Our retrospective, standard EEG study tries to answer to the prognostic need in the single patient whenever EEG is recorded in the range 12–72 h. Using standardised definitions of EEG pat-

terns we showed, in agreement with other studies, that the prognostic value of single patterns changes over time at least until 48 h after CA. We also found that in each time-frame there is at least one pattern which is specific to good or poor outcome.

These results are encouraging and should be explored further in larger samples, as even recent prognostic guidelines (Sandroni et al., 2014) still do not include detailed chronology of the prognostic value of specific EEG patterns and do not consider prognostication of good outcome.

Conflict of interest

None of the authors have potential conflict of interests to be disclosed.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2016.04.008.

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