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Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Value of EEG reactivity for prediction of neurologic outcome after cardiac arrest: Insights from the Parisian registry

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Abstract

Purpose: To evaluate the predictive value of EEG reactivity assessment and confounders for neurological outcome after cardiac arrest.

Methods: All consecutive patients admitted in a tertiary cardiac arrest center between 2007 and 2016 still alive 48 h after admission with at least one EEG recorded during coma. EEG reactivity was defined as a reproducible waveform change in amplitude or frequency following standardized stimulation. Each EEG was classified based on American Clinical Neurophysiology Society nomenclatures and classified in highly malignant (including status epilepticus), malignant, or benign EEG. We assessed the predictive values of EEG reactivity and sedation effect for neurologic outcome at ICU discharge using the Cerebral Performance Category scale (with CPC 1–2 assumed as favorable outcome and CPC 3-4-5 considered as poor outcome).

Results: Among 428 patients, a poor outcome was observed in 80% patients. The median time to EEG recording was 3 (1–4) days and 51% patients had a non-reactive EEG. The positive predictive value (PPV) of a non-reactive EEG to predict an unfavorable outcome was 97.1% (IC95% 93.6–98.9), increasing to 98.3% (IC95 94.1–99.8) when the EEG had been performed without sedation. In multivariate analysis, a non-reactive EEG was associated with poor outcome (OR 12.6 IC95% 4.7–33.6; $p < 0.001$). In multivariate analysis, concomitant sedation was not statistically associated with EEG non-reactivity. The PPV of a benign EEG to predict favorable outcome was 49.7% (IC95% 41.5–57.9), increasing to 66.2% (IC95% 54.3–76.8) when EEG was recorded earlier, with ongoing sedation.

Conclusions: After cardiac arrest, absence of EEG reactivity was predictive of unfavorable outcome. By contrast, a benign EEG was slightly predictive of a favorable outcome. Reactivity assessment may have important implications in the neuroprognostication process after cardiac arrest and could be influenced by sedation.

Keywords: Cardiac arrest, Prognosis, Therapeutic hypothermia, Reactivity, Electroencephalography, Persistent coma

Abbreviations: CA, cardiac arrest; CPC, cerebral performance category; EEG, electroencephalogram; ESM, electronic supplementary material; FPR, false positive rate; GCS, glasgow coma scale; ICU, intensive-care-unit; IQR, interquartile-range; NPV, negative predictive value; PPV, positive predictive value; RASS, Richmond-Agitation-Sedation-Scale; ROSC, return of spontaneous circulation; SD, standard deviation; SSEP, short-latency somatosensory evoked potentials; TTM, targeted temperature management; WLST, withdrawal-of-life-sustaining-treatments.

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https://doi.org/10.1016/j.resuscitation.2019.06.009
Received 5 March 2019; Received in revised form 7 June 2019; Accepted 7 June 2019

Introduction

A vast majority of patients who are resuscitated after a cardiac arrest (CA) are still comatose after return of spontaneous circulation (ROSC) because of transient or definitive anoxic-ischemic brain injury. Among these comatose patients, a significant proportion of them remain unconscious after rewarming from targeted temperature management (TTM) and discontinuation of sedation. Despite the improvement of post-CA care, most of these comatose patients will die following withdrawal of life-sustaining treatment (WLST) for irreversible post-anoxic encephalopathy.[1,2] European guidelines recommend to delay the initiation of WLST until exclusion of potential confounders, focusing mostly on residual sedation.[3,4] Indeed, predictive value of clinical indicators can be influenced by remaining effects of sedatives, as illustrated by clinical studies that reported a high rate of delayed awakening.[5,6] Consequently, a combination of prognostic tools that are independent of sedation should always be combined to avoid premature WLST.

Electroencephalogram (EEG) is broadly used both as a diagnostic and a prognostic tool in post-CA comatose patients.[7] This bedside investigation is widely available, non-invasive and provides real-time investigation of electrical brain activity. In post-CA comatose patients, EEG may reveal a large spectrum of abnormalities carrying prognostic information, such as malignant patterns indicating brain injury. In addition, ischemia-induced neuronal damage is associated with decreased amplitude and slowing of background EEG activity, and these abnormalities are correlated with the degree of neuronal injury.[8] Data from the literature are heterogeneous regarding the predictive value of EEG non-reactivity for prediction of a poor outcome in post-anoxic patients.[9–13] By contrast, some authors have reported that the presence of EEG reactivity could also identify patients with good outcome.[14,15] However, most of these prior studies have included heterogeneous populations and did not permit to assess the interaction between sedation and background reactivity.

The aim of the present study was to evaluate the prognostic value of EEG reactivity for neurological outcome after CA and to assess the potential confounding effect of sedation.

Materials and methods

Population

We considered for inclusion all consecutive adult patients who were admitted between January 2007 and October 2016 in the intensive care unit (ICU) of the Cochin University Hospital (Paris, France) with coma (Glasgow coma scale [GCS] $\leq$8) after resuscitation from CA and in whom at least one EEG was performed during coma. We excluded patients investigated for brain death diagnosis and those who had an EEG performed after awakening. Patients who died within 48 h post-CA (before any reliable neurological examination could be made) were also excluded. Patients' next of kin were informed that data were collected for clinical research purposes. According to the French legislation, the institutional review board waived the need for written informed consent.

Data collection

We performed a retrospective analysis of prospectively collected data from our CA registry that has previously been described.[1,16] The following data were recorded for each participant: patient's characteristics and cardiac arrest management data using Utstein style,[17] in-hospital parameters including, TTM modalities, type of sedation, timing for discontinuation of sedation, clinical indicators of neurological status (pupillary light reflex and motor component of the GCS, status epilepticus, timing for awakening) and short-latency somatosensory evoked potentials (SSEP). Length of ICU stay, cause of death and vital status at 1 year were also reported. For the present study, we used the first EEG performed during the ICU stay.

ICU management

Our management protocol for patients admitted after CA has previously been described (see ESM) and did not change throughout the study period except for sedation.[18] In the absence of contraindication, TTM was immediately started after ICU admission, targeting a core temperature of 32–34 °C for 24 h using an external cooling device. For sedation, we used midazolam and fentanyl between 2007 and 2014. Following updated guidelines, we then shifted towards propofol and remifentanil. The Richmond Agitation-Sedation Scale (RASS) was assessed every 3 h and the sedation level was titrated to maintain a RASS level of -5 (no response to voice or physical stimulation) all along the TTM period. Sedatives were interrupted after rewarming.

Neurological prognostication and WLST

Neurological status was evaluated twice-daily by ICU physicians until death or ICU discharge. Sedation level was assessed by nurses every 3 h and awakening was defined by the presence of 3 consecutive RASS scores of at least −2 (patient briefly awakens with eye contact to voice), as previously reported.[19] In patients who were still comatose 72 h after sedation discontinuation, a multimodal prognostication protocol was used, according to current guidelines (ESM).[3,20–22] Burst suppression or refractory status epilepticus were part of our algorithm. Importantly, EEG reactivity was not part of our prognostication algorithm during the study period.

EEG assessment

Intermittent EEG was recorded for at least 20 min by a skilled technician using a standardized protocol with 19 externals electrodes. In order to facilitate the interpretation of tracings, physicians in charge specified several clinical data to the board-certified neurologists, such as GCS, pupillary and corneal reflexes, presence of myoclonus, timing of sedation weaning, and drugs administered during EEG recording.

Presence of EEG reactivity was defined as the reproducible evidence of increase or decrease in amplitude or frequency of EEG waveforms. Appearance of muscle activity or eye blink artifacts was not considered as reactive patterns. The reactivity was tested at bedside in a standardized way, by auditory stimulation (hands clap, patient name call) and nociceptive (pressure on the nail or nipple pinching only if no reactivity was obtained with other stimuli) every 2 min during EEG recording.[23]

EEG findings were collected from the daily report of neurologists in the medical record of each patient, and tracings were not re-analyzed. EEG patterns were retrospectively classified by two authors (and a third one in case of disagreement) based on the American Clinical Neurophysiology Society (ACNS) terminology.[24] Highly malignant pattern was defined as electrical status epilepticus, burst suppression or suppression. Electrical status epilepticus was considered as

continuous rhythmic discharges like spikes, or spike-waves; burst suppression was defined as isoelectric voltage background with burst, and suppression as isoelectric voltage or suppressed background (<10 microvoltages) without discharges waveforms. Malignant patterns were defined as malignant periodic or rhythmic patterns, malignant background (discontinuous background, low voltage background <20 microvoltages) or non-reactive EEG. Finally, EEG was considered benign in the absence of any malignant features stated above and with the presence of reactivity EEG.

The primary outcome was the neurological status at ICU discharge using the cerebral performance categories (CPC) scale, dichotomized in good (CPC 1 or 2) or poor (CPC 3–5) outcome.[25]

Statistical analysis

Continuous variables were summarized using medians and inter-quartile range (IQR), and categorical variables were reported as proportions.

We first investigated the association between relevant patients' characteristics and neurologic outcome (CPC 1–2 vs CPC 3–5), including patient demographics, Utstein variables and EEG patterns. We performed Pearson's Chi2 test for categorical variables, and Wilcoxon test, when appropriate, for continuous variables. Secondly, a multivariate analysis was performed to assess independent predictors of poor outcome using logistic regression including factors with a p-value < 0.15 in univariate analysis.

Specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV) and false positive rate (FPR) corresponding to 1- specifity using an exact binomial 95% confidence interval (CI), were calculated in order to assess the predictive performance of each clinical and EEG indicator. We evaluated the predictive values for unfavorable outcome of non-reactivity, benign pattern, highly malignant pattern, malignant pattern on EEG, and bilaterally absence of N20 potentials on SSEP. To take into account the influence of potential confounders on non-reactive EEG, we stratified analysis according to the presence or absence of sedation and according to presence or absence of TTM use during EEG recording.

Finally, we assessed the predictors of EEG non-reactivity, using logistic regression including factors associated with EEG non-reactivity identified in univariate analysis with a p value < 0.15.

All tests were two-sided, with $p < 0.05$ considered statistically significant. We performed analysis using STATA/SE 14.0 software (College Station, TX, USA).

Results

Patients

From January 2007 to October 2016, 1426 patients were admitted after CA, of them 529 patients had at least one EEG performed during their ICU stay and were potentially eligible for the present analysis. Among them, 101 patients were excluded for the following reasons: 16 patients died during the first 48 h; 45 patients were already awake at time of EEG recording; in 40 additional patients, the indication of EEG was confirmation of a brain death diagnosis (Fig. 1).

Patients' characteristics are described in Table 1 for the 428 patients retained in the analysis. Patients were mostly male (71%), with a median age of 63 years. Initial cardiac rhythm was shockable in 212 (49%) patients, and epinephrine was used during resuscitation in 320 (76%) cases. TTM was used in 96% of patients, with a median duration of sedation 1.1 (0.7–1.5) days, using mostly midazolam (81%). A poor outcome was observed in 344/428 patients (80%) at ICU discharge and in 342/411 patients (83%) at 1 year. Causes of death are listed in ESM.

EEG and SSEP findings

Patients' status at time of EEG recording is detailed in Table 2 and EEG results according to neurologic outcome are reported in Table 3. Median time to EEG assessment was 3 days (2–4). Two-hundred and forty-three patients (57%) were weaned from sedation at time of EEG recording: the median delay between CA and EEG examination was 4 days (3–4) in patients assessed after weaning of sedation versus 1 day (1–2) in patients assessed with ongoing sedation $p < 0.001$.

In the whole population, 209/409 (51%) patients had a non-reactive EEG. Non-reactive EEG was far less frequent in patients with good outcome as compared with those with poor outcome (7% vs 63%, $p < 0.001$). Characteristics of the 6 patients who had a good outcome despite non-reactivity on EEG are listed in ESM.

Based on the ACNS nomenclature, 113/428 patients (26%) had highly malignant patterns, 162/428 (38%) had malignant patterns and 153/428 patients (36%) had a benign EEG. As compared with the good outcome group, malignant patterns were more frequently observed in the poor outcome group (9.5% vs 45%, $p < 0.001$), and all highly malignant patterns were observed in the poor outcome group (0% vs 33%).

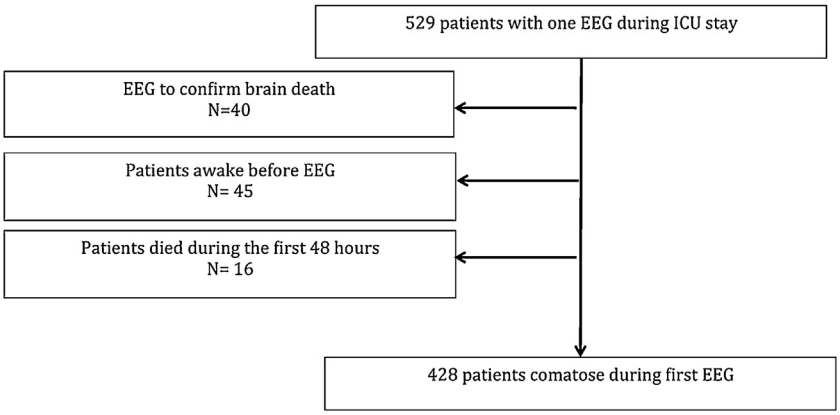

Fig. 1 – Flow chart.

Table 1 – Patients' characteristics.

Patients' characteristics	All patients n = 428	CPC 1–2 n = 84	CPC 3–5 n = 344	p
Male gender, n (%)	304 (71)	66 (77)	239 (69)	0.15
Age >63 years, n (%)	214 (50)	32 (38)	182 (53)	0.02
CA in a public area, n (%)	136 (32)	35 (42)	101 (29)	0.03
Witnessed CA, n (%)	375 (89)	75 (93)	300 (88)	0.26
Bystander CPR, n (%)	255 (61)	49 (61)	206 (61)	0.96
Initial shockable rhythm, n (%)	212 (49)	64 (76)	148 (43)	<0.001
Use of epinephrine, n (%)	320 (76)	35 (44)	285 (84)	<0.001
Dose of epinephrine >2 mg, n (%)	165 (39)	18 (22)	147 (43)	0.001
Time from CA to CPR > 5 min, n (%)	201 (52)	31 (40)	170 (55)	0.02
Time from CPR to ROSC > 20 min, n (%)	210 (50)	27 (33)	183 (55)	<0.001
Serum lactate at admission >4.5 mmol L-1, n (%)	183 (49)	17 (23)	166 (55)	<0.001
TTM, n (%)	412 (96)	80 (95)	332 (97)	0.58
Post-resuscitation shock, n (%)	209 (48)	44 (52)	165 (48)	0.47
Duration of sedation, days, median (IQR)	1.1 (0.7–1.5)	1.1 (0.6–1.6)	1.1 (0.7–1.5)	0.68
ICU length of stay, days, median (IQR)	7.2 (5.2–9.9)	8.9 (5.5–13.9)	7 (5.2–9.0)	0.008

Table 2 – Status at time of EEG recording.

Status at time of EEG recording	All patients n = 428	CPC 1–2 n = 84	CPC 3–5 n = 344	p
Glasgow motor response 1 or 2, n (%)	324/375 (86)	55/78 (71)	269/297 (91)	<0.001
No pupillary reflex, n (%)	158/428 (37)	18/84(21)	140/344 (41)	<0.001
Ongoing hypothermia, n (%)	91/428 (21)	31/84 (37)	60/84 (17)	<0.001
Ongoing sedation, n (%)	185/428 (43)	53/428 (63)	132/428(38)	<0.001

Table 3 – EEG and SSEP findings.

EEG and SSEP findings	All patients n = 428	CPC 1–2 n = 84	CPC 3–5 n = 344	p
Non-reactive EEG, n (%) Missing data 19	209/409 (51)	6 (7)	203(63)	<0.001
Highly malignant pattern, n (%)	113 (26)	0	113 (33)	–
Burst suppression or suppression, n (%)	58 (14)	0	58 (17)	–
Status epilepticus, n (%)	55 (13)	0	55 (16)	–
Malignant pattern, n (%)	162 (38)	8 (9)	154 (45)	<0.001
Benign pattern, n (%)	153 (36)	76 (90)	77(22)	<0.001
Bilaterally absence of N20 on SSEP, n (%)	103/206 (50)	0	103/190 (54)	–

EEG for prediction of poor outcome

PPV of a non-reactive EEG for prediction of a poor outcome was 97.1% (93.6–98.9) (Table 4). The PPV reached 98.3% (94.1–99.8) if reactivity was tested in non-sedated patients (p = 0.41). In multivariate analysis, ongoing sedation during EEG was not associated with a higher risk of non-reactive EEG (OR 1.3; IC95 (0.8–2.1) p = 0.35) (ESM).

In multivariate analysis, non-reactive EEG was significantly associated with a higher risk of poor outcome (OR 12.56; IC 95% (4.7–33.6) p < 0.001). Predictive values of other EEG patterns for poor outcome are reported in Table 4 and ESM.

Table 4 – Prognostic value of EEG parameters and SSEPs for poor outcome.

Parameters for poor outcome	Sensitivity (IC95%)	Specificity (IC95%)	NPV (IC95%)	PPV (IC95%)	FPR (IC95%)
Non-reactive EEG (all patients) n=209	62.5 (57–67.7)	92.9 (85.1–97.3)	39 (32.2–46.1)	97.1 (93.6–98.9)	7.1 (2.7–14.9)
Non-reactive EEG (without concomitant sedation) n= 120	57.6 (50.5–64.4)	93.5 (78.6–99.2)	25 (17.4–33.9)	98.3 (94.1–99.8)	6.5 (0.8–21.4)
Non-reactive EEG (with concomitant sedation) n= 89	70.8 (61.8–78.8)	92.5 (81.8–97.9)	58.3 (47.1–7)	95.5 (88.9–98.8)	7.5 (2.1–18.2)
Highly malignant pattern n= 113	32.8 (27.9–38.1)	100 (95.7–100)	26.67 (21.9–31.9)	100 (96.8–100)	0 (0–4.3)
Malignant pattern n=162	44.8 (39.4–50.2)	90.5 (82.1–95.8)	28.6 (23.2–34.4)	95.1 (90.9–97.8)	9.5 (4.2–17.9)
Bilaterally absence of N20 n=103	54.2 (46.8–61.4)	100 (79.4–100)	15.5 (9.2–24)	100 (96.5–100)	0 (0–20.6)

EEG patterns for prediction of a good outcome

The PPV of a benign EEG to predict a good outcome was 49.7% (41.5–57.9). This PPV increased up to 66.2% (54.3–76.8) when sedation was present, as compared to benign EEG without sedation, with PPV of 34.2% (23.9–45.7) $p < 0.001$. In the subgroup of patients under TTM and still sedated during EEG recording (n = 96), this PPV increased to 72.9% $p = 0.33$. (ESM).

Discussion

In this population of post-CA comatose patients, we found that EEG non-reactivity was observed in half of the population, being predictive of unfavorable outcome. Sedation had a modest effect on the predictive value of EEG non-reactivity, with a slightly higher PPV and lower FPR even if this difference was not significant. This would suggest that sedation might partly alter EEG reactivity, a fact that should be taken into account in the interpretation of EEG for neuroprognostication after CA. Interestingly, predictive value of a benign reactive EEG for good outcome seems to be better if EEG was assessed earlier, despite ongoing sedation.

The first step of neuroprognostication after CA is based on neurological examination performed after exclusion of confounders, particularly residual sedation.[26] In this context, other reliable tools are needed. Bilateral absence of N20 potentials on SSEP is highly correlated with poor neurologic outcome.[27] However, SSEP have a low sensitivity and remain underused.[28] Conventional EEG is more widely available, contributes to diagnose persistent coma with subclinical seizure and serves also as a prognostic tool after CA. In our population, EEG was performed in 37% of patients admitted for a CA, a rate that is in line with previous studies.[29,30]

The present work highlights that sedation might interfere with reactivity assessment even the results are not statistically significant. In our population, 43% of EEG recordings were performed with ongoing sedation, mostly because EEG was performed during the first 24 h. This is concordant with other recent studies suggesting that EEG within the first 24 h after ROSC might be associated with a good prognostic accuracy.[31] In fact, sedation could probably be a confounding factor for absence of EEG reactivity, with a trend to a lower PPV regarding prediction of poor neurologic outcome. As a matter of fact, midazolam and propofol are not only sedatives drugs but they are also active against seizures and can modify EEG patterns.[32] Some studies highlighted that sedation increases suppression ratio and decreases amplitude-integrated EEG.[33,34] In a clinical study in which 8/22 post-CA patients with burst suppression survived with good outcome, all cases were possibly confounded by the concomitant use of propofol.[13] Physicians should cautiously interpret the lack of reactivity during this period because of the risk of interference with sedation.[9,12] This is mostly important when the first tracing is non-reactive in a sedated patient. We reported 6 patients with an initial non-reactive EEG who later awoke and who had a favorable outcome. Interestingly, all these 6 patients were sedated with midazolam and EEG assessment was performed 1 day after CA in median, with ongoing sedation in 67% of cases. We could probably explain our statistically negative results with the under estimation of sedative effect on EEG reactivity because EEG was not systematically performed in all comatose post-CA patients.

We reported the presence of a highly malignant EEG pattern in 26% of patients, which was a very strong EEG indicator of poor outcome, in agreement with previous studies.[15,33] However this should be interpreted cautiously since presence of a status epilepticus was considered as a highly malignant pattern and was a part of our criteria for WLST although some study described good outcome after this event.[35] A malignant EEG pattern was strongly associated with poor outcome but with a higher rate of false positive rate, confirming that detection of low voltage and discontinuous background could be difficult.[30]

Concerning prognostication of good outcome, we found a moderate predictive value of a reactive EEG (39%) and a benign EEG (50%) in comparison with Rossetti et al. reporting a 72% PPV of presence of reactivity on early EEG and 86.2% PPV of early benign EEG for good outcome.[15] Our population differed significantly since we only included patients who had an EEG performed in case of neurological concern. This may have selected a population with a higher risk of severe brain injury. This may explain that only 20% of our patients recovered a CPC 1–2 level as opposed to 50% in Rossetti's population. Second, the diversity of reactivity testing modalities and interpretation with a possible inter-rater variability could also explain these differences.[36] Third, timing for EEG assessment was different. Interestingly, the PPV of a benign EEG regarding good outcome seems to be better when a benign EEG was obtained earlier, despite ongoing sedation and TTM.

Our study has several strengths. First, we studied a large number of patients with inclusion criteria in concordance with current guidelines for neuroprognostication. Second, reactivity was tested in a standardized way by the same technician and the interpretation was blinded to other prognostic tools and performed by the same electrophysiologists all along the study period. Both were external consultants, thus limiting the risk of bias. Moreover, definition of EEG reactivity respected ACNS's standardized critical care EEG terminology.[24]

This study also has some limitations. First, this is a retrospective and monocentric study in which the timing for EEG assessment was not strictly uniform, even if the median delay from CA was 3 days as recommended. EEG recordings performed under sedation were obtained earlier as compared with those performed without ongoing sedation. The difference may have influenced the results on sedation effect on EEG. EEG patterns may fluctuate and evolve, and temporal dynamic changes of EEG over time are common.[8] Second, categorization between highly malignant, malignant or benign patterns was scored retrospectively according to the detailed EEG report. We cannot exclude the risk of missing data in EEG description. Third, neurophysiologists who interpreted EEG tracings were not totally blinded for all clinical data and it could have influenced their interpretation. However, they were blinded to outcome at time of EEG interpretation. Fourth, there is a risk of subjective assessment of EEG reactivity.[23,37,38] Quantitative methods might increase reproducibility and objectivity of EEG reactivity assessment, though they are rarely used in routine practice.[39,40] Fifth, we did not use continuous EEG in our study. However, it has been reported that two standard EEG recordings of 20–30 min duration, including reactivity testing, are as informative as continuous EEG, while being less demanding on resources.[10,41] Then, we changed our sedation protocol during the 9 years collection period, which could have theoretically influenced our results. Sixth, self-fulfilling prophecy is a common bias in this setting. The treating physicians were not blinded to the results of reactivity testing. However WLST decisions were not based on EEG reactivity assessment, since it was not part of our prognostication algorithm during the study period. Median ICU length of stay was

7 days in the group of patients with poor outcome, illustrating the low risk of early WLST in this population. Finally, the outcome was assessed at ICU discharge for analysis while long-term outcome would have been more adapted.

Conclusion

Among comatose patients after CA, a non-reactive EEG was predictive of unfavorable outcome but this indicator has to be used in a multimodal approach for prognostication. Assessment of reactivity was slightly influenced by concomitant sedation. Conversely, early benign EEG seems to be a promising tool for prediction good outcome but further studies are required to confirm this finding.

Conflict of interest

None.

Acknowledgment

We thank Nancy Kentish-Barnes for her help in preparing the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.06.009.

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