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Clinical paper

Benign EEG for prognostication of favorable outcome after cardiac arrest: A reappraisal

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Abstract

Aim: The current EEG role for prognostication after cardiac arrest (CA) essentially aims at reliably identifying patients with poor prognosis ("highly malignant" patterns, defined by Westhall et al. in 2014). Conversely, "benign EEGs", defined by the absence of elements of "highly malignant" and "malignant" categories, has limited sensitivity in detecting good prognosis. We postulate that a less stringent "benign EEG" definition would improve sensitivity to detect patients with favorable outcomes.

Methods: Retrospectively assessing our registry of unconscious adults after CA (1.2018–8.2021), we scored EEGs within 72 h after CA using a modified "benign EEG" classification (allowing discontinuity, low-voltage, or reversed anterio-posterior amplitude development), versus Westhall's "benign EEG" classification (not allowing the former items). We compared predictive performances towards good outcome (Cerebral Performance Category 1–2 at 3 months), using 2x2 tables (and binomial 95% confidence intervals) and proportions comparisons.

Results: Among 381 patients (mean age 61.9 ± 15.4 years, 104 (27.2%) females, 240 (62.9%) having cardiac origin), the modified "benign EEG" definition identified a higher number of patients with potential good outcome (252, 66%, vs 163, 43%). Sensitivity of the modified EEG definition was 0.97 (95% CI: 0.92–0.97) vs 0.71 (95% CI: 0.62–0.78) ($p < 0.001$). Positive predictive values (PPV) were 0.53 (95% CI: 0.46–0.59) versus 0.59 (95% CI: 0.51–0.67; $p = 0.17$). Similar statistics were observed at definite recording times, and for survivors.

Discussion: The modified "benign EEG" classification demonstrated a markedly higher sensitivity towards favorable outcome, with minor impact on PPV. Adaptation of "benign EEG" criteria may improve efficient identification of patients who may reach a good outcome.

Keywords: Prognosis, Anoxic-ischemic encephalopathy, Background, Amplitude, Electroencephalogram, Cardiac arrest

Introduction

The role of electroencephalogram (EEG) to prognosticate unconscious patients after cardiac arrest (CA) was described more than 50 years ago[1]. Added to neurological examination, cortical somatosensory evoked potentials (SSEP), serum biomarkers (such as neuron-specific enolase, NSE) and neuroimaging, EEG represents one of the most widely used prognostic tools[2]. EEG interpretation in an intensive care unit (ICU) environment has been increasingly guided by recommendations of the American Clinical Neurophysiology Society (ACNS)[3–4], allowing a high generalizability of the findings. It has been shown that EEG interpreted according to these guidelines may orient on poor and good outcome[5–6]. In particular, the definition of "highly malignant" patterns by Westhall and colleagues in 2014[7–8] shows a high specificity towards poor prognosis. However, the definition of a "benign" EEG by exclusion of any "malignant" and "highly malignant" feature seems less robust, as its sensitivity is relatively low[7].

We postulated that this definition may be too stringent, especially in terms of background continuity, amplitude, and anterio-posterior amplitude reversal (i.e., when, as opposed to physiological activity, the EEG background shows higher amplitude in the front than in the back), which can be influenced by sedation, and that timing

Abbreviations: ACNS, American Clinical Neurophysiology Society, CA, Cardiac Arrest, CHUV, Centre Hospitalier Universitaire Vaudois, CPC, Cerebral Performance Category, EEG, Electroencephalogram, cEEG, continuous Electroencephalogram, FOUR, Full Outline of UnResponsiveness, ICU, Intensive Care Unit, NSE, Neuron-Specific Enolase, PPV, Positive Predictive Value, ROC, Receiver Operating Characteristic, ROSC, Return of Spontaneous Circulations, SIRPID, Stimulus Induced Rhythmic, Periodic or Ictal Discharges, SSEP, Somatosensory Evoked Potentials

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may be critical to detect patients with favorable outcome. Our hypothesis was that the removal of the three aforementioned items would strengthen the sensitivity of benign EEG for identifying good outcomes. The aim of the present study is therefore to propose and test a modified "benign" EEG definition with features associated with good outcome, in order to increase sensitivity without major compromise on false positivity (positive predictive value, PPV). This would potentially impact prognostic evaluation of post-CA patients, allowing earlier and improved sensitivity of detection of those with likely favorable outcome.

Methods

Study design

We analyzed our institutional (CHUV, Lausanne University Hospital, Switzerland), monocentric, prospectively acquired registry of consecutive adult patients treated after CA in our ICU, not dying within 24 h, and receiving at least one EEG recording within 72 h of CA, between January 2018 and August 2021 (44 months). The registry is approved by the local ethics committee (CER-VD), with consent waiver (procedures and treatments are part of standard care).

ICU management and EEG analysis

The protocol (as previously described[5,9]included temperature management during the first 24 h targeting 35–36 °C, with sedation by propofol (2–3 mg/kg/h) or midazolam (0.1–0.15 mg/kg/h), and analgesia by fentanyl (1.5mcg/kg/h), with a case-dependent adaptation. Neuromuscular blocking agents and noradrenaline (mean arterial pressure target: ≥65 mmHg) were administered if needed. Clinical and nonconvulsive (electrical) seizures were treated with valproate or levetiracetam as primary agents; in selected cases, propofol was added[10].

The in-house protocol foresaw repeated routine (20 min) video-EEGs. The first routine recording occurred at 12–36 h, repeated at 36–72 h (NicOne, Viasys Neurocare; after December 2020 XLtek, Natus Medical Inc., Middleton WI) using 21 electrodes (10–20 international system), with systematic reactivity testing by physicians or certified EEG technologists[11]. In some cases, continuous EEG (cEEG) war used (according to changing internal guidelines during definite time periods). Median nerve SSEP were recorded after 24 h following CA; serum NSE was collected at 24 and 48 h. Clinical examination (Glasgow Coma Scale, FOUR -Full Outline of UnResponsiveness- score) was performed routinely at 72 hours, off sedation, by certified neurologists.

During patients' recruitment, life-sustaining-therapy withdrawal was considered, per house-internal protocol based on previous studies, in the presence of at least two reliable unfavorable prognostic factors (assessed off sedation and at 72 h following CA), such as absence of pupillary or corneal reflexes, treatment-resistant myoclonus / status epilepticus, unreactive EEG background in normothermia and off-sedation, bilateral absence of cortical somatosensory-evoked potentials[12]; brain MRI and serum NSE (threshold: 75 μg/l) represented additional supporting criteria[5,9,13]. Decisions of withdrawal of intensive treatment were multi-disciplinarily, including discussion with relatives[5,9].

EEGs were prospectively interpreted by two authors (JN, AOR) and entered in the registry according to ACNS recommendations, before knowing the patient's outcome. For those patients, the registry was prospectively scored using the time for reactivity testing corresponding to the routine recordings (12–36 hours, then 36–72 hours). Each recording had prospectively been assigned to the three prognostic Westhall's categories[14]; continuity, reactivity, amplitude (categorized as normal, low or suppressed), anterio-posterior gradient, and occurrence of repetitive epileptiform discharges were also entered separately. For this study, HF and AOR re-evaluated all tracings with pre-specified modified criteria of good prognosis (Fig. 1), blinded for outcome and cardiac arrest details. We focused on following elements: background continuity, anterio-posterior gradient, reactivity[11] (excluding stimulus-induces rhythmic, periodic or ictal discharges (SIRPIDs)[15], and occurrence of repetitive epileptiform elements (spikes, spike-waves, sharp waves, including triphasic appearance). The registry, with full EEG reports, as well as original and EEG tracings were accessed for clarification.

Information on temperature and sedation during EEG recordings (and reactivity testing) was retrieved from the registry, as were results of SSEP, peak serum NSE, and FOUR scores. No tests were specifically performed for the means of this study.

Outcomes

The outcome was prospectively assessed, for clinical follow-up, using Cerebral Performance Categories (CPC[16] at 3 months by semi-structured interviews with patients, relatives, or primary care physicians, performed by a blinded investigator; good outcome was defined as CPC 1–2[17]). Patients for whom outcome could not be obtained were excluded.

	Westhall Definition	Modified Definition
Benign EEG	**1. Reactive background** **2. Absence of:** -Malignant periodic or rhythmic patterns (abundant periodic discharges, abundant rhythmic polyspike-/spike-/sharp-and-wave; unequivocal electrographic seizure). *-Malignant background (discontinuous with suppression periods; low voltage; reversal of anterior–posterior amplitude gradient).*	**1. Reactive background** **2. Absence of:** -Malignant periodic or rhythmic patterns (abundant periodic discharges; abundant rhythmic polyspike-/spike-/sharp-and-wave; unequivocal electrographic seizure).

Fig. 1 – Benign EEG ûWesthall criteriaý and û Modified criteria ý for good outcome. The difference lies in the second items group of Westhall criteria (in italic).

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Statistics

Clinical variables were compared with Fisher, chi^2 or 2-sided t-tests, as needed. Predictive performances of "Westhall" and the modified criteria for "benign EEG" for good outcomes (CPC 1–2) and awakening with contact (CPC 1–3) at 3 months were calculated, using 95% binomial confidence intervals. Performances of the two approaches were assessed by comparisons of proportions, and comparisons of areas under the Receiver Operating Characteristic (ROC) curves. Results with a p-value < 0.05 were considered statistically significant. Calculations were performed using Stata version 16 (College Station, TX).

Results

During the study period of 44 months, 381 patients were included in our registry (suppl. flowchart); their characteristics are summarized in Table 1. Of them, 363 (95%) had an early EEG within the first 24–36 h and 313 (82%) at 36–72 h (Table 2); the majority (292 patients, 77%) had both recordings. The lower number of recordings performed at 72 h was due to patient deceasing or regaining consciousness during this period of time. A continuous EEG (cEEG) was recorded in 32 patients (8%). We conducted the data analysis for both early and late EEG, as well as for "any EEG", meaning a benign EEG occurring at any time-point.

The modified definition of "benign EEG" allowed identifying a greater number of patients with a benign recording as compared to the original one (252 (66%) versus 163 (43%) of 381); the distribution of clinical variables was however comparable in both groups of "benign EEGs" (Table 1). Sensitivities and positive predictive values for good functional outcome (CPC 1–2) and awakening reaching contact to the environment (CPC 1–3) are illustrated in Tables 3 and 4. Comparisons of these performances showed a marked improvement of sensitivities at any time-point and for each outcome, paralleling a slight, statistically non-significant of PPV reduction (Table 5). Comparing ROC curves, the modified definition showed higher areas towards survival (0.796 vs 0.757, p = 0.066) and good outcome (0.746 vs 0.723, p = 0.295), in both cases however not reaching statistical significance.

Discussion

This analysis shows that a comprehensive definition of "benign EEG" not including the criteria of amplitude, anterio-posterior amplitude gradient, and allowing discontinuity of the background, appears to be more sensitive to identify post CA patients with favorable prognosis than the original definition[7–8].

Identification of patients with favorable outcome after CA has received increasing attention in the last years[18–19], but is still scarcely mentioned in current prognostic recommendations[12]. Recent studies[20–21] already highlighted the importance of background reactivity. However, our goal in the present work was to provide an improved definition of benign EEG using several criteria, not just reactivity, with increased sensitivity (48% in the original study, however on a very limited number of patients with good outcome)[7–8], and similar PPV; higher sensitivities lead to non-significantly higher ROC areas.

Our cohort appears relatively similar to those described in other studies, including the original description[7–8]: mean age 67 years (62 in ours), 70% male (73%), 72% shockable rhythm (reflecting the targeted recruitment towards this rhythm in the TTM trial; 45% in ours), median time to ROSC 30 minutes (17 minutes). The higher time to ROSC in the original cohort could reflect that some TTM trial centers possibly performed EEG more frequently in unclear prognostic situations, thus somewhat concentrating poor prognosis patients, which would be in line with the worse outcome: (24% CPC 1–2, clearly lower than most CA cohorts, versus 55% in ours). Timing of EEG recording, reactivity testing as well as sedation did not differ between the cohorts.

It could be argued that sensitivity is not more important than specificity to identify subjects with potential good outcome, as active care would not be discontinued in the absence of an isolated benign EEG. Identification of good outcome, however, practically relies on

Table 1 – Patients characteristicsROSC = return of spontaneous circulation, SSEP = somatosensory evoked potentials, CPC = cerebral performance category scale, SD = standard deviation.

	All patients 381	Benign EEG after Westhall (15) 163	Modified benign EEG 252	p (test)
Age, years	61.9 (SD:15.4)	61.6 (SD: 16.0)	62.4 (15.2)	0.596 (t)
Female sex	104 (27.2.%)	45 (27.6%)	63 (25.0%)	0.554 (Chi^2)
Shockable cardiac rhythm	173 (45.4%)	65 (39.8%)	116 (46.0%)	0.217 (Chi^2)
Cardiac origin	240 (62.9%)	121 (75%)	181 (72%)	0.590 (Chi^2)
Time to ROSC (minutes, median)	17 (IQR:8–27)	15 (IQR: 8–28)	17 (IQR: 8–27)	0.891 (U)
Bilaterally absent SSEP (tested n = 340)	87/340 (25.5%)	1/143 (0.7%)	5/220 (2.2%)	0.501 (Fisher)
Bilaterally absent pupillary reflex (tested n = 381)	90 (23.6%)	9 (5.5%)	18 (7.1%)	0.549 (Fisher)
CPC 1	101 (24.3%)	45 (27.6%)	56 (22.2%)	0.317 (Fisher)
CPC 2	129 (31.0%)	52 (31.9%)	77 (30.5%)	
CPC 3	91 (21.9%)	37 (22.7%)	54 (21.4%)	
CPC 4	1 (0.2%)	0	1 (0.4%)	
CPC 5	93 (22.4%)	29 (17.7%)	64 (25.4%)	

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Table 2 – Details regarding EEG: early (12–36 h after CA, EEG1) and late (36–72 h after CA, EEG2). SD: standard deviation; other sedation: ketamine, thiopental.

Total patients n = 381	EEG 1 (n = 363) 95%	EEG 2 (n = 313) 82%
Mean timing of recording (h)	19.0 (SD: 5.75)	51.1 (SD: 9.5)
Mean temperature (°C)	35.6 (SD: 0.8)	36.7 (SD: 0.6)
Propofol (%)	221 (61%)	70 (22%)
Midazolam (%)	152 (42%)	53 (17%)
Other sedation (%)	3 (0.8%)	5 (1,5%)

Table 3 – Original definition (Westhall): Sensitivity and PPV (positive predictive value) (95% confidence interval) of good outcome and awakening with contact. CPC = cerebral performance category scale.

	EEG	Total scored	True positive	False positive	True negative	False negative	Sensitivity	PPV
CPC 1–2 (good outcome)	Early	362	66	27	205	64	0.51 (0.42–0.59)	0.71 (0.61–0.80)
	Late	313	74	55	155	29	0.72 (0.62–0.80)	0.57 (0.48–0.66)
	Any	381	97	66	179	39	0.71 (0.62–0.78)	0.59 (0.51–0.67)
CPC 1–3 (survival)	Early	362	78	15	156	113	0.41 (0.34–0.49)	0.84 (0.75–0.91)
	Late	313	107	22	135	49	0.68 (0.61–0.76)	0.83 (0.75–0.89)
	Any	381	134	29	153	65	0.67 (0.60–0.73)	0.82 (0.75–0.67)

Table 4 – Modified definition; sensitivity and PPV (positive predictive value) (95% confidence interval) of good outcome and awakening with contact. CPC = cerebral performance category scale.

	EEG	Total scored	True positive	False positive	True negative	False negative	Sensitivity	PPV
CPC 1–2 (good outcome)	Early	362	120	79	153	10	0.92 (0.86–0.96)	0.60 (0.53–0.67)
	Late	313	96	92	118	7	0.93 (0.86–0.97)	0.51 (0.43–0.58)
	Any	381	133	119	126	3	0.97 (0.93–0.99)	0.53 (0.46–0.59)
CPC 1–3 (survival)	Early	362	160	39	132	31	0.84 (0.78–0.89)	0.80 (0.74–0.86)
	Late	313	143	45	112	13	0.91 (0.86–0.95)	0.76 (0.69–0.82)
	Any	381	188	64	118	11	0.94 (0.92–0.97)	0.74 (0.68–0.78)

maximizing sensitivity (minimizing false negatives, or in other words not missing patients with good outcome), rather than specificity[18,22]. The latter does represent a key element of poor outcome prognostication, where minimizing false positives is paramount[22]; however, identifying patients with favorable prognosis may not be efficient using high specificity (e.g., serum NSE, where 65% of good outcome patients were missed applying highly specific thresholds[23]).

We thus opted to optimize sensitivity (which is independent from the prevalence of the considered outcome in the studied population, and includes false negatives in the denominator) rather than PPV; this, including false positives in the denominator, was only slightly and non-significantly decreased with the modified definition, and remains relatively low for both "benign EEG" approaches, especially for identification of CPC 1–2. In case of false positives for good outcome, patient's evolution or additional prognostic tests[24] would likely contribute to correct the overestimation.

Comparison of clinical characteristics of patients selected according to the original or the modified ûbenign EEGý definition did not show any relevant difference, suggesting that these two populations are comparable, and supporting that the modified "benign EEG" definition allows a more efficient identification of subjects with favorable outcome.

We conducted our analyses on two different time-points (12–36 hours, 36–72 hours), as well as together ("any EEG"), for our initial hypothesis was that early and late recordings might show different performances, with better accuracy at the early time-point[5–6]. Indeed, sensitivities of the original definition between early or late EEG showed a striking difference (Table 3), whereas they remained relatively stable over the two different time-points for the modified version (Table 4). This may be the consequence of EEG amplitude reduction and background discontinuity during sedation. It can be conversely inferred that sedation (mostly present early after resuscitation) did not bias EEG prediction using the modified criteria, in line with recent data at normally prescribed doses[6]. This suggests that not only the modified definition is more sensitive, but also that it is more robust over time, including at an early stage of prognostication. Indeed, the modified ûbenign EEGý definition was based on the assumption that the items of background continuity, amplitude, and

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Table 5 – Comparisons (P-values) of proportions of performances between the two definitions of benign EEG. CPC = cerebral performance category scale.

	CPC 1–2 (good outcome)		CPC 1–3 (awake)	
	Sensitivity	PPV	Sensitivity	PPV
Early	<0.001	0.077	<0.001	0.477
Late	<0.001	0.269	<0.001	0.140
Any	<0.001	0.178	<0.001	0.070

reversal of anterior-posterior amplitude gradient were too easily impacted by sedation and without robust evidence upon their description[8].

In the 5 patients with conflicting prognostic information having a "benign EEG" (new definition) but bilaterally absent SSEPs, 1 reached CPC 3, while the other 4 died, underscoring that discordant prognostication warrants watchful waiting.

The inclusion of background discontinuity (attenuation < 50%) as a malignant item in the original classification was described in the original analysis[8] to be responsible for several false positive predictions, as opposed to burst-suppression (attenuation > 50%), which has very high specificity to poor prognosis. Other studies[6,25–26] also found that discontinuous background can be associated with good outcome. Normal background voltage has been associated with good prognosis[6,25], but the relationship of early low-voltage with poor outcome is inconstant[25], especially in the first 24 hours post CA. The limited predictive value of low voltage was also highlighted in the original analysis as responsible for false prediction of negative outcomes[8]. Recent work indeed suggests that, especially if at least nearly continuous, low voltage background may be related to favorable outcome[27]. Finally, to our knowledge, there is no validation of the predictive value of the anterior-posterior amplitude development; its inclusion in the original criteria drew a parallel with the alpha coma pattern, which also includes lack of reactivity[7,14,28].

The use of positive items (such as reactivity) to define a "benign EEG" instead of merely the absence of items associated to bad prognosis, which probably overstates the value of voltage development and low-voltage background, as had already been observed[29]. The elements of discontinuity (burst-suppression) and background voltage remain however of unchanged importance for the "highly malignant" category[7–8], which has been convincingly validated[5,30–31].

Our results should be interpreted in the light of limitations. They are based on a single cohort, albeit sizeable and with characteristics similar to others[5–6,25,32]; this suggests a good generalizability (note that ethnic information is not included in our registry, which is representative of a cohort of White, European individuals).The limited inter-rater reliability for the evaluation of reactivity on EEG in post-CA patients should be acknowledged[8]. However, reactivity has been independently related to favorable outcome in this setting[33]; it was tested uniformly across patients[11] and interpreted by two experienced authors (AOR, JN) working together for many years, supporting internal validity. It is possible that some EEG features, such as reactivity, may have influenced patients' management and lead to a self-fulfilling prophecy. This seems however less probable than in studies analyzing poor outcome, as to our knowledge there are no widely recognized multimodal recommendations to forecast good prognosis (and there is still no protocol in this sense at our center). Of relevance, EEG scorings were conducted without knowledge of prognosis, and inspection of the raw EEG recordings was performed on selected cases to address unclear reports. We basically scored the amplitude regarding the item of anterior-posterior gradient, not the frequency. Unfortunately, our registry does not contain details on death cause. The retrospective design does not allow testing whether this modified EEG scoring may influence patient care: a prospective design would be needed. Another issue is that the post-test probability is somewhat similar compared to the pre-test probability of a good outcome (which was 55% in this cohort). The vast majority of patients did not undergo cEEG; however, repetitive routine EEG probably bears similar predictive information[34] and does not seem to influence outcome[35–36]. One last point is that a "burst-suppression" pattern directly classifies EEGs into the "highly malignant" category, which was not put into question for this study; a small number of these recordings (5 cases) showed however distinct reactivity to stimuli. This should be further investigated in a larger dataset.

Conclusion

"Benign EEG" after CA may be defined in a more comprehensive way, regardless of background amplitude, anterior-posterior amplitude development and discontinuity, allowing a high sensitivity in identification of patients with favorable outcome, with reasonable PPV. Further studies are warranted to develop the present results in order to refine current knowledge on identification of patients with favorable prognosis, including a more granular analysis of the different EEG items (potentially considering cEEG), addressing interrater reliability, and including other clinical items for a multi-modal analysis.

Conflicts of Interest

The authors of this study have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2022.11.003.

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