Title: Standardized EEG interpretation in patients after cardiac arrest: Correlation with other prognostic predictors.

Authors: Beuchat I, Solari D, Novy J, Oddo M, Rossetti AO

Journal: Resuscitation

Year: 2018 May

Issue: 126

Pages: 143-146

DOI: 10.1016/j.resuscitation.2018.03.012

Standardized EEG interpretation in patients after cardiac arrest: correlation with other prognostic predictors

Isabelle Beuchat, MD[1], Daria Solari, MD[2], Jan Novy[1] MD PhD, Mauro Oddo[2] MD, Andrea O. Rossetti[1] MD FAES

[1] Department of Clinical Neuroscience, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne University Hospital, Lausanne, Switzerland
[2] Department of Intensive Care Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne University Hospital, Lausanne, Switzerland

Contents:
Title: 110 characters
Abstract: 245 words
Main text: 1500 words
Tables: 3; Supplementary Tables: 2, Supplementary figure: 1
References: 20

Corresponding author
Pr Andrea Rossetti
Service de Neurologie; CHUV-BH07
CH-1011 Lausanne, Switzerland
Email andrea.rossetti@chuv.ch
Phone: + 41 21 314 12 20
Fax: +41 21 314 12 90

Abstract

Introduction

Standardized EEG patterns according to the American Clinical Neurophysiology Society (ACNS) (“highly malignant”, “malignant” and “benign”) demonstrated good correlation with outcome after cardiac arrest (CA). However, this approach relates to EEGs after target temperature management (TTM), and correlation to other recognized outcome predictors remains unknown.

Objectives

To investigate the relationship between categorized EEG and other outcome predictors, during and after TTM, at different temperatures.

Methods

In a prospective adult CA registry between 01.2014 and 06.2017, EEG at day one and two after CA were reclassified into pre-defined categories. Correlations between EEG and clinical, biochemical, neurophysiological outcome predictors, and prognosis (CPC at three months; good: 1-2), were assessed.

Results

Of 203 CA episodes, 31.5% were managed targeting 33°C, 60.6% targeting 36°C, and 7.9% with spontaneous temperature. “Highly malignant” EEG was found in 36.7% of patients at day one (predicting poor prognosis with 91% specificity -95%CI: 83%-97%-, and 63% sensitivity -95% CI 53%-72%), and 27.1% at day two. “Benign” EEG occurred in 19.2% at day one (sensitivity to good prognosis: 35% -95%CI: 26%-46%, positive predictive value: 89% -95% CI: 75%-97%), and in 33.2% at day two. Categorized EEG showed robust correlations with all prognostic predictors. Results were similar between EEGs recorded at day one or two, and, especially for poor prognosis, across TTM targets.

Discussion

Standardized EEG categorization after CA shows strong correlation with other outcome predictors, without marked variation across EEG recording time or TTM targets, underscoring its prognostic role in a multimodal approach.

Introduction

Cardiac arrest (CA) has a yearly incidence of 38-84/100'000 and survival of 10% in Europe (1-3); withdrawal of life-sustaining treatment (WSLT) is the leading cause of death (4). A multimodal approach combining clinical and neurophysiological examinations, blood biomarkers, and brain imaging is recommended for early outcome prediction (5, 6). EEG is one of the most commonly used tool either to assess prognostication or to detect epileptiform activity (6, 7).

Three predefined EEG categories based on the recent American Clinical Neurophysiology Society (ACNS) standardized critical care terminology (8) ("highly malignant", "malignant", "benign") show good correlation with poor and good outcome (9-12). However, to the best of our knowledge, the relationship between these patterns and other commonly used outcome predictors is unknown. Furthermore, this standardized approach was originally described in patients receiving EEG after target temperature management (TTM), and occurrence of self-fulfilling prophecy could not be formally excluded.

Our aim was to investigate the relationship of pre-defined standardized EEG categories with other outcome predictors in patients during and after TTM, with different temperature targets.

Methods

Subjects were retrospectively identified from our prospective CA registry including consecutive comatose adults admitted between January 2014 and June 2017. Details on patient's management are published (9, 13). Following variables were extracted: demographics; TTM (hypothermia; 33°C, normothermia: 36°C, or none); CA etiology (cardiac versus other); time to return of spontaneous circulation; neurological examination off sedation at 72 hours (corneal and pupillary reflexes, any myoclonus, motor reaction better than extension posturing) (5); cortical somatosensory evoked potentials (SSEP);

serum neuron-specific enolase (NSE) peak value within 72 hours; quantitative pupillometry (PLR, as in (14)), and functional outcome at 3 months according to a semi-structured phone interview using Glasgow-Pittsburg Cerebral Performance Categories (CPC: 1-2 good; 3-5: poor) (15). PLR, SSEP and routine EEG were recorded at day one (during) and two (after TTM).

EEGs were specifically reviewed and reclassified into pre-defined categories (9-12), mutually exclusive and exhaustive:
1-“Highly malignant”: suppressed background with or without continuous periodic discharges; burst-suppression.
2-Malignant”: abundant periodic discharges, or rhythmic epileptiform transients; electrographic seizure; discontinuous or low-voltage background; reversed anterior–posterior gradient; unreactive EEG to stimuli.
3-“Benign” EEG (absence of all malignant features stated above)

WLST decisions occurred using a previously described multimodal approach (9, 13, 16), after more than 72h after CA, in normothermia, off sedation, in the presence of at least two variables related to poor prognosis. Neither EEG during TTM nor PLR were considered.

We analyzed correlations between “highly malignant” or “benign” EEG patterns, and other commonly used outcome predictors: clinical (corneal, clinical and PLR pupillary reflexes, early myoclonus), biochemical (peak NSE), neurophysiological (SSEP), and functional prognosis, using the Excel software, with Student t, Wilcoxon, Chi-square or Fisher exact tests as needed. Bonferroni correction was applied to correct for multiple comparisons, targeting a global alpha error of 0.05. Predictive performances were estimated using exact binomial distributions.

Results

Of 208 CA episodes, 5 patients did not have any EEG: we studied 203 episodes corresponding to 202 patients (**Table 1)**. At three months, 88 had died; one was vegetative (CPC 4), 16 had severe disability (CPC 3), 30 were moderately disabled (CPC 2), and 68 reported complete recovery (CPC 1).

EEG at day one was performed 20.1 ± 7.1 hours, and at day two 39.4 ± 14.9 hours after CA. It was recorded only on day one in 13 patients, and only on day two in five: these were thus considered only in the corresponding groups. Missing data were distributed as follows: SSEP (18), NSE in (24), PLR (103), clinical examination off sedation within 72 hours (2), brainstem reflexes (1, ocular melanoma). “Highly malignant” EEG was found in 36.7% of patients at day one, and in 21.7% at day two; “malignant EEG” in 43.9% at day one, and 45.2% at day two; 19.2% patients presented a “benign” pattern at day one, and 33.2% at day two.

Tables 2a and 3a summarize analyses of “highly malignant” vs. “benign” or “malignant” EEG. “Highly malignant” EEG, on day one, showed 91% (95%CI: 83%-97%) specificity and 63% sensitivity (95% CI: 53%-72%) to poor prognosis. On day two, “specificity was 98% (95%CI: 92%-100%), sensitivity was 40% (95%CI: 31%-51%).There was a strong correlation with other predictors of unfavorable prognosis.

Tables 2b and 3b show assessments of “benign” vs. “malignant” or “highly malignant” EEG On day one, sensitivity towards good outcome was 35 % (25%CI 26%-46%), with positive predictive value of 89% (75%-97%), and specificity of 96% (95% 90%-99%). At day two, sensitivity was 57% (95% CI: 47%-68%), with 84% (95% CI: 72%-92%) positive predictive value, and 57% (95% CI: 47%-68%) specificity. “Benign” EEG was also robustly associated with other predictors of favorable outcome, especially at day two.

Stratification after TTM target temperatures did not alter the prognostic performance of “highly malignant” EEG patterns, nor their correlation with other predictors of poor outcome (apart from PLR at both temperatures and early myoclonus at 33°C) (**supplementary Tables 1 and 2**). The correlation of “benign” EEG patterns with other predictors was however lost (except from corneal reflexes and SSEP in normothermia,

and motor reaction at both temperatures), while correlation with prognosis remained significant (**supplementary Tables 3 and 4)**.

Discussion

This study shows that predefined “highly malignant” and “benign” EEG patterns according to the ACNS nomenclature strongly correlate with other recognized prognostic predictors, especially regarding poor prognosis, and underscores EEG ability to predict poor or favorable prognosis after CA, during and after TTM.

Current guidelines propose multimodal prognostic approaches, in order to minimize risks of false positive prediction of poor outcome (5, 6, 17); however, clinical examination is not quantitative, biomarkers are limited by the lack of clear cutoffs (5, 18), and lack of standardization of clinical EEG may impair reliability (10-12). The remarkable correlation with other recognized prognostic predictors strengthens the concept that all variables should tend towards the same direction, in order to offer robust prognostication. Of note, PLR recently appeared to be predictive of poor outcome, but showed lower accuracy for favorable prognosis (14): this might explain the limited correlation between”benign” EEG and PLR on day one.

In the TTM trial, associations between EEG patterns and outcome were studied only after rewarming. Like a previous multicenter study, with 102 patients overlapping with the present one (9) , we included patients in whom EEG were recorded both during and after TTM. Our findings suggest that the specificity of “highly malignant” EEG is not significantly altered by TTM. Furthermore, robust correlation with other predictors of unfavorable prognosis was maintained across TTM targets, except for early myoclonus and PLR, which might be influenced by analog-sedation and hypothermia. There was conversely a loose correlation of “benign” features with other predictors across temperatures; this may reflect better EEG performances in predicting poor prognosis, but is also probably due to relatively low numbers of patients, and the fact that the vast majority of available predictors identify subjects with poor prognosis. Finally, “malignant” EEG, as described

earlier, can occur during the early post CA period, TTM and sedation in patients with good outcome (12, 16, 19); moreover, lack of specificity and considerable variability between interpreters exist (11, 12); therefore, “malignant” features were not considered in our study.

According to assessments on the TTM study cohort, “highly malignant” EEG predicted poor outcome with a sensitivity of 50%, no false positives, and substantial intra- and interrater agreement (11, 12). We confirm the reliability of these EEG patterns to predict unfavorable outcome, with even higher sensitivity but also some false positives on day one, while on day two, sensitivity was somewhat lower (10-12). Only 1% of poor outcome were described in patients with “benign” EEG (12); we confirm strong correlations between “benign” EEG and favorable outcome. Sedation could account for the few false positive “highly malignant” patterns, and the lower sensitivity of “benign” EEG on day one, reinforcing recommendation of prognostication after day 3-5, rewarming and sedation withdrawal (6). EEG prediction within 24h is still debated: some authors advocating it for poor and good outcome prediction (9, 20), whereas other reporting false-positive malignant EEG patterns (21). Discrepancies across studies may be accounted for by patient heterogeneity, timing of EEG and different EEG criteria: furthermore, in a previous study (12) and in the present analysis “malignant” EEG could not be reliably applied for prognostication.

This study has limitations. We did not consider the amount of sedation during EEG recordings; while this may affect EEG activity (22), predictive ability of benign and malignant patterns seem more robust (9, 12). EEG reports and clinical data were available to caregivers, and EEG assessment for this study was not formally blinded to outcome: this could have led to self-fulfilling prophecy. However, the excellent correlation between EEG patterns and other outcome predictors should temperate this possibility. Importantly, we never use EEG on its own to decide upon discontinuation of life supporting measures (16).

In conclusion, standardized EEG interpretation presents strong correlations with other validated outcome predictors, with some few exceptions. EEG being a broadly available,

non-invasive tool, pre-defined “highly malignant” and “benign” features could be routinely incorporated in the multimodal approach for decision on WLST.

References

1. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation. 2005;67(1):75-80.
2. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation. 2010;81(11):1479-87.
3. Grasner JT, Lefering R, Koster RW, Masterson S, Bottiger BW, Herlitz J, et al. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. Resuscitation. 2016;105:188-95.
4. Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche JD, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med. 2013;39(11):1972-80.
5. Rossetti AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome in patients in coma after cardiac arrest. Lancet Neurol. 2016;15(6):597-609.
6. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Resuscitation. 2014;85(12):1779-89.
7. Friberg H, Cronberg T, Dunser MW, Duranteau J, Horn J, Oddo M. Survey on current practices for neurological prognostication after cardiac arrest. Resuscitation. 2015;90:158-62.
8. Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol. 2013;30(1):1-27.
9. Rossetti AO, Tovar Quiroga DF, Juan E, Novy J, White RD, Ben-Hamouda N, et al. Electroencephalography Predicts Poor and Good Outcomes After Cardiac Arrest: A Two-Center Study. Crit Care Med. 2017;45(7):e674-e82.
10. Westhall E, Rosen I, Rossetti AO, van Rootselaar AF, Kjaer TW, Horn J, et al. Electroencephalography (EEG) for neurological prognostication after cardiac arrest and targeted temperature management; rationale and study design. BMC Neurol. 2014;14:159.
11. Westhall E, Rosen I, Rossetti AO, van Rootselaar AF, Wesenberg Kjaer T, Friberg H, et al. Interrater variability of EEG interpretation in comatose cardiac arrest patients. Clin Neurophysiol. 2015;126(12):2397-404.
12. Westhall E, Rossetti AO, van Rootselaar AF, Wesenberg Kjaer T, Horn J, Ullen S, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology. 2016;86(16):1482-90.
13. Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med. 2014;42(6):1340-7.
14. Solari D, Rossetti AO, Carteron L, Miroz JP, Novy J, Eckert P, et al. Early prediction of coma recovery after cardiac arrest with blinded pupillometry. Ann Neurol. 2017;81(6):804-10.
15. Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. JAMA. 2004;291(7):870-9.
16. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol. 2010;67(3):301-7.
17. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive Care Med. 2015;41(12):2039-56.

18. Stammet P, Collignon O, Hassager C, Wise MP, Hovdenes J, Aneman A, et al. Neuron-Specific Enolase as a Predictor of Death or Poor Neurological Outcome After Out-of-Hospital Cardiac Arrest and Targeted Temperature Management at 33 degrees C and 36 degrees C. J Am Coll Cardiol. 2015;65(19):2104-14.
19. Rundgren M, Westhall E, Cronberg T, Rosen I, Friberg H. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med. 2010;38(9):1838-44.
20. Hofmeijer J, Beernink TM, Bosch FH, Beishuizen A, Tjepkema-Cloostermans MC, van Putten MJ. Early EEG contributes to multimodal outcome prediction of postanoxic coma. Neurology. 2015;85(2):137-43.
21. Amorim E, Rittenberger JC, Baldwin ME, Callaway CW, Popescu A, Post Cardiac Arrest S. Malignant EEG patterns in cardiac arrest patients treated with targeted temperature management who survive to hospital discharge. Resuscitation. 2015;90:127-32.
22. Crepeau AZ, Rabinstein AA, Fugate JE, Mandrekar J, Wijdicks EF, White RD, et al. Continuous EEG in therapeutic hypothermia after cardiac arrest: prognostic and clinical value. Neurology. 2013;80(4):339-44.

Table 1: Clinical characteristics of the studied population of 203 episodes of post-cardiac arrest coma (202 patients)

Age	64.99 ± 14.5
Women, n (%)	59 (29.1%)
Cardiac etiology, n (%)	145 (71.4%)
ROSC (minutes ± SD)	22.2 ± 17.4
TTM n (%)	
Hypothermia (target: 33°C)	64 (31.5%)
Normothermia (target: 36°C)	123 (60.6%)
Spontaneous temperature	16 (7.9%)

Results are expressed as mean +/- SD unless otherwise specified.

ROSC, time to return of spontaneous circulation; TTM, targeted temperature management

Table 2a: Distribution of EEG scored after (9–11) on day 1 after cardiac arrest, according to "highly malignant" patterns.

	Highly malignant	Not Highly malignant	p	test
Total patients	73	125		
Absent corneal reflex.*	39 (54.2%)	18 (14.6%)	<0.001**	Chi2
Pupillary reflex *				
- absent on clinical observation	29 (40.3%)	9 (7.3 %)	<0.001**	Chi2
- pupillometry (% reaction), mean+/- SD	16.6 ± 10.4	23.1 ± 13.0	<0.001**	t-test
Presence of early myoclonus*	25 (34.2%)	7 (5.7%)	<0.001**	Chi2
Peak NSE (ug/l), median (IQR)*	75 (31.9-151)	23.5 (16.9-31.7)	<0.001**	Wilcoxon
Absent N20 on SSEP *	38 (55.9%)	9 (7.9 %)	<0.001**	Chi2
CPC at 3 months, median (IQR)	5 (5-5)	2 (1-3)	<0.001**	Wilcoxon

Table 2b: Distribution of EEG scored after (9–11) on day 1 after cardiac arrest, according to "benign" patterns.

	Benign	Not Benign	p	Test
Total patients	38	160		
Present corneal reflex.*	33 (91.7%)	105 (66%)	0.004**	Chi2
Pupillary reflex *				
- present on clinical observation	35 (97.2%)	122 (76.7%)	0.005**	Chi2
- pupillometry (% reaction), mean+/- SD	26.6 ± 14.2	19.6 ± 11.8	0.023	t-test
Motor reaction (better than flexion) *	31 (86.1 %)	84 (53.8 %)	<0.001**	Chi2
Peak NSE (ug/l), median (IQR)*	23.7 (13.1-15.1)	31.6 (19.5-76.1)	0.002**	Wilcoxon
Present N20 on SSEP *	30 (100%)	104 (68.9%)	<0.001**	Chi2
CPC at 3 months, median (IQR)	1 (1-2)	5 (1.25-5)	<0.001**	Wilcoxon

**SSEP were not assessed in 17 cases, NSE in 22, pupillometry in 98 and 2 patients did not have a clinical examination off sedation after 72 hours. Corneal and pupillary reflexes were not reliable in 1 patient due to ocular melanoma. Motor reaction was not assessed in 6 patients.*

*** Significant after Bonferroni correction (p value <0.007).*

Data are expressed as n (%) unless otherwise specified.

Table 3a: Distribution of EEG scored after (9–11) on day 2 after cardiac arrest, according to "highly malignant" patterns.				
	Highly malignant	**Not Highly malignant**	**p**	**Test**
Total patients	41	149		
Absent corneal reflex.*	23 (57.5 %)	32 (21.8 %)	<0.001**	Chi2
Pupillary reflex *				
- absent on clinical observation	19 (47.5 %)	16 (19.9 %)	<0.001**	Chi2
- pupillometry (% reaction), mean+/- SD	12.8 ± 7.8	22.1 ± 12.6	<0.001**	t-test
Presence of early myoclonus*	13 (31.7%)	16 (10.8%)	<0.001**	Chi2
Peak NSE (ug/l), median (IQR)*	81.9 (40-184.5)	24.5 (17.1-36.9)	<0.001**	Wilcoxon
Absent N20 on SSEP *	28 (71.8 %)	17 (12.5%)	<0.001**	Chi2
CPC at 3 months, median (IQR)	5 (5-5)	2 (1-5)	<0.001**	Wilcoxon
Table 3b: Distribution of EEG scored after (9–11) on day 2 after cardiac arrest, according to "benign" patterns.				
	Benign	**Not Benign**	**p**	**Test**
Total patients	63	127		
Present corneal reflex.*	56 (91.8%)	76 (88.4%)	<0.001**	Chi2
Pupillary reflex *				
- present on clinical observation	59 (96.7 %)	93 (73.8%)	<0.001**	Fisher
- pupillometry (% reaction), mean+/- SD	25.2 ± 14.2	17.7 ± 10.4	<0.001**	t-test
Motor reaction (better than extension) *	47 (78.3 %)	43 (29.9 %)	<0.001**	Chi2
Peak NSE (ug/l), median (IQR)*	23.7 (16.4-31.1)	38.3 (21.3-97.4)	<0.001**	Wilcoxon
Present N20 on SSEP *	55 (100%)	75 (91.5%)	<0.001**	Chi2
CPC at 3 months, median (IQR)	1 (1-2)	5 (2-5)	<0.001**	Wilcoxon

**SSEP were not assessed in 15 cases, NSE in 19, pupillometry in 95 and 2 patients did not have a clinical examination off sedation after 72 hours. Corneal and pupillary reflexes were not reliable in 1 patient due to ocular melanoma. Motor reaction was not assessed in 5 patients.*

*** Significant also after Bonferroni correction (p value <0.007).*

Data are expressed as n (%) unless otherwise specified.

Supplementary table 1 : Distribution of EEG scored after (9–11) on day 1 after cardiac arrest, according to "highly malignant" patterns in patients treated with TTM 33°C.

	Highly malignant	Not Highly malignant	p	test
Total patients	21	39		
Absent corneal reflex.*	9 (42.9%)	4 (10.3 %)	0.006**	Fisher
Pupillary reflex *				
- absent on clinical observation	6 (28.6 %)	0 (0%)	0.001**	Fisher
- pupillometry (% reaction), mean+/- SD	16.9 ± 8.7	21.5 ± 7.9	0.113	t-test
Presence of early myoclonus*	5 (23.8%)	3 (7.8%)	0.114	Fisher
Peak NSE (ug/l), median (IQR)*	77.3 (27.2-110.6)	22.6 (16.4-30.2)	<0.001**	Wilcoxon
Absent N20 on SSEP *	9 (42.9%)	1 (2.6%)	<0.001**	Fisher
CPC at 3 months, median (IQR)	5 (4-5)	1 (1-2)	<0.001**	Wilcoxon

**SSEP were not assessed in 1 case and pupillometry in 22 patients.*
*** Significant after Bonferroni correction (p value <0.007).*
Data are expressed as n (%) unless otherwise specified.

Supplementary table 2 : Distribution of EEG scored after (9–11) on day 1 after cardiac arrest, according to "highly malignant" patterns in patients treated with TTM 36°C.

	Highly malignant	Not Highly malignant	p	test
Total patients	44	78		
Absent corneal reflex.*	26 (60.5%)	12 (12.2 %)	<0.001**	Chi2
Pupillary reflex *				
- absent on clinical observation	17 (39.5 %)	8 (8.2 %)	<0.001**	Chi2
- pupillometry (% reaction), mean+/-	17.2 ± 9.8	24.5 ± 8.3	0.007	t-test
Presence of early myoclonus*	18 (40.9%)	4 (5%)	<0.001**	Fisher
Peak NSE (ug/l), median (IQR)*	63.2 (31.3-186.1)	23.9 (16.9-32.9)	<0.001**	Wilcoxon
Absent N20 on SSEP *	22 (55%)	8 (11.9 %)	<0.001**	Chi2
CPC at 3 months, median (IQR)	5 (5-5)	2 (1-5)	<0.001**	Wilcoxon

**SSEP were not assessed in 15 cases, NSE in 18, pupillometry in 67 and 2 patients did not have a clinical examination off sedation after 72 hours. Corneal and pupillary reflexes were not reliable in 1 patient due to ocular melanoma.*
*** Significant after Bonferroni correction (p value <0.007).*
Data are expressed as n (%) unless otherwise specified.

Supplementary table 3 : Distribution of EEG scored after (9–11) on day 1 after cardiac arrest, according to “benign” patterns in patients treated with TTM 33°C.

	Benign	Not Benign	p	test
Total patients	13	47		
Corneal reflex (present)*	13(100%)	34(72.3%)	0.032	Chi2
Pupillary reflex *				
- clinical observation (present)	13(100%)	41(87.2%)	0.17	Chi2
- pupillometry (% reaction), mean (SD)	27.6 ± 6.8	18.7 ± 8.1	0.03	t-test
Motor reaction (better than flexion) *	11 (84.6%)	15 (31.9 %)	<0.001**	Chi2
Peak NSE (ug/l), median (IQR)*	23.8 (16.4-29.1)	30.2 (19.2-77.2)	0.013	Wilcoxon
SSEP (present)*	12 (100%	37 (78.2%)	0.09	Chi2
CPC at 3 months, median (IQR)	1 (1-1)	3 (1-5)	<0.001**	Wilcoxon

**SSEP were not assessed in 1 case and pupillometry in 22 patients.*
*** Significant after Bonferroni correction (p value <0.007).*
Data are expressed as n (%) unless otherwise specified.

Supplementary table 4 : Distribution of EEG scored after (9–11) on day 1 after cardiac arrest, according to “benign” patterns in patients treated with TTM 36°C.

	Benign	Not benign	p	test
Total patients	23	99		
Corneal reflex (present)*	20 (95.2%)	61 (62.2%)	0.003 **	Chi2
Pupillary reflex *				
- clinical observation (present)	21 (100%)	73 (74.5%)	0.009	Chi2
- pupillometry (% reaction), mean (SD)	26.2 ± 9.8	20.7 ± 9.8	0.097	t-test
Motor reaction (better than flexion) *	19 (90.5 %)	45 (47.4%)	<0.001**	Chi2
Peak NSE (ug/l), median (IQR)*	22.6 (12.8-33.4)	31.3(19.7-67.2)	0.123	Wilcoxon
SSEP (present)*	16 (100%)	61 (67%)	0.006**	Chi2
CPC at 3 months, median (IQR)	1 (1-2)	5 (1-5)	<0.001**	Wilcoxon

**SSEP were not assessed in 15 cases, NSE in 18, pupillometry in 67 and 2 patients did not have a clinical examination off sedation after 72 hours. Corneal and pupillary reflexes were not reliable in 1 patient due to ocular melanoma. Motor reaction was not assessed in 6 patients.*

*** Significant after Bonferroni correction (p value <0.007).*
Data are expressed as n (%) unless otherwise specified.

Supplementary Figure 1 legend

EEGs example with “highly” malignant patterns. Please note that calibration in given on top of each trace; all arranged as longitudinal bipolar montage using 21 electrodes arranged after the international 10-20 system.

a) Suppressed background (amplitude <10 μV, 100% of the recording) intermixed by electrographic seizures, unreactive to nociceptive stimulus (black marker).

b) Suppressed background (amplitude <10 μV, 100% of the recording) without epileptiform discharges, unreactive to nociceptive stimulus (black marker).

c) Burst-suppression (periods of suppression with amplitude <10 μV, >50% of the recording) with superimposed epileptiform discharges associated with myoclonic eye blinking (black marker).

d) Suppressed background with superimposed generalized periodic discharges, unreactive to nociceptive stimulus (black marker).