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Postanoxic alpha, theta or alpha-theta coma: clinical setting and neurological outcome**

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Runnig title: Alpha and theta coma in CRA

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ABSTRACT

Aim: The aim of this study was to determine the prognosis of 26 consecutive adults with alpha coma (AC), theta coma (TC) or alpha-theta coma (ATC) following CRA and to describe the clinical setting and EEG features of these patients.

Methods: We retrospectively analyzed a prospectively collected cohort of adult patients diagnosed as having AC, TC or ATC after CRA between January 2008 and June 2016. None of the patients included in this analysis underwent therapeutic hypothermia (TH). Neurological outcome was expressed as the best score 6 months after CRA using the five-point Glasgow-Pittsburgh Cerebral Performance Categories (CPC)

Results: Twenty-six patients were identified with a diagnosis of postanoxic AC, TC or ATC coma. There were 20 (77%) men and 6 (23%) women. The mean age was 63 ± 16 years. The most frequent EEG pattern was TC (21 patients, 80%), followed by AC (3 patients, 12%) and ATC (2 patients, 8%). The cardiac rhythm as primary origin of the CRA was ventricular fibrillation (VF) in 16 patients (61.5%), asystole in 8 patients (34.6%) and ventricular tachycardia (VT) in one patient (3.8%). The presence of EEG reactivity was present in 8 patients (30%). The mortality rate was 85%. Of the 4 surviving patients, two (3.8%) had moderate disability (CPC 2), one (3.8%) had severe disability (CPC 3) and one (3.8%) reached a good recovery. The age was significantly lower in survivors 46.2 ± 10.8 versus nonsurvivors 63.3 ± 15.5 ($p=0.04$). There was increased association of EEG reactivity with survival ($p=0.07$).

Conclusion: Hypoxic-ischemic AC, TC and ATC are associated with a poor prognosis and a high rate of mortality. In younger patients with AC, TC and ATC and incomplete forms showing reactivity on the EEG, there is a greater probability of clinical recovery.

Abbreviations: Alpha coma (AC); Alpha-theta coma (ATC);

Cardiorespiratory arrest (CRA); Electroencephalogram (EEG); Hypoxic-ischemic encephalopathy (HIE) ; Therapeutic hypothermia (TH), Theta coma (TC);

KEYWORDS: anoxia, coma, electroencephalogram, prognosis, alpha coma, theta coma

Introduction.

Cardiorespiratory arrest (CRA) is a severe clinical condition that is a frequent cause of coma and admission to the intensive care unit (ICU). Supportive care imposes a high economic burden and this effort is balanced against the chance and quality of neurological recovery and the expectations of the patient's family.¹

It is now widely accepted that accurate prognostication in comatose patients after CRA is on a multimodal assessment that includes clinical, electrophysiological, laboratory and neuroimaging data is warranted.² The utility of electroencephalography (EEG) in determining outcome in hypoxic-ischemic encephalopathy (HIE) has been the subject of extensive investigation over the past dozen years.³⁻²¹ Hence, much effort has been directed at determining those EEG patterns or specific EEG alterations that carry prognostic significance. It has been reported that a uniform, continuous, diffuse, unreactive pattern with alpha and theta frequencies (complete alpha coma (AC), theta coma (TC) or alpha-theta coma (ATC)), with frontal predominance, has been associated with poor outcome.²²⁻²⁶ Incomplete or atypical variants of these patterns are not rare and, in these cases, neurological recovery may be possible.^{26,27} The interpretation of the EEG changes in AC, TC and ATC may not be straightforward and there is a spectrum of variants to these patterns that may have different prognostic significance.

The aim of this study was to determine the prognosis of 26 consecutive adults with AC, TC or ATC following CRA and to describe the clinical setting and EEG features of these patients.

Methods

Data collection and patients

This investigation is a retrospective analysis of a prospectively collected series. The Department of Clinical Neurophysiology at Marqués de Valdecilla University Hospital

provides adult neurophysiologic service to 591,886 inhabitants in an urban and rural area of the region of Cantabria, located in the north of Spain. It is the only neurophysiology department in the area. Between January 2008 and June 2016, we prospectively identified all those patients older than 18 years with a diagnosis of AC, TC or ATC after CRA. Other patients with coma from toxic or metabolic causes, and de-efferented states resulting from brainstem lesions were excluded. None of patients included in this analysis underwent therapeutic hypothermia (TH) since this technique was not routinely used in our hospital.

All clinical data were gathered from chart review, EEG reports and protocols, discharge summaries, and resident sign-out notes. Baseline demographic data (age, gender), past medical history, focusing our attention on cardiovascular antecedents including the shockable cardiac rhythm as primary origin of the CRA were recorded. When we had 26 consecutive patients, we retrospectively analyzed all our data.

EEG inclusion criteria

Electroencephalography was performed with 21 needle or surface electrodes placed according to the International 10-20 System at the ICU. Routine video-EEG was obtained for at least 30 minutes including manual eye opening, photic, auditory, tactile and noxious stimuli. All tracings were reviewed by one board-certified clinical neurophysiologist (JLF-T), and the frequency of the cerebral rhythms, distribution and reactivity were analyzed. Reactivity was defined as any reproducible change in amplitude or frequency in the cerebral EEG activity, excluding stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs) and muscle artifacts, related to patient sensory stimulation.²⁸ In the majority of subjects follow-up EEGs were done.

All EEGs recordings carried out in CRA comatose patients showing continuous widespread rhythms of alpha (8-13 Hz), theta (4-7 Hz) or both frequencies, in comatose

patients following CRA were selected. This pattern was present throughout the full recording. We used the term ATC when AC and TC patterns were observed in the same recording. All patients were without sedation at the moment of the EEG. Although AC, TC and ATC are classically characterized by the lack of reactivity, in our study, the presence of EEG reactivity was not an exclusion criterion since partially reactive EEG recordings have been observed in subjects with incomplete forms of AC and TC.^{24,26,27}

Outcome assessment

Neurological outcome was expressed as the best score 6 months after CRA using the five-point Glasgow-Pittsburgh Cerebral Performance Categories (CPC) (1= good recovery, 2= moderate disability, 3= severe disability with dependency for daily life activity, 4= comatose or vegetative state, and 5= death).²⁹ Neurological state was collected from the clinical visits, medical records and EEG charts. Outcome was dichotomized between “good” and “poor”. Good outcome was defined as a CPC score of 1 or 2 and poor outcome as a CPC score of 3, 4 or 5. CPC scores were determined after 6 months of CRA.

Statistical analysis

All data were coded and entered into a database in SPSS 20.0 for statistical purposes. Quantitative variables were expressed as mean and standard deviation (SD), or median and interquartile range. Qualitative variables were presented as total number of events and percentages. The comparison of qualitative variables was done by Chi-square test or 2x2 tables. Quantitative variables were compared by Student t test or non-parametric Mann–Whitney U test, as appropriate, verified by Kolmogorov–Smirnov test.

Results

Twenty-six patients were identified with a diagnosis of postanoxic AC, TC or ATC coma. All demographic, clinical, EEG and neuroimaging features are summarized in table 1.

There were 20 (77%) men and 6 (23%) women. The mean age was 63 ± 16 years (range 30 to 82 years). The median duration of the presumed time of CRA was 20.2 minutes (IQR, 10-30 minutes). In 5 patients the duration of the CRA could not be reliably determined. The median time from admission to the first EEG was 48.0 hours (IQR 24-72 hours). The median time of hospitalization was 10 days (IQR, 7-16 days). The most frequent EEG pattern was TC (21 patients, 80.7%), followed by AC (3 patients, 11.5%) and ATC (2 patients, 7.6%) (fig. 1). EEG features included widespread predominantly monotonous, more frequently nonreactive (70%), alpha or theta frequencies with or without frontal predominance. Occasionally, delta waves or brief episodes of generalized electrodecremental events were also observed (fig. 2). The median number of EEGs was 2 (IQR 1-3). Eighteen patients (69%) had a second EEG. In 9 (50%) the EEG remained invariable, in 2 patients (11%) EEG evolved in to a burst-suppression pattern and in 7 (39%) a moderate or severe encephalopathy was present. Seven subjects had a third EEG, 5 had a fourth EEG and in 2 cases we carried out 5 EEGs. Thirteen patients (50%) had arterial hypertension, 8 (31%) coronary heart disease, 5 (19%) had diabetes mellitus, 4 (15%) had alcoholism and 3 (12%) had dyslipidemia. The cardiac rhythm as primary origin of the CRA was ventricular fibrillation (VF) in 16 patients (61.5%), asystole in 8 patients (34.6%) and ventricular tachycardia (VT) in one patient (3.8%) (fig. 1). The presence of EEG reactivity was present in 8 patients (30%). Five (63%) of these patients died and 3 (38%) survived (fig. 3). In one subject (patient 7) that survived with a favourable evolution with moderate disability (CPC 2), the EEG was unreactive. Neuromaging was obtained in only 16 patients (61%). Brain computed

tomography (CT) scan was done in 15 of these patients, and only two had a brain magnetic resonance imaging (MRI). In all cases neuroimaging was unremarkable. The mortality rate was 85% (22/26) including 19 TC (90%), 2 ATC (100%) and 1 AC (33%). Four subjects (15%) survived counting 2 TC and 2 AC. Two subjects (3.8%) had moderate encephalopathy and disability (CPC 2), one (3.8%) had severe disability (CPC 3) and one (3.8%) reached a good recovery. In three (75%) of these patients, we observed reactivity in the EEG. The age was significantly lower in survivors 46.2 ± 10.8 versus nonsurvivors 63.3 ± 15.5 ($p=0.04$). In addition, AC in comparison with TC and ATC was associated with lower rate of mortality, 33% versus 91.3 % ($p=0.05$). However, the number of patients with AC was too few to make definite conclusions. Lack of background reactivity was more common in the poor outcome group; 94.4% versus 62.5%. There was increased association of reactivity with survival ($p=0.07$). The duration of hospitalization was longer among survivors, ($p=0.002$). Similarly, the number of EEGs was higher in the survivor group ($p=0.01$). The duration of CRA was not significantly different between survivors and nonsurvivors, 17.5% versus 20 ($p=0.8$). There was a trend toward asystole associated with higher rate of mortality than with ventricular fibrillation ($p=0.2$).

One of the major limitations of EEG as a prognostic tool in comatose resuscitated patients is its sensitivity to the effects of sedative drugs used in the ICU. Profound sedation may significantly affect EEG interpretation.³⁰ In our series, 20 out 26 (77%) patients were sedated: 12 patients with propofol, 3 patients with midazolam , 4 patients with midazolam and propofol and one patient with intravenous diazepam (table 2). In six cases (23%) general anesthesia was not employed. Of note, sedation with propofol was stopped at least one hour before the onset of the EEG recording in all 16 patients (table 2). However, the interruption of midazolam varied from 2 hours in 2 patients, 12

hours in one patient to 24 hours in one patient. Intravenous diazepam was stopped 48 hours before the EEG recording.

Discussion

Over the last dozen years, several investigators have carried out studies directed at determining the prognostic value of EEG in HIE.³⁻²¹ Most of this research has focused on “malignant, highly malignant or unfavorable EEG patterns” that include isoelectric, low voltage, burst-suppression with or without identical burst, status epilepticus and, in some cases, unreactive ATC.^{3,7,10,11,12,16,17,19,20} The use of a benign (favorable) versus malignant (unfavorable) EEG stratification has been criticized by some experts for its lack of sensitivity and accuracy in prognostication.⁹ There is a scarcity of recent detailed studies in patients with complete or incomplete forms of AC, TC and ATC, while older studies may contain greater detail.^{22,23,24,25,26} In several studies, some of the EEG patterns have been classified generically as being “diffusely slow”. Assessment of reactivity and anterior-posterior differentiation were not included in the definition of normal patterns.^{12,14,20} This might explain the poor outcome in subjects with *a priori* favorable EEG patterns.

Our study offers an overview of a uniform series of patients in the pre-hypothermia era of HIE management and AC, TC or ATC. Therapeutic hypothermia is now a standard care but it was not used in our patients. However, it may be important to know in detail the prognosis of patients with different EEG patterns (even if TH has not been used) because these different patterns most likely represent diverse degrees of cerebral hypoxic injury, and they can give information on the underlying pathophysiology. Some studies have shown that continuous rhythms within first 24 hours after CRA are a reliable predictor of outcome but a more detailed classification of these continuous EEG patterns has been absent.^{12,14,20} In our study, the rate of mortality was high (85%),

despite the existence of background continuity on the EEG. This rate is similar to that reported by others.^{24,25,26} Our investigation confirms the conclusion that AC, TC and ATC are associated with poor outcome. Of note, 4 (15%) patients survived; three had a good functional outcome (one with a CPC score of 1 and two with a CPC score of 2) and one (CPC 3) had a severe disability with dependence on others for daily activity. Therefore, the neurological outcome of the survivors was not universally poor.

The lack of EEG reactivity in HIE is associated with poor outcome^{7,10,17,19,31} while not surprisingly, the presence of reactivity correlated with survival in AC, TC and ATC.^{24,25} Reactivity might be overemphasized as an invariant indicator of favorable outcome. In our study, 8 (30%) out of 26 patients had reactive EEGs. However, 5 of these patients despite the presence of EEG background reactivity, died (fig. 2). These results are consistent with those reported by Berkhoff et al.²³ who found that incomplete forms of AC or TC are often associated with poor outcome. In the study by Tsetsou et al.³¹, nonsurvivors with reactive EEGs had greater cerebral damage (higher levels of serum neuron-specific enolase), but similar degrees of systemic injury (procalcitonin levels) as compared to survivors with reactive EEG. It could be hypothesized that thalamo-cortical networks might be temporally functional but with the passage of time such function declines. Kaplan et al.²⁵ reported 21 patients with AC following CRA. Six (29%) showed reactivity in the EEG and only 2 patients survived. These authors observed that reactivity occurred in AC with many different causes, indicating its independence of etiology. Our findings are similar (30% of reactive EEGs), suggesting that reactivity in AC, TC and ATC is more frequent than classically thought and, that these patients meet criteria for incomplete (reactive) forms of AC, TC and ATC.

Alpha coma and TC had been considered grade 3 (severe) in a recently published EEG severity grading system for continuous EEG monitoring findings following CRA

undergoing TH.¹⁰ A grade 3 pattern (including AC and TC) during TH and normothermia correlated with poor outcome. In this study, one patient with a nonreactive TC during TH recovered reactivity during rewarming and had good neurological outcome, suggesting that reactivity can fluctuate during the clinical course of HIE. Conversely, a recent study using a single routine EEG to investigate outcome in comatose patients after CRA, proposed that AC and TC without reactivity showing reversed anterior-posterior gradient constituted a malignant EEG pattern.¹⁶ In the study by Westhall et al.¹⁶ reversed anterior-posterior gradient was not a reliable predictor of outcome, however, more detailed information on EEG frequencies, reactivity or evolution was absent.

Young and colleagues³ observed that AC, TC and ATC are almost always transient patterns. In their study, the EEG changed to an alternate pattern in 96% of the cases. Of note, the change occurred from 3 to 17 days of coma onset. In our study, in the half of patients with a second EEG, the recording remained invariable but evolution towards other encephalopathic patterns were also observed. The use of continuous EEG monitoring may provide further detailed information on the evolution of these EEG patterns that could have utility in prognostication.

In our study, younger patients had a more favorable prognosis since the age was significantly lower in survivors. Our investigation is not the only one with this result. Roest and associates⁵ studied 115 patients with postanoxic coma and they found that younger patients (<50 years) showed a significant better outcome at 180 days, concluding that age is an important variable determining the prognostic value of the EEG in HIE and should be taken into consideration.

Sedation is an important confounder and EEG patterns may be affected by sedative drugs such as propofol and midazolam. This point was also made in a recent paper in

which the authors found that most patients were still under the effect of sedation at the time of EEG.¹⁶ The predictive value of their malignant EEG patterns was not significantly affected. In the present study, 20 subjects received sedation with intravenous anesthetics or benzodiazepines but it had been stopped in all of them before the beginning of the recording. In our institution, propofol is more frequently used than midazolam; however, protocol was stopped in all cases a minimum 1 hour before the EEG. In five patients the withdrawal was 2 hours before the EEG, in two it was stopped 4 hours before, and in one it had been stopped during the prior 48 hours. Hence, the possible confounding effects of propofol were minimized. However, some of our patients could have been on propofol for more than 48 hours and being a tri-compartment drug it (or its metabolites) may still be active, particularly in those with deranged metabolism. Propofol induces fast rhythm in beta range and alpha oscillations on the EEG and it could affect EEG interpretation, in particular, for AC (cases 7, 8 and 17) or ATC (cases 1 and 15). Nevertheless, in our series, none of these patients had received prolonged doses of propofol. Indeed, only 3 out 5 of these patients were sedated with propofol.

Nonventricular fibrillation initial rhythm has been associated with poor outcome.¹² In our study, there was increased association of asystole (100%) with mortality compared to ventricular fibrillation (76.5%).

The pathophysiology of the AC, TC and ATC is incompletely understood. Animal data have suggested a crucial role of the amygdala in the origin of the alpha frequencies in diffuse HIE. Other investigations propose that the mid-brain tegmentum plays also a role. A study comparing the alpha pattern in normal subjects and in AC, found a lack of right-left coherence in AC supporting that pacemakers operated independently in each hemisphere as consequence of significant thalamo-cortical disruption.³² More recently,

Abusleme and Chen³³ using independent component analysis and dipole fitting algorithm localized cerebral generators in AC and normal subjects. They found important differences in the distribution of dipole locations between normal and abnormal alpha activity indicating that alpha frequencies could be produced by different generators and circuitry pathways. Thus, the dipoles of alpha rhythms of postanoxic coma were localized to the anterior neocortical and subcortical (caudate nucleus, hypothalamus and midbrain) regions. In contrast, the normal rhythms were generated by posterior neocortical generators.

This study has some limitations: first, despite including a long period for analysis (8 years), the number of patients is relatively small; second, the study was carried out in patients that did not undergo TH, thus our results should be considered in this clinical context; third, somatosensory evoked potentials were not performed systematically and we lost its potential predictive value for AC, TC and ATC; fourth, the evaluation of reactivity can be heavily subjective in both administration and assessment of EEG recordings; fifth, a potential limitation of all studies investigating diagnostic accuracy is the self-fulfilling prophecy. In our case, attending physicians were not blinded to the EEG results regarding management of epileptiform phenomena.

Conclusions

Hypoxic-ischemic AC, TC and ATC are associated with a poor prognosis and a high rate of mortality. Nevertheless, a few patients may survive and outcome may be favorable. In our study, the age and presence of EEG reactivity were associated with survival, suggesting that in younger patients with AC, TC and ATC and incomplete forms showing reactivity on the EEG, there is a greater probability of clinical recovery.

Conflict of interest

None

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Figure

Figure 1. Types of coma and cardiac rhythm as primary origin of the CRA in our series.

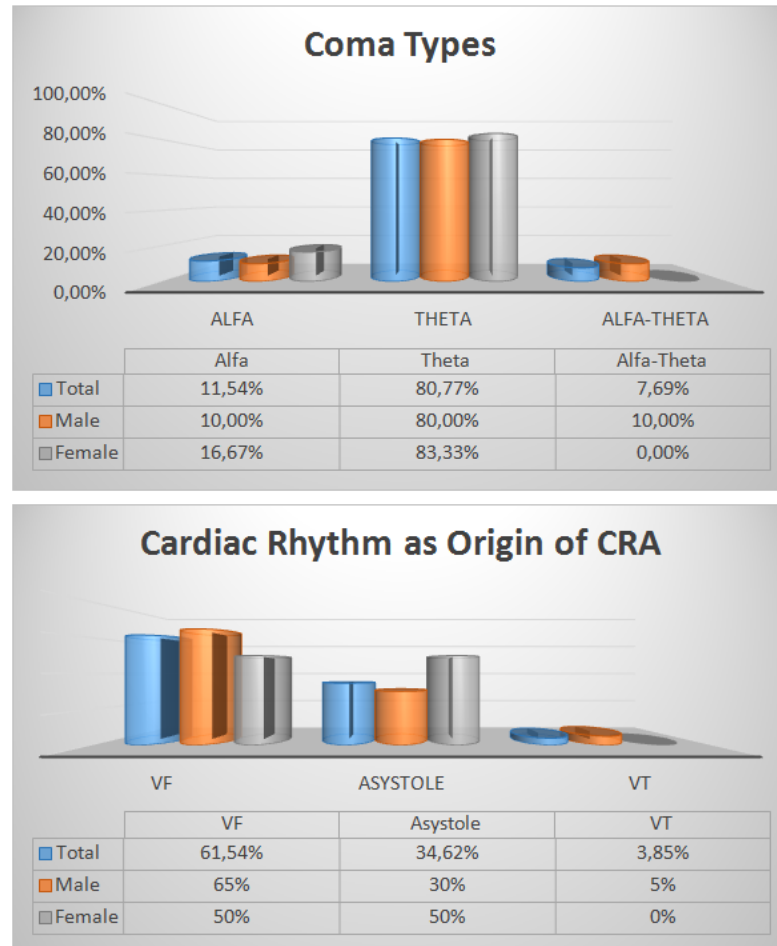
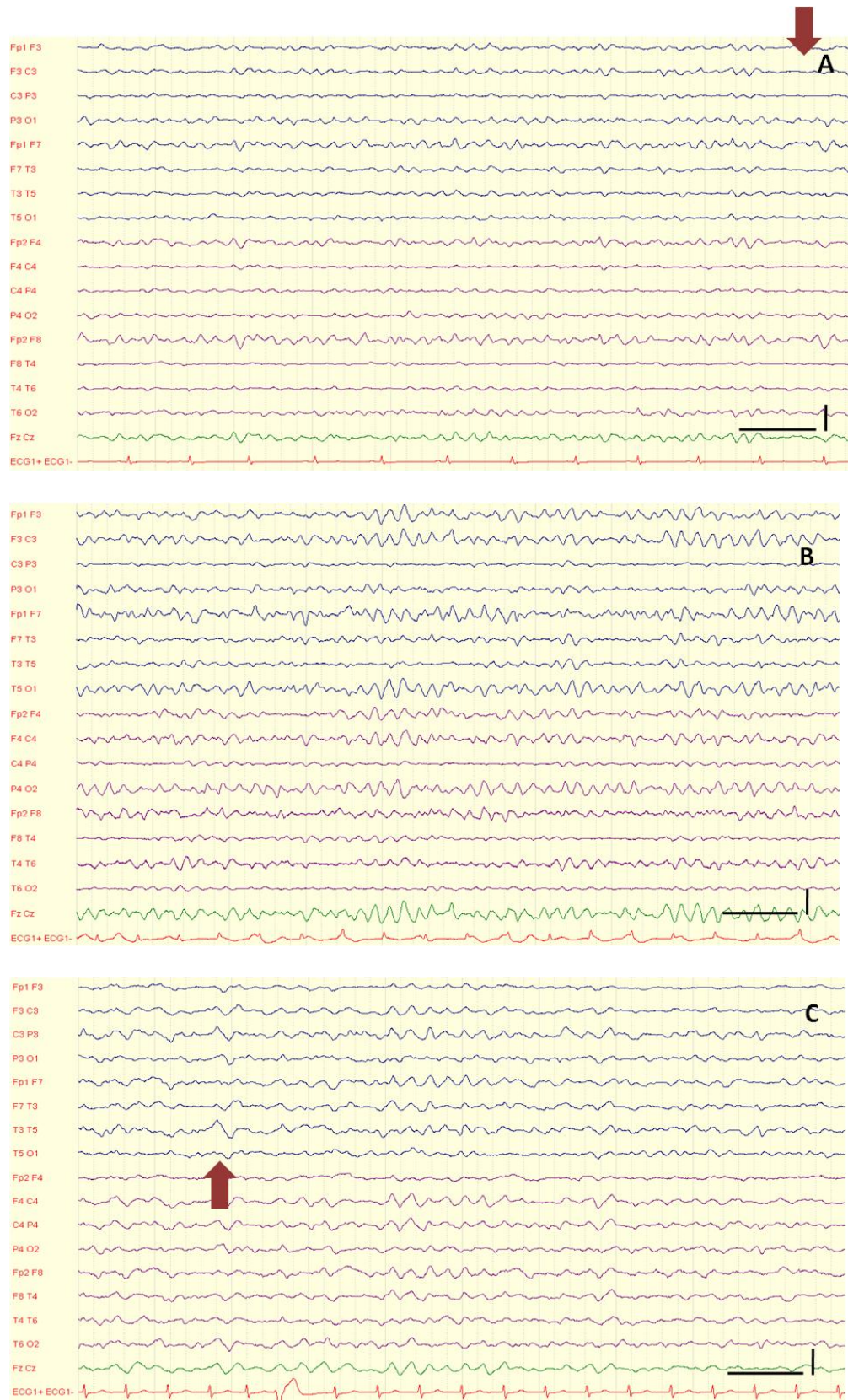


Figure 2. Examples of EEGs in cases of TC and AC. A) Monotonous theta frequencies with occasional generalized electrodecremental events (arrow); B) Widespread theta rhythm with frontal predominance; C) TC with occasional slow waves; D) Nonreactive widespread alpha rhythms in keeping with postanoxic AC. LF: 0.53 Hz; HF: 70 Hz; NF: 50 Hz.



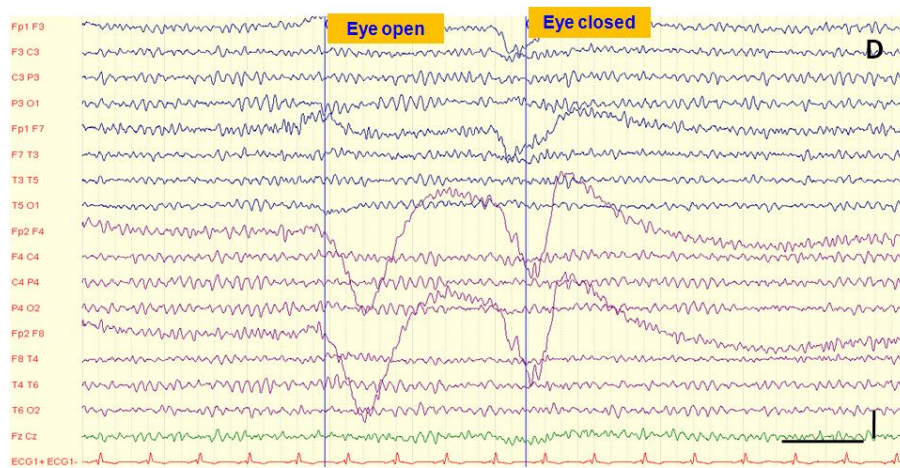
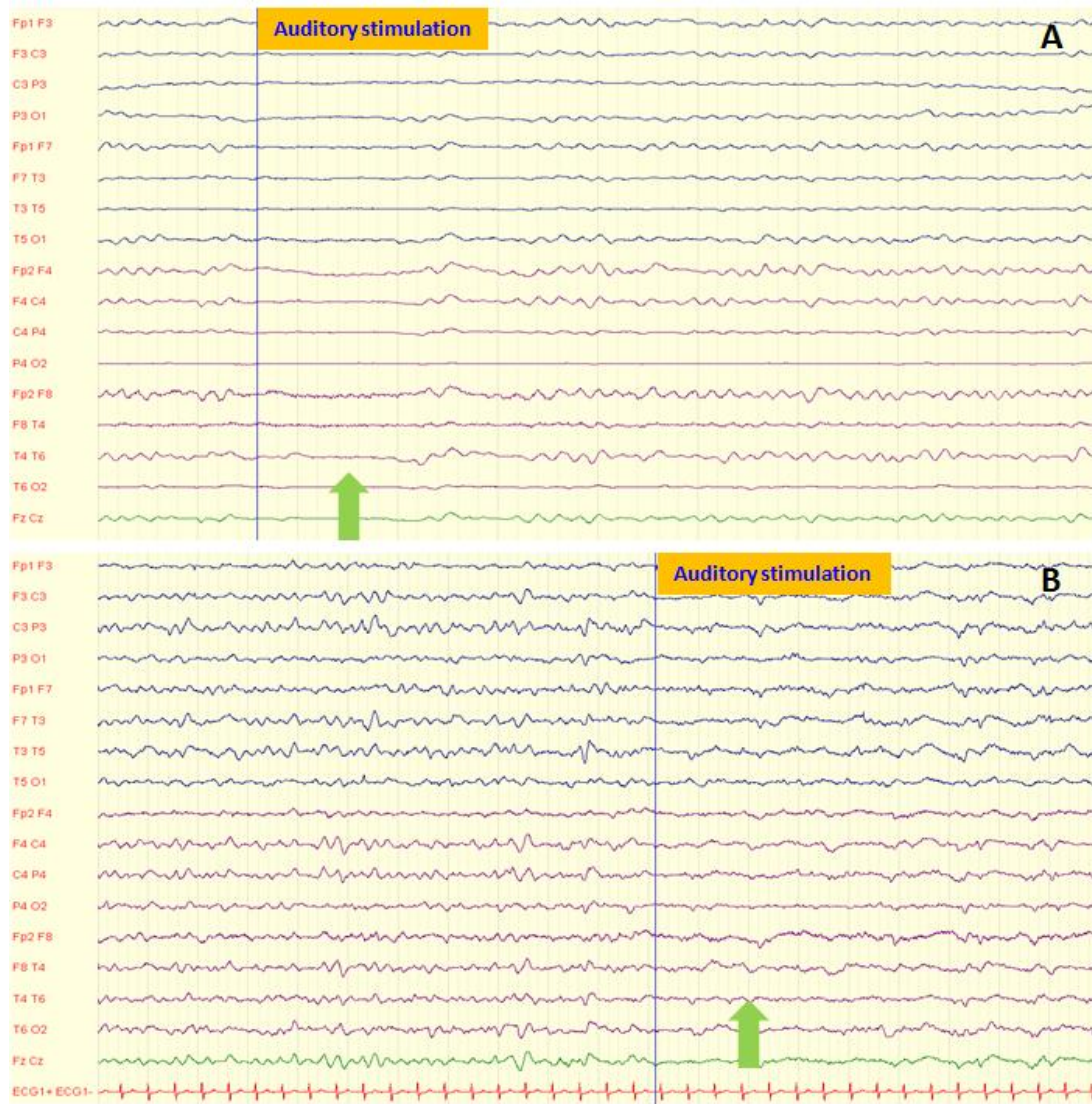


Figure 3. Four examples of EEG reactivity obtained of our patients. A and B showed EEG reactivity (arrow) after auditory stimulation in 2 patients that died. C and D showed EEG reactivity (arrow) in 2 patients that survived. LF: 0.53 Hz; HF: 70 Hz; NF: 50 Hz; sensitivity: 100 μ V/cm, speed: 30 mm/s (in A, C y D) 15 mm/s (in B).



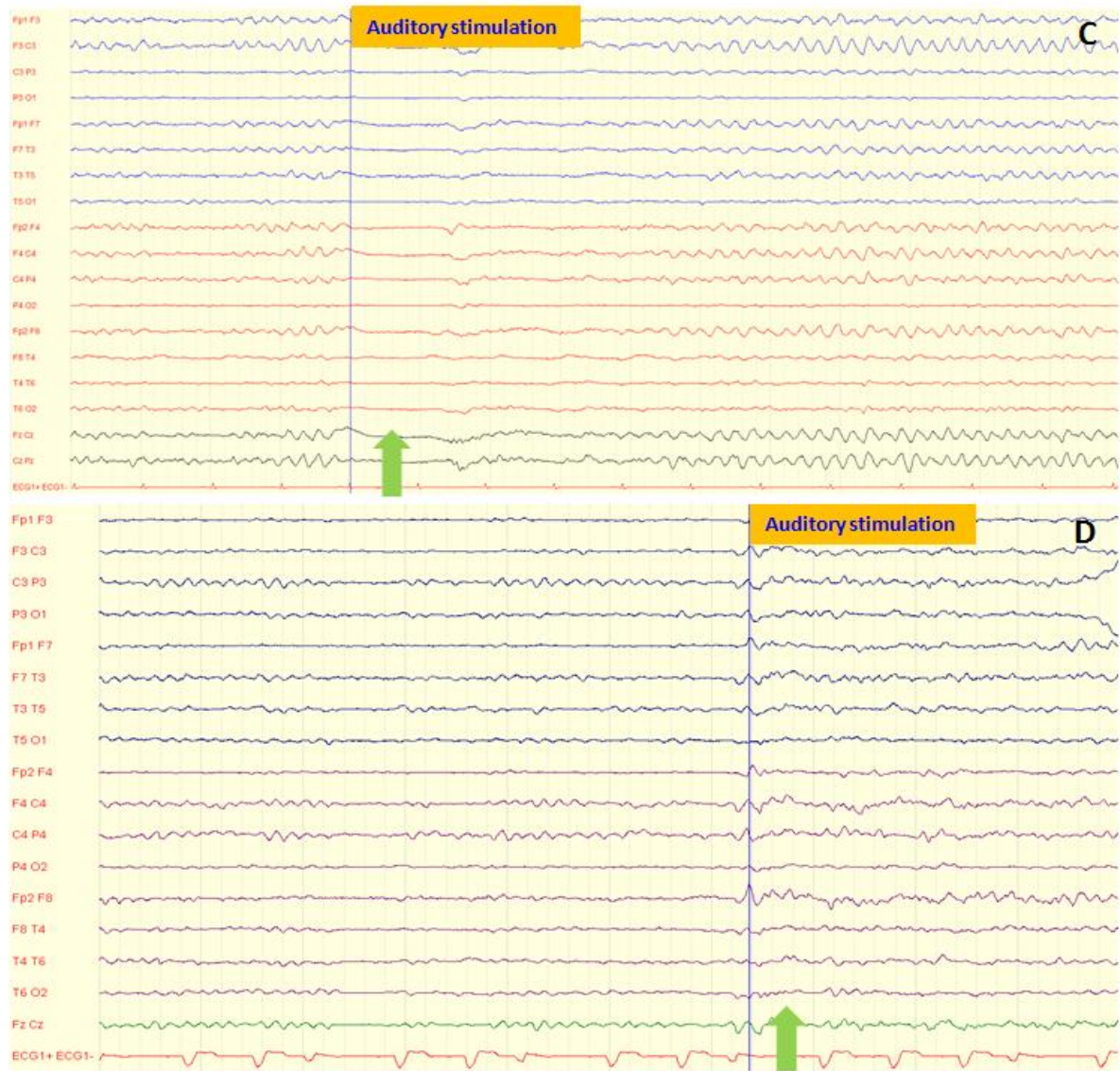


Table 1. Demographic, clinical, EEG, neuroimaging and outcome data of our 26 patients.

Patient	Sex	Age	CRA Cause	HTN	DM	CRF CHD	OH	DLP	CRA Duration (min)	Time of admission	Coma type	EEG timing (hours)	N° EEGs	EEG Reactivity	Disability scale	Neuroimaging
1	M	80	Asystole	YES	-	YES	-	-	10	8	Alfa-Theta	96	2	NO	5	No
2	M	71	VF	-	-	-	-	-	35	14	Theta	96	1	YES	5	CT
3	F	70	VF	-	-	-	-	-	25	15	Theta	58	1	NO	5	No
4	F	67	VF	YES	YES	-	-	-	NR	15	Theta	24	2	NO	5	No
5	M	72	VF	YES	-	YES	-	-	8	11	Theta	20	1	NO	5	No
6	M	55	Asystole	-	-	-	YES	-	10	7	Theta	48	1	YES	5	No
7	M	51	VF	-	-	-	-	-	10	48	Alfa	48	2	NO	2	MRI
8	F	30	VF	-	-	-	-	-	10	30	Alfa	72	4	YES	1	CT/MRI
9	M	53	VF	YES	-	-	-	-	25	49	Theta	48	5	YES	3	CT
10	M	47	Asystole	-	-	-	-	YES	25	8	Theta	48	2	YES	5	CT
11	M	75	VF	YES	YES	YES	YES	-	NR	8	Theta	72	2	YES	5	No
12	M	57	VF	-	-	YES	-	-	20	3	Theta	48	1	NO	5	No
13	F	68	Asystole	YES	-	-	-	-	NR	20	Theta	72	2	NO	5	No
14	M	72	Asystole	YES	-	-	-	-	30	7	Theta	72	1	NO	5	CT
15	M	74	VT	YES	-	YES	-	-	20	12	Alfa-Theta	24	3	NO	5	CT
16	M	78	VF	YES	-	YES	-	-	35	2	Theta	24	1	NO	5	CT
17	M	50	VF	YES	YES	-	YES	-	30	9	Alfa	48	2	NO	5	No
18	M	74	VF	-	-	-	-	-	NR	8	Theta	48	1	NO	5	No
19	M	37	VF	-	-	-	-	-	20	5	Theta	48	2	NO	5	CT
20	M	79	Asystole	YES	YES	-	-	YES	15	2	Theta	20	2	NO	5	CT
21	F	34	Asystole	-	-	-	-	-	NR	14	Theta	16	4	NO	5	CT

22	M	82	Asystole	-	-	-	-	-	5	71	Theta	48	1	NO	5	CT
23	M	71	VF	YES	YES	YES	-	-	5	5	Theta	20	2	NO	5	CT
24	M	51	VF	YES	-	-	YES	YES	45	68	Theta	72	5	YES	2	CT
25	M	57	VF	-	-	YES	-	-	30	9	Theta	72	3	YES	5	CT
26	F	30	Asystole	NO	NO	NO	NO	NO	10	11	Theta	36	5	NO	5	CT

CT: Computed tomography; CRA: cardiorespiratory arrest; CRF: cardiovascular risk factors; CHD: coronary heart disease; DM: diabetes mellitus; DLP: dyslipidemia; EEG: electroencephalogram; F: female; M: male; HTN: hypertension; MRI: magnetic resonance imaging; NR: not recorded; OH: alcohol; VF: ventricular fibrillation.

Table 2. Numbers of EEGs and sedation employed in relation to the disability scale and survival.

Patient	Number of EEGs	Sedation
1	2	DZP (>48h)
2	2	Propofol (48h)
3	1	-
4	2	Propofol (2h)
5	1	Propofol (2h)
6	1	-
7	2	Propofol (2h)
8	4	Propofol (2h)
9	4	MDZ+Propofol (24h)
10	2	MDZ (48h)+Propofol (2h)
11	2	Propofol (4h)
12	1	MDZ (2h)
13	2	Propofol (2h)
14	1	Propofol (24h)
15	3	-
16	1	Propofol (1h)
17	2	Propofol (1h)
18	1	-
19	2	MDZ+Propofol (20h)
20	2	Propofol (1h)
21	4	MDZ (12h)

22	1	MDZ (24h)
23	2	-
24	5	Propofol (4h)
25	3	-
26	5	MDZ+Propofol (2h)

DZP: diazepam; MDZ: midazolam

In brackets, the period of time from interruption of the sedation to the first EEG.