EEG patterns associated with present cortical SSEP after cardiac arrest

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Abstract

Background

After cardiac arrest (CA), present cortical somatosensory evoked potentials (N20 response of SSEPs) have low predictive value for good outcome, and might be redundant with EEG.

Aims

To determine if specific features, or rather global, standardized EEG assessments, are reliably associated with cortical SSEP occurrence after cardiac arrest (CA).

Methods

In a prospective CA registry, EEGs recorded within 72 hours were scored according to the ACNS-nomenclature, and also categorized into "benign", "malignant", "highly malignant". Correlations between EEGs and SSEPs (bilaterally absent versus present), and between EEGs/SSEPs and outcome (good: CPC 1-2) were assessed.

Results

Among 709 CA episodes, 532 had present N20 and 366 "benign-EEGs". While EEG categories as well as background, epileptiform features, and reactivity differed significantly between patients with and without N20 (each $p<0.001$), only "benign EEG" was almost universally associated with present N20: 99.5% (95%CI: 97.9-99.9%) PPV. The combination of "benign EEG" and present N20 showed similar PPV for good outcome as "benign" EEG alone: 69.0% (95%CI:65.2-72.4) vs. 68.6% (95%CI:64.9-72.0).

Conclusion

Global EEG ("benign") assessment, rather than single EEG features, can reliably predict cortical SSEP occurrence. SSEPs adjunction does not increase EEG prognostic performance towards good outcome. SSEP could therefore be omitted in patients with "benign EEG".

Introduction

In comatose patients following cardiac arrest (CA), multimodal prognostication based on clinical examination, neurophysiological, biological and neuroradiological data is recommended (1). Bilateral absent cortical somatosensory evoked potentials (the N20-response of SSEPs) represents one of the strongest predictors for poor outcome, but present N20 has limited prognostic performance towards good outcome (1, 2). Conversely, standardized EEG categorization ("benign", "malignant", "highly-malignant") has showed a good correlation with both good and poor outcome (3, 4). As the "toolbox" for multimodal prognostication in post-anoxic coma is increasing, an important practical question is whether each available exam should be performed in every patient or not, especially in resource-limited settings. While a recent study suggested that SSEPs may be redundant with "benign-EEG" for good outcome prediction (5) others reported that SSEPs cannot be predicted by EEGs except for present N20-responses in normal EEGs (6). We aimed to determine on a larger sample if early EEG can reliably predict SSEP occurrence, and identify the relevant EEG features.

Methods

Patients

Consecutive comatose adults admitted to our ICU after CA from all etiologies (2006-2019), who had SSEP and EEG recordings within 72 hours from CA, were identified from our prospective CA registry (approved by our Ethic Commission; consent waived in view of the observational character). Details on clinical management have been previously described (7). Withdrawal of life support (WLST) decisions is made using a multimodal approach, after ≥72 hours, in normothermia and off sedation, if at least two variables related to poor prognosis occur, including EEG or SSEP (1). Outcome at three months is prospectively scored through a semi-structured phone interview, according to Glasgow-Pittsburg Cerebral Performance Categories (CPC: 1-2 good; 3-5: poor) (8).

EEG

Per protocol, patients undergo at least two 20 minutes video-EEGs, with 21 electrodes arranged after the international 10-20 system, during targeted temperature management (TTM) (12-36h) and

after (36h-72h). EEGs were interpreted using the American Clinical Neurophysiology (ACNS) terminology (9); for this study, IB and GB rescored, blinded for the clinical outcome, all traces recorded before 2014, when this classification became routine at our center. After 2014, we used EEG reports at the time of CA. EEGs were defined "epileptiform" in the presence of periodic or rhythmic spikes, sharp waves or spike and waves (9). EEG background was categorized as suppressed (<10μV), burst-suppression (suppression ≥50%) or discontinuous (suppression 10-49%) (9). Reactivity was tested through auditory (loud clapping, name's calling), visual (eye opening with light), and nociceptive (bilateral nail compression, nipple pinching) stimulations and defined as reproducible change in amplitude or frequency, excluding SIRPIDS and muscle artifacts. EEGs were further classified into pre-defined categories (4):

-"Highly malignant": suppressed background, with or without continuous periodic discharges; burst-suppression.

-"Malignant": abundant periodic discharges/ rhythmic epileptiform transients/ unequivocal electrographic seizure/ discontinuous or low-voltage background/ reversed anterior–posterior gradient/ unreactive EEG.

-"Benign EEG": absence of all above features.

For this study, we considered the best (less malignant) EEG within 72 hours from CA, or the earliest one if the two recordings were similar.

SSEP

Per protocol, median nerve stimulation at the wrist are performed after TTM (mostly between 36-48h, with exclusion of week-end). Recording electrodes are fixed over the supraclavicular fossa (NErb), C5 (N13a), and CP3/CP4, referenced at Fz. A minimum of 200 stimulations (at 3-5 Hz) per recording are averaged, with intensity adjusted to produce visible thumb twitches (or according to Erb amplitudes, if neuromuscular blocking agents were administered). The cortical N20 response was prospectively identified visually at the time of recording as a reproducible, biphasic waveform occurring at least 4ms after the N13, and dichotomized as absent (bilaterally) or present (unilaterally or bilaterally). In the few patients who had two SSEP recordings (due to technical reason), discordant SSEPs were considered as present.

Statistical analysis

Correlation between EEGs patterns and cortical SSEPs were analyzed with t, U or χ^2 tests, as needed. Bonferroni correction was applied to correct for multiple comparisons. Calculations were performed on Stata 14 (College Station, TX).

Results

Of 786 consecutive CA episodes, SSEPs recordings were not performed in 72, and EEGs in another 6; 709 CA episodes (corresponding to 703 patients) were therefore included (**table 1**). SSEPs were performed after a median of 48 hours (range 12-168) after CA, 81.9% within 48 hours. Although the incidence of all considered EEG features (EEG background categorized as continuous, discontinuous, BS or suppressed; reactivity; epileptiform features; "benign" vs "malignant" vs "highly malignant" EEG) differed significantly ($p<0.001$) between patients with and without cortical SSEPs, only "benign EEG" could almost perfectly predict present SSEP (**table 1**). Two patients had absent SSEPs despite "benign EEGs": one with a cervical medullary lesion regained consciousness; the other, with fatal outcome, had a first EEG showing major, unreactive slowing on the right hemisphere (the left was reactive), his EEG became "malignant" the next day. "Benign EEG" predicted SSEP presence with 98.7% (95%CI 95.9-99.9%) specificity and 99.5% (95% CI 97.9-99.9%) PPV (**table 2**).

While outcome was almost always fatal in the absence of SSEP (174/176, 98.9%) only 283/533 (53.1%) of patients with N20 responses reached good outcome (**table 1**). Cortical SSEPs presence was associated with good outcome with only 42.9% (95%CI:38.0-47.9) sensitivity and 54.9% (95%CI:52.8-56.9) PPV. Furthermore, the combination of "benign EEG" and present SSEP did not improve the PPV of "benign EEG" alone: 69.0% (95%CI: 65.2-72.4) vs. 68.6% (95%CI: 64.9-72.0) (**table 3**).

Conclusion

This study confirms in a markedly larger cohort the recent finding that "benign EEG" is robustly associated with cortical SSEP responses (5), and suggests additionally that an EEG global assessment (using ACNS guidelines and integrating several parameters (4)) seems more reliable than single EEG features in post-CA coma evaluation. This highlights the importance to integrate

standardized EEG categorization into post CA prognostication, offering high interrater agreement and strong correlation with outcome and other prognostic predictors (3, 4).

It is known that cortical SSEPs have lower prognostic performance towards good outcome than EEGs with benign features (1); we observed indeed that adding them to "benign EEG" does not increase EEG prediction of good outcome. A recent paper reported N20-responses in all 20 patients having continuous >8 Hz EEGs (6). These results are also reminiscent of a study showing no improvement after SSEP addition in a prediction model including EEG, neurological examination and serum NSE for poor outcome (7). However, others reported that SSEPs and EEGs are complementary for poor outcome (6). Intriguingly, despite preserved EEG reactivity at some time, 19 patients had absent N20-responses. Since we considered the best EEG, it is possible that EEG reactivity was lost at the time of SSEP recording. Also, in case of alteration of nociceptive pathways, auditory or visual pathways might remain intact. Anyway, 2 of these patients, both presenting "malignant-EEG", reached CPC 1 and 3, underscoring that no test is always 100% specific, hence the importance of multimodal prediction before deciding WLST.

Despite their high specificity for poor outcome, SSEP present a low sensitivity (1, 2, 7). Indeed, N20 may even co-occur EEG with patterns clearly associated with unfavorable prognosis (10). It has been postulated that synaptic inputs of thalamo-cortical cells are sufficient to generate N20 responses, as opposed to the EEG signal that offers a refined picture of cortico-cortical neuronal networks (10). As the integrity of complex thalamo-frontal networks seems critical to recover consciousness (11), it is not surprising that a focus on thalamo-parietal afferent pathways is not performant in this context.

This study has limitations. N20 were dichotomized as present or absent, without amplitude threshold or frequency analysis (12). Early EEG were rescored retrospectively, but blinded to outcome and using the same criteria than subsequent recordings. The absence of formal blinding to the respective results of SSEP and EEG might have led to overinterpretation of EEGs as "benign" in case of known present SSEPs, or consideration of "doubtful" SSEPs as present in patients with "benign EEG". However, EEGs interpretation followed the ACNS nomenclature, which shows excellent interrater agreement (13). Also, "doubtful" SSEPs occur rarely in our experience, and in

such cases, results are discussed among two interpreters. While a systematic bias in EEGs/SSEPs interpretation cannot be excluded, it should not represent a major impact. Until 2009, as per institution protocol, no EEGs were recorded within the first 24 hours after cardiac arrest, 140 patients therefore did not have EEG during TTM. Also, lack of a strict standardization of EEG timing represents a limitation. However, the used EEG classification demonstrates a good consistency across time and TTM (3), and sedation does not alter significantly EEG prediction performance in this context (14). EEGs and/or SSEPs were not performed in 78 patients, as they were probably deemed futile (clear prognostic situation, such as early WLST or awakening). As such, exclusion of these patients seems unlikely to have biased the results. As EEG and SSEP reports were available to caregivers and integrated in the WLST discussion, a self-fulfilling prophecy, almost inevitable in this kind of study, cannot be excluded; anyway, EEG and SSEP interpretation occurred without knowledge of the outcome.

Under consideration of the aforementioned limitations, “benign” EEG seems reliably associated to cortical SSEP responses. EEGs, broadly used in post-CA prognostication (15), are often performed early after CA (during TTM) (1, 4, 5, 7) and could be used to stratify patients, particularly in resource-limited settings. SSEP may be omitted in those with “benign” EEG, and rather reserved to inform on poor outcome prediction in patients with “malignant” or “highly malignant” EEG, where multimodal assessment is paramount to prevent premature WLST.

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Table 1. Clinical and EEG characteristics of 708 episodes of post-cardiac arrest coma stratified according to SSEP.

	Present SSEP (n=533)		**Absent SSEP (n=176)**			
	n	**%**	**n**	**%**	**p**	**test**
Gender (female)	130	24,4	61	34.7	0.010	Chi2
Mean age (SD)	62,6 (14,4)		60,9 (14,3)		0.170	t
Shockable rhythm	340*	63,8	54	30,5	**< 0.001**	Chi2
Cardiac etiology	430*	80,7	88	50,00	**< 0.001**	Chi2
Median time to ROSC, min (range)	20 (1-180)		25 (4-90)		**< 0.001**	U
PLR present	484 **	90,8	76*	43,2	**< 0.001**	Chi2
Motor reaction better than flexion	322**	60,4	6	3,4	**< 0.001**	Chi2
Myoclonus	55**	10,3	83	47,2	**< 0.001**	Chi2
Median hours to SSEP (range)	24 (12-168)		48 (18-144)		**0.997**	U
Best EEG within 72 hours						
Median hours to EEG (range)	24 (1-72)		25 (6.5-72)		0.120	U
continuous	401	75,2	41	23,3		
discontinuous	103	19,3	45	25,6		
burst-suppressed	22	4,1	71	40,3		
suppressed	7	1,3	19	10,8	**< 0.001**	Fisher
reactive	467	87,6	19	10.8	**< 0.001**	Chi2
epileptiform	63	11,8	77	43,8	**< 0.001**	Chi2
"Highly Malignant"	31	5,8	91	51,7		
"Malignant"	138	25,9	83	47,2		
"Benign"	363	68,1	2	1,1	**< 0.001**	Fisher
CPC at three months ***						
CPC 5	167	31,3	174	98,9	**< 0.001**	Fisher
Good (CPC 1-2)	283	53,1	1	0,6		
Poor (CPC 3-5)	233	43,7	175	99,4	**< 0.001**	Fisher

In bold significant after Bonferroni correction (p value <0.0033)

PLR= pupillary light reflex. ROSC=return of spontaneous circulation

** 1 patient with missing data. ** 5 patients with missing data. *** 15 patients with missing data*

Table 2. EEG features associated with present cortical SSEP

Model	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
Continuous EEG background	75.2% 71.3-78.8	76.7% 69.5-82.7	90.7% 88.1-92.8	50.8% 46.6-55.0
Reactive EEG	87.6% 84.5-90.3	89.2% 83.7-93.4	96.1% 94.1-97.4	70.6% 65.6-75.2
Non-epileptiform EEG	88.2% 85.1-90.8	43.8% 36.3-51.4	82.5% 80.4-84.3	55.2% 48.1-62.2
"Benign" EEG	68.3% 64.2-72.2	98.9% 96.0-99.9	99.5% 97.9-99.9	50.7% 47.6-53.9

Table 3. Outcome prediction model integrating EEG and SSEP

Parameters for good outcome (CPC 1-2) at three months after cardiac arrest	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
Benign EEG	85.2% 80.5-89.1	72.8% 68.2-77.1	68.6% 64.9-72.0	87.6% 84.2-90.4
Present SSEP	99.7% 98.1-100.0	42.9% 38.0-47.9	54.9% 52.8-56.9	99.4% 96.1-99.9
Present SSEP + Benign EEG	85.2% 80.5-89.1	73.3% 68.7-77.5	69.0% 65.2-72.4	87.7% 84.3-90.5