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ORIGINAL ARTICLE

The potential role of pain-related SSEPs in the early prognostication of long-term functional outcome in post-anoxic coma

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ABSTRACT

BACKGROUND: Cardiac arrest (CA) is a common cause of disability. Multimodal evaluation has improved prognosis but precocious biomarkers are not appropriate in determining long-term functional outcome.
AIM: To identify early prognostication markers of long-term functional outcome in post-anoxic coma.
DESIGN: Retrospective assessment of outcomes.
POPULATION: Individuals older than 18 years with post-anoxic coma hospitalized in intensive care units after cardiac arrest (CA) regardless of cause (cardiac or non-cardiac) and location of event (in or out-of-hospital).
METHODS: Clinical, biological and neurophysiological data were collected within 48 hours from CA. Clinical data included time of no and low flow, CA rhythm, pupillary reflex, Glasgow motor score at admission and hyperthermia. Biological marker was the highest creatinine level. Neurophysiological parameters included EEG pattern and reactivity, Somatosensory Evoked Potential (SSEP), and Middle-Latency (ML) SSEP evoked at low (10 mA) and high (50 mA) intensity stimulation. Level of Cognitive Functioning Scale (LCFS), Disability Rating Scale and recovery from coma (Revised coma Recovery Scale [CRS-R]) were collected at 12 months. A LASSO multiple regression analysis was fitted to data to investigate the best predictors of LCF, DRS and CRS-R. In-sample prediction was obtained to verify the quality of fitting, and accuracy indices (*i.e*., total error rate) produced.
RESULTS: Presence of short and medium latency SSEPs with low and high stimulation intensity were identified as prognostic predictors of outcome for all the scales. Error rate was 4.5% for CRS and LCF, and 9.1% for DRS.
CONCLUSIONS: Middle latency somatosensory evoked potentials associated with short latency somatosensory evoked potentials during the first 48 hours after a cardiac arrest are strong predictors of functional outcome at 12 months from the event. Replication on larger cohorts is needed to support their routine use as prognostic markers.
CLINICAL REHABILITATION IMPACT: These markers could inform more appropriate allocation of resources, provide a basis for realistic goal-setting, and help the family to adjust its expectations.

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Key words: Neurophysiological monitoring - Evoked potentials - Heart arrest - Disability evaluation - Coma.

Cardiac arrest (CA) is a common cause of disability.[1] Current prognostication guidelines recommend multimodal monitoring,[1, 2] combining clinical neurological examination with median nerve somatosensory evoked potentials (SSEP), electroencephalography (EEG) and cerebral computed tomography (CT) scan. The combination of different techniques attempts to overcome the potential limitation of each one.

Recent studies provided evidence of the prognostic value of EEG abnormalities recorded during therapeutic hypothermia. These findings were based on continuous EEG recordings started during hypothermia and continued throughout rewarming.[3] Earlier data suggested that EEG was not significantly altered by this procedure.[4] A combination of biochemical markers with neurophysiological and neuroimaging data has been suggested,[5] but results of this specific study could only predict poor outcomes. Recently, the same authors focused on early predictors of good recovery, demonstrating a role for EEG background and reactivity.[6] Short latency SSEP (SL-SSEP, also known as N20/N25) have a limited sensitivity in predicting an unfavorable prognosis, as almost half of those with preserved N20 have a poor neurological outcome.[7] Middle-latency somatosensory evoked potentials (ML-SSEP), represented by cortical potentials in the range of 40-70 ms, seem to be more sensitive than short-latency SSEP to detect the extension of ischemic injury; their preservation is thought to reflect a less severe brain damage.[8-10] ML-SSEP associated with blood pressure (BP) reactivity triggered by painful median nerve electrical stimulations were shown to predict good neurological outcome and survival.[11, 12]

The current focus is to rehabilitate individuals to regain premorbid functional status. The identification of early prognostic markers correlating with long term functional outcome is important to guide physicians in designing individual-tailored rehabilitative programs, to inform families and to allocate healthcare system resources appropriately.

This study aims to identify early (<48 hours) neurophysiological and clinical prognostication markers of long term (12 months from cardiac arrest) functional outcome in people who suffered an anoxic-ischemic insult.

Materials and methods

This is a retrospective assessment of outcomes study. Neurophysiology, anesthesiology, clinical and laboratory data were retrospectively obtained by the same experienced physician evaluating subjects at 12-months clinical follow-up.

Subjects

Inclusion criteria were: age older than 18 years; admission either to cardiac surgery ICU and general ICU of Treviso Regional Hospital after a cardiac arrest; disorder of consciousness defined as a Glasgow Coma Scale score <8; cause of cardiac arrest both cardiac (myocardial infarct or arrhythmias) or non-cardiac; location of event both in-hospital and out-of-hospital.

Those with a previous history of neurological disease were excluded. The study was approved by the local Ethical Committee of the Regional Hospital of Treviso, Italy (no. 100, 30/09/2014).

Intervention

The Lund University Cardiac Arrest System (LUCAS) was used as a bridge for extracorporeal membrane oxygenation (ECMO) in subjects not achieving the return of spontaneous circulation (ROSC) with conventional cardiopulmonary resuscitation. After ICU admission participant were evaluated and subjected to targeted temperature management with Arctic Sun© 5000.[13]

Clinical and biochemical parameters

Time from cardiac arrest (CA) to return of spontaneous circulation (ROSC) was divided into no flow (time from CA to cardiopulmonary resuscitation [CPR]) and low flow (time from CPR to ROSC or to the start of ECMO). The initial CA rhythm was categorized into ventricular tachycardia (VT), ventricular fibrillation (VF), pulseless electrical activity (PEA) and asystole (AS). Pupillary reflex (PR) assessment and the Glasgow Scale motor score were performed by the intensive care physician at ICU admission. Hyperthermia occurrence (tympanic temperature >37.8 °C) and the highest value of creatinine within 48 hours from CA were recorded.

Neurophysiological evaluation

Neurophysiological recordings were performed within 48 hours of CA. They consisted of EEG (background pattern and reactivity) and SSEP, recorded during the same session. SSEP were recorded at low (10 mA) and high (50 mA) intensity stimulation to trigger the appearance of ML-SSEP. ML-SSEP were considered present if a deflection with an amplitude >0.5 mV was recorded between 30 and 90 ms. The painful stimulation (50 mA) was used to trigger EEG reactivity. EEG and SSEP were recorded using the NIM-Eclipse© Nerve Monitoring

System (Medtronic Xomed, Jacksonville, FL, USA). The ground electrode was placed on the left shoulder for both EEG and SSEP recordings. The impedance was kept below 1 kΩ.

EEG recording parameters and classification

EEG was recorded from eight bipolar channels, with needle electrodes placed at standard scalp sites (F3/F4-Cz, C3'/C4'-Cz, T3/T4-Cz, P3/P4-Cz). EEG data were digitized at a sampling rate of 250 Hz and hardware band-pass filter was applied with a bandwidth of 1-100 Hz. EEG patterns were categorized according to established criteria [14] by two independent and experienced neurophysiologists (A.D.F. and P.Z.) revising the recordings and resolving discordances by consensus. The final revision of EEG included the classification of main term 1 and 2 plus modifiers, major and minor modifiers, categorization of epileptiform discharges and definition of background characteristics.

SSEP recording parameters

SSEPs were recorded by four bilateral channels (C4'/C3'-Fpz, right Erb's point/left Erb's point-C4'/C3', Fpz-Cv and Fpz-right Erb's point/left Erb's point). Filtering was kept between 30 and 500 Hz. 100 sweeps were averaged for any trace; a minimum of three traces were registered during every step. The stimulus duration was 1000 μs to increase the activation of Aδ fibers.[15, 16] Median nerves were stimulated simultaneously at 3.3 Hz using needle electrodes at 10 mA (low-intensity stimulus) and at 50 mA (high-intensity stimulus); each block of stimulation lasted 120 s. ML-SSEP was considered present if any reproducible potential was detected on one or both sides in the range of 30-90 ms and with amplitude over 0.5 mV. SL-SSEP was defined as bilaterally absent if no reproducible potentials could be identified on either side at a maximum gain of 1 mV per division in the presence of the brachial plexus potential. Both SL and ML-SSEP were analyzed on recording windows of 100 ms.

Decision to treat

Status epilepticus, with normal short latency SSEP (SL-SSEP) was treated with incremental doses of midazolam (0.03-0.2 mg/kg/h). If ineffective, propofol was associated (1.5-2.5 mg/kg bolus and then 4-12 mg/kg/h). The most resistant cases were treated with thiopental to achieve the burst suppression pattern for 48 hours. Levetiracetam (1 g *b.i.d.*) was also used during the weaning off period of the anesthetic. Other antiepileptic drugs were administered according to EEG patterns.

Functional evaluation

Scales were administered by the same trained physician (SB) at 12 months' follow-up in the Neuro-rehabilitation Unit. Functional scale values at admission were not retrieved: the aim of the study was to identify precocious markers of long-term prognosis, whereas the time course of functional recovery was beyond the scope of this work. Examinations were routinely performed during late morning hours to reduce the confounder of circadian fluctuations. Validated scales were used to assess Level of Cognitive Functioning Scale (LCFS), Disability Rating Scale [17] and recovery from coma (Revised Coma Recovery Scale [CRS-R]).[18]

Statistical analysis

Descriptive statistics are reported for demographic, neurophysiological and clinical parameters. Results were reported with 95% confidence intervals (CI) if appropriate.

Three continuation ratio models,[19] were fitted to data to model the effects of covariates on LCF, DRS and CRS-R scores at 12 months. Independent variables considered as covariates include: CA rhythm, cause heart failure, place heart failure, cardio-surgery ICU, hypothermia, hyperthermia after 24 hours, pupillary reflex, first motor response, EEG, N20/P25 presence, medium latency at basal stimulus (10-mA intensity) SSEP (MLb SSEP), medium latency at painful stimulus (50-mA intensity) SSEP (MLp SSEP), consciousness recovery, and EEG data (Main.term.1, Main.term.2, Modifier, sporadic epileptiform discharges [SED], Symmetry, Background EEG frequency, Anteroposterior gradient, Variability, Reactivity, Voltage, Continuity, EEG benign/malignant criteria).

To reduce bias and variance in the model, we selected explanatory variables by estimating regression param-

eters through a LASSO procedure based on penalization of the log-likelihood.[20] The final model is chosen by minimizing the BIC criterion [21] to select the most appropriate set of covariates for each score. No standard errors are provided for the estimates of these models. Penalized estimation is a procedure that, although appropriate to obtain good estimates when size of data is small by reducing the variance of estimators, introduces substantial bias; this is not considered when the standard errors are computed and sufficiently precise estimates of bias are not available. On this ground, standard errors were not provided.

A LASSO multiple regression analysis was fitted to data to investigate the best predictors of LCF, DRS and CRS-R.

In-sample prediction has been obtained to verify the quality of fitting, and accuracy indices (including total error rate, sensitivity and specificity for each level of the three scales) produced.

Statistical analysis was performed with R software.[22]

Results

Twenty-two subjects (57.3±15 years; 6 females, 16 males) were included from January 2013 to January 2015. Demographic, neurophysiologic and clinical characteristics are reported in Table I. Mean time from event to neurophysiological testing was 32.18 hours. During hospitalization, 13 out of 22 subjects (59.09%, 95% CI: 38.73-76.74%) regained consciousness.

At 12 months' follow-up, 12 subjects (54.55%) had a 8-6 LCF score, 1 (4,55%) had a 5-4 LCF score and 9 (40.91%, 95% CI: 23.26%-61.27%) had a 3-1 LCF score. All subjects with LCF score 8-4 presented MLp-SSEP within 48 hours of CA, whereas those with LCF score 3-1 did not. At 12 months' follow-up, 11 subjects (50.00%) had a 0-6 DRS score, 6 (27.27%) had a 7-21 DRS score 5 (22.73%) had a 22-30 DRS score. All subjects with DRS score 0-21 presented MLp-SSEP within 48 hours of CA, whereas those with DRS score 22-30 did not. At 12 months' follow-up, 12 subjects (54.55%) had an absent or light disability at CRS, 5 (22.73%) were diagnosed with minimally consciousness state (MCS), and 5 (22.73%) with persistent vegetative state (PVS). All subjects with absent or light disability at CRS presented MLp-SSEP within 48 hours of CA, whereas those diagnosed with PVS did not. Among the subjects diagnosed with MCS, one presented high voltage medium latency SSEP within 48 hours of CA, whereas 4 did not. Twelve months follow-up LCF, DRS and CRS-R scores for the whole cohort are reported in Table II. Neurophysiological

TABLE I.—*Demographic, neurophysiologic and clinical characteristics of the included subjects.*

Characteristics	Descriptive statistics
Age	57.36±15.05
Cardiac arrest rhythm	VF: 15 (68.2%); PEA: 5 (22.7%); AS: 2 (9.1%)
Cause heart failure	C: 17 (77.3%); NC: 5 (22.7%)
	C: 1 WPWS; 16 MI
	NC: 1 Pheo; 4 pulmonary thromboembolism
Place heart failure	O: 18 (81.8%); I: 4 (18.2%)
CS ITU	Y: 11 (50%); N: 11 (50%)
Time no flow (min)	6.55±5.46
Time low flow (min)	34.05±29.18
Hypothermia	Y: 10 (45.5%); N: 12 (54.5%)
Highest creatinine 24 h (mg/dL)	1.54±1.10
Start hypothermia 2 h	Y: 5 (22.7%); N: 5 (22.7%)
Hyperthermia after 24 h	Y: 10 (45.5%); N: 12 (54.5%)
Pupillary reflex	Y: 20 (90.9%); N: 2 (9.1%)
First motor response	Y: 5 (22.7%); N: 17 (77.3%)
Time EEG SSEP (hours)	32.18±21.03
EEG	Normal: 14 (63.6%); Epileptiform: 6 (27.3%); Poor: 2 (9.1%)
N20/P25 presence	Y: 17 (77.3%); N: 5 (22.7%)
MLb SSEP	Y: 5 (22.7%); N: 17 (77.3%)
MLp SSEP	Y: 13 (59.1%); N: 9 (40.9%)
Consciousness recovery	Y: 13 (59.1%); N: 9 (40.9%)
LCF	5.32±2.89
DRS	11.82±10.66
CRS-R	15.73±9.09

AS: asystole; C: cardiac; WPWS: Wolff-Parkinson-White syndrome; MI: myocardial infarction; CRS-R: Revised Coma Recovery Scale; CS ITU: Cardiosurgery Intensive Care Unit; DRS: Disability Rating Scale; EEG: electroencephalography; I: in hospital; LCF: level of cognitive functioning; ML SSEP: medium latency somatosensory evoked potentials; N: no; NC: non-cardiac; Pheo: pheochromocytoma type 1; O: out of hospital; PEA: pulse less electrical activity; VF: ventricular fibrillation; SSEP: somatosensory evoked potentials; Y: yes.

TABLE II.—*Twelve-month follow-up scores of Level of Cognitive Functioning Scale (LCFS), Disability Rating Scale (DRS) and Coma Recovery Scale-Revised (CRS-R).*

	Outcome	N.	Percentage and CI
LCF	Score 8-6	12	54.55% CI: 34.36-73.08
	Score 5-4	1	4.55% CI: –
	Score 3-1	9	40.91% CI: 23.26-61.27
DRS	Score 0-6	11	50.00% CI: 30.72-69.28
	Score 7-21	6	27.27 CI: 13.15-48.15
	Score 22-30	5	22.73% CI: 10.12-43.44
CRS-R	Absent or light disability	12	54.55% CI: 34.36-73.08
	MCS	5	22.73% CI: 10.12-43.44
	PVS	5	22.73% CI: 10.12-43.44

CRS-R: Revised Coma Recovery Scale; DRS: Disability Rating Scale; LCF: level of cognitive functioning; MCS: minimally conscious state; PVS: persistent vegetative state.

details and outcome for each included subject are reported in Table III.

Considering LCF as dependent variable, a model that included the variable high voltage medium latency SSEP (MLp-SSEP) was selected. For DRS the variables were place of heart failure, basal and high voltage medium latency SSEP (MLb-SSEP and MLp-SSEP), N20/P25 presence, consciousness recovery and frequent sporadic epileptiform discharges. For CRS-R the variables were high voltage medium latency SSEP (MLp-SSEP), N20/P25 presence and consciousness recovery.

Presence of short and medium latency SSEPs with low and high stimulation intensity were identified as prognostic predictors of outcome for all the scales. Prediction accuracy of these factors was very high for all three scores, with only one misclassified subject for CRS and LCF and two for DRS corresponding to error rates of 4.5% for CRS and LCF, and 9.1% for DRS. Of note, for a single subject all three score were incorrectly predicted. The regression coefficients (β) are listed in Table IV.

TABLE III.—*Neurophysiological details and outcome data for each subjects. Classification based on the American Clinical Neurophysiological Society's standardized Critical Care EEG terminology: 2012 version.*[14]

Subject #	EEG	SED	SL-SSEP	MLb-SSEP	MLp-SSEP	LCF 12 months	DRS 12 months	CRS
1	E	A	Yes	Yes	Yes	8	2	L/A d
2	E	A	Yes	Yes	Yes	8	1	L/A d
3	N	F	Yes	No	Yes	8	4	L/A d
4	N	R	Yes	No	Yes	4	19	MCS
5	N	F	Yes	No	Yes	8	3	L/A d
6	N	R	Yes	No	Yes	8	3	L/A d
7	N	R	Yes	No	Yes	8	2	L/A d
8	E	A	Yes	Yes	Yes	8	3	L/A d
9	N	R	Yes	Yes	Yes	8	2	L/A d
10	N		Yes	No	Yes	8	2	L/A d
11	N	A	Yes	Yes	Yes	8	2	L/A d
12	N	R	Yes	No	Yes	6	10	L/A d
13	N	R	Yes	No	Yes	8	0	L/A d
14	N	R	Yes	No	No	2	18	MCS
15	E	A	Yes	No	No	2	18	MCS
16	P	R	Yes	No	No	3	19	MCS
17	N	A	Yes	No	No	2	18	MCS
18	E	A	No	No	No	2	28	PVS
19	N	R	No	No	No	2	29	PVS
20	E	A	No	No	No	2	25	PVS
21	P		No	No	No	2	26	PVS
22	N	R	No	No	No	2	26	PVS

E: epileptiform; N: normal; P: poor; SED: sporadic epileptiform discharge; A: abundant; F: frequent; R: rare; SL-SSEP: short-latency SSEP; MLb SSEP: medium-latency basal (10-mA stimulus) SSEP; MLp-SSEP: medium-latency pain (50-mA stimulus) SSEP; L/A d: light/absent disability; MCS: minimal conscious state; PVS: permanent vegetative state.

TABLE IV.—*Predictive values for each functional score (LSF, DRS, CRS-R): high amplitude, painful medium latency SSEP are predictive for all scores; N20/P25 components are predictive for DRS and CRS-R; DRS is predicted also by the presence of frequent SED, basal medium latency SSEP and the location of heart failure.*

	Variables	Beta
LCF	MLp SSEP	3.397
DRS	Site of heart failure	1.449
	N20/P40 presence	3.532
	MLb SSEP	1.665
	MLp SSEP	1.810
	Frequent SED	1.250
CRS-R	MLp SSEP	2.09
	N20/P40 presence	1.96

MLp: medium-latency at painful stimulus (50-mA intensity) somatosensory evoked potentials; MLb: medium-latency at basal stimulus (10-mA intensity) somatosensory evoked potentials; SED: sporadic epileptiform discharges.

Discussion

Middle latency somatosensory evoked potentials associated with short latency somatosensory evoked potentials during the first 48 hours after a cardiac arrest are strong predictors of functional outcome at 12 months from the event.

Short latency SSEPs [23-26] have a limited sensitivity in predicting long term functional outcome after coma: while bilateral absence of N20/P25 responses has been shown to correlate with poor outcome in multiple studies,[23-25] almost half of individuals with preserved N20 have a poor neurological outcome.[7]

N20/P25 response reflects the integrity of thalamocortical projections. The N70 potential, part of medium latency SSEP, reflects cortico-cortical projections and bears a different pathophysiological significance, reflecting integrity of polysynaptic, long range connections. It has not been commonly used due to technical challenges limiting its generalizability.[27]

ML-SSEPs have already been demonstrated to predict good neurological outcome and survival.[11, 12] The proof of their utility in predicting good long-term functional outcome adds to their overall prognostic value, and provides the intensive care and rehabilitation physicians with an additional tool.

Recent studies assessed long term functional outcome after acquired brain injury,[28, 29] but variables were collected at admission to the neuro-rehabilitation Unit, preventing a real early prognostication. Among factors predicting return to home, age, etiology, and DRS score at neuro-rehabilitation unit admission had the highest predictive values.[28] The anoxic cohort had an overall worse prognosis than other categories with different etiologies of acquired brain injury.[30, 31]

The current American Academy of Neurology (AAN) guidelines for prognostication after cardiopulmonary resuscitation [2] have been tentatively integrated with a multimodal approach after the introduction of targeted temperature management (TTM),[5] which included clinical examination, electroencephalography, short latency somatosensory-evoked potentials, and serum neuron-specific enolase. The suggested paradigm in fact strengthened the accuracy only in predicting a poor outcome.

Middle-latency somatosensory evoked potentials (ML-SSEP), in the range of 40-70 ms, reflect higher-order brain processes.[27, 32, 33] These connections are required for consciousness recovery and good outcome after an acquired brain injury.[12, 34-37] ML-SSEPs are altered after more severe ischemic injury than short-latency SSEP (SL-SSEP, commonly named N20/P40, or N20/P25 according to which deflections are primarily considered), and their preservation reflects a less severe brain damage:[8-10] longer latency evoked potentials assume the integrity of polysynaptic, sub-cortical connections.[38-40]

We observed good correlation between the early presence (<48 hours from cardiac arrest) of ML-SSEPs and a good functional outcome after 12 months from the anoxic brain injury. This was measured by the Level of Cognitive Functioning Scale (LCFS), the Disability Rating Scale (DRS) and the Coma Recovery Scale-Revised (CRS-R).

A sound correlation with functional outcome was found also for short latency SSEPs (N20), except for LCFS. The cortical generator of N20 has been identified in the Brodmann areas 3b and 1 of the primary somatosensory cortex:[41] N20 indicates the structural and functional integrity of this area. The lack of correlation between N20 presence and LCFS outcome is not surprising. The scales explore different abilities: the DRS tests mainly motor actions with a limited level of complexity, and CRS tests basic functions. LCFS, conversely, attempts to evaluate the cognitive status of the individual: cognitive processes require a comprehensive integration of diverse intra- and interhemispheric cortical areas [42, 43] which are dependent on the integ-

rity of subcortical, long range fibers, and not just on the preservation of sensorimotor areas.

The only outcome measure appearing to depend on the interaction of multiple factors was DRS: good outcome was related to the presence of N20/P25, ML-SSEPs, place of heart failure (*i.e.*, events which happened in hospital were treated more precociously and thus more effectively), recovery of consciousness and frequent sporadic epileptiform discharges (SED). Whereas the pathophysiological significance of these biomarkers is clear, less clear-cut is the positive correlation of SED with outcome. A possible hypothesis is that a brain with frequent epileptiform signals a suffering but still viable and functioning tissue.

Surprisingly, creatinine values were not a biomarker for outcome in our model. High creatinine values signal a potential renal failure, implying a systemic involvement. Indeed, kidneys, along with the brain, are the most oxygen-consuming organs. During anoxia, both the brain and the kidneys are the first compromised organs. This finding is well established in cardiac surgery and during open-heart surgery (*i.e.*, extracorporeal circulation): in this setting, organ hypoxia is a recognized risk, and creatinine levels are in many centers routinely collected to precociously identify signs of organ dysfunction related to decreasing oxygen saturation.[44, 45] On this ground, creatinine levels are part of the routine biochemical markers after a cardiac arrest in our ICU, tracking a hypoxia-anoxia that occurred over the previous 24 hours. We included it among our covariates to strengthen information on possible severe sufferance of the most oxygen-consuming organs.

No data have been reported on an early prognostication of functional recovery in this population, with the exception of a study on post-anoxic brain injury with prolonged disorder of consciousness. Short latency SSEPs were recorded during the first two weeks of admission at the neuro-rehabilitation Unit (mean 43 days from event).[46] No correlation could be found with N20 and Functional Independence Measure (FIM). The result could be explained by the timing of the neurophysiological examination, which deviate from the AAN guidelines,[2] and the sample population, deliberately chosen among the worst scoring subjects in the ICU.

Our mortality rate is lower than in another recent report (48% *vs*. 70%).[47] This difference could rest on the lower rate of withdrawal therapy in other studies,[5, 25] which likely results in a higher number of persistent vegetative states. This could also explain the better outcome at DRS of our subjects compared to those of previous series:[28, 29] (DRS 11.82±10.66 and LCF of 5.32±2.89 in our cohort, *versus* 18±7 for DRS and 4±2.02 for LCF). It should be noted that these scores were recorded at discharge, with a mean time from admission of 128±85 days for our data and 78±55 days for other studies. Our longer follow-up could have allowed a longer recovery time, and thus a more favorable outcome.

Limitations of the study

A technical limitation in recording ML-SSEPs could have been the C4'/C3'-Fpz standard montage. The N60/N70 potential consists of two responses, a N60 generated by the pre-SMA and primary somatosensory cortex (SI) over the fronto-central region, and a N70 generated by the secondary sensory cortex (SII) over the temporal region. With recording electrodes at C3' and C4', we recorded probably mostly activity from SI, rather than SII, possibly missing the reverberation of circuits projecting exclusively to SII.

We stimulated at a rate of 3.3 Hz, instead of 1.5 Hz. This stimulation paradigm did not decrease the amplitude of ML-SSEP, as previously reported, but potentially increased the yield of the 50 mA stimulation. This may be due a possible compensatory mechanism of a suboptimal stimulation paradigm in brain-injured subjects.

The limited size of our sample was a major limitation, but the very strong statistical significance of results points to a promising direction for research. The fact that a single subject was misclassified for the three functional scale models suggest that intrinsic conditions (*i.e.*, associated comorbidities) could have played a role, additionally strengthening our findings. These data could be used as a proof of concept to design large trails.

Conclusions

ML-SSEPs, combined with SL-SSEP, are early prognostication markers of long-term (12 months) functional outcome in post anoxic comatose subjects. These markers could inform more appropriate allocation of resources, provide a basis for realistic goal-setting, and help the family to adjust its expectations.

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