Pain-related middle-latency somatosensory evoked potentials in the prognosis of post anoxic coma: a preliminary report

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ABSTRACT

Background. Regarding hypoxic-ischemic encephalopathy, while the bilateral absence of N20/P25 somatosensory evoked potentials (SEPs) is considered to be the best indicator of adverse outcomes, the presence of middle latency evoked potentials (MLCEPs) is associated with a favourable neurological prognosis. The main aim of the present study was to investigate whether painful electrical stimulation might be considered a provocative test in producing MLCEPs and predictor of patient's outcomes after cardiac arrest.

Methods. Retrospective pilot study. SEPs with and without pain-related electrical stimulation in both median nerves were recorded in 17 patients with post anoxic coma after cardiac arrest. Glasgow Coma Scale, electroencephalograms, heart rate and blood pressure changes were also recorded at the same time. Three months after cardiac arrest the same measures with inclusion of Glasgow Outcome Scale Extended were also performed only in the remaining patients with severe neurological outcome. No one intervention was made.

Results. Patients who showed MLCEPs had a good outcome, while patients without N20/P25 SEPs but with increases in blood pressure remained in a vegetative state. Patients who did not show N20/P25 SEPs and increase in blood pressure died within one week. Only one patient who showed N20/P25 SEPs was minimally conscious.

Conclusion. These preliminary data suggest that MLCEPs elicited by painful electrical stimulation seem to be a sensitive method to predict the neurological outcome of patients in the acute phase of coma. Blood pressure response might be a prognostic physiological measure of survival in the vegetative state in patients without N20/P25 SEPs. *(Minerva Anestesiol 2012;78:749-56)*

Key words: Evoked potentials, somatosensory - Electroencephalography - Hypoxia-ischemia, brain.

Accurate prediction of the neurological outcome for comatose patients after cardiac arrest is important in intensive care for early prognosis of the functional outcome. In addition to standard clinical examination, the somatosensory evoked potentials (SEPs) improve the accuracy of neurological prognosis of comatose patients after cardiopulmonary resuscitation for cardiac arrest.[1, 2] Indeed, the bilateral absence of the early cortical SEP (*i.e.*, N20/P25) is related to adverse outcomes such as death or survival in a vegetative state. However, the presence of N20/P25 is not sensitive for predicting a good neurological outcome.[3] It is well established that only event-related evoked potentials (*i.e.*, P300) can be reliably used in detecting awareness markers in minimally responsive patients.[4] There is also evidence that the presence of middle-latency cortical somatosensory evoked potentials (MLCEPs) strongly correlates with a favourable

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neurological prognosis in patients affected by either cardiac arrest or severe stroke.[5, 6] Moreover, although treatment cannot be determined on the basis of MLCEPs presence, Zandbergen *et al*. (2006) observed that the absence of the N70 potential provides evidence for poor prognosis.[7]

Recently, it has been shown that during anaesthesia, it is possible to induce the appearance of MLCEPs during painful electrical stimulation in the median nerves, suggesting that SEP responses can reflect a more integrated cerebral processing of pain.[8] Nonetheless, the effectiveness of this method in predicting neurological outcomes in comatose patients is not fully known.

Therefore, the main aim of the present study was to evaluate whether pain-related MLCEPs might be a reliable and accurate tool to predict the neurological prognosis of patients in the acute phase of post-anoxic coma. Neurovegetative responses were also investigated as a prognostic physiological measure of survival in the vegetative state in patients without N20/P25.

Materials and methods

Patients

Approval for the present study was obtained from our Institution Ethical Committee. Seventeen comatose patients after cardiac arrest due to an acute coronary syndrome were enrolled into this study after admittance in the Intensive Care Unit according to availability of the neurophysiologist. The patients were predominantly male (79%) with a mean age of 60±13 years. The etiopathogenetic mechanism of cardiac arrest was ventricular fibrillation and asystole for 88% and 12% of the patients, respectively. Sixty-five percent of patients had the indication to undergo hypothermia according to the International Guidelines for Resuscitation.[9]

Both clinical and neurophysiological evaluations were performed in two steps. The Glasgow Coma Scale (GCS),[10] electroencephalograms (EEG) and SEPs were performed on day 2 after cardiac arrest after re-warming from moderate hypothermia (first step). GCS, Glasgow Outcome Scale Extended (GOS-E),[11] EEG and SEPs were performed three months after cardiac arrest on patients with adverse neurological prognosis (second step). Clinical outcome evaluation was not performed in patients with good neurological outcome. All clinical and neurophysiological evaluations were performed in normothermia, and in stable hemodynamic, metabolic, normoglycemic and respiratory gas exchange conditions for each patient. SEPs and the EEG were recorded with muscle paralysing medications to reduce the signal-to-noise ratio induced by movements; in the second step, the neurophysiological evaluation was performed without sedation. The SEPs recording was performed at 10 and 50 mA electrical stimulation. Blood pressure and heart rate were also recorded during the electrical stimulation. Blood pressure and heart rate responses at 50 mA stimulation were defined as an increase of 10% with respect to baseline values recorded at 10 mA stimulation.

The status epilepticus was initially treated with sedation with intravenous continuous infusion of incremental doses of midazolam with or without propofol and with the barbiturate coma in the most resistant patients. Phenytoin, valproic acid and levetiracetam were used to replace the midazolam/propofol for controlling epileptic activity.

Neurophysiological recording

1. The four bilateral channels of SEPs were: Fpz-C4'/C3', right Erb's point/left Erb's point-C4'/C3', Fpz-Cv and Fpz-right Erb's point/left Erb's point. The recording parameters for SEPs were 30 and 400 Hz for the low frequency filter (LFF) and high frequency filter (HFF), respectively, at 10 ms/div with 100 sweeps, a further bandpass averaging filter (30-400 Hz) was applied. The sampling rate was 20 KHz and the hardware bandwidth was 1 to 4 KHz. The stimulus duration was 200 ms and the stimulus frequency was 3.3 Hz. Electrical stimulation was performed simultaneously, using needle electrodes placed on both wrists.

2. Eight bipolar channels for the EEG were recorded with needle electrodes placed at the standard scalp sites (F3/4-Cz, C3'/C4'-Cz, T3/T4-Cz, P3/P4-Cz); C3' and C4' were positioned 2 cm posterior to C3 and C4, according to the

10/20 International System. The recording parameters of the EEG were 1 Hz LFF, 40 Hz HFF, sampling rate 250 Hz and hardware bandwidth 1 to 100 Hz.

The ground electrode was placed on the left shoulder for both EEG and SEP recordings. The impedance was kept below 1 KΩ. The EEG and SEPs were recorded using the Eclipse Neurological Workstation-Axon System (80/5 Davis Drive Haupage, 11788, NY, USA).

The patients were bilaterally subjected to an increasing intensity of electrical stimulation of the median nerve in two steps: 10 and 50 mA. Each block of stimulation lasted 120 s. At each step, the following parameters were simultaneously recorded during both 10 and 50 mA stimulation: cortical short latency SEP (N20/P25) and MLCEPs (P45/N55 – P60/N70), EEG, heart rate and blood pressure.

Statistical analysis

Fisher's exact test was performed in order to estimate whether neurological outcomes were different between patients who had shown MLCEPs or not. Fisher's exact test was also conducted to investigate whether the presence or absence of blood pressure response might be associated with a vegetative state or death in patients who did not show N20/P25, respectively. Sensitivity and specificity with 95% confidence intervals (95% CIs) were calculated for MLCEPs (presence, absence) and BP response (presence, absence). Sensitivity measures the proportion of actual positives which are correctly identified as such whereas specificity measures the proportion of negatives which are correctly identified. Sensitivity and specificity can range from 0% to 100% and it is necessary that both be as high as possible. A P-value <0.05 was considered to be statistically significant. STATISTICA 6.1 software (Stat. Soft Inc., Tulsa, OK, USA) was used for the statistical analysis. All levels of significance reported in the following sections are two-tailed values.

Results

On day 2 after cardiac arrest, all patients had a GCS score of 3. Eight patients displayed convulsive or non-convulsive status epilepticus (NCSE), two had alpha, one had theta, four had delta, one had burst suppression and one an isoelectric EEG brain rhythm. After one month, patient 2 underwent a barbiturate coma to treat a resistant status epilepticus. No patients showed EEG responses to painful stimulation.

No patients had a myoclonus. Neurophysiological evaluation at 50 mA electrical stimulation showed both N20/P25 and MLCEPs in six patients, only N20/P25 in two patients and neither N20/P25 nor MLCEPs in the remaining nine patients; the MLCEPs were induced only with the electrical stimulation at 50 mA (Figure 1), (Table I).

At three months after cardiac arrest, two patients (patients 10 and 11) with both N20/P25 and MLCEPs died within fifteen days after cardiac arrest due to multi-organ failure after a subsequent cardiac arrest, and a pulmonary haemorrhage respectively. The remaining patients who had shown the appearance of MLCEPs peaking between 45 and 70 ms during the 50 mA electrical stimulation in the first step evaluation (N.=4) had a good recovery (GCS score of 15 and GOS-E of 8). These patients had no motor or sensitive deficit and completely recovered from post anoxic coma. Patient 2 suffered from bronchopneumonia and sepsis.

In the patients (N.=5) who had an adverse neurological outcome (GCS <10 and GOS-E <4), four in a vegetative state and one minimally conscious, NCSE was persistent (Figure 2).

The pain-related N20/P25 and MLCEPs were only recorded in the patient in a minimally conscious state three month after cardiac arrest (patient 5), while the bilateral pain-related N20/P25 was not recorded in the other four patients in a vegetative state. All these patients also showed preserved hemodynamic response. One patient (patient 12) with N20/P25, detected in the first step evaluation, died within fifteen days because of a brain haemorrhage during extracorporeal membrane oxygenation.

The remaining patients (N.=8) died within 15 days. Four of the five patients, who died within seven days after cardiac arrest because of brain death, did not show N20/P25 and hemodynamic reactivity to painful stimulation.

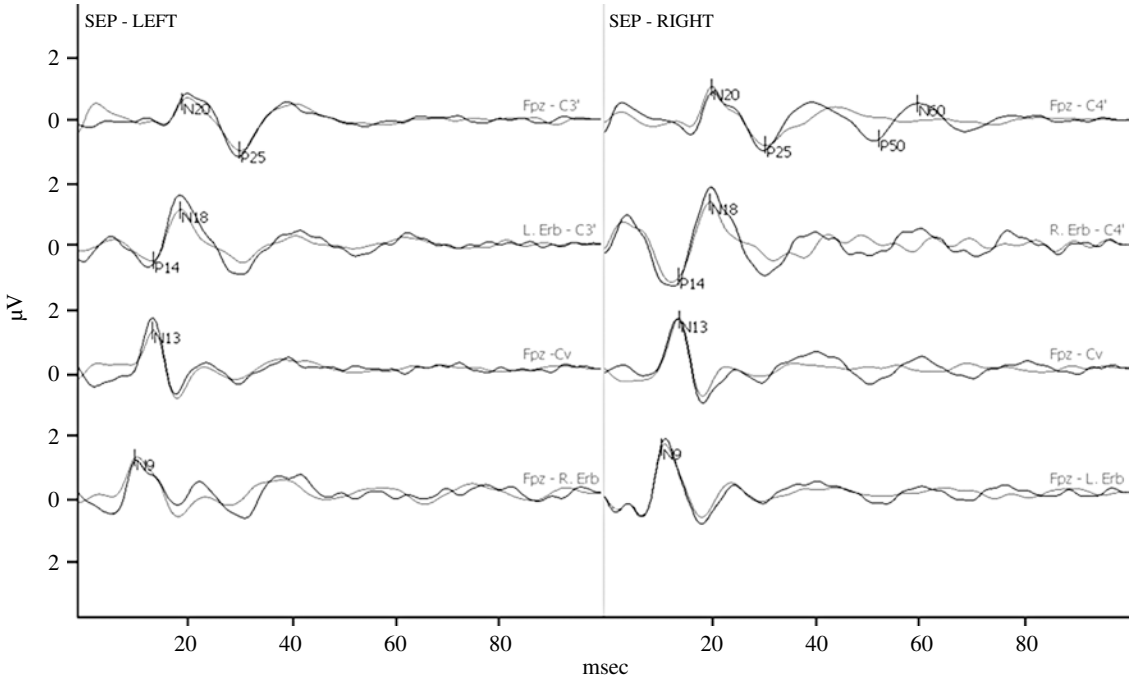

Figure 1.—Patient 1: four bilateral somatosensory evoked potential (SEPs) channels: Fpz- C3'/C4', left Erb's/right Erb's - C3'/ C4', Fpz- Cv; Fpz- right Erb's/left Erb's. Note the appearance of the right MLCEP (P50/N60) at 50 mA of stimulation (black line) with respect to the baseline (red line) at 10 mA.

Table I.—*Latency and amplitude of the right and left middle-latency cortical somatosensory evoked potentials.*

Patients	Right hemisphere MLCEP				Left hemisphere MLCEP			
	P45/N55		P60/N70		P45/N55		P60/N70	
	Latency (ms)	Amplitude (uV)	Latency (ms)	Amplitude (uV)	Latency (ms)	Amplitude (uV)	Latency (ms)	Amplitude (uV)
1	50/59	0.5	-	-	-	-	-	-
2	46/57	1	-	-	45/56	0.5	-	-
3	-	-	-	-	-	-	66/77	0.5
4	-	-	-	-	52/67	0.4	-	-
10	-	-	-	-	-	-	62/72	4.4
11	51/60	1.4	-	-	49/58	1.7	-	-

MLCEP: middle-latency cortical somatosensory evoked potential.

Outcome and neurophysiological details of patients are reported in Figure 3.

The percentage of patients with an adverse (*i.e.*, a minimally conscious state, vegetative state or death) or a good neurological outcome significantly differed between patients who had shown MLCEPs or not (Fisher's exact test, P=0.006). Indeed, 23.5% of patients with MLCEPs had a good neurological outcome compared to 0% of patients without MLCEPs, while only 11.8% of patients with MLCEPs had an adverse neurological outcome compared to 64.7% of patients without MLCEPs. The presence of MLCEPs showed 100% of sensitivity (95% CI=100% - 100%), identifying good neurological outcome in all patients with MLCEPs, whereas the absence of MLCEPs had 85% of specificity (95% CI = 65% - 105%) in identifying adverse neu-

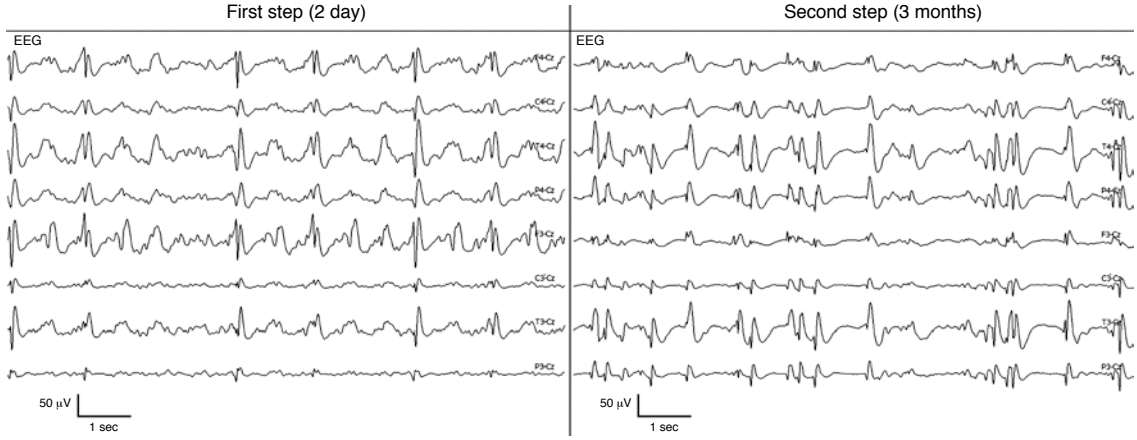

Figure 2.—Patient 8: electroencephalographic non-convulsive status epilepticus (NCSE) patterns on day two and at three months.

Patients	Age	Cardiac arrest rhythym	Hypothermia	Death Time (days)	Consciouness recovery (days)	Outcome	first step (2 day)						second step (3 month)						
							GCS	EEG	N20/P25	MLCEP	BP reactivity	HR reactivity	GCS	GOS-E	EEG	N20/P25	MLCEP	BP reactivity	HR reactivity
1	58	VF	yes	-	10	Recovery	3	NCSE	yes	yes	yes	yes	15	8	-	-	-	-	-
2	69	VF	no	-	54	Recovery	3	C/NCSE	yes	yes	yes	no	15	8	-	-	-	-	-
3	54	VF	yes	-	5	Recovery	3	DELTA	yes	yes	yes	yes	15	8	-	-	-	-	-
4	49	VF	yes	-	5	Recovery	3	ALPHA	yes	yes	yes	yes	15	8	-	-	-	-	-
5	71	VF	yes	-	-	MCS	3	C/NCSE	yes	no	yes	yes	9	3	NCSE	yes	yes	yes	no
6	48	VF	yes	-	-	VGS	3	C/NCSE	no	no	yes	no	9	2	NCSE	no	no	yes	no
7	59	VF	yes	-	-	VGS	3	C/NCSE	no	no	yes	no	6	2	NCSE	no	no	yes	no
8	64	AS	yes	-	-	VGS	3	NCSE	no	no	yes	yes	6	2	NCSE	no	no	yes	no
9	60	FV	no	-	-	VGS	3	NCSE	no	no	yes	no	6	2	NCSE	no	no	yes	no
10	67	FV	no	15	-	Died	3	DELTA	yes	yes	no	no	-	1	-	-	-	-	-
11	61	FV	yes	12	-	Died	3	THETA	yes	yes	yes	yes	-	1	-	-	-	-	-
12	54	FV	yes	3	-	Died	3	DELTA	yes	no	no	no	-	1	-	-	-	-	-
13	64	FV	yes	4	-	Died	3	BURST	no	no	no	no	-	1	-	-	-	-	-
14	55	FV	no	2	-	Died	3	ISO	no	no	no	no	-	1	-	-	-	-	-
15	35	FV	no	2	-	Died	3	ALPHA	no	no	no	no	-	1	-	-	-	-	-
16	89	FV	no	5	-	Died	3	C/NCSE	no	no	no	no	-	1	-	-	-	-	-
17	63	AS	yes	7	-	Died	3	DELTA	no	no	yes	no	-	1	-	-	-	-	-

Figure 3.—Description of the outcome differences in relation to neurophysiological evaluations at 50 mA and clinical data. The four different colours refer to the four different outcomes: good neurological outcome (light gray), minimally conscious state (dark gray), vegetative state (white) or death (gray). MLCEP: middle-latency cortical somatosensory evoked potential; Amp: amplitude of N20/P25; Lat: latency of N20/P25; HR: heart rate; BP: blood pressure; GCS: Glasgow Coma Scale; GOS-E: Glasgow Outcome Scale Extended; VF: ventricular fibrillation; AS: asystole; C/NCSE: convulsive/non-convulsive status epilepticus; ISO: isoelectric EEG pattern.

rological outcome (*i.e.*, minimally conscious or vegetative states).

Moreover, the percentage of patients without N20/P25 SEPs who remained in a vegetative state or died significantly differed from patients who had shown BP response or not (Fisher's exact test, P=0.048): 44.5% of patients with BP response were in a vegetative state compared to 0% without BP response while 11% of patients with BP response died compared to 44.5% without BP response. The presence of BP response had 100% of sensitivity (95% CI=100% - 100%), identifying adverse neurological outcome (*i.e.*, minimally conscious or vegetative states) instead of death in all patients with BP response, whereas the absence of BP response showed 80% of specificity (95% CI=41% - 119%) in identifying death.

The percentage of patients who had an adverse (*i.e.*, a minimally conscious state, vegetative state or death) or a good neurological outcome did not significantly differ between patients who were subjected to hypothermia or not (Fisher's

exact test, P=0.99); the percentage of patients who died or survived did not significantly differ between patients with or without hypothermia (Fisher's exact test, P=0.33). At the same time, the percentage of patients who showed MLCEPs or not did not significantly differ between patients who had undergone hypothermia or not (Fisher's exact test, P=1).

Discussion

The present study investigated whether MLCEPs and neurovegetative measures during intense electrical stimulation on both median nerves were accurate tools for predicting the neurological outcome of patients with hypoxic-ischemic encephalopathy in the acute phase.

It is well-established that clinical responses to painful stimuli are widely used to explore consciousness in routine clinical practice. The GCS represents the most widely used clinical scale in exploring this issue.[10] Since pain is an unpleasant experience that involves the conscious awareness of noxious sensations,[12] we considered the aims of our research to be ethically justified in comatose patients because most of them were in NCSE or had an unresponsive EEG to painful stimulation.

The appearance of MLCEPs seemed to be an expression of cortical processing of painful stimuli.[8] This network includes the primary and secondary somatosensory cortices, the insular, anterior cingulate and prefrontal cortex.[13] In the comatose condition, the dissociation between N20/P25 and MLCEP suggests the dysfunction of the cerebral network (*i.e.*, cortico-cortical and cortico-subcortical connections) involved in the perception of pain. In line with previous studies, the MLCEP was in the range of 45 to 70 ms after onset of stimulus;[5, 6] MLCEPs might represent the pain cortical processing induced by the activation of the A delta nerve fibers.[8] The MLCEPs was not prolonged in latency compared to the previous data suggesting that MLCEPs induced by pain may activate brain networks much more strongly with respect to the lower-intensity stimulation routinely used.[14, 15]

Our preliminary results suggest that pain-related MLCEPs might be an accurate measure to predict good neurological outcomes in comatose patients, as demonstrated by previous studies without a pain-related method.[5, 6] Indeed, the presence and the absence of MLCEPs showed high sensitivity (*i.e.*, 100%) and specificity (*i.e.*, 85%) in predicting good and adverse neurological outcomes in comatose patients, respectively. MLCEPs reflects the integrity of brain pathways beyond the primary somatosensory cortex. Given that the only high intensity stimulation at 50 mAmp could generate MLCEPs, the present neuropathic pain method might allow the detection of the brain network quiescent in the ischemic penumbra. Therefore, by detecting brain cortex somatosensory responses induced through painful electrical stimulation, pain-related SEPs may represent a sort of neurophysiological GCS that neurophysiologists can use to assess cortical reactivity in response to painful stimulation.

The potential effectiveness of MLCEPs in predicting a good neurological outcome might be underestimated in this study because two patients with MLCEPs died after 12 and 15 days due to pulmonary hemorrhage and cardiovascular failure, respectively. Furthermore, the presence of bilateral MLCEPs in two patients suggests that patients may have a different sensitiveness to median nerve nociceptive stimulation which, in turn, may reflect the extent or the severity of the global ischemic brain injury.

Although status epilepticus after anoxic coma represents an independent adverse outcome predictor as observed in vegetative state patients,[16] this assumption was not true for patients with good neurological prognosis. The current finding is in line with more recent evidence showing a lack of correlation between the EEG rhythms and good neurological outcome.[17, 18] Indeed, the recovery of consciousness in patients with preserved SEPs may depend on the time of recovery of normal EEG rhythm.[18]

Interestingly, this method might also be a useful tool to evaluate brain connectivity in patients without normal spontaneous cortical EEG activity (*e.g.*, the NCSE). Indeed, SEPs are less influenced by sedation and intravenous anaesthesia and, therefore, can be considered as a measure to evaluate the integrity of somatosensory system

independent of anaesthetic medications which, turn, suppress the spontaneous cortical excitability assessed with EEG.[8, 19-21]

Moreover, electrical stimulation of the median nerves can be considered a good experimental model of pain in comatose patients because the highly intense stimulation induced an increase in blood pressure, suggesting an autonomic response to stress. Heart rate did not change during stimulation, probably due to cardiovascular medications (*i.e.*, beta-blockers). The absence of blood pressure response seemed to be strongly associated with early brain death in patients who did not show N20/P25. Hence, in patients without N20/P25, it might be suggested that blood pressure response to painful stimulation represents a useful and accurate index for predicting an adverse outcome (*i.e.*, survival in a vegetative state or death) during the early phase of hypoxic ischemic encephalopathy due to cardiac arrest. Indeed, the presence and the absence of blood pressure response showed high sensitivity (i.e., 100%) and specificity (*i.e.*, 80%) in predicting adverse neurological outcome and death in comatose patients, respectively. Blood pressure response to stressful stimulation seemed to be related to the preserved brainstem and sub-cortical functioning. More importantly, the absence of the neurovegetative response was associated with a very high incidence of mortality for brain death within one week after cardiac arrest.

We appreciate that pain-related method derived from our intraoperative neurophysiological experience (*e.g.*, needles electrodes, filter settings, sedation, curarization) can reduce the signal to noise ratio which, in turn, may influence inter-observer variation in the interpretation of the N70 potential.[7, 22] Our method also provides evidence for the effectiveness of an integrated multidisciplinary approach linking neurophysiology and intensive care medicine and put the basis to introduce the basic neurophysiology in the domain of anaesthesiology and intensive care physician as for the intraoperative setting.[23]

Moreover, the high variability in good neurological outcome in patients with N70 potential might be explained by the high percentage of NCSE and antiepileptic treatments which were not taken into account in previous studies.[7] Our findings suggest that the NCSE should be treated in the early phase after cardiac arrest in patients with preserve SEPs. Indeed, the proposed pharmacological treatment might be effective in restoring of consciousness in patients who had shown the integrity of the thalamus-cortical and cortico-cortical network assessed with pain-related MLCEPs.

There are some limitations that have to be recognized in interpreting our data. A large number of patients, control groups and long-term clinical outcome follow-up (performed with GOS-E) should also be carried out in order to fully estimate the effectiveness of pain-related MLCEPs in predicting the neurological outcome of patients with hypoxic-ischemic encephalopathy. Correlation analysis between MLCEPs amplitude and clinical outcome measures (*e.g.*, GCS or GOS-E) should be also conducted to provide further evidence for pain-related MLCEPs prognostic value. Moreover, future studies should also assess neuropsychological performance along with clinical outcome to evaluate the potential predictive value of MLCEPs for cognitive status of patients with good neurological outcome after post anoxic coma. A large number of neurophysiological evaluations should also be performed within the first week after cardiac arrest to accurately detect when the neurovegetative reserve is lost.

Conclusions

Although our small sample data need to be confirmed by further research, the present study provides evidence that painful electrical stimulation of the median nerves might be a useful method for exploring neurophysiological responses of the nervous system and predicting adverse or good neurological outcomes in patients in the acute phase of hypoxic-ischemic coma.

Key messages

— The present study investigated whether pain-related middle-latency cortical somatosensory evoked potentials may allow a better prediction of neurological outcome in patients with post anoxic coma after cardiac arrest.

— The absence of neurovegetative responses to painful stimulation seems to be associated with a high incidence of mortality for brain death within one week after cardiac arrest.

— Since a particular setting (e.g., needles electrodes, filter settings, sedation, curarization) is needed to perform a neurophysiological evaluation with the best signal to noise ratio, the present study provides evidence for the effectiveness of an integrated multidisciplinary approach between neurophysiology and intensive care medicine.

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Conflicts of interest.—None.

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