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Stimulus Induced Rhythmic, Periodic or Ictal Discharges (SIRPIDs) in comatose survivors of cardiac arrest: characteristics and prognostic value.

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Highlights:

- SIRPIDs are a newly described group of EEG pattern, which is still not well characterized, and this study help clinicians to integrate this neurophysiologic information in clinical practice.
- This study suggest that considerable brain insult is necessary to induce SIRPIDs
- Our findings provide new elements in the field of outcome prognosis in cardiac arrest survivors.

Keywords: EEG pattern, neurocritical care, hypoxic brain injury, prognosis, hypothermia, outcome

Abstract

Objectives: To analyze the prevalence of Stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs) in patients with coma after cardiac arrest (CA) and therapeutic hypothermia (TH) and to examine their potential association with outcome.

Methods: We studied our prospective cohort of adult survivors of CA treated with TH, assessing SIRPIDs' occurrence and their association with 3-month outcome. Only univariated analyses were performed.

Results: 105 patients with coma after CA who underwent electroencephalogram (EEG) during TH and normothermia (NT) were studied. Fifty-nine patients (56%) survived, and 48 (46%) had good neurological recovery. The prevalence of SIRPIDs was 13.3% (14/105 patients), of whom 6 occurred during TH (all died), and 8 in NT (3 survived, 1 with good neurological outcome); none had SIRPIDS at both time-points. SIRPIDs were associated with discontinuous or non-reactive EEG background and were a robustly related to poor neurological outcome ($p<0.001$).

Conclusion: This small series provides preliminary univariate evidence that in patients with coma after CA, SIRPIDs are associated with poor outcome, particularly when occurring during in therapeutic hypothermia. However, survival with good neurological recovery may be observed when SIRPIDs arise in the post-rewarming normothermic phase.

Significance: This study provides clinicians with new information regarding the SIRPIDs prognostic role in patients with coma after cardiac arrest.

Introduction:

While “stimulus-sensitive” neurological manifestations have been known for a long time in survivors of cardiac arrest (CA) (Niedermeyer et al., 1977), a spectrum of stimulation-induced electroencephalographic patterns, called stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs) has recently been described (Hirsch et al., 2004); in the original report, these were found in 22% critically ill patients (including one subject with post anoxic coma out of 33 with SIRPIDs). As stated by the authors, neither the prognostic role nor the clinical implications of SIRPIDs were known, and this has not changed in the following years. To explore these aspects, the role of SIRPIDs was analyzed in comatose patients surviving a CA and treated with therapeutic hypothermia (TH).

Methods

Patients and procedures:

We prospectively studied a cohort of consecutive adults treated in our 32-bed multidisciplinary intensive care unit (ICU) between April 2009 and February 2012 (34 months). This observational registry has been described elsewhere (Rossetti et al., 2010a), and has full approval by our ethics commission. Briefly, all patients treated with TH were included; TH was started immediately in the emergency room and continued in the ICU. Patients were cooled to 33 ± 1°C for 24 hours using ice packs and cold infusions for hypothermia induction and an automated surface-cooling device (Arctic Sun Temperature Management System, Medivance, Louisville, CO) for maintenance of stable mild hypothermia. All patients were given a standardized sedation-analgesia with midazolam (0.1 mg/kg/hr) and fentanyl (1.5 µg/kg/hr). Vecuronium was used to prevent shivering. Patients diagnosed as brain dead after rewarming were excluded. Withdrawal of care was decided after interdisciplinary discussion, based on clinical and electrophysiological findings, as recently described (Rossetti et al., 2010a); SIRPIDs occurrence was not considered for this decision.

Neurological assessment

A neurologist examined all patients after rewarming, off sedation. Neurological examination included testing of principal brainstem reflexes (pupillary, oculocephalic, corneal) and motor reactivity to painful stimulation. As often as possible, an electroencephalogram (EEG) was also obtained during TH (limited EEG technologist availability during overnight), and all patients had at least one EEG after rewarming and off sedation, in normothermia. Both recordings were realized with auditory and noxious stimulations performed by a physician at bedside. Most EEGs were recorded for 20 to 60 minutes (some for a longer time) on a portable digital machine (Viasys Neurocare, Madison, WI), using 21 (occasionally, 9 or 14) electrodes arranged in accordance to the international 10-20 system. EEGs were interpreted by certified electroencephalographers at bedside and post hoc, using bipolar and referential montages, with a filters setting of 0.5 and 70Hz, and a notch filter (50Hz). Bilateral median nerve somatosensory evoked potentials (SSEP) recordings were also performed by a certified technologist using a cephalic (Fpz) and extracephalic (contralateral ear) reference and interpreted by a certified neurologist. Serum neuron-specific enolase (NSE) was sampled at 24 and 48 with an automated imunofluorescent assay.

Variables:

Demographics, CA etiology, duration of CA (defined as the time from collapse to the return of a spontaneous circulation (ROSC)) were prospectively collected. Brainstem reflexes were categorized as all present or not. The motor response to pain was categorized as no response or extension posturing, vs. flexor response or better. Antiepileptic drugs (AED) administration was also recorded.

EEG findings were categorized by experienced certified electroencephalographers according to three variables, as previously described (Rossetti et al., 2010b): 1) EEG background reactivity, defined as a clear and reproducible change in background frequency or amplitude following auditory or noxious stimulation, excluding SIRPIDs (see below) and muscle artifacts; 2) spontaneous discontinuous (burst-suppression) pattern, defined as an EEG background interrupted by very low-voltage (<5 μV) periods; 3) epileptiform activity, defined as any periodic or

rhythmic spikes, sharp waves, spike-waves, or rhythmic waves evolving in amplitude, frequency, or field. SIRPIDs were defined by the occurrence of rhythmic, periodic or ictal discharges after a stimulus, according to the original description (Hirsch et al., 2004); the time relation between the SIRPIDs and the stimuli needed to be clearly within few seconds and reproducible. All EEG recordings with SIRPIDs that were also scored as "epileptiform" were reviewed to confirm this aspect independently of SIRPIDs.

The N20 response on the SSEP was categorized as present or not. A negative deflection between 18 and 25 ms after the simulation followed by a clear positive deflection was needed for the N20 to be considered as present. If the exam was not evaluable it was performed again. In case of doubtful interpretation, N20 was considered present.

Outcome was assessed with mortality rate (during hospital stay) and with the Glasgow-Pittsburgh Cerebral Performance Categories (CPC) at three months, where good outcome is defined as CPC 1 (no impairment) or 2 (moderate impairment) (Booth et al., 2004).

Statistical analysis:

Analyses were performed using two-tailed Fisher's exact, $\chi 2$, or t tests, as required. Significance was assumed at $p<0.05$. Given the relatively low number of events (14 patients had SIRPIDs), no multivariable analysis was performed.

Results

During the studied period, 144 patients were treated with TH; 105 had an EEG during both TH and normothermia, the latter were recorded within 72 hours following CA. **Table 1** illustrates demographics, etiology of CA and outcome of the studied cohort. Most patients were men and suffered from ventricular fibrillation. In hospital mortality was 46/105 (43.8%), while nearly half of patients (48/105; 45.7%) reached a good neurological outcome (CPC of 1-2) at 3 months. The mean delay between CA and the hypothermic EEG was 16 ± 6.6 hours.

The prevalence of SIRPIDs was 13.3% (14/105 patients). Eight of them had a periodic pattern, while the others were equally distributed between rhythmic or ictal patterns (see figure 1 for examples). No patient showed SIRPIDs during both hypo- and normothermia. Comparison

between patients with SIRPIDs and controls is shown in **Table 2**. Baseline demographics, including age, initial CA rhythm and the time to ROSC did not differ significantly between patients with vs. without SIRPIDs. In contrast, subjects with SIRPIDs during TH were more likely to have a discontinuous (p=0.005) EEG background, while those with SIRPIDs during NT had a higher proportion of EEG with epileptiform background (p<0.001). SIRPIDs at any time were associated with elevated NSE > 33 µg/l (62% vs. 29% in patients without SIRPIDs, p=0.02), but this relationship was not found when the cut off was set at 80 µg/l (15.4% VS 18.2%, p=0.43).

Regarding AED administration, seven patients received levetiracetam, five valproic acid (all were also treated with levetiracetam) and three propofol, in various combinations.

Overall, SIRPIDs were associated with poor prognosis at 3 months (**Table 3**). When considering the time of SIRPIDs occurrence (during TH vs. NT), we found that none of the six patents with SIRPIDs during TH survived. In contrast, 3 out of 8 patients with SIRPIDs after rewarming during NT survived (all 3 had a reactive EEG background and presence of N20 on SSEP and two had present brainstem reflexes within 72 hours from CA). Only one of them had a favorable outcome (CPC 2): all his brainstem reflexes were present, without any myoclonus, his EEG background was reactive independently from SIRPIDs, which had a rhythmic pattern of SIRPIDs, N20 was bilaterally present and his NSE level was 10 µg/l.

Discussion

The principal finding of this study is that SIRPIDs are not uncommon in comatose survivors of CA (observed in 14 patients, corresponding to 13.3% of our cohort) and, in this series this pattern appears to be associated with a poor prognosis, particularly when occurring during TH. Survival and favorable functional ouctcome, however, may be observed when SIRPIDs appear after rewarming and in normothermic conditions, as it was the case in one out of 14 patients with SIRPIDs of our prospective cohort.

The prevalence of SIRPIDs in our cohort (13.3%) is lower than previously reported in a more heterogeneous group of neurological critically ill patients (Hirsch et al., 2004); this may be related the our homogenous etiology of brain dysfunction.

Before the SIRPIDs' definition, a small series of four patients presenting "stimulus-sensitive seizures" after CA also mentioned a catastrophic outcome with a mortality of 100% (Van Cott et al., 1996). Those findings and our results are in line with the hypothesis that SIRPIDs are associated with a dysfunction of subcortico-cortical projections secondary to severe brain damage and hyper-excitability (Hirsch et al., 2004). The strong associations of SIRPIDs with highly abnormal EEG background and with elevated serum NSE, both strong markers of neuronal injury as previously reported by our group (Rossetti et al., 2012), corroborate this hypothesis. Of note, the fact that a NSE level > 33 µg/l was associated with SIRPIDs and not a level > 80 µg/L possibly reflects that the injury should be severe enough to produce SIRPIDs, but not too serious. If the injury is too severe, neurons may be unable to produce those EEG pattern. Indeed, half of the patients from the control group with a NSE > 80 µg/L had value > 130 µg/L (max. 291 µg/L).

The transient nature of SIRPIDs, with no patient showing this pattern during both hypo- and normothermia, suggests a dynamic process during hypoxic-ischemic injury. The fact that necrosis is generally induced by a more severe brain aggression than apoptosis (Banasiak et al., 2000) could explain the worse prognosis associated with earlier appearance of SIRPIDs: stimulus-induced patterns appearing early (during TH) might reflect severe irreversible damage with neuronal loss in thalamo-cortical loops due to necrosis, whereas SIRPIDs in normothermia could be due to a slower neuronal death due to apoptosis, and thus may reflect a less severe and potentially reversible process leading to brain damage. The timing of the "necrosis-apoptosis continuum" described in several in vitro and in vivo models may corroborate this hypothesis. Indeed the entire process involved in neuronal apoptotic cell death may take several days while necrosis occurs after several hours only (Martin et al., 1998). Finally, the worse prognosis of patients with SIRPIDs during HT seems congruent with the inhibitory potential of TH towards seizures (Corry et al., 2008); therefore, SIRPIDs appearing despite TH may reflect a more severe damage and thus a worse outcome in analogy with seizures (Rossetti et al., 2012).

The ictal nature of SIRPIDs is still a matter of debate (Kaplan and Duckworth, 2011; Rossetti and Dunant, 2007; Zeiler et al., 2011), possibly because it is a group of different patterns: some are clearly ictal, showing electric seizures induced by stimulation (figure 1C), but other - may be classified as “periodic patterns” (figure 1B), whose ictal nature is very debatable. However, we found a strong association of SIRPIDs with a discontinuous/non-reactive EEG background in the early phase during TH, while, interestingly, later occurrence of SIRPIDs during NT was closely related to an epileptiform EEG background. This interesting observation supports the notion that periodic elements represent an “unstable interictal–ictal continuum” (Pohlmann-Eden et al., 1996).

Our group previously reported favorable outcome in some selected patients with post-anoxic myoclonic status epilepticus in the immediate post-rewarming normothermic phase who had preserved brainstem reflexes and cortical SSPE responses, and a reactive EEG background (Rossetti et al., 2009). Here, we observed that survival may be possible with acceptable functional recovery at 3 months in patients with SIRPIDs during NT: because in this subset of patients SIRPIDs were associated with “epileptiform” EEG pattern, it could be inferred that patients with SIRPIDs during normothermia and with the previously described clinical and electrophysiological profile may warrant intensive care and AED therapy for a limited time. Indeed, the only patient who survived with good functional outcome presented the profile described above, and was given levetiracetam therapy.

Our findings are partially limited by the relatively low numbers of patients with SIRPIDs and the exploratory nature of this study. Indeed, we were not able to address whether SIRPIDs had an independent prognostic value. Secondly, most patients had two punctual EEG and not continuous EEG monitoring. So it is possible that some SIRPIDs may have been missed due to their transient nature shown by our data. Also because of the limited EEG evaluation, we were not able to precise the duration of the SIRPIDs susceptibility. However, this analysis relies on a prospective EEG assessment and, to the best of our knowledge, represents the first attempt to answer to the relevant question of SIRPIDs’ relationship on prognosis in ICU patients.

In conclusion, SIRPIDs seems to reflect a severe brain damage. If appearing during therapeutic hypothermia after CA, this EEG pattern seems related to mortality, whereas survival can be hoped for some selected patients presenting SIRPIDs after rewarming. Our analysis expands current knowledge on electrophysiological prognostication in patients after cardiac arrest, but larger confirmatory studies assessing SIRPIDs in this setting are needed.

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Figure 1: examples of SIRPIDs in comatose patients after cardiac arrest on bipolar montage. Colored marks on the top represent the time of painful stimuli. **A)** Rhythmic pattern. **B)** Periodic pattern. **C)** Ictal pattern; this evolving periodic pattern lasted for one minute, then decreased in amplitude and frequency over 30 seconds, and the suppressed background reappeared.

Table 1: Demographics of 105 patients treated with TH

Age, mean (+/-SD)	61.1 (12.8)
Male gender, n (%)	78 (74.3)
Cardiological variables	
Cardiac arrest due to ventricular fibrillation, n (%)	70 (66.6)
Time to ROSC, mean (SD)	23.8 (20.2)
Outcome	
In-hospital mortality, n (%)	46 (43.8)
CPC 1–2 at 3 months, n (%)	48 (45.7)

ROSC: return of spontaneous circulation – CPC: Glasgow-Pittsburgh Cerebral Performance Categories

Table 2: SIRPIDs characteristics and comparison between patients with SIRPIDs and controls.

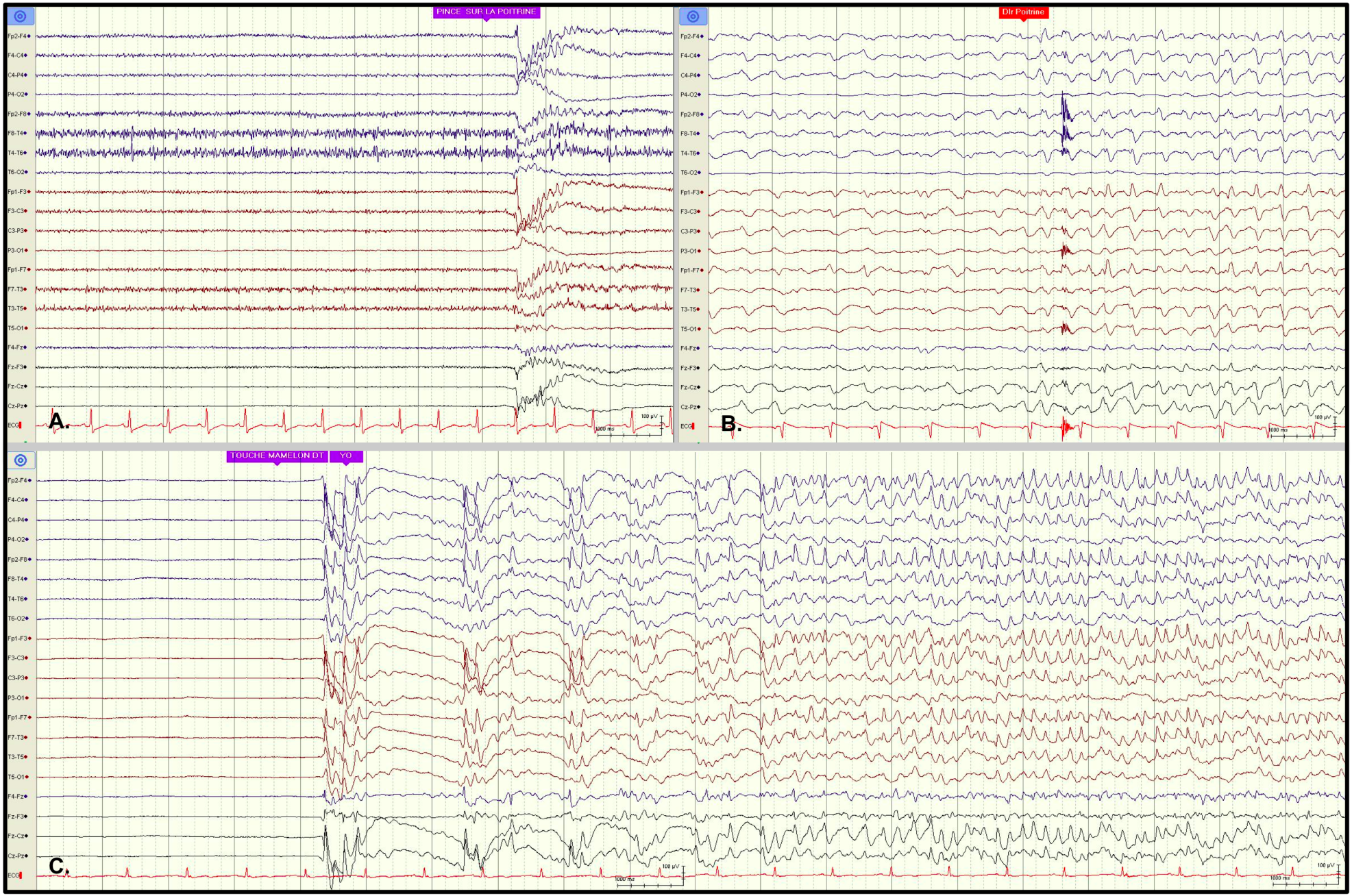
	SIRPIDS	Controls	p
n=105	14/105 (13.3)*	91/105 (86.7)*	
SIRPIDs characteristics			
Rhythmic, n (%)	3 (21.4)**		
Periodic, n (%)	8 (57.2)		
Ictal, n (%)	3 (21.4)		
Male gender, n (%)	10 (71.4)**	68 (74.7)**	0.241 (Fisher)
Age, mean (SD)	59.2 (12.2)	62.4 (12.9)	0.39 (t)
Cardiological variables			
Ventricular fibrillation cardiac arrest, n (%)	10 (71.4)	60 (65.9)	0.685 (Fisher)
Mean time to ROSC, in minutes (SD)	21.5 (9.48)	24.1 (21.3)	0.65 (t)
EEG background in hypothermia			
Non-reactive, n (%)	8(57.1)	31 (34.1)	0.096 (χ2)
Discontinue – non-epileptiform, n (%)	12(85.7)	41 (40.1)	**0.005** (χ2)
Epileptiform (Epileptiform transients, PEDs or electrical seizures), n (%)	3 (21.4)	12 (13.2)	0.226 (Fisher)
EEG background in normothermia			
Non-reactive, n (%)	2 (14.3)	15 (16.5)	0.835 (Fisher)
Discontinue – non-epileptiform, n (%)	2 (14.3)	15 (16.5)	0.835 (Fisher)
Epileptiform (Epileptiform transients, PEDs or electrical seizures), n (%)	11 (78.6)	14 (15.4)	**<0.001** (Fisher)
SSEP			
Tested, n (%)	12 (85.7)	86 (94.5)	
Bilateral absence of N20, n (%)	4/12 (33.4)	18/86 (20.1)	0.17 (Fisher)
NSE			
Available, n (%)	13 (92.9)	77 (84.6)	
Mean µg/l (SD)	47.5 (34)	44 (54.6)	0.82 (t)
>33 µg/l, n (%)	8/13 (61.5)	22/77 (28.6)	**0.02** (χ2)
>80 µg/l, n (%)	2/13 (15.4)	14/77 (18.2)	0.43 (Fisher)
Clinical signs			
Absence of one or more brainstem reflexes, n (%)	8 (57.1)	31 (34.4)	0.103 (χ2)
Absence of motor response, n (%)	10 (71.4)	37 (41.1)	0.14 (Fisher)
Presence of early myoclonus, n (%)	5 (35.7)	14 (15.6)	0.059 (χ2)

EEG: electroencephalogram – NSE: neuron-specific enolase – PEDs: periodic epileptiform discharges – ROSC: return of spontaneous circulation – SSEP: somatosensory evoked potentials – SIRPIDs: stimulus-induced rhythmic, periodic or ictal discharges. *Row percentages; ** Column percentages

Table 3: Frequency of SIRPIDs occurrence and relation with therapeutic hypothermia in patients with good versus poor functional outcome

	CPC 1-2 (good outcome)	**CPC 3-5 (poor functional outcome)**	**p**
n=105	48/105 (45.7)*	57/105 (54.3)*	
SIRPIDs			
In hypothermia, n (%)	0 (0)**	6 (10.5)**	**0.023** (Fisher)
In normothermia, n (%)	1 (2.1)	7(12.3)	**0.046** (Fisher)
In hypothermia or normothermia, n (%)	1 (2.1)	13 (22.8)	**<0.001** (Fisher)

CPC: Glasgow-Pittsburgh Cerebral Performance Categories
* Row percentages; ** Column percentages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