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The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia☆,☆☆

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ABSTRACT

Aim: The incidence and timing of electrographic seizures and epileptiform activity in comatose, adult, post-cardiac arrest syndrome (PCAS) patients treated with therapeutic hypothermia (TH) have not been extensively investigated. We hypothesized that onset most frequently occurs within the first 24 h post-arrest and is associated with poor neurologic outcome.

Methods: Single-center, retrospective analysis of a cohort of 38 comatose PCAS patients treated with TH and continuous-EEG-monitoring (cEEG), initiated as soon as possible after ICU admission. All raw cEEG waveform records were cleared of annotations and clinical information and classified by two fellowship-trained electroencephalographers.

Results: Twenty-three percent (9/38) of patients had electrographic seizures (median onset 19 h post-arrest); 5/9 (56%) had seizure-onset prior to rewarming; 7/9 (78%) had status epilepticus. Forty-five percent (17/38) had evidence of epileptiform activity (electrographic seizures or interictal epileptiform discharges), typically occurring during first 24 h post-arrest. Interictal epileptiform activity was highly associated with later detection of electrographic seizures (6/14, 43%, $p = 0.001$). Ninety-four percent (16/17) of patients with epileptiform activity had poor neurologic outcome or death at discharge (Cerebral Performance Category scale 3–5; $p = 0.002$) as did all (9/9) patients with electrographic seizures ($p = 0.034$).

Conclusions: Electrographic seizures and epileptiform activity are common cEEG findings in comatose, PCAS patients treated with TH. In this preliminary study, most seizures were status epilepticus, had onset prior to rewarming, evolved from prior interictal epileptiform activity, and were associated with short-term mortality and poor neurologic outcome. Larger, prospective studies are needed to further characterize seizure activity in comatose post-arrest patients.

1. Introduction

Cardiac arrest results in a high rate of mortality and neurologic morbidity. Historically, mortality for comatose, post-cardiac arrest syndrome (PCAS) patients has ranged from 30% to 69%[1] and a substantial proportion regaining consciousness have significant neurologic deficits.[1–3] Therapeutic hypothermia (TH) is the only intervention demonstrated to significantly improve neurologic morbidity and mortality in comatose ventricular fibrillation (VF) patients, and is now considered standard of care.[1,4]

Seizures are common after cardiac arrest. It remains unclear whether they contribute to poor neurologic outcomes or are simply a marker of an irreversibly damaged brain. Acute seizures occur in between 15% and 44% of post-arrest patients.[3] They often occur as status epilepticus, which is frequently nonconvulsive, difficult to control, and associated with higher rates of morbidity and mortality.[5] An American Academy of Neurology practice parameter examining pre-TH data reached the conclusion that the clinical diagnosis of myoclonus status epilepticus (MSE) during the first

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Table 1
Continuous electroencephalogram (cEEG) terminology [6,11].

Term	Definition	Comment
Electrographic seizure (ESz)	At least 10 s of rhythmic activity unrelated to the patient's typical background pattern, which begins abruptly and then evolves in frequency and/or anatomical localization. In cases of periodic discharges, evolution of frequency to >2 Hz in discrete epochs >10 s is classified as ESz	
Epileptiform discharge	A waveform that is spike- or sharp wave-shaped and easily discriminated from the background. This waveform type most often implies interictal discharges (i.e. between discrete seizures), but it also is used for waveforms that compose an electrographic seizure	Present in a patient who is at increased risk for a seizure
Periodic epileptiform discharge (PED)	The repeated and regular appearance of a monomorphic-appearing epileptiform discharge throughout the EEG recording with a recurrence of at least once per 2 s (0.5 Hz or more)	PEDs are often present in the region of a structural lesion or known brain injury. Patient considered at relatively high risk for seizures for several days after discover of PED
PLED	Periodic lateralized epileptiform discharge. A PED that is lateralized to one hemisphere	
BiPLED	Bilateral periodic lateralized epileptiform discharge. A PED occurring bilaterally simultaneously	
GPED	Generalized periodic epileptiform discharge. A PED occurring bilaterally and diffusely	
Epoch	A defined duration of EEG	
Burst suppression (BS)	An abnormal EEG pattern present throughout long durations (several minutes or more of recording) where >0.5-s-long bursts of cerebral activity are separated by periods of no clear cerebral activity where the EEG amplitude is <10 mV	BS is associated with diffuse brain injury and significant anesthetic administration and is associated with poor outcome in comatose post-arrest patients
Myoclonic status epilepticus (MSE)	A clinical, not an EEG, term, describing at least 5–30 min of spontaneous, continuous, generalized and repeated axial, limbs, and or face muscle jerks	When MSE occurs during first 24 h post-arrest in comatose patients, it has been associated with poor long-term neurologic outcome

24 h post-arrest is a predictor of poor outcome with a very low false positive rate.[6]

Recent studies examining electrographic seizures in PCAS patients treated with TH have yielded similar results.[7] However, cases of recovery after MSE have been documented.[8,9] Continuous-EEG (cEEG) monitoring has been recommended for comatose PCAS patients treated with TH.[10] However, cEEG-monitoring is resource-demanding and is not available at all institutions performing TH. Identification of the timing of seizures and other epileptiform patterns and associated outcomes might help optimize cEEG use. We hypothesized that a substantial number of comatose PCAS patients treated with TH have epileptiform cEEG patterns (i.e. seizure patterns or interictal epileptiform discharges) in the first 24 h post-arrest and that these cEEG findings are associated with poor outcomes. Our objectives were to determine the incidence and timing of epileptiform activity and electrographic seizures and demonstrate their association with poor short-term neurologic outcomes.

2. Methods

After obtaining IRB approval, we utilized a pre-existing cardiac arrest database to identify consecutive, comatose, adult (>18-years-old), PCAS patients treated with TH and monitored with cEEG or frequent routine EEGs, between 5/1/2005 and 1/1/2009 at the Hospital of the University of Pennsylvania (HUP) in Philadelphia, PA. Therapeutic hypothermia was induced with infusion of two liters of 4 °C normal saline solution via peripheral intravenous (IV) catheters, ice bags, and water-filled surface cooling wraps. Target temperature of 33 °C was achieved as soon as possible after return of spontaneous circulation (ROSC) and was maintained for 24 h, before the patients were actively rewarmed to 36 °C over 12–18 h. Paralysis with neuromuscular blocking agents was maintained throughout TH; adequate sedation was achieved with some combination of IV propofol, fentanyl, lorazepam, or midazolam to maintain a bispectral index monitor (BIS) reading of 40–60. The HUP PCAS protocol recommends early initiation of cEEG monitoring but an order for the cEEG must be placed by the treating physician. All patients were monitored by EEG upon arrival to the ICU with the goal of monitoring being initiated within 12 h post-arrest and continued until after return to normothermia. During monitoring, cEEG interpretations made by electroencephalographers were communicated to the treating medical teams at least twice a day. Treatment decisions based on cEEG findings including choice of anti-epileptic drugs and sedatives were at the sole discretion of the primary team. Most patients with electrographic seizures or frequent epileptiform activity had cEEG continued for additional days to help guide clinical management. The international 10–20 system electrode configuration displaying 16–18 channels of EEG data was utilized.

For this study, all raw EEG waveform records were cleared of annotations and clinical information and prospectively, systematically, and independently reviewed by two neurophysiology fellowship-trained electroencephalographers (RM and SS), who were blinded to clinical course and neurologic outcomes. In cases of discrepancies of seizure, epileptiform, or background classification, a consensus decision was made by the two reviewers. Status epilepticus and electrographic seizures were defined by existing criteria[11]: status epilepticus was defined as seizure activity occurring for >30 min; electrographic seizures were defined as epileptiform activity demonstrating frequency, amplitude, and/or spatial evolution occurring in periods of >10 s. Amplitude evolution alone was not sufficient for a seizure definition. Periodic discharge consistently >2 Hz in epochs >10 s were counted as seizure activity. Onset of epileptiform activity and electrographic seizure activity was documented. EEG reactivity was not noted because of lack of reliable stimulation records (Table 1 provides definitions of EEG terms).

Medications (anesthetics, antiepileptic drugs [AEDs], meperidine, IV antibiotics and vasopressors) and their administration

Table 2
Characteristics of EEG cohort.

Characteristic	Value
Age (y)	58 (45–65)
Female	18 (47%)
Initial arrest PEA or asystole rhythm	18/32[a] (56%)
Initial arrest VF or VT rhythm	14/32[a] (44%)
Time to ROSC (min)	20 (10–30; range 3–80 min; 25 subjects)
Interval from arrest to goal hypothermia (h)	6.8 (3.9–12.1)
EEG monitoring duration (h)	47.5 (38–67.6; range 0.7–329)
Interval from arrest to EEG monitoring initiation (h)	14.8 (7.5–21.3)
Patients with good neurologic outcome at discharge (CPC 1–2)	12 (32%)
Patients with awareness at discharge (CPC 1–3)	15 (39%)
Mortality in-hospital	20 (53%)
Withdrawal of ventilator support	12 (32%)
Discharge to home or acute care rehabilitation facility	8 (21%)
Discharge to long-term care facility or hospice	10 (26%)
Hospital length of stay (d)	10 (5–19)
Interval from arrest to withdrawal of ventilator support (d)	7 (3–14)

Values from 38 patients are given unless otherwise specified. Medians with interquartile ranges or percentages and proportions are documented.
[a] 6 patients were missing these data.

times in the first three days post-arrest were abstracted from the electronic medical record (EMR). Care level changes to "do not resuscitate/intubate" (including withdrawal of ventilator support), demographic data (gender, age), and cardiopulmonary resuscitation (CPR) details (initial arrest rhythm, bystander CPR, time to ROSC), electrographic seizure clinical correlates, cooling and rewarming times, and discharge outcomes were abstracted from the EMR. Cerebral Performance Category (CPC) was used to categorize outcomes, dichotomized as good short-term neurologic outcome (CPC 1 or 2) vs. poor (CPC 3–5). Secondary analysis included comparing patients with CPC 1–3 (recovery of awareness at discharge) vs. CPC 4–5 (vegetative state, brain death, or dead).

Data were analyzed using STATA v. 10.0 (STATA Corp, LP, College Station, TX) and described using frequencies, medians, and the interquartile ranges (IQR). The kappa statistic was calculated according to a non-weighted method, also using STATA v. 10.0. Groups were compared using Fisher's exact test or the Wilcoxon rank-sum test. Hypothesis tests were two-sided and used a type I error rate of 0.05. For key results, 95% confidence intervals were constructed.

3. Results

Between 5/1/2005 and 1//1/2009, 41 consecutive comatose PCAS patients were treated with TH at our hospital. Thirty-six patients had cEEG monitoring and two patients had frequent routine EEGs. In three patients only one routine EEG was obtained and they were excluded from further analysis. Therefore, a cohort of 38 patients was included in the analysis.

3.1. Demographics, EEG-recording, and outcomes

Clinical and treatment characteristics of the cohort are presented in Table 2. The average age of the patients was 58 years (IQR 45–65), 47% were female, and 44% had VF as their initial rhythm.

Electrographic seizures occurred in 9/38 patients (23%; 95% CI 11–40%). The kappa coefficient for agreement between the two electroencephalographers on presence of electrographic seizure activity was 0.85 ($p < 0.0001$), which connotes very good level of agreement. Any epileptiform discharges (interictal, ictal or both) were present in 17/38 (45%; 95% CI, 28–61%). Median time from arrest to onset of any epileptiform activity was 16.9 h (IQR, 10.0–21.6 h). Median time from arrest to onset of electrographic seizures was 19.0 h (IQR, 16.7–47 h). The epileptiform discharges consisted of periodic lateralized epileptiform discharges (PLEDs) (4/38; 11%), generalized periodic epileptiform discharges (GPEDs) (8/38; 21%), and isolated non-periodic spikes or sharp waves (8/38; 21%). Samples of EEG labeled as electrographic seizure are showed in Fig. 1a and b.

Median duration of cEEG activity interpreted as electrographic seizure activity was 12.3 h (IQR 2.5–22 h). The majority of seizure patients (5/9; 56%) had electrographic seizure onset in the maintenance phase of TH. Seven of nine patients (78%) with electrographic seizures had an eventual clear clinical correlate documented in the medical record. (Table 3 describes EEG features and clinical characteristics of patients with electrographic seizures.)

Table 4A shows associations between presence or absence of electrographic seizures and clinical, treatment, and outcome characteristics. Patients with electrographic seizures had increased EEG recording duration, were more likely to have interictal epileptiform discharges, and were more likely to have received conventional AEDs and receive greater number of anesthetic and conventional AEDs compared to those without seizures. Epileptiform activity in the first hour of EEG was detected in 89% (8/9) of patients with electrographic seizures (interictal [5/9; 56%]; ictal [3/9; 33%]). This early epileptiform activity consisted of easily identifiable periodic discharges in 78% (7/9) of the patients. The one patient with later detection of epileptiform activity and seizures had cEEG started 5 h after arrest vs. a median of 15 h post-arrest (IQR 10–24) in the remaining 8 patients.

None of the patients with electrographic seizures had good neurologic outcome. However, one regained awareness, demonstrating that early electrographic seizures are not incompatible with recovery of consciousness (Table 3). Patients with electrographic seizures were more likely to have withdrawal of ventilator support but the time from cardiac arrest to this change in care did not differ between those with and without seizures. At that point in the clinical course all but two of the patients who survived with good neurologic outcome were extubated, awake, and alert. Trends in the associations between electrographic seizures and either in-hospital mortality ($p = 0.13$) or remaining comatose ($p = 0.16$) were not statistically significant.

Table 4B displays associations between the presence of any epileptiform activity (i.e. electrographic seizures or interictal epileptiform discharges) and clinical, treatment, and outcome characteristics. In general, the presence of any epileptiform activity had similar associations with clinical variables as did electrographic seizures. The occurrence of electrographic seizures or epileptiform activity was associated with poor neurologic outcome in this cohort of comatose PCAS patients treated with TH (sensitivity, 61%, specificity, 92%).

4. Discussion

In a cohort of 38 consecutive comatose PCAS patients treated with TH and monitored with cEEG or frequent routine EEGs, we found that interictal and ictal epileptiform activity are fairly common (17/38 [45%] and 9/38 [23%] respectively). Nearly all of the epileptiform activity had onset detected within 24 h post-arrest. Interictal epileptiform discharges are associated with evolution to electrographic seizures, and the majority of the electrographic seizures have onsets resembling generalized status epilepticus. Many of the patients with electrographic seizures initially do not have a clinical correlate noted; eventually most, but not all, patients manifest clinical correlates with MSE being the most common. As was noted in comatose PCAS patients in the pre-TH era,

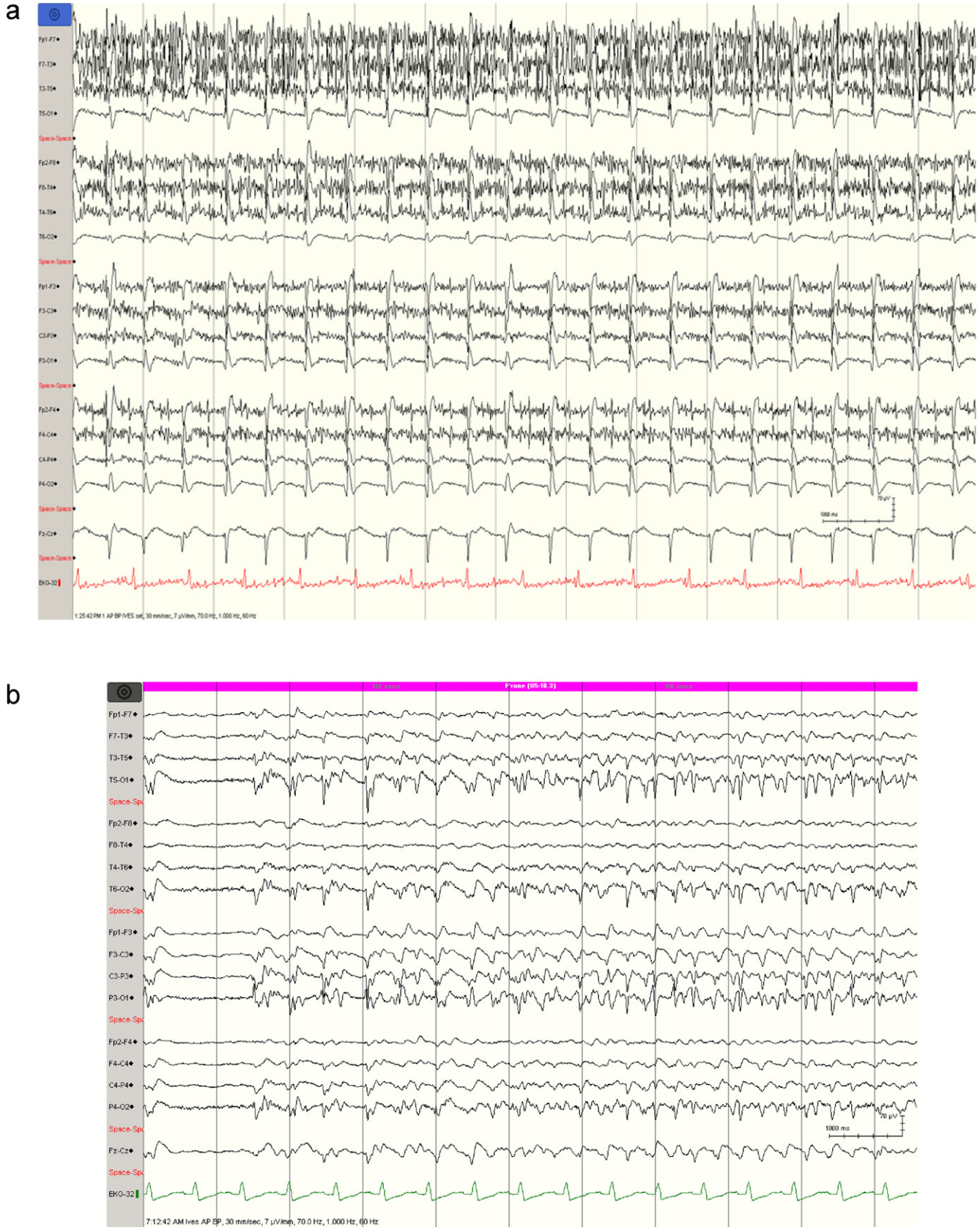

Fig. 1. (a) Generalized epileptiform activity with myoclonus artifact labeled as seizure. Varying frequency (1-3 Hz) GPEDs appearing during the course of prolonged epileptiform activity labeled as seizure. The patient had torso and face myoclonus noted. (b) Left posterior quadrant discrete electrographic seizure activity, occurring repetitively, lasting for 30–60 s at a time, over a 24 h period.

Table 3
EEG and clinical details of patients with electrographic seizures.

Age (y)	Time from CA to EEG monitoring[a]	Time from CA to onset of ED	Time from CA to ESz onset	TH phase @ ESz onset	cEEG background[*]	ESz morphology	ESz clinical correlation	Status epilepticus	AEDs	Duration of ESz and/or continuous ED[a]	Did ED Continue @ EEG termination	LOS #	CPC	Destination @ discharge
51	12.3	12.3	13.7	M	BS w/high amplitude spikes	BiPLEDS evolving >6 Hz w/associated semi-rhythmic fast activity	MSE (diffuse jerks)	Yes	PROP, MDZ, LEV, PHT	44	Yes; BiPLEDs @ 1.8–3 Hz	7	5	Death
62	23.7	23.7	32.7	R	BS w/GPEDs	GPEDs increasing to 2 Hz	Left arm shaking and eye-blinking	Yes	PROP, MDZ, LZP, PHT	3	Yes; 1–2 Hz intermittent GPEDs	19	3	Nursing home
52	10	10	19	M	<10 uV delta and rare L > R occipital spikes	Discrete episodes of posterior spikes that evolve in frequency to 5–6 Hz and generalize	Chest wall and torso MSE	Yes	MDZ; LZP; LEV; PHT	20	No	18#	5	Death
51	9.5	9.5	47.5	P-R	BS w/GPEDs of polyspikes	GPEDs increase up to 5 Hz in brief epochs	MSE	Yes	LZP	17	Yes; GPEDs	4#	5	Death
59	17.8	17.8	17.8	M	BS w/GPEDs	GPEDs increasing in frequency >2 Hz in brief epochs	None	Yes	LZP; PHT; PHB	7.5	Yes; GPEDS	10#	5	Death
42	47	47	47	R	GPEDs on moderate voltage theta background	GPEDs increase >3 Hz in frequency	Possible (R leg stiffening & shaking; biting ETT)	Yes	LZP; LEV; PHT	2	Yes; GPEDs	7	4	Hospice
69	24.5	24.5	111.4	P-R	Low-moderate voltage theta-delta; PLEDs	Posterior predominant bilateral evolving in frequency and space; sharp waves in discrete epochs	Eyebrows raising, head deviation, body shaking	No	LZP; PHT	0.2	No	15#	5	Death
64	4.8	13.7	16.7	M	BS w/occasional bifrontal spike-wave	Spike-wave GPEDs continuous and evolving to >2 Hz	None	Yes	PHT	24	Yes; GPEDs	3#	5	Death
63	10	10	10	M	BS w/GPEDs”	BiPLEDs evolving to >4 Hz	GPEDs later correlate w/MSE (diffuse jerks)	No	PROP; PHT	N/A	GPEDs absent on routine EEG done 3 d post-arrest	25#	5	Death

[a] Time is in hours; #indicates care withdrawn in hospital. I, induction; M, maintenance; R, rewarming; P-R, post-rewarming; CA, cardiac arrest; ESz, electrographic seizure; ED, epileptiform discharges; ETT, endotracheal tube; AED, antiepileptic medication; LZP, lorazepam; MDZ, midazolam; PROP, propofol; PHT, phenytoin; LEV, levetiracetam; PHB, phenobarbital; GPED, generalized periodic epileptiform discharge; Bck, EEG background; biPLED, bilateral periodic lateralizing epileptiform discharge; MSE, myoclonus status epilepticus; BS, Burst suppression; LOS, Length of stay, in days; CPC, cerebral performance category.

[*] Denotes intermittent routine EEG performed not cEEG.

Table 4A
Clinical and electrographic associations with electrographic seizures.

Variable	Patients with electrographic seizures ($n=9$)	Patients without electrographic seizures ($n=29$)	p-value
Age (y)	59 (51–63)	57.5 (43.5–67)	NS
PEA or asystole arrest rhythm	4/8 (50%)	14/24 (58%)	NS
Interval from arrest to hypothermia temperature goal achievement (h)	5.2 (4–13)	7.6 (3.4–12)	NS
Interval from arrest to EEG monitoring initiation (h)	12.3 (10–23.7)	14.8 (7.2–20.8)	NS
EEG monitoring duration (h)	**84.5 (49.5–205)**	**44.5 (34.8–62.5)**	**0.008**
Interictal epileptiform discharges[a]	**6/9 (67%)**	**8/29 (28%)**	**0.01**
Epileptiform activity in first hour of EEG	8/9 (89%)	6/29 (21%)	0.0005
Interval from arrest to epileptiform discharge onset (h)	13.7 (10–22.7)	18.8 (4.8–21.3; 7 patients)	NS
Number of acute AEDs received per patient	3 (1–4)	1 (1–2)	0.001
Time from arrest to delivery of first anesthetic AED (h)	2.2 (1.6–16)	6.6 (1.3–15.9)	NS
Received conventional AEDs in first 3 d after arrest	**8/9 (89%)**	**4/25 (16%)**	**0.003**
Good neurologic outcome at discharge (CPC 1–2)	**0/9 (0%)**	**12/29 (41%)**	**0.034**
Awareness at discharge (CPC 1–3)	1/9 (11%)	14/29 (48%)	0.06
Mortality in-hospital	7/9 (78%)	13/29 (45%)	0.131
Discharge to home or acute care rehabilitation facility	0/9 (0%)	8/29 (28%)	0.16
Length of hospital stay after arrest (d)	10 (7–18)	10 (5–19)	NS
Withdrawal of ventilator support	**6/9 (67%)**	**6/29 (21%)**	**0.02**
Interval from arrest to withdrawal of ventilator support (d)	11 (3.9–17.7)	4 (1.9–9.6)	NS

Data are reported as medians with interquartile ranges or percentages with proportions. NS represents p-values > 0.20. Statistically significant values are presented in bold-faced type.

[a] Interictal epileptiform discharge were seen before development of possible electrographic seizures in 6/9; 67% of patients the other 3 patients had electrographic seizures at onset of EEG hookup.

these electrographic seizures and associated clinical phenomena are very refractory to treatment and highly associated with poor short-term neurologic outcome despite increased EEG monitoring duration, administration of multiple anesthetic and conventional antiepileptic drugs, and extended periods of aggressive clinical care.[5]

Our study's incidence of electrographic seizures and status epilepticus is similar to that reported (26–38%) in the few systematic studies of cEEG in adult PCAS patients treated with TH.[9,12–14] Electrographic seizures were reported in 41% of patients in a pediatric series of PCAS patients with similar etiology and treatment conditions.[7] Differences between seizure incidences in these studies are likely due to injury severity differences, definitions of electrographic seizure used, EEG-monitoring timing, EEG montages, and random error. In our study, in addition to the 9 patients identified as having electrographic seizures, 8 more had EEGs with periods of continuous, potentially epileptiform activity (i.e. rhythmic delta waves, low-frequency GPEDs, blunted triphasic morphology waveforms distinguishable from spikes and sharp waves). However, none of these had spatial or frequency evolution, stereotypic runs, or high enough frequency (i.e. >2 Hz) to be classified as electrographic seizures by the *a priori* definitions used in this study.

Only one of these 8 "non-ictal" patients had a good short-term neurologic outcome. This patient had intermittently appearing focal sharp waves within 24 h post-arrest that transformed to intermittently appearing PLEDs. These data suggest that there may be a spectrum of epileptiform and other abnormal waveform features correlating with short-term neurologic outcome.

Early epileptiform activity can assist in prognostication in the first 24–36 h post-arrest in comatose PCAS patients treated with TH. The presence of any frequent or continuous epileptiform activity serves as an indicator of potential poor neurologic outcome. However, this indicator is neither highly sensitive nor sufficiently specific and does not capture all patients who go on to have a poor neurologic outcome (sensitivity 61%; specificity 92%). Forty-three percent (9/21) of patients who had no epileptiform activity died during their post-arrest hospitalization and only 6% (1/17) of patients with early epileptiform activity had a good neurologic recovery. Therefore, early epileptiform activity is neither sufficient

Table 4B
Clinical and electrographic associations with epileptiform discharges (interictal and seizure activity).

Characteristic	Patients with any epileptiform activity ($n=17$)	Patients without any epileptiform activity ($n=21$)	p-value
Age (y)	54 (50–62)	60 (43.5–69.5)	NS
PEA or asystole arrest rhythm	6/12 (50%)	12/20 (60%)	NS
Interval from arrest to hypothermia temperature goal achievement (h)	6 (3.9–12.6)	7.2 (4.2–11.2)	NS
Interval from arrest to EEG monitoring initiation (h)	16 (9.5–21)	13.5 (7.2–22.5)	NS
EEG monitoring duration (h)	**60.1 (42–95.5)**	**43.6 (28.8–61.5)**	**0.03**
Length of stay (median days)	10 (5–18)	10 (5–21)	NS
Withdrawal of ventilator support	7/17 (41%)	5/21 (24%)	NS
Arrest to withdrawal of ventilator support(d)	9.3 (1.2–17.7)	4.5 (3.4–9.6)	NS
Good neurologic outcome at discharge (CPC 1–2)	**1/17 (6%)**	**11/21 (52%)**	**0.002**
Awareness at discharge (CPC 1–3)	**3/17 (18%)**	**12/21 (52%)**	**0.02**
Mortality in-hospital	12/17 (70%)	8/21 (38%)	0.059
Discharge to home or acute care rehabilitation facility	1/17 (6%)	7/21 (33%)	0.053
Received conventional AEDs in first 3 days	**10/16 (63%)**	**2/18 (11%)**	**0.003**
Number of conventional and anesthetic AEDs received in first 3 days per patient	3 (1–4)	1 (1–2)	0.001

Statistically significant values are presented in bold-faced type.

to determine futility of care nor when absent predictive of good outcomes. Rather, it is one of many data points that should be examined when considering a particular PCAS patient's prognosis.

Additionally, this study refutes a common belief that seizures do not occur until the rewarming phase of TH. Animal and limited human data showing that hypothermia can abort status epilepticus may have fostered this belief.[15] Recently three studies[13,14,16] presented data suggesting that seizures may occur while the patient is in the maintenance phase of TH. Our study supports the finding that the majority of the patients had their first electrographic seizure detected while in the maintenance phase of TH (at target temperature, 33 °C).

Our study has a number of limitations. Given that three of the five patients with seizures detected early in their monitoring had their initial seizure activity within 90 min of onset of EEG monitoring, it is possible that seizures may have begun before TH initiation or during the induction phase of TH. Further, we excluded three patients who had only one routine EEG during their treatment. None of these EEGs demonstrated ictal or interictal epileptiform discharges. It is possible that these patients had seizure activity that was not captured on this limited EEG.

The median time from ROSC to cEEG initiation (15 h) and duration of cEEG monitoring (48 h) may be different from those at other institutions and limits the generalizability of our findings. Further, in our study, we used a conservative definition of electrographic seizures and may have underestimated their true incidence. There is a growing understanding that the definition of status epilepticus should not be limited to the classic definition of >30 min of seizure activity. For example, Rossetti[8,9] defined status epilepticus as seizure activity lasting for >5 min. Applying this more liberal definition of status epilepticus to our cohort, one patient we classified as having interictal epileptiform discharges would have been reclassified as having status epilepticus. This person had a bad neurologic outcome. The cEEG appearance several days after arrest for all the patients is unknown. In addition, for a significant period of time (mean, 8 h) our patients were hypothermic without cEEG monitoring. We do not know if they had seizures during that period of time. The fact that 89% of those who had seizures had them detected within the first hour of the cEEG, raises the possibility that they may have been seizing for hours before seizure detection. Alternatively, they may have had seizures for a period of time and these seizures stopped before the cEEG was initiated, which subsequently detected either interictal epileptiform activity or no abnormalities at all, placing them in the "non-epileptiform" subgroup. Thus, there is potential for significant overlap between the subgroups. The relatively high proportion of patients in our cohort presenting with PEA and asystole as their initial arrest rhythms may limit generalizability of seizure timing findings because patients with an initial rhythm of VF may have lower seizure incidence or may have good recovery after seizures.

Further, the true incidence of seizures in the patient population has not been delineated since the routine clinical use of drugs with anti-epileptic properties may mask seizure activity on cEEG in some patients; no post-arrest, seizure management algorithm was utilized during the study period; and the researchers had no input into medication choice. However, this would lead us to underestimate the true incidence of seizures. Finally, ominous cEEG findings can be a self-fulfilling prophecy – withdrawal of care was more frequent in the patients with electrographic seizures, the presence of which was available daily to the treating team. Reduction in ICU care and withdrawal of ventilator support did not occur until a median of 11 days after cardiac arrest in this group, which did not differ significantly from the group of patients without seizures. However, these are limited measures of whether a self-fulfilling prophesy occurred and that possibility exists.

Whether continuous epileptiform patterns and electrographic seizures have an impact upon further neuronal death or add to systemic disturbances (i.e., increased lactate, increased cerebral edema, or worsened cardiac dysfunction) is not known. Despite the sequential addition of antiepileptic agents including lorazepam, propofol, phenytoin, and levetiracetam, these patterns were associated with poor neurologic outcome. In Rossetti's study[8] of post-arrest TH patients, only six percent (6/107) of PCAS patients with status epilepticus survived to discharge, 50% (3/6) of whom had good neurologic function (CPC 1–2) at six months follow up. In our study, there were two survivors of status epilepticus: one remained vegetative; the other regained awareness but with severe neurologic disability (CPC 3).

5. Conclusion

In this preliminary study, electrographic seizures and epileptiform activity were common cEEG findings in comatose, PCAS patients treated with TH. Onset of these patterns was, in general, during the first 24–48 h post-arrest for patients monitored with cEEG for 2–3 days. Most seizures had onset prior to rewarming, were associated with prior interictal epileptiform activity, manifest as status epilepticus, and were associated with short-term mortality and poor neurologic outcome despite multiple antiepileptic drugs. Further, large-scale, prospective studies reporting the timing and incidence of seizures and epileptiform activity and their ability to predict neurologic outcomes are needed to confirm our findings as well as those of recently published studies (13,14,16) and add precision to these estimates. A multimodal assessment combining neurologic examination, cEEG findings, and somatosensory evoked potentials, as in Rossetti's prospective study,[9] may help determine if there are indicators predictive of who may awake and recover from post-anoxic status epilepticus and prevent premature withdrawal of care based upon a single predictive modality. If these patients can be further sub-grouped early in hospitalization, this may lead to more reliable prognostication for patients who cannot be reliably assessed clinically because of paralytic agents, lingering anesthetic effects, and hypothermia depressant effects. This would also allow for more focused triaging of two categories of patients: (1) those with a higher probability for recovery suggesting potential efficacy of an extended period of antiepileptic treatment, supportive care, and prognostic assessment; and, (2) those with an extremely low probability for recovery, which could help clinicians and families choose less aggressive care.

Conflict of interest statement

None.

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