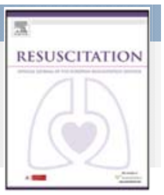

Clinical Paper

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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Introduction

- Cardiac arrest results in a high rate of mortality and neurologic morbidity
- post-cardiac arrest syndrome (PCAS) patients
  - mortality - 30% to 69%
  - significant neurologic deficits

- Therapeutic hypothermia (TH)
  - significantly improve neurologic morbidity and mortality in comatose ventricular fibrillation (VF) patients
  - standard of care

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seizure

- **Seizures** are common after cardiac arrest
  - 15% and 44% of post-arrest patients.
  - poor neurologic outcomes?
  - an irreversibly damaged brain?
  - often occur as status epilepticus
    - nonconvulsive
    - difficult to control
    - associated with higher rates of morbidity and mortality

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Pre-TH

- An American Academy of Neurology practice parameter
- Myoclonus status epilepticus (MSE)

  \- predictor of poor outcome (with a very low false positive rate)

- Continuous- EEG (cEEG) monitoring
  - recommended for comatose PCAS patients treated with TH
  - Resource demanding

objectives

- Determine the incidence and timing of epileptiform activity and electrographic seizures

→help optimize cEEG use

- association with poor short-term neurologic outcomes

Methods

- Patients
  - comatose, adult (>18-yearsold), PCAS treated with TH
  - monitored by cEEG or frequent routine EEGs
  - Date: 5/1/2005 and 1/1/2009
  - At: Hospital of the University of Pennsylvania (HUP) in Philadelphia, PA

Therapeutic hypothermia

- After ROSC
  - infusion of 2 L. of 4 ◦C N/S by IV
  - ice bags
  - water-filled surface cooling wraps
- Target temperature: 33 ◦C
- Maintain: 24 h
- Given during TH: neuromuscular blocking agents and sedation

cEEG

- within 12h post arrest
- Until: return to normothermia once abnormal→ additional days
- interpretations by 2 electroencephalographers (blinded)

- status epilepticus
  - seizure activity occurring for >30 min
- electrographic seizures
  - epileptiform activity demonstrating frequency, amplitude, and/or spatial evolution occurring in periods of >10 s

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

Results

- 41 consecutive comatose PCAS patients were treated with TH between 5/1/2005 and 1/1/2009
- 36 pt - cEEG monitoring
  2 pt - frequent routine EEGs
- Excluded: 3 pt- only one routine EEG

➔a cohort of 38 patients was included!

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)

- Electrographic seizures : 9/38 patients (23%)
- epileptiform discharges (interictal, ictal or both) :17/38 (45%)
- arrest to onset of electrographic seizures :19.0 h
- arrest to onset of any epileptiform discharge : 16.9
- 5 pt of seizure patients (5/9; 56%) onset in the maintenance phase of TH.

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[c]	ESz morphology	ESz clinical correlation	Status epilepticus	AEDs	Dura and/ cont
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
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
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
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
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
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
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
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
63	10	10	10	M	BS w/GPEDs[e]	BiPLEDs evolving to >4 Hz	GPEDs later correlate w/MSE (diffuse jerks)	No	PROP; PHT	N/A

- 9 Pt with electrographic seizures (increased EEG recording duration) have more
  - interictal epileptiform discharges
  - conventional AEDs
  - greater number of anesthetic and conventional AEDs

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

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

electrographic seizures

- Epileptiform activity in the first hour of EEG
  - 89% (8/9) of patients with interictal [5/9; 56%]; ictal [3/9; 33%]).
- None of the patients with electrographic seizures had good neurologic outcome.

- Patients with electrographic seizures were more likely to have withdrawal of ventilator support
- the time from cardiac arrest to this change in care did not differ
- Electrographic seizures and either inhospital mortality ($p = 0.13$) or remaining comatose ($p = 0.16$) were not statistically significant

Discussion

- Interictal and ictal epileptiform activity are fairly common
  - within 24 h post-arrest.
  - ➔ electrographic seizures➔generalized status epilepticus.
- Many of the patients with electrographic seizures initially do not have a clinical correlate noted
  - most patients manifest clinical correlates with MSE being the most common.

incidence

- similar to the few systematic studies : 26–38%
- Differences between seizure incidences in these studies are due to
  - injury severity differences
  - definitions of electrographic seizure
  - EEG-monitoring timing
  - EEG montages
  - random error

indicator of poor neurologic outcome?

- Early **epileptiform activity** can assist in prognostication in the first 24–36 h post-arrest in comatose PCAS patients treated with TH.
- neither highly sensitive nor sufficiently specific! (sensitivity 61%; specificity 92%)
- **it is one of many data points** that should be examined when considering a PCAS patient's prognosis.

maintenance phase of TH!

- a common belief
  - seizures occur at the rewarming phase of TH
- Our study
  - the majority of the pts had their first electrographic seizure detected while in the maintenance phase of TH (target temperature, 33 ◦C).

limitations

- seizures may began before TH initiation or during the induction phase of TH
- seizures may began after TH but without cEEG monitoring
- The median time from ROSC to cEEG initiation (15 h) and duration of cEEG monitoring (48 h) may be different
- conservative definition of electrographic seizures and may have underestimated their true incidence

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- PEA and asystole as initial arrest rhythms may limit generalizability
- Lower the true incidence: anti-epileptic drug mask seizure

Characteristic	Value
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Conclusion

- electrographic seizures & epileptiform activity - common cEEG findings in PCAS patients treated with TH
- Onset : first 24–48 h post-arrest
- Most seizures had onset prior to rewarming
  - prior interictal epileptiform activity, manifest as status epilepticus,
  - poor neurologic outcome
- the timing and incidence of seizures and epileptiform activity and their ability to predict neurologic outcomes are needed but not the only indicator

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- A multimodal assessment combining NE, cEEG findings, and somatosensory evoked potentials
  - predictive of who may awake and recover from post-anoxic status epilepticus
  - prevent premature withdrawal of care based upon a single predictive modality.
- more focused triaging of two categories of patients:

(1) higher probability for recovery

(2) extremely low probability for recovery

THANK YOU ~