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Clinical Paper

Malignant EEG patterns in cardiac arrest patients treated with targeted temperature management who survive to hospital discharge☆

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ABSTRACT

Background and purpose: Cardiac arrest patients treated with targeted temperature management (TTM) have improved neurological outcomes, however mortality remains high. EEG monitoring improves detection of malignant EEG patterns (MEPs), however their prevalence in patients surviving to hospital discharge is unknown.
Design/methods: We examined consecutive cardiac arrest subjects who received TTM and continuous EEG monitoring at one academic center. Only subjects surviving to hospital discharge were included in the analysis. MEPs were defined as seizures, status epilepticus, myoclonic status epilepticus, or generalized periodic discharges. Subjects with suppression-burst (SB) without concomitant MEPs were categorized as having a "pure" SB pattern. Demographic, survival, hospital discharge disposition, and neurological function data were recorded retrospectively. Outcomes were assessed using the Glasgow-Pittsburgh Cerebral Performance Category (CPC). A CPC score of 1–2 was considered "good" neurological function, and a CPC of 3–4 "poor".
Results: Of 364 admissions due to cardiac arrest screened, 120 (29.9%) survived to hospital discharge and met inclusion criteria. MEPs and pure SB were observed in 19 (15.8%) and 22 (18.3%) survivors respectively. Two subjects with MEP and eight subjects with pure SB had good neurological function at discharge, however all SB cases were confounded by the use of anesthetic agents. Presence of MEPs was not an independent predictor of poor neurological function ($p = 0.1$).
Conclusions: MEPs are common among cardiac arrest patients treated with induced hypothermia who survive to hospital discharge. Poor neurological function at discharge was not associated with MEPs. Prospective studies assessing the role of EEG monitoring in cardiac arrest prognostication are warranted.

1. Introduction

Mild induced hypothermia (IH) became a major therapy for out-of-hospital cardiac arrest (OHCA) attributable to ventricular fibrillation after 2002, and its application expanded to non-shockable rhythms.[1,2] Recent data demonstrate similar outcomes between IH and targeted temperature management (TTM) of 36 °C in the out of hospital VF/VT population.[3] Despite the increased survival rates and improved long-term neurological function shown in randomized controlled trials with TTM, identifying which comatose patients will have a favorable outcome remains challenging.[1,2,4,5]

Malignant EEG patterns (MEPs) such as seizures, status epilepticus (SE), and suppression-burst (SB) are considered predictors of poor neurological function in cardiac arrest.[6–10] For this reason, the American Heart Association guidelines and the American Academy of Neurology practice parameters for prognostication in cardiac arrest consider EEG monitoring a helpful tool for cardiac arrest prognostication.[2,7,10] However, the prognostic value of EEG monitoring when TTM is utilized has been challenged more recently, as

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reports of good neurological function despite the presence of MEP have emerged.[11]

The aim of this study was to identify the incidence of MEPs, SB, and other relevant EEG features in cardiac arrest patients treated with TTM who survive to hospital discharge.

2. Methods

2.1. Subjects

All consecutive adult subjects (≥18 years) admitted to a single tertiary care center after being successfully resuscitated from either in-hospital or out-of-hospital cardiac arrest were prospectively enrolled in a quality improvement database from 08/28/2009 to 06/04/2013. Only subjects undergoing IH for cardiac arrest who survived to hospital discharge and had more than 10 h of continuous EEG monitoring were included in this study.

2.2. Hypothermia protocol

In our institution, subjects that remain comatose after return of spontaneous circulation following cardiac arrest will be treated with IH according to our local protocol.[5] The study period occurred before the results of the TTM trial, thus all patients received IH. IH is achieved by intravenous infusion of rapid cold saline (4 °C) infusion and maintained by surface cooling (Arctic Sun, Temperature Management System, CR Bard, Louisville, CO) to a goal temperature of 33 °C for 24 h. Sedation is performed with propofol (25–60 mcg kg^{-1} h^{-1}), and titrated to suppress shivering. In cases where propofol infusion is insufficient, fentanyl is added (25–100 mcg h^{-1}). In subjects who do not tolerate propofol because of hypotension, midazolam (0.1 mg kg^{-1} h^{-1}) is utilized. Neuromuscular paralysis is employed during induction of hypothermia and is rarely continued during maintenance or rewarming phases. Gradual rewarming is performed at a target rate of 0.25 °C h^{-1} to normothermia. This retrospective analysis of clinical and EEG data was part of a quality improvement project, and was deemed an exempt activity by the University of Pittsburgh Institutional Review Board.

2.3. EEG monitoring, analysis, and antiepileptic therapy protocol

At our institution, comatose subjects receive EEG monitoring during IH for at least 48 h (until completion of rewarming), and EEG may continue for longer duration based on the presence of worrisome EEG patterns. Digital EEG was recorded using 22 electrodes according to a 10–20 system. Video EEG monitoring was available in limited cases. All EEG records were interpreted during patient care by board certified electroencephalographers.

EEG reports were analyzed and classified under three EEG categories depending on the presence of MEPs, pure SB, or non-malignant EEG patterns. The following EEG patterns were identified as MEPs (Table 1): seizures, generalized periodic discharges (GPD), status epilepticus (SE), myoclonic status epilepticus (MSE). The EEG classification definitions are based on the ACNS standardized critical care EEG terminology to defining equivocal periodic, rhythmic, quasi-periodic, quasi-rhythmic and fluctuating patterns seen in encephalopathy patients.[12] The status epilepticus definition was based on Guidelines for the evaluation and management of status epilepticus.[13]

EEG records with SB in the absence of MEPs were categorized as having a "pure" SB pattern. Suppression-burst was defined as a discontinuous EEG background with the presence of alternating periods of bursts of cerebral activity with periods of suppression of <10 μV. For SB pattern cases in which SB developed during infusion of an anesthetic agent such as propofol or midazolam, SB was categorized as "likely confounded by medication-effect". Remaining EEG records were categorized as "non-malignant". Records with epileptiform discharges, focal lateralized periodic discharges (LPD) were part of the non-malignant group. Epileptiform discharges were defined as spikes, polyspikes, sharp waves, spike-and-wave or sharp-and-slow wave occurring outside a SB pattern and not meeting criteria for a malignant EEG pattern. To avoid inclusion of subjects with chronic hypoxic myoclonus (Lance-Adams syndrome), subjects developing stimulus-induced myoclonus or reflex myoclonus beyond 48 h after cardiac arrest were not included in the MEP category.[14] Background reactivity was defined as change in EEG background frequency or amplitude after a noxious or auditory stimulus, and it was defined as "present", "absent" or "not tested".[12] EEG findings were reported to the critical care team and treatment decisions were made according with our institution cardiac arrest antiepileptic drug protocol and treating physician's discretion.

2.4. Data collection and outcome measures

Clinical and demographics data were collected retrospectively, and a subset of records was reviewed separately to confirm data reliability. Discrepancies were resolved by consensus. We stratified patients by gender, location of cardiac arrest, and initial cardiac rhythm, which was dichotomized as shockable and non-shockable (including asystole, pulseless electrical activity, and unknown). Based on their initial neurological examination and Sequential Organ Failure Assessment (SOFA) score on admission, subjects were categorized using the validated Pittsburgh Cardiac Arrest Category (PCAC): PCAC I: awake and following commands, PCAC II: coma with preserved brainstem reflexes, PCAC III: coma with preserved brainstem reflexes and severe cardiopulmonary failure, and PCAC IV: coma with loss of some or all brainstem reflexes.[15] Patient outcomes consisted of level of neurologic function at discharge and discharge disposition and were scored by one of the PCAS physicians. Neurologic function at discharge was graded retrospectively using the Glasgow-Pittsburgh Cerebral Performance Categories (CPCs) scale. "Good" neurological function was defined as a CPC score of 1 or 2 and "poor" as CPC of 3 or 4. Subjects with CPC score of 5 were not evaluated, as only subjects surviving to hospital discharge were included in the data analysis. Discharge disposition was dichotomized as "good" disposition outcome if subjects were discharged home or to an acute rehabilitation facility, and "poor" if discharged to a long-term acute care facility, or hospice. We report both outcomes as they assess different aspects of recovery.[16] Local practice requires patients to be able to tolerate more than 3 h of physical therapy per day to qualify for rehabilitation. Locally, most patients are discharged home from the acute rehabilitation facilities.

In our facility, a Post Cardiac Arrest Service attending sees almost all patients successfully resuscitated from cardiac arrest. Neurologic prognostication consists of serial examinations, computerized tomography of the brain, continuous EEG, and in select cases, somatosensory evoked potentials and magnetic resonance imaging of the brain. We have previously reported on the lack of specificity of these tests, therefore, no single test result is utilized for withdrawal of care.[8,15,17–19]

2.5. Statistical analysis

Data were analyzed using Pearson χ^2 for categorical variables and independent *t*-test for continuous variables. Logistic regression was performed to identify whether EEG category (presence of MEPs, pure SB, or non-malignant) were independent predictors of poor neurological function (CPC 3–4) and poor discharge disposition. Age, OHCA, presence of a shockable rhythm, and EEG

Table 1
EEG classification definitions.

EEG classification	Description
Seizure	Repetitive or periodic generalized or focal spikes, sharp waves, spike-and-wave or sharp-slow wave complexes at greater than or equal to 3 Hz or sequential rhythmic, periodic, or quasi-periodic waves at ≥1 Hz with unequivocal evolution in frequency, morphology, or location lasting at least 10 s
SE	Seizures lasting longer than 5 min or recurrent electrographic seizures for over 30 min
GPD	Generalized periodic discharges at a rate of <3 Hz not satisfying criteria above
MSE	Electroclinical syndrome defined as multifocal or generalized myoclonic jerks or subtle facial movements, including eye opening, locked in with bursts in a suppression-burst pattern or myoclonic jerks associated with electrographic seizures, status epilepticus, generalized periodic discharges, or epileptiform discharges in a comatose patient
SB	Discontinuous EEG background with the presence of alternating periods of bursts of cerebral activity with periods of suppression of <10 μV
ED	Spikes, polyspikes, sharp waves, spike-and-wave or sharp-and-slow wave occurring outside a SB pattern and not meeting criteria for a malignant EEG pattern

SE, status epilepticus; GPD, generalized periodic discharges; MSE, myoclonic status epilepticus; SB, suppression-burst; ED, epileptiform discharges.

category were simultaneously included as candidate variables in this model. Goodness of fit of the final model was evaluated with the Hosmer–Lemeshow test. Unadjusted odds ratios and 95% confidence intervals were calculated. Statistical significance was determined at the α level of 0.05. All analysis was conducted with SPSS, version 21.0.1 software package (SPSS, Chicago, IL, USA).

3. Results

Medical charts from 364 consecutive admissions of 362 subjects presenting with cardiac arrest were screened. Two subjects were admitted after cardiac arrest in two different occasions, and in both cases did not survive the second admission. Subjects who did not survive to hospital discharge (239 subjects), or those who had insufficient EEG monitoring (five subjects) were excluded from the final analysis. Insufficient EEG monitoring occurred due to early clinical improvement in two subjects who started following commands before continuous EEG was started, and could not be determined for three subjects.

The mean age of the 120 subjects surviving to hospital discharge (29.9%) and included in the final analysis was 56 years (SD 15) and 87 (73.1%) were OHCA. Baseline patient characteristics are summarized in Table 2. Median continuous EEG monitoring duration was of 2 days (interquartile range 1,3), and 51 (42.5%) subjects had MEPs, pure-SB or epileptiform discharges recorded. MEPs and pure SB were identified in 19 (15.8%) and 22 (18.3%) subjects, respectively. Interictal epileptiform discharges without association with MEPs were present in 10 (8.3%) subjects. One subject later diagnosed with Lance-Adams syndrome developed seizures on day six from admission. As continuous EEG monitoring had already been discontinued by the time seizures emerged, this subject did not meet criteria for inclusion in the MEP group.

All cases of SB were considered "likely confounded by medication-effect". MEP emerged during the hypothermia-phase with temperatures under 34 °C in 8 (42.1%) patients, 4 (21.1%) during rewarming, and 4 (21.1%) with temperatures above 36 °C. Detailed temperature data could not be retrieved for three subjects. Reactivity was tested in 98 (81.7%) subjects, and was present in 85 (70.8%) of them. Six patients with good CPC at discharge and five patients discharged to home or rehabilitation had a nonreactive background in the first day of EEG monitoring. The distribution of EEG findings and stratification by clinical outcome are displayed in Table 3.

Eighty (66.7%) subjects had poor neurological function at discharge, and 47 (39.2%) had poor hospital discharge disposition. Seven subjects with good neurological function were discharge to a long-term acute care facility. No subjects with MSE or SE had good neurological function at discharge, however four were discharged to a rehabilitation facility. Among subjects with pure SB, eight (36.4%) subjects had good neurological function at discharge, and 14 (66.6%) were discharged to home or to rehabilitation.

EEG category (MEPs, pure SB, and non-malignant) was not associated with poor neurological function at discharge (Pearson χ^2: 5.3; $p = 0.07$), or poor disposition outcome (Pearson χ^2: 3.3; $p = 0.19$). The odds ratios (OR) and confidence intervals (CI) of the multivariate logistic regression are given in Table 4. EEG category did not correlate to neurological function or discharge disposition. Poor neurological function at discharge was associated with age (OR: 1.03; 95% CI 1.01–1.06; $p = 0.03$), and inversely associated with presence of a shockable rhythm (OR: 0.4; 95% CI 0.2–0.99; $p = 0.046$). OHCA (OR 0.22; 95% CI 0.08–0.54; $p = 0.001$) and presence of a shockable rhythm (OR 0.3; 95% CI 0.1–0.7; $p = 0.01$) were inversely associated with poor disposition outcome.

4. Discussion

In this study, we demonstrated that MEPs and pure SB are commonly seen in cardiac arrest subjects who survive to hospital discharge. Moreover, the presence of MEPs was not correlated with functional outcome. Several subjects with MEPs were discharged to home or rehabilitation, including two subjects with myoclonic status epilepticus.

Epileptiform activity is prevalent in cardiac arrest patients treated with TTM, and these EEG findings are associated with high in-hospital mortality and poor outcome.[6,8,9,20,21] Twenty-nine (24.2%) subjects in our study had epileptiform features recorded on EEG, and only three had good neurological function at discharge. The two subjects with good neurological function despite presence of MEPs had GPD. In cardiac arrest literature, GPD have been associated with poor outcome, however this EEG pattern has not been studied as systematically as its "more malignant" counterparts MSE and SE.[6,22,23,24] Few reports of awakening and good outcome despite electrographic confirmation of MSE and SE have been published.[11,25–30] This study extends these prior reports with six subjects with MEPs, including two subjects with MSE, being discharged to home or rehabilitation despite having a CPC score of three at discharge. We have previously shown that recovery from cardiac arrest continues for the first year following cardiac arrest.[16] A more aggressive care plan, including use of TTM and anesthetic agents to suppress MEPs, may have contributed to the good outcomes encountered.

Suppression-burst is considered a strong predictor of poor outcome by some authors, but most of the data available precedes the temperature management era.[7,21] Several studies have described no chance of survival if SB is present, however more recent data indicate that good outcome, despite infrequent, is still possible.[31,21,32,33,34,8,35] All cases of pure SB in our study were likely confounded by medication-effect, and not necessarily due to brain injury. In our cohort, a "pure" SB pattern was associated with good

Table 2
Baseline characteristics.

	Survivors	Non-survivors	*p*	Total admissions (*N* = 359)
Age (mean ± SD)	56.2 ± 15.1	58 ± 17.4	0.09	57.4 ± 16.7
Female	45 (37.5%)	90 (37.7%)	0.98	135 (37.6%)
OHCA	87 (72.5%)	193 (80.8%)	0.08	280 (78%)
Shockable rhythm	63 (52.5%)	44 (18.4%)	<0.001	107 (29.8%)
Category of illness severity			<0.001	
Category II	60 (50%)	33 (13.8%)		93 (25.8%)
Category III	30 (25%)	20 (8.3%)		50 (13.9%)
Category IV	24 (20%)	175 (72.9%)		199 (55.3%)
Category unknown	6 (5%)	12 (5%)		18 (5%)
Length of stay, days (median; IQR)	18; 12,24	4; 3,6	<0.001	6; 3,13

OHCA: out-of-hospital cardiac arrest; IQR: interquartile range.

Table 3
EEG patterns distribution by outcome.

	CPC		Disposition		Total (*N* = 120)
	CPC 1–2	CPC 3–4	Good	Poor	
MEPs	2	17	8	11	19 (15.8%)
- MSE	0	4	2	2	4 (3.3%)
- SE	0	5	2	3	5 (4.2%)
- GPED	2	8	4	6	10 (8.4%)
- Seizure	0	0	0	0	0
Pure-SB	8	14	14	8	22 (18.2%)
Epileptiform discharges	1	9	5	5	10 (8.4%)
Non-malignant	29	40	46	23	69 (57.5%)
Background reactivity	27	58	29	56	85 (70.8%)

MSE, myoclonic status epilepticus; SE, status epilepticus; GPD, generalized periodic discharges; SB, suppression-burst.

neurological function in eight subjects and 14 were discharged home or to rehabilitation. Medications such as propofol and midazolam can induce SB, therefore the prognostic value of this EEG pattern may be misleading if different circumstances are not taken into account. Propofol is the standard anesthetic agent used in our shivering-control protocol, and therefore likely determinant for the high incidence of SB in the good neurological function group.

Limited data is available on the prognostic role of other EEG patterns such as epileptiform discharges and LPD in cardiac arrest.[6,9,14,31,36,37] Our findings support that epileptiform discharges when not accompanied by MEPs are not necessarily associated with poor outcome, underscoring the fact that EEG changes alone cannot provide certainty in prognostication in cardiac arrest subjects treated with hypothermia.[6,38]

More recently, increased attention has been given to the analysis of the EEG background reactivity as a predictor of good outcome[7,9,21]. In our cohort, over seventy percent of subjects had reactivity present, however six subjects had good neurological function at discharge despite the absence of reactivity in the first day of EEG monitoring. The shorter duration of EEG monitoring in subjects that do not develop MEP might have contributed to these findings, as reactivity emergence might be protracted by hypothermia and use of sedatives.

Our report has several limitations. The main shortcoming of this single-center series is the fact that EEG monitoring duration was not uniform and some electroencephalographers who were not blinded to clinical outcome reviewed the records. Therefore bias in the EEG interpretation might have occurred. Electroencephalogram was also used to guide treatment decisions while being acquired, making a "self-fulfilling prophecy" one potential source of bias, because many subjects with MEPs might have had life sustaining therapies withdrawn prematurely. In an attempt to minimize this effect, in our facility no single test is used as justification for limiting life-sustaining therapy, with length of stay in the non-survivors group above five days.

In this study, a different approach was utilized from previous work published in cardiac arrest prognostication involving the use of continuous EEG monitoring. By only including subjects surviving to hospital discharge, we aimed to avoid prognostication confounders related to withdrawal of care and non-neurological factors. Determining the CPC at discharge is correlated with other measures of functional recovery and with long-term survival, although continued improvement in CPC occurs over time after discharge.[16,39] We acknowledge that many subjects with devastating neurological injury, and therefore expected to have significant EEG changes, were not evaluated. This limitation underpowers

Table 4
Multivariable analysis of characteristics associated with poor functional outcome (CPC) and poor discharge disposition outcome.

	CPC 3–4		Poor disposition	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.03 (1.01–1.06)	0.03	1.01 (0.99–1.04)	0.37
OHCA	0.3 (0.09–1.03)	0.06	0.2 (0.08–0.54)	0.001
Shockable rhythm	0.4 (0.2–0.99)	0.046	0.3 (0.1–0.7)	0.01
EEG category		0.3		0.66
Malignant EEG patterns	3.9 (0.78–19.2)	0.1	1.6 (0.5–5.2)	0.4
Pure suppression-burst	1.1 (0.39–3.3)	0.8	0.9 (0.33–2.8)	0.8
Non-malignant (reference)	1		1	

OHCA, out-of-hospital cardiac arrest; VF, ventricular fibrillation; MEPs, malignant EEG patterns; SB, suppression-burst.

an analysis with the objective of determining poor outcome predictors. The intent of this approach, however, was to attempt to demonstrate that subjects with significant EEG changes might have good neurological and discharge outcomes. That was true even in cases with MEPs and pure-SB, which until recently have been reported to be of invariably poor prognostic value.

Historically, myoclonic and nonconvulsive SE have been considered markers of irreversible injury. Some authors consider that they might not be a meaningful contributor to direct brain injury and that its treatment is futile.[10,14] The impact of sedation on EEG features and the fact that subjects received anti-seizure treatment differently might have influenced the development of EEG changes and outcomes. Since the relationship between electroencephalographic changes related to post-anoxic injury and meaningful response to anti-seizure treatment remains poorly understood, aggressive treatment remains the standard practice in our institution.[8,11,21,25,34] Determining patients most amenable to therapy remains a goal for the resuscitation community.

5. Conclusion

MEPs and pure SB are common features in EEG recordings of cardiac arrest patients treated with TTM who survive to hospital discharge. The fact that MEPs were not uniformly associated with unfavorable outcomes suggests that EEG data should be interpreted with caution and integrated with a multimodal approach to prognostication. Prospective studies including long-term outcomes are needed to evaluate the role of prolonged EEG monitoring in prognostication of cardiac arrest subjects treated with targeted temperature management.

Conflict of interest statement

The authors have no conflict of interest to report.

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Appendix A.

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