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Clinical paper

Continuous EEG monitoring enhances multimodal outcome prediction in hypoxic–ischemic brain injury☆

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ABSTRACT

Objective: Hypoxic brain injury is the largest contributor to disability and mortality after cardiac arrest. We aim to identify electroencephalogram (EEG) characteristics that can predict outcome on cardiac arrest patients treated with targeted temperature management (TTM).

Methods: We retrospectively examined clinical, EEG, functional outcome at discharge, and in-hospital mortality for 373 adult subjects with return of spontaneous circulation after cardiac arrest. Poor outcome was defined as a Cerebral Performance Category score of 3–5. Pure suppression–burst (SB) was defined as SB not associated with status epilepticus (SE), seizures, or generalized periodic discharges.

Results: In-hospital mortality was 68.6% ($N=256$). Presence of both unreactive EEG background and SE was associated with a positive predictive value (PPV) of 100% (95% confidence interval: 0.96–1) and a false-positive rate (FPR) of 0% (95% CI: 0–0.11) for poor functional outcome. A prediction model including demographics data, admission exam, presence of status epilepticus, pure SB, and lack of EEG reactivity had an area under the curve of 0.92 (95% CI: 0.87–0.95) for poor functional outcome prediction, and 0.96 (95% CI: 0.94–0.98) for in-hospital mortality. Presence of pure SB ($N=87$) was confounded by anesthetics use in 83.9% of the cases, and was not an independent predictor of poor functional outcome, having a FPR of 23% (95% CI: 0.19–0.28).

Conclusions: An unreactive EEG background and SE predicted poor functional outcome and in-hospital mortality in cardiac arrest patients undergoing TTM. Prognostic value of pure SB is confounded by use of sedative agents, and its use on prognostication decisions should be made with caution.

Introduction

Sudden cardiac arrest (CA) is the leading cause of death in North America in adults over the age of 40, with about 360,000 cases of non-traumatic out-of-hospital cardiac arrest (OHCA) each year.[1] Over the past decade, bundles of care including targeted temperature management (TTM) has become the standard treatment of patients who remain comatose after resuscitation, yielding significant improvement in survival rates and improved neurological function.[2] Despite the advancements in care with implementation of TTM, prognostication remains difficult, and a significant number of patients have withdrawal of life-sustaining therapies prior to formal prognostication, or are labeled with indeterminate outcome.[3] Moreover, the role of several well-established markers of poor prognosis has been challenged, hindering the determination of patient characteristics that indicate potential for neurological recovery.[4]

Electroencephalogram (EEG) is a widely used tool for neurological prognostication in cardiac arrest.[5–9] It can provide real-time continuous monitoring of brain physiology, and is both non-invasive and convenient to use in unstable patients. Clinical and subclinical seizures along with other epileptiform patterns or pres-

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ence of a suppression–burst (SB) background have been shown to be robust predictors of poor neurological function in cardiac arrest.[6,7,9,10] More recent data, however, indicates that good neurological outcome can be present despite the presence of these patterns.[11,12] Other EEG features have emerged as powerful predictive factors for neurological recovery, and more attention has been given to other aspects of EEG background, in particular EEG background reactivity (EBR).[6,12,13]

The aim of this study is to estimate the association of epileptiform patterns and EEG background features with functional outcome of comatose cardiac arrest subjects treated with TTM.

Methods

Patients and Targeted Temperature Management

Adult subjects that remained comatose after successful resuscitation from either in-hospital (IHCA) or out-of-hospital cardiac arrest (OHCA) were prospectively included on a quality improvement database from January 2009 to June 2013. At the time of this study, all patients receiving TTM had a goal temperature of 33 °C. Patients that did not undergo TTM to a goal temperature of 33 °C, or who had continuous EEG monitoring for less than ten hours, were excluded. During the study period, our institution's TTM protocol included induction with intravenous infusion of cold saline followed by application of external cooling pads for 24 h of hypothermia maintenance.[14] Neuromuscular paralysis is frequently employed during induction of TTM, however, it is not routinely continued through hypothermia and rewarming phases. Sedation is performed primarily with propofol infusion (25–60 mcg/kg/h), however, midazolam (0.1 mg/kg/h) and fentanyl (25–100 mcg/h) can be utilized at the treating physician's discretion. The University of Pittsburgh Institutional Review Board deemed this retrospective analysis of quality improvement data including demographic, clinical and EEG data exempt from requirements for informed consent.

EEG monitoring and classification

Our long-term continuous EEG monitoring protocol is initiated during TTM and continues until completion of rewarming.[14] Digital EEG was recorded using 22 electrodes according to a 10–20 system. EEG monitoring was performed for clinical indications and was interpreted by board certified electroencephalographers during standard care. EEG reports were retrospectively reviewed and categorized based on the presence of malignant EEG patterns (MEP), pure SB, or non-malignant EEG patterns as reported previously.[12] Malignant EEG patterns included: status epilepticus (SE), seizures, or generalized periodic discharges (GPD). EEG nomenclature was based on the "ACNS standardized critical care EEG terminology," and the "Guidelines for the evaluation and management of status epilepticus" were used for the SE definition.[12,15,16] Suppression–burst was defined following ACNS criteria, and was described as "present" if SB was present for over 30 min and if "more than 50% of the record consisted of attenuation or suppression with bursts alternating with attenuation or suppression".[15] In cases of SB in the absence of MEP, records were categorized as containing a "pure" SB pattern. Further subclassification of the bursts regarding presence of embedded "highly epileptiform" discharge was not performed. If SB was present in the same day in which propofol or midazolam were administered, SB was categorized as "likely confounded by medication." EEG recordings in which neither MEP or SB were present were considered "non-malignant", even if epileptiform discharges or focal lateralized periodic discharges (LPD) were present. Chronic post-hypoxic myoclonus (i.e., Lance–Adams syndrome) was defined as action myoclonus in a conscious patient that develops 48 h or more after cardiac arrest or respiratory arrest, and was not included as part of the MEP category.[17] The routine EEG monitoring protocol in our institution includes once daily neurological assessments performed by EEG technicians. These assessments include auditory and noxious stimulation in case patients are unresponsive. Noxious stimulation consisted of unilateral or bilateral fingernail compression performed at least once. Electroencephalogram background reactivity was reviewed in the first 72 h of EEG monitoring and was defined as "change in EEG background frequency or amplitude after a noxious or auditory stimulus". EBR was tested once a day and was scored as "reactive," "unreactive," or "not tested" by a board certified neurophysiologist during the hospital stay as per local protocol.[15] In cases in which EBR was not specifically attested, adjudication was performed by two board-certified neurophysiologist (M.E.B and A.P.), and discrepancies were resolved by consensus. Best EBR scoring during entire duration of EEG monitoring duration was used for final EBR categorization. EEG background reactivity testing associated with stimulus induced rhythmic, periodic or ictal discharges (SIRPDS), isolated muscle artifact without association with synchronized epileptiform discharges, or SB were not scored as reactive.

Data collection and neurological evaluation

Clinical and demographics data were collected, 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 (in- or out-of-hospital), and initial cardiac rhythm, which was dichotomized as shockable (ventricular fibrillation or ventricular tachycardia) or 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 Service 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.[18,19] Patient outcomes consisted of level of neurologic function at discharge and discharge disposition, and were scored by one of the PCAS physicians or a trained technician using a standard algorithm.[18] Neurologic function at discharge was graded retrospectively using the Glasgow–Pittsburgh Cerebral Performance categories (CPC) scale. "Good" functional outcome was defined as a CPC score of 1 or 2 and "poor" as CPC of 3–5. Subjects discharged home or to a rehabilitation institution were considered having "good disposition," and those discharged to a skilled-nursing facility, long-term acute care facility, hospice, or who were deceased at discharge were categorized as having "poor disposition." In order to qualify for rehabilitation referral, patients have to be able to tolerate more than three hours of physical therapy per day.

In our institution, 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.[10,18,20–22]

Statistical analysis

Univariate comparison of good and poor outcome groups was performed using Pearson χ^2 for categorical variables and independent *t*-tests for continuous variables. The variables