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Short paper

Awakening from post anoxic coma with burst suppression with identical bursts

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Abstract

Background: Electroencephalography (EEG) is commonly used after cardiac arrest. Burst suppression with identical bursts (BSIB) has been reported as a perfectly specific predictor of poor outcome but published case series are small. We describe two patients with BSIB who awakened from coma after cardiac arrest.

Methods: We identified two out-of-hospital cardiac arrest (OHCA) patients with coma and BSIB. We determined the etiology of arrest, presenting neurological examination, potential confounders to neurological assessment, neurodiagnostics and time to awakening. We reviewed and interpreted EEGs using 2021 American Clinical Neurophysiology Society guidelines. We quantified identicality of bursts by calculating pairwise correlation coefficients between the first 500 ms of each aligned burst.

Results: In case one we present a 62-year-old man with OHCA secondary to septic shock. EEG showed burst suppression pattern, with bursts consisted of high amplitude generalized spike waves in lock-step with myoclonus (inter-burst correlation = 0.86). He followed commands 3 days after arrest, when repeat EEG showed a continuous, variable and reactive background without epileptiform activity. Case two was a 49-year-old woman with OHCA secondary to polysubstance overdose. Initial EEG revealed burst suppression with high amplitude generalized polyspike-wave bursts with associated myoclonus. She followed commands on post-arrest day 4, when repeat EEG showed a continuous, variable and reactive background with frequent runs of bifrontal predominant sharply contoured rhythmic delta activity.

Conclusion: These cases highlight the perils of prognosticating with a single modality in comatose cardiac arrest patients.

Keywords: Cardiac arrest Anoxic brain injury Anoxic coma Prognostication Electroencephalography Outcome Burst suppression

Introduction

Hypoxic-ischemic brain injury from cardiac arrest often results in coma after return of spontaneous circulation (ROSC).[1] Prognostication in this population is challenging, with few highly specific tests available in the first days after ROSC.[2] Electroencephalography (EEG) is a commonly used diagnostic and prognostic test after cardiac arrest. The EEG observation of burst suppression with identical bursts (BSIB) is an ominous finding observed in 10 to 18% of comatose post-arrest patients.[3–7] Initially described by Hofmeijer, *et al.*,[6] the histopathological correlate of BSIB is severe cortical, deep brain and cerebellar necrosis.[8] These observations and available outcomes data support the concept that BSIB is a sign of irrecoverable brain injury. A recent systematic review found BSIB to be a perfectly specific predictor of poor outcome,[2] but noted broad

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confidence intervals reflective of limited sample size in published case series. Here we describe two patients with BSIB who awakened after cardiac arrest.

Methods

The University of Pittsburgh Human Research Protections Office approved this study. The University of Pittsburgh Post-Cardiac Arrest Service (PCAS) is consulted systematically for patients hospitalized at our large regional receiving center, as we have described previously.[9] At this hospital, we have identified 243 cases of BSIB over an eight-year period (2010–2018), accounting for 10% of the overall and 18% of the comatose post-arrest population. Since 2019, PCAS has offered telemedicine consultation for patients treated elsewhere in our health system, which includes 42 hospitals across Western Pennsylvania and neighboring portions of Ohio, New York, West Virginia and Maryland.[9,10] The health system has a catchment area of approximately 5.7 million people.[10] Across the 42 hospitals, there are approximately 900,000 emergency department encounters 355,000 inpatient and observation admissions annually. Six facilities offer continuous EEG monitoring while other facilities have access to intermittent EEG monitoring. Because we are not consistently consulted in the care of patients treated at outlying hospitals, the total volume of post-arrest patients in the system is unknown.

Historically, we have not observed recovery from BSIB.[5] We evaluated both patients reported here via telemedicine. We determined the etiology of arrest,[11] presenting neurological examination, potential confounders to neurological assessment, neurodiagnostic testing and time to awakening from coma. For research purposes, our group, which included neurointensivists and neurologists board certified in either clinical neurophysiology or epilepsy, reviewed both patients' EEGs and interpreted results using American Clinical Neurophysiology Society guidelines.[12] We defined BSIB as described by Hofmeijer, et al.[6]

To quantify burst identicality, we identified bursts on EEG by detecting deviations > 6 standard deviations above the baseline then visually inspecting to confirm accurate identification of burst onset. We aligned individual bursts within patients by optimizing cross-correlations, then calculated correlation coefficients across all channels for the first 500 ms of each pairwise combinations of in-phase bursts. We used Matlab for quantitative analyses (MathWorks, Natick, MA). We used Persyst 13 to quantify suppression ratio in the first 30 minutes of artifact free EEG recording using software default settings (Persyst Development Corporation, Solana CA).

Results

Case 1

This patient was a 62-year-old man with tetraparesis secondary to remote cervical spinal cord injury, neurogenic bladder, and spasticity who had been treated chronically with sertraline, gabapentin and baclofen. On the day of his arrest, the patient was found by his wife to be difficult to arouse with sonorous respirations followed by apnea. Emergency medical services (EMS) were summoned. First responders found the patient to be apneic and pulseless so started cardiopulmonary resuscitation (CPR). An automated defibrillator was placed and no shock was advised. Approximately ten minutes later, paramedics arrive and noted a pulse with narrow complex rhythm on cardiac monitoring, though the patient remained apneic. Paramedics intubated the patient and transported him to the emergency department (ED).

Neurological evaluation after initial stabilization in the ED revealed small, equal and reactive pupils, absent corneal, cough and gag reflexes and intermittent truncal and facial myoclonus. The patient was noted to be febrile and received broad-spectrum intravenous antibiotics (pipercillin-tazobactam and vancomycin). His ECG was unremarkable. Computerized tomographic (CT) imaging of the brain and chest were unrevealing, and abdominal imaging revealed colitis. He was admitted to the intensive care unit (ICU) for ongoing care with septic shock as the presumed etiology of arrest. An endovascular cooling catheter was placed, the patient received targeted temperature management (TTM) to 33 °C for 24 hours and a propofol infusion was started to suppress shivering. Continuous video EEG monitoring was initiated 18 hours after arrest (Fig. 1). His EEG showed burst suppression pattern, with a suppression ratio of 63% in both right and left hemispheres and bursts initiated with high amplitude generalized spike waves and prior to administration of neuromuscular blockade was associated with myoclonus noted on video recording. His neurological exam was unchanged over the next 24 hours and EEG monitoring was discontinued.

On the third hospital day, the patient's bedside nurse noted him to be following commands. Repeat EEG showed continuous, normal amplitude, variable and reactive EEG background without epileptiform features (Fig. 1). He was extubated and transferred out the ICU. Magnetic resonance imaging (MRI) of the brain was ordered but could not be completed because of ferromagnetic spinal hardware. His interval course was complicated by recurrent septic shock, ventilator dependent respiratory failure. He required diverting colostomy and debridement of decubitus ulcer. Forty-five days later, he was discharged home with the care of his family. He was at his baseline neurological function, awake and grossly cognitively intact.

Case 2

This patient was a 49-year-old woman with a history significant for depression and anxiety on escitalopram, quetiapine, baclofen, cerebellar degeneration, neurogenic bladder, polysubstance use. On the morning of her arrest, she was found by her husband unresponsive in their home beside several empty bottles of her psychiatric medications. He could not palpate a pulse and noted her to be apneic, so called EMS and started CPR. Paramedics arrived 10 minutes later and find her with pulse and shallow breathing. She received bag valve mask ventilation en route to the ED where she was intubated on arrival. Brain CT was unrevealing. Her ECG was benign. Urinary toxicology revealed escitalopram, quetiapine and midazolam. Serum was negative for ethanol, salicylates, acetaminophen and her serum baclofen level was 12 mcg/dl. She was admitted to the ICU for management of cardiac arrest secondary to presumed medication overdose.

Examination on ICU arrival demonstrated absent pupillary light reflex, absent corneal reflex, no cough or gag, intermittent facial and upper extremity myoclonus. A routine EEG was obtained in the afternoon given this exam (Fig. 2), which revealed burst suppression pattern with high amplitude generalized polyspike-wave bursts with associated myoclonus noted on video recording. The median suppression ratio of this recording were 78% for the right hemisphere

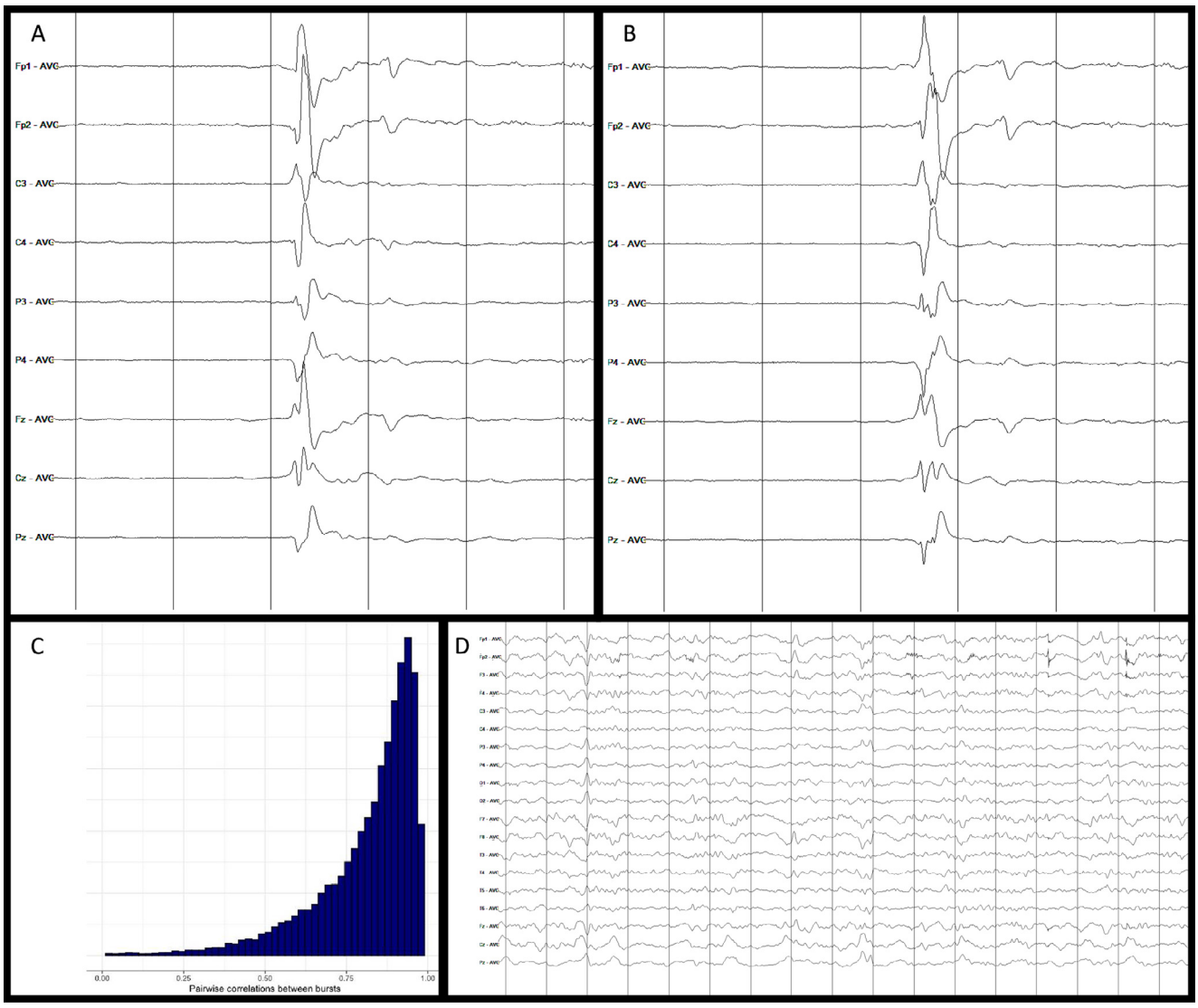

Fig. 1 – EEG obtained on Patient 1's admission to the ICU after neuromuscular blockade. (A,B) Two representative bursts with identical initiation concerning for BSIB are shown. Prior to administration of neuromuscular blockade these bursts were observed to occur in lock-step with orofacial myoclonus. (C) Histogram of cross-correlation values between bursts (inter-burst correlation = 0.86 among 124 bursts). (D) EEG obtained on post-arrest day 3 showed continuous, normal amplitude, variable and reactive EEG background without epileptiform features BSIB-Burst suppression with identical bursts.

and 75 % for the left. She underwent TTM to 36 °C, was sedated with propofol and fentanyl and received several bolus doses of midazolam to suppress myoclonus. She underwent one session of intermittent hemodialysis to clear potential toxins.

After 24 hours of TTM she was rewarmed to 37 °C. Interval EEG obtained after rewarming was essentially unchanged though she was started on levetiracetam on post arrest day 2. An MRI brain obtained the same day revealed no diffusion restriction. The following day her EEG evolved to generalized periodic discharges at a frequency of 1.5 to 2 Hz, concerning for possible nonconvulsive status epilepticus. The patient was then transferred to tertiary care for continuous EEG monitoring.

On arrival to the receiving facility, she was placed on continuous video EEG monitoring. There was concern for worsening seizures related to acute baclofen withdrawal, and her home baclofen dose was restarted. Over the next day her mental status improved, EEG at that time showed continuous, normal voltage generalized delta slowing and frequent generalized rhythmic delta activities (GRDA) with bifrontal predominance, intermixed with intermittent generalized theta beta activities, and was reactive and variable **(**Fig. 2**).** She was weaned from mechanical ventilation and extubated. On post cardiac arrest day 4, she was alert to self, followed commands though was weak in her extremities.

Her trajectory continued to improve and she was discharged from the ICU. Over the subsequent hospital days levetiracetam was weaned off. On post-arrest day 13 she was alert to month and year, but demonstrated poor memory and attention. Given these neurological deficits and weakness, as well as the need for psychiatric care,

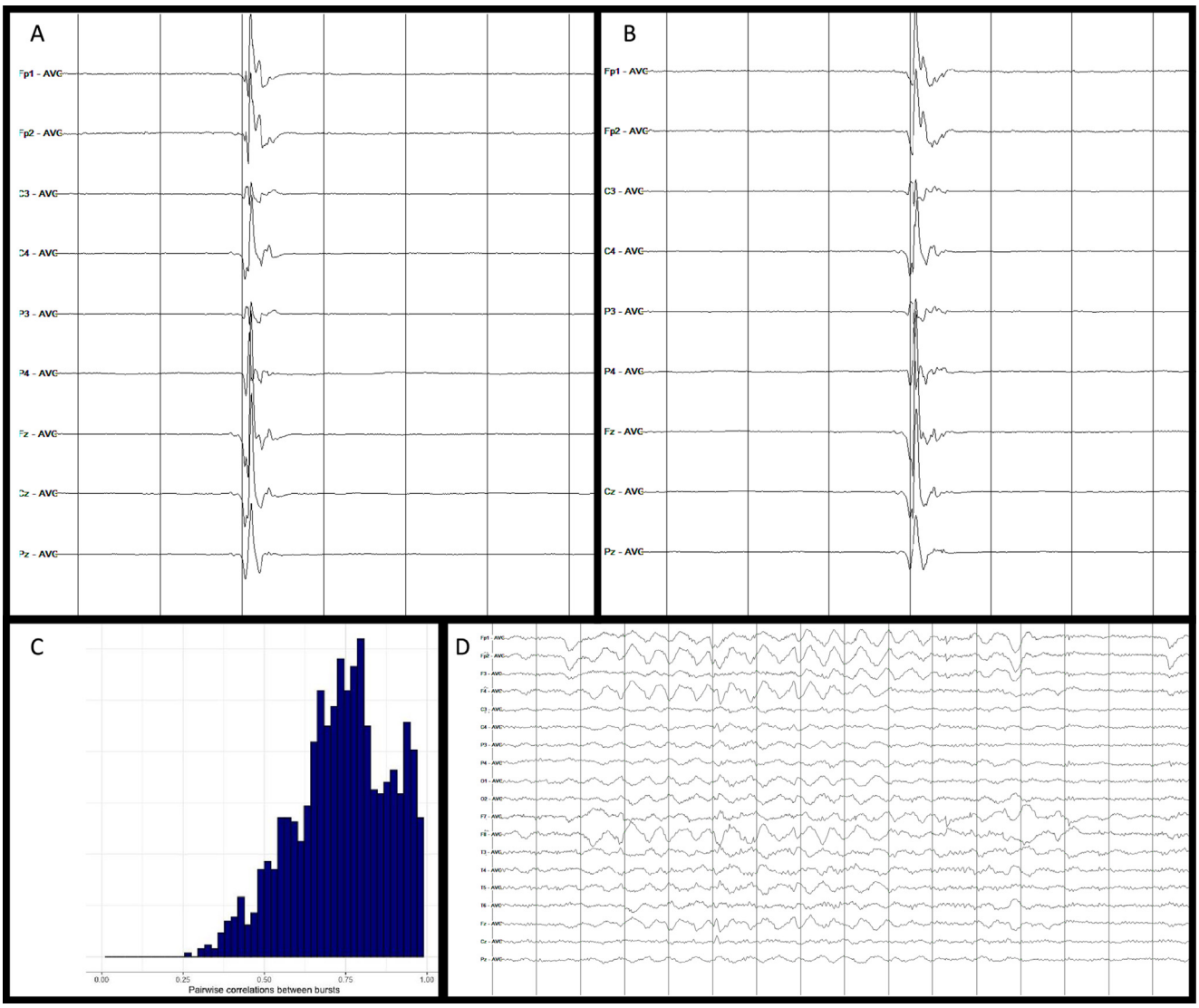

Fig. 2 – EEG obtained 18 hours after cardiac arrest in Patient 2. (A,B) Two representative bursts with identical initiation concerning for BSIB are shown. Facial and axial myoclonus was observed in lock-step with the initiation of these bursts. (C) Histogram of cross-correlation values between bursts (inter-burst correlation = 0.84 among 23 bursts). (D) EEG obtained on post arrest day 3 showed continuous generalized delta slowing and frequent generalized rhythmic delta activities (GRDA) with bifrontal predominance, intermixed with intermittent generalized theta beta activities. BSIB- Burst suppression with identical bursts.

she was discharged to brain injury rehabilitation for further care. After two weeks of inpatient rehabilitation, she was discharged home in the care of family. On discharge from rehabilitation, she was independent for most activities of daily living and per family was at her cognitive baseline.

Discussion

Burst suppression with identical bursts is an ominous prognostic finding in post anoxic coma, though series describing it as a perfectly specific predictor of poor outcome are small.[2] Here we report two cases of BSIB who emerge from post-anoxic coma and enjoyed favorable recoveries. Because the total denominator of patients from which these cases were identified is unknown, we cannot report quantitative test characteristics for BSIB except insofar as confirming it is not a perfectly specific predictor of poor outcome.

In both presented cases, medications including selective serotonin reuptake inhibitors (SSRIs) and baclofen and/or medication withdrawal may have altered the EEG. SSRI overdose may cause myoclonus, but neither case exhibited other signs of serotonin syndrome.[13] Medications that activate gamma-aminobutyric acid (GABA) receptors induce burst suppression, but are not known to cause BSIB.[14] BSIB is believed to represent widespread irrecoverable synaptic failure resulting in low-dimensional cortical networks with deterministic behavior.[6,15] While excessive GABA activation reduces network density and size, small-worldness does not appear to be influenced.[16] The seratonin axis has been implicated in both seizure and sudden unexpected death in epilepsy,[17] though SSRIs have been associated with possibly reduced seizure frequency in

epilepsy patients.[18] Moreover, increased serotonin transmission shortens post-ictal suppression and does not cause burst suppression.[19] Neither case had a history of seizures or epilepsy prior to arrest.

Both cases had generalized myoclonus for > 30 minutes, meeting the clinical criteria for post-anoxic "status myoclonus". Previously, we described EEG characteristics that may differentiate malignant myoclonus (i.e. myoclonus associated with BSIB) from early Lance-Adams syndrome.[4] Cases of Lance-Adams syndrome typically show a continuous EEG background with parasagittal spikes in step lock with myoclonus, unlike the cases we report here.[4,20] Moreover, during follow-up examinations neither patient continued to have myoclonus. In our experience patients with Lance-Adams syndrome often required at least some long-term pharmacotherapy to manage myoclonus.

Ruijter and colleagues identified ominous variants of burst suppression under the concept of "synchronous pattern with 50% suppression".[21] These patterns are characterized by abrupt, synchronous bursting activity ranging from BSIB to generalized periodic discharges on a suppressed background. Post-mortem histopathological analysis in these cases reveals diffuse supra- and infratentorial necrosis, though the exact pathophysiology is not fully understood.[8]

Conclusion

These cases highlight the importance of multimodality neuroprognostication and thoughtful consideration of potential confounders to testing.[22–24] EEG obtained after achieving normothermia showed improved background for both cases. Serial or continuous EEG should be considered in cases with prognostic uncertainty.

Ethical statement

The University of Pittsburgh Human Research Protections Office approved this study.

Conflicts of interest

None.

CRediT authorship contribution statement

Patrick J. Coppler: Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Visualization, Writing - original draft, Writing - review & editing, Project administration. **Amanda E. Kusztos:** Methodology, Software, Formal analysis, Investigation, Writing - review & editing. **Mark Andreae:** Investigation, Writing - original draft. **Brad W. Butcher:** Investigation, Writing - original draft. **Ankur Doshi:** Investigation, Writing - original draft. **Maria E. Baldwin:** Investigation, Writing - original draft. **Niravkumar Barot:** Investigation, Writing - original draft. **James F. Castellano:** Investigation, Writing - original draft. **Joanna S. Fong-Isariyawongse:** Investigation, Writing - original draft. **Alexandra Urban:** Investigation, Writing - review & editing, Visualization. **Clifton W. Callaway:** Writing - review & editing, Supervision. **Alexis Steinberg:** Investigation, Writing - review & editing. **Jonathan Elmer:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Supervision. : .

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