



Mechanistic Wager on Outcome in Coma After Cardiac Arrest: The EEG Signature in Burst Suppression Provides Some Clues

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Independent Functional Outcomes After Prolonged Coma Following Cardiac Arrest: A Mechanistic Hypothesis

Forgacs PB, Devinsky O, Schiff ND. *Ann Neurol.* 2020;87:618-632. doi:10.1002/ana.25690.

Objective: Survivors of prolonged (>2 weeks) post-cardiac arrest (CA) coma are expected to remain permanently disabled. We aimed to investigate 3 outlier patients who ultimately achieved independent functional outcomes after prolonged post-CA coma to identify electroencephalographic (EEG) markers of their recovery potential. For validation purposes, we also aimed to evaluate these markers in an independent cohort of post-CA patients. **Methods:** We identified 3 patients with late recovery from coma (17-37 days) following CA who recovered to functionally independent behavioral levels. We performed spectral power analyses of available EEGs during prominent burst suppression patterns (BSP) present in all 3 patients. Using identical methods, we also assessed the relationship of intraburst spectral power and outcomes in a prospectively enrolled cohort of post-CA patients. We performed chart reviews of common clinical, imaging, and EEG prognostic variables and clinical outcomes for all patients. **Results:** All 3 patients with late recovery from coma lacked evidence of overwhelming cortical injury but demonstrated prominent BSP on EEG. Spectral analyses revealed a prominent theta (~4-7 Hz) feature dominating the bursts during BSP in these patients. In the prospective cohort, similar intraburst theta spectral features were evident in patients with favorable outcomes; patients with BSP and unfavorable outcomes showed either no features, transient burst features, or decreasing intraburst frequencies with time. **Interpretation:** Burst suppression patterns with theta (~4-7 Hz) peak intraburst spectral power after CA may index a recovery potential. We discuss our results in the context of optimizing metabolic substrate availability and stimulating the corticothalamic system during recovery from prolonged post-CA coma.

Commentary

I suspect that everyone who utilizes the electroencephalogram (EEG) to assist in the prognostication of patients comatose after cardiac arrest may have a regretful sense that in retrospect, perhaps life sustaining therapy in some patients was withdrawn too prematurely. This may in part be due to the phenomenon of the “self-fulfilling prophecy” in which a test believed to have high negative predictive value for poor outcome increasingly, and perhaps falsely, gains significance as each withdrawal of care reinforces the potentially false value of this test.

Such is the sense I had when reading manuscript by Forgacs et al in which the authors present a detailed study of 3 extraordinary survivors of coma after cardiac arrest.¹ Each of these patients had EEGs that would typically point to extraordinarily poor expected outcomes. All patients had burst suppression patterns, one of them just in relation to sedative use, another for 3 days after anesthetic medication was discontinued, and in one patient for 62 days. All of the patients had prominent and persistent burst suppression pattern and status epilepticus (one patient was in super-refractory status epilepticus). None of the raw EEG traces are shown, but one of the patients was

published as a case report previously.² In my review, that tracing would be considered highly malignant, consistent with persistent burst suppression and status epilepticus.³ It is unclear whether the EEGs of the other two patients had equally clear patterns that would typically portend an extremely poor prognosis. In particular, burst suppression in one patient was present only with concurrent use of anesthetic drips so it is unclear whether this can be considered prominent and persistent. All had extremely poor neurological examinations upon rewarming, including absent corneal and most importantly, absent motor responses.

The social context under which the patients were supported is informative. In one patient, goals of care were not changed because the family was living abroad. The family of another patient continued active care despite the declaration of extreme poor prognosis by multiple experts. Interestingly, the third was supported due to the similarities to the first 2 patients.

All 3 patients eventually achieved what most neurologists would consider a good outcome. All of them regained consciousness were able to functionally interact with the environment, hold a conversation, and appear to be able to perform



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activities of daily living independently, though none of them were able to return to work. Despite the profound burst suppression patterns, there were signs in several domains in all 3 patients that portended potentially good prognosis. Two of the patients were young, being in their early 50s. Two had shockable pulseless rhythms, and 2 had short time to return of spontaneous circulation. Pupillary reflexes were present early in each of these patients, though its presence is not a sign of high positive predictive value of good recovery after targeted temperature management. Neurophysiologically, EEG reactivity during acute hospitalization was present in 2 patients; in one of them, the burst suppression pattern was not sustained. Electroencephalograms were continuous at some points of the recordings, and in the 2 patients in whom it was obtained, the somatosensory evoked potentials were present. Most importantly, magnetic resonance imaging scans did not reveal any evidence of substantial anoxic brain injury.

What is remarkable is the time it took for recovery to occur. Coma recovery (eg, spontaneous eye opening) occurred between days 17 and 37, and recovery of conscious awareness (eg, following commands) between days 52 and 71. The authors point out that this phenomenon had been previously observed in traumatic brain injury patients⁴; rare instances of delayed coma recovery have previously been reported,⁵ but not of such markedly delayed recovery of conscious awareness.


In terms of EEG analysis, the authors carefully evaluated the burst portion of the burst suppression pattern using spectral analysis. They demonstrated a prominent power peak in the theta range in all 3 patients, which they surmise is an indication of a corticothalamic network with potential for recovery. More interestingly, the frequency of this peak appeared to increase as the patient recovered from coma. They confirmed these findings in a retrospective analysis of 17 other patients who were comatose after cardiac arrest and displayed a burst suppression pattern. In patients with an eventual favorable outcome, the prominent theta feature was always present, and increased in frequency over time. In patients without favorable outcome, the theta feature was either not present, was transient, or decreased in frequency over time.

The key hypothesis postulated by the authors is that in patients with a theta peak and a prominent theta pattern, there is potential for neurons to either move toward programmed cell death, as demonstrated by slowing frequency of the theta feature and its eventual disappearance. Alternately, there may be recovery, associated with increasing frequency of the theta feature, sometimes back into the alpha spectrum, and that burst suppression itself is a potential neuroprotective mechanism. This is primarily based on a biophysical computational model developed by Ching et al⁶ that aims to unify the various physiological and disease states in which burst suppression is seen, including anesthesia, hypothermia, and anoxic brain injury. This model explains some of the features seen in burst suppression: the nearly periodic onset/offset of bursts, the relatively slow time scale (of seconds) of burst/suppression alteration, and the modulation of suppression duration by depth of sedation or degree of injury. The model features an ATP-gated


potassium channel which cyclically modulates neuronal activity by intracellular ATP levels. There is experimental evidence that selective opening of these channels had neuroprotective effects against ischemia–reperfusion injury in the brain.⁷ Thus, this paradigm models ischemic injury leading to impaired cerebral metabolism, depletion of ATP, and resultant burst suppression.

One may argue with some features of the experimental as well as interpretational results in this manuscript. The bursts were selected by visual examination of artifact-free data, thus it may introduce selection bias. That the burst suppression is a protective mechanism is still theoretical, and there are competing, though not necessarily incompatible, biophysical models.^{8–10} The biophysical model demonstrates that the frequency of the spectral content within bursts is maintained through different levels of hypothermia and anesthesia, thus it does not necessarily explain the shift toward faster theta activity with improving neuronal function and slowing of the theta feature in patients who have poor outcome. The findings in the current manuscript suggest that frequency slows with cellular death and increases with reafferentation and restoration of normal background. The authors suggest that since prolonged burst suppression may be linked to metabolic impairment, that caloric intake and hydration be maintained. While that is sound clinical advice in general, linking it to this putative mechanism is speculative.

These minor points aside, this work elegantly describes the mechanisms of a potentially intact corticothalamic network in burst suppression, a feature that may portend potentially good outcome in these patients. The overarching clinical theme returns to the self-fulfilling prophecy of potential premature withdrawal of care—an unacceptable (but ultimately potentially unknowable) outcome. Careful examination of the bursts in the EEG of burst suppression may provide us clues to where prolonged care can be maintained, tilting the odds in this small group of patients.

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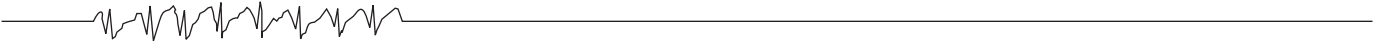
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