

Independent functional outcomes after prolonged coma following cardiac arrest: a mechanistic hypothesis

Running title: Mechanism of recovery from prolonged cardiac arrest coma

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Abstract:

Objective: Survivors of prolonged (> 2 weeks) post-cardiac arrest (CA) coma are expected to remain permanently disabled. We aimed to investigate three 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 three 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 three patients. Using identical methods, we also assessed the relationship of intra-burst spectral power and outcomes in a prospectively enrolled cohort of post-CA patients. We performed chart reviews of common clinical, imaging, EEG prognostic variables and clinical outcomes for all patients.

Results: All three patients with late recovery from coma lacked evidence of overwhelming cortical injury but demonstrated prominent BSP on EEG. Spectral analyses revealed a prominent theta (~4-7Hz) feature dominating the bursts during BSP in these patients. In the prospective cohort, similar intra-burst 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 intra-burst frequencies with time.

Interpretation: BSP with theta (~4-7Hz) peak intra-burst spectral power after CA

may index a recovery potential. We discuss our results in the context of optimizing metabolic substrate availability and stimulating the cortico-thalamic system during recovery from prolonged post-CA coma.

Introduction:

Improved acute management of comatose post-cardiac arrest patients using targeted temperature management (TTM) strategies – including therapeutic hypothermia - has changed expected neurological outcomes^{1,2}. Such major shifts from prior outcome statistics³⁻⁷ likely reflect a poorly characterized effect of TTM on neuronal cell-types exposed to hypoxic-ischemic conditions. In this context, many studies have identified physiological markers that remain associated with poor prognosis⁵⁻¹⁰ to guide management (e.g. loss of brainstem reflexes on exam, burst-suppression pattern (BSP) or refractory status epilepticus on electroencephalogram (EEG)). However, following the widespread use of TTM an increasing number of reports describe unexpected recoveries despite evidence of poor prognostic markers¹¹⁻¹⁶. In addition, a lack of imaging-based evidence of anoxic cortical or white matter injuries after cardiac arrest may portend better outcomes¹⁷, even in patients remaining in coma for more than 7 days¹⁸. The poorly characterized physiological protective factors related to TTM¹⁹ suggest the possibility that in comatose post-cardiac arrest patients with wide preservation of cerebral structure, some negative predictive markers may only indicate a sustained abnormal state of global neuronal functions without permanent loss of potential to recover integrative cerebral functions. Collectively, these observations raise the question of whether global dysfunction of large-scale cerebral networks indexed by negative physiological predictive markers (e.g. BSP, refractory status epilepticus) may hide a latent capacity for broad functional recovery across the cortico-thalamic system in patients with prolonged

coma after cardiac arrest.

We first identified three patients with independent functional outcomes following very prolonged coma (range 17-37 days) after out-of-hospital cardiac arrests. Notably, all three patients had prominent BSP on EEG and one patient had prolonged super-refractory status epilepticus; physiological patterns that are typically associated with poor outcomes after cardiac arrest²⁰⁻²³. However, recent studies of the physiological basis of BSP arising with anesthesia in healthy controls have shown that BSP arises as a general mechanism when low levels of adenosine triphosphate (ATP) are present and may lead to protection of membrane integrity and cellular preservation in the setting of severe limitations of metabolic substrate availability²⁴. Based on these considerations, we carefully characterized the burst structure in each patient applying spectral analysis methods; we find a dominant theta (~4-7Hz) or higher frequency feature within the burst component of the BSP in all three patients. Based on prior studies, the presence of a similar theta feature in resting EEG activity may index evidence of remaining functional integrity of the cortico-thalamic system^{25,26}. To further evaluate these observations in the late coma recovery patients, we reviewed clinical variables and EEG recordings in a prospectively enrolled cohort of 53 post-cardiac arrest patients; EEG records from patients with BSP (n=17) were further analyzed to examine potential association of theta-bursting within BSP and clinical outcome. We discuss our findings in the context of the role of metabolic substrate availability in the generation of BSP and provide several directions for further investigations and strategies for initial management of

patients with prolonged coma following cardiac arrest based on these considerations.

Methods:

Patient selection and procedures:

Three patients who showed recovery to independent functional level after remaining in coma for at least two weeks (17, 37, 30 days, respectively; Figure 1 and Table 2) following a cardiac arrest were identified through clinical or research encounters. Patient 1 was assessed twice under a research protocol (at 7 and 19 months after cardiac arrest) at Rockefeller University Hospital (RUH) in an ongoing multi-modal research study of patients after severe, chronic brain injuries using EEG, behavioral and neuroimaging evaluations. Patient 2 was followed longitudinally during in- and outpatient clinical encounters by co-authors OD and NDS. Patient 3 was enrolled as part of a longitudinal research protocol at New York Presbyterian/Weill Cornell Medical College (NYP/WCMC) that involves acute post-cardiac arrest patients during the initial hospitalization. In a subsequent investigation informed by the results obtained in the initial subset of three patients, we reviewed all post-cardiac arrest patients (n= 53) who were prospectively enrolled under acute care EEG monitoring and inpatient post-cardiac arrest research protocols at NYP/WCMC. Consents for research protocols and permission to use clinical data for research purposes were obtained from or provided by the patient's legally authorized representatives. All

research procedures were approved by the NYP/WCMC and RUH Review Boards.

Clinical and behavioral data collection:

For all patients involved in the study, we identified key elements of clinical history that are relevant to prognosis of coma following cardiac arrest via systematic chart review. The information extracted from charts focused on the circumstances of the cardiac arrest (e.g. initial rhythm and time to return of spontaneous circulation); elements of routine neurological examinations that are relevant to prognostication after cardiac arrest; reports of all neuroimaging or electrophysiological studies as evaluated by the clinicians; anesthetic or sedative use; presence of major metabolic derangements and clinical outcomes, including goals of care discussions. Functional outcomes were quantified using the Cerebral Performance Categories (CPC)²⁷ scale at the time of hospital discharge and at best known functional state, when available. Two of the three late coma-recovery patients underwent standardized behavioral and cognitive tests in addition to the routine clinical examinations. In patients 1 and 3, these included serial assessments using the Coma Recovery Scale–Revised (CRS-R)²⁸ and Mini-Mental State Examination (MMSE)²⁹. In patient 1, a range of additional standardized cognitive tests (Mississippi Aphasia Screening Test (MAST)³⁰ and elements of the Confusion Assessment Protocol (CAP)³¹) were obtained at multiple time points during research admissions.

EEG recordings and quantitative analyses:

All EEGs collected for clinical and research purposes were recorded using a standard video-EEG system (Natus Medical, San Carlos, CA) using collodion-pasted electrodes placed by certified technicians. At a minimum, electrode arrangement consisted of the conventional 19-electrode montage for EEGs collected for clinical purposes. An augmented montage (with an additional 18 electrodes) was used for EEGs collected for research purposes³². EEG recordings of the three patients with late recovery after post-cardiac arrest coma and all patients who had BSP at any time during EEG monitoring in the prospective cohort (n=17) underwent additional quantitative analyses.

Methodological details of the analysis of bursts and suppression periods from EEG segments containing BSP was published earlier by our group²⁶. Briefly, during times when EEG showed a BSP with periods of suppression longer than 3 seconds, burst and suppression periods were analyzed separately from the same EEG segment. Alternatively, if the suppression periods were shorter than 3 seconds during BSP, only burst periods were analyzed. During times when the EEG background was continuous, consecutive 3-second long segments were used for spectral analysis. Frequency spectral content of visual inspected artifact-free EEG segments were quantified using a multi-taper method³³ as implemented by the Chronux toolbox³⁴ of Matlab (MATLAB R2013b, The MathWorks, Natick, MA). Power spectra between 0-24 Hz were plotted for each day when recording was available. Spectral features of EEG were visually assessed using the midline central, parietal or occipital electrodes that are

typically least affected by myogenic or technical artifacts. In addition, based on earlier studies, the midline central and parietal electrodes are expected to first reflect signal properties related to cortico-thalamic integrity²⁵.

To operationalize and automate the definition of a “hump” or “peak” in the power spectra and to quantify the peak frequency of such features when present in the intra-burst period of BSP, we employed the approach of Gottselig et al.³⁵. We first fit a best-fitting spline to the shape of the power spectrum and then calculated a “normalized” spectra defined as the difference between the power spectrum and the Gottselig spine (custom Python code, available on request). Following this step we determined the frequency at the maximal normalized spectral power spectra within the 4-8 Hz range to return the nominal peak frequency (if the peak value was at the edge (i.e. 4 or 8), then the window was extended to 3-9 Hz).

Results

Clinical summary of three patients with late recovery after prolonged post-cardiac arrest coma:

The overview of relevant baseline clinical characteristics clinical and neurological examination findings most commonly used in prognostication of comatose post-cardiac arrest patients as well as timeline of clinical milestones related to recovery of consciousness as are presented in Table 1 and 2 and shown in Figure 1. Additional information on long-term functional outcomes and details of goals of care discussions are presented in Table 2. Briefly, each patient had

relatively short time to return of spontaneous circulation (10-20 minutes range) and underwent a therapeutic hypothermia protocol with target temperature of 33 °C; no patient had more than minimal evidence of hypoxic-ischemic injury to the cortex on CT or MRI. A preserved cortical response on the median somatosensory evoked potential (SSEP) exam was measured in two patients (patients 1 and 2). In two patients (patients 2 and 3), there was a considerably delayed time to recovery of spontaneous eye opening after cessation of all sedative or anesthetic medications (23-26 days). All three patients showed a remarkably delayed time to recovery of conscious awareness (i.e. command following with a range of 37-67 days after cessation of sedatives). These timeframes considerably exceeded the expected clearance of the sedative medications used based on known half-lives and documented hepatic and renal function in each subject. EEG reactivity was present for patient 1 by day 3 after cardiac arrest, however, patient 2 showed very late recovery of EEG reactivity (by day 73) and patient 3 had recovery of EEG reactivity by day 8. All three patients had persistent epileptiform discharges present on EEG starting during hypothermia throughout the last available observation point (19 months in patient 1, 4.5 years in patient 2; 3 months in patient 3). In all three patients, non-convulsive status epilepticus emerged on day 2. Patient 1 developed super-refractory status epilepticus²⁸ despite escalating treatment with anti-seizure and anesthetic medications. Status epilepticus resolved after initiation of ketamine on day 14. All 3 patients had prominent BSP on EEG. Remarkably, BSP in patient 2 persisted until day 62 after cardiac arrest (48 days after last anesthetic use). In

patient 3, BSP persisted for an additional 3 days after cessation of anesthetic medication use, and in patient 1, BSP emerged in relation to concurrent use of anesthetic drips only. All three patients continued to improve after discharge from hospital and were eventually able to perform activities of daily living and recover to functionally independent levels (Table 2).

Assessment of late cognitive and functional recovery after cardiac arrest:

For Patient 1, detailed longitudinal neuropsychological evaluations revealed continued recovery of cognitive functions at 7 and 19 months following the cardiac arrest as part of research assessments. While hospital records charted the patient to be in coma until day 17 and vegetative state until at least day 54 after the cardiac arrest, the patient continued to progressively improve after hospital discharge and emerged from minimally conscious state to the level of confusional state by 7 months after the cardiac arrest as evidenced by near-maximal (22.5 out of 23) score on the Coma-Recovery Scale – Revised (CRS-R) examination. However, while marked cognitive disturbances were still evident at this point with impaired communication/language skills (MAST (Mississippi Aphasia Screening Test) score), attention, vigilance and memory functions (CAP (Confusion Assessment Protocol) subscores), the patient demonstrated significant improvements in all tested cognitive domains by 19 months after the cardiac arrest. Remarkably, e.g. an increase in overall cognitive function reflected in the Mini-Mental State Examination (MMSE) showed a ~16-point change from 14/28 to 29.5/30 between 7 months to 19 months. Notably, overall

improvements were most delayed in exams (and exam elements) requiring sustained attention and working memory (i.e. GOAT (Galveston Orientation and Amnesia Test)). While standardized neurophysiological assessments were not obtained for the other two patients, patient 2 and 3 both also recovered to functional independence (see details in Table 2).

Characterization of EEG dynamics in patients with late recovery from coma after cardiac arrest:

To track recovery of brain function we quantified the resting EEG activity in each patient with late recovery from coma after cardiac arrest (Figure 2). In patient 1, a ~7 Hz feature was present in bursts of BSP during hypothermia protocol (day 0) as well as during utilization of sedative drips to treat super-refractory status epilepticus (e.g. day 7 and day 14). On intervening days when EEG was continuous, a mixture of delta/theta/alpha activity rendered the spectra relatively flat (e.g. days 2, and 12). A re-emergence of a ~7 Hz peak in the resting EEG spectrum appeared by day 23 (not shown). Recovery of a normal 8-10 Hz (alpha) frequency background rhythm appeared by one month and remained stable with repeat measurements at 7 and 19 months after the cardiac arrest.

Patient 2 showed a ~5-6 Hz peak in the EEG power spectrum on day 1 during the hypothermia protocol. During a subsequent period of non-convulsive status epilepticus emerging on day 2 and during high doses of sedative medications no dominant features were observed. Ensuing periods of prolonged BSP revealed bursts with ~6-7 Hz (day 10) and 8 Hz (day 14) intra-burst peak features in the

EEG power spectrum. Two months after the cardiac arrest, the resting EEG demonstrated a shallow peak ~6-7 Hz in the power spectrum.

Patient 3 showed a concentration of spectral power below 4 Hz (delta) frequency range during hypothermia (day 1) and non-convulsive status epilepticus emerged during rewarming (day 2). During ensuing BSP, a ~5-6 Hz (theta) intra-burst frequency dominated the burst periods (day 3) that persisted over the next several days until day 6. On subsequent weeks an EEG spectra dominated by low delta frequency activity was persistently present. Subsequently a slow, gradual emergence of ~6-8 Hz (theta) and ~16-20 Hz (beta) features tracked behavioral recovery with only shallow features seen at two months and more prominent evidence of these peaks within the power spectrum emerging at three months.

Evaluation of cohort of post-cardiac arrest patients for dominant intra-burst frequency during BSP:

Based on the findings shown in Figure 2, we sought to determine whether intra-burst frequency peaks during BSP showed an association with outcomes of cardiac arrest. In a cohort of 53 prospectively-enrolled cardiac arrest patients we identified 17 patients who had BSP present during acute EEG monitoring after cardiac arrest. Overview of the most commonly assessed baseline clinical variables, neurological exam findings, prognostic tests and outcomes of groups of patients within this cohort are presented in Table 3. Within the 17 patients with BSP in the prospective cohort, 14 patients had unfavorable outcomes (CPC of 4

in one patient and CPC of 5 in 13 patients), and three had favorable outcomes with recovery to functional independence (CPC of 2), by the time of hospital discharge (2 patients) or discharge from acute inpatient rehabilitation (1 patient). Importantly, intra-burst spectral features in all three patients with favorable outcomes revealed the presence of a persistent and prominent theta (~4-7 Hz) spectral peak within the burst period of the BSP; these features remained present throughout the observation period for each patient and showed increasing peak frequency over time (see Figure 3, panel A and Figure 4, right side of the inverted U-shape)). Among the 14 patients with BSP and unfavorable outcomes, 5 patients had either a transient un-sustained theta or slightly higher feature within the intra-burst structure at some point during BSP (i.e. present at one time point only) or the intra-burst frequencies decreased over time. The remaining 7 patients with unfavorable outcomes and BSP had featureless, flat spectra or in two patients a shallow feature at low (~4 Hz) frequencies (for representative examples, see Figure 3, panel B and Figure 4, left side of the inverted U-shape).

Discussion:

Neurological outcomes in comatose patients following cardiac arrest have steadily improved over the last decades with advancements in intensive care, especially since the implementation of therapeutic hypothermia and other TTM protocols^{5,7}. Current guidelines recommend multi-modal assessments and timely reevaluations of prognostic factors but they do not provide clear direction for

maintaining life-support in patients with discordant findings who remain comatose for more than 2 weeks after cardiac arrest^{5,8,10}. However, a general rule of thumb that guides current clinical practice is that longer durations of elapsed time are probative of worsening outcomes⁸. Nevertheless, reports of late recoveries from prolonged post-cardiac arrest coma suggest that recovery of neuronal function can extend over much longer time periods¹¹⁻¹⁶. The three patients with late recovery presented here all remained in coma for more than two weeks following cardiac arrest (17, 37, 30 days, respectively; see Figure 1 and Table 2), and yet achieved independent functional outcomes. In two patients (patient 2 and 3), non-medical reasons (i.e. family wishes and logistical limitations of obtaining a legally authorized decision-maker) prohibited withdrawal of life sustaining therapy; in the third patient (patient 1), knowledge of the outcomes and clinical profiles of these first two patients provided the basis for the prolonged wait period to allow late emergence from coma (Table 2). While it is unclear what underlying factors determined recovery in our late recovery patients, there are several common clinical features (Table 1). Furthermore, all three showed one or more EEG features³⁶ that are considered to be strong predictors of poor outcomes based on current clinical guidelines^{8,9}, including prominent or persistent BSP (all three patients), status epilepticus (in all three patients; including super-refractory status epilepticus lasting until day 14 in one patient). However, none demonstrated more than minimal evidence of hypoxic-ischemic injury on MRI.

Here we find a prominent theta (~4-7Hz) peak spectral power within the initial intra-burst period of BSP in all three patients with late recovery from coma

after cardiac arrest. Two of these subjects showed increasing nominal peak frequencies with the intra-burst spectrum as well (Figure 2). In addition, we tested the association of intra-burst theta frequency peaks and outcomes in a prospective cohort of 53 patients and find that patients with BSP and favorable outcomes within this cohort also demonstrated prominent and persistent theta (~4-7Hz) intra-burst spectral features, while patients with BSP and unfavorable outcomes showed either no features, transient burst features or decreasing intra-burst frequencies with time. Furthermore, in a previous, retrospective, limited study involving an independent cohort of 73 post-cardiac arrest patients²⁶, we also found a link between theta-bursting during BSP and outcomes after cardiac arrest. These findings collectively support the hypothesis that a well-defined theta (~4-7Hz) peak present in the bursting phase of the BSP (Figures 2, 3 and 4) may indicate a recovery potential in comatose post-cardiac arrest patients. Importantly, such theta dominated resting EEG activity has been linked to a range of dynamic regimes as cortico-thalamic integrity improves in patients recovering consciousness after severe brain injuries³⁷ including patients after post-cardiac arrest coma²⁵.

The clinical recovery after a very prolonged BSP (lasting for several weeks after discontinuation of sedatives) in one of the patients reported here led Becker et al.¹¹ to hypothesize that a mechanism similar to BSP during anesthesia in the intact brain may play a key role in protracted coma in patients with late good recoveries. Ching et al.²⁴ originally proposed that burst-suppression may serve as an innate protective mechanism to conserve energy within neurons facing

limited availability of adenosine triphosphate (ATP). As such, this mechanism may result in maintained cellular integrity and act to avoid neuronal membrane collapse. In addition, in healthy subjects in general anesthesia induced BSP, as seen by Ching et al., the brief reconstitution of the background EEG within the BSP reflects the transient restoration of baseline cellular energetics and expression of intrinsic cortico-thalamic network dynamics. Other network models of BSP generation have been proposed³⁸ but do not challenge the core role of intracellular ATP production in this setting; these models suggest the further possibility that synaptic depletion may play a role at the network level that may offer additional future testable measures of BSP. We emphasize that the intra-burst spectral theta feature may mark the preservation of network dynamics in patients with BSP. The presence of a theta feature in the continuous EEG of some patients with such an intra-burst feature supports this hypothesis. Moreover, increasing frequencies over time into the alpha range, as seen in Patient 2 (Figure 2) are further consistent with normalization of the corticothalamic network following the interpretation of Ching et al. (2012).

Extending these ideas, and following Westover et al.³⁹, we assessed the dominant frequencies of bursts separated from suppression periods during BSP to assess evidence of potential for early functional preservation of cortico-thalamic connections^{25,26}, and followed evolution of these spectral EEG features longitudinally (Figures 2, 3 and 4). Our findings suggest a generalization of the Ching et al. model to examine the dynamics of recovery in post-cardiac arrest patients through evolution of intra-burst frequencies during BSP. The inverted U

curve shown in Figure 4 infers a point of equal potential for neurons to recover or move toward programmed cell death. The prominent theta spectral peaks appearing in these post-cardiac arrest patients suggests that effective cellular preservation of the neurons by BSP as proposed in the Ching et al. model is marked by the emergence of theta rhythms as opposed to slower delta (<4Hz) spectral features. As the power spectrum averages over large neuronal populations the specific dominant intra-burst frequency may therefore be a sensitive index of the overall impact of ~~hypoxia-hypoxic-ischemic on the~~ brain injury. Taken together, in patients without evidence of widespread cortical injury, ongoing BSP along with a slow evolution of a severely disorganized EEG background activity (including measurable improvements in the mean frequency of intra-burst activity; Figure 4) may reflect an effort by the brain to maintain cellular survival^{24,26}. However, the correlation of changes in intra-burst nominal frequencies will require further larger, prospective studies.

Although no specific characterization of such a process is known for neurons, a “stunning” of another excitable cell type, the cardiac myocyte, is described after hypoxic-ischemic injury and is associated with specific patterns of associated gene expression⁴⁰. Changes in gene expression typically occur within 2-4 weeks, a similar timeframe to several observed clinical evolutions in our patients with late recovery from coma presented here, suggesting possible correlations⁴¹. Although the possible significance of these considerations in relation to the remarkable recoveries reported here is unknown, they support systematic studies of prolonged post-cardiac arrest coma and provide a potential

measure for further investigation.

The late but continued slow neurological recovery seen in all three post-cardiac arrest patients with prolonged coma presented here bears a strong resemblance to the natural history of recovery after severe traumatic brain injuries mostly described in patients with prolonged disorders of consciousness⁴². In such patients, slow recovery from coma through minimally conscious state to emergence into interactive communication typically occurs over several months and can give way to independent levels of functioning after one year. While continued clinical improvement months to years after the cardiac arrest was evident in all three patients presented here (Table 2), detailed neuropsychological tests were performed at 7 and 19 months after cardiac arrest, respectively, in Patient 1. Cognitive functions in domains with known correlation of neuronal structures sensitive to hypoxia or anoxia, such as working memory and sustained attentional function⁴³ lagged for months compared to other neuropsychological domains. This suggests that neuronal subtypes known to be sensitive to ~~hypoxia~~ hypoxic-ischemic injury may recover function more slowly than generally anticipated. Whether this time lag reflects effects of local deafferentation from loss of neighboring neurons that undergo programmed cell death or an intrinsic subcellular alteration broadly affecting neuronal signaling functions in selectively vulnerable neuronal populations is unknown. In this context, however, the wide preservation of neuronal volume in all three subjects suggest that at least part of their prolonged recovery process originates from such intrinsic alterations of cell function. Collectively, however, our findings

challenge traditional understanding of post-anoxic recovery potential of such post-cardiac arrest patients and invite further investigation of the long-term recovery processes in neurons exposed to anoxia or severe ~~hypoxia~~hypoxic-ischemic conditions.

The timeframes of recovery from prolonged coma in the patients reported here are considered to be significant outliers against the currently published large studies^{15,16,36,44-56}, case reports¹²⁻¹⁴ and reviews/guidelines^{3,5-10}. The importance of these patients is underlined by the fact that in present clinical practice withdrawal of life sustaining therapy in comatose post-cardiac arrest patients most typically occurs within 5-7 days⁵⁰ and rarely exceeds two weeks even in the setting of some favorable prognostic factors^{6,44,46,51,57}. As a result, most studies are hindered by self-fulfilling prophecy⁵⁸ as withdrawal of life sustaining therapy practices in post-cardiac arrest patients with prolonged coma^{53,59} limit the evaluation of the natural course of their recovery potential or cellular survival mechanisms. Furthermore, the marked change in clinical outcomes generally associated with TTM of post-cardiac arrest coma^{5,7} indicates that such therapies can significantly shift the probabilities of permanent neuronal death or dysfunction¹⁹ after cardiac arrest and hence, the possibility of favorable outcomes.

Current practice recommendations offer limited guidance for continued care and treatment options for patients who remain comatose for over 2 weeks after cardiac arrest⁶⁻⁹. Nevertheless, our findings and the proposed mechanism offer some immediate potential implications for patients in prolonged post-cardiac

arrest coma and lack of overwhelming cortical injury on MRI or CT. As discussed earlier, prolonged BSP may be linked to impaired metabolism in post-hypoxic neurons, therefore maintaining caloric intake and hydration during recovery may be important in post-cardiac arrest patients with these clinical features. As decisions to limit both hydration and gastrostomy feeding often arise coincident with early observational periods^{36,46,47,55}, these patients may benefit from maintaining available metabolic substrates during an extended observation period. In addition, as done for patient 1, institution of a time-limited trial of pharmacologic activation, such as amantadine, should be considered to drive anterior forebrain activity. The broad activation of fronto-striatal systems via the NMDA antagonists effects of amantadine are thought to underlie its positive effects on disorders of consciousness in patients following traumatic brain injuries^{60,61}, however, case reports demonstrate behavioral activation patients with in post-hypoxic-ischemic brain injury⁶². Furthermore, in the computational model of BSP²⁴, wide functional or structural deafferentation modulated ATP dynamics within neurons. Thus, interventions aimed at reversal of marked functional dysfacilitation⁶³ via increasing the glutamatergic tone may alter intrinsic neuronal metabolic requirements and allow for a reset of network dynamics in such patients as described here.

Beyond BSP, similar considerations may be relevant to patients with other persistently abnormal electroencephalographic activity patterns that are linked to increased metabolic demand, including refractory seizures⁶⁴ or sustained rhythmic and periodic epileptiform discharges⁶⁵. In addition, recent studies have

shown that super-refractory status epilepticus, as seen in Patient 1, may remit with the use of ketamine, another NMDA-antagonist agent^{66,67}. Lastly, ketogenic diet is increasingly used as an effective treatment for refractory seizures in adults⁶⁸ another treatment modality thought to alter metabolic substrate availability even though the basic underlying mechanism ~~are-is~~ not completely understood^{69,70}.

Perhaps most importantly, our findings in conjunction with emerging clinical trials of neuroimaging markers of structural integrity in post-cardiac arrest comatose patients^{17,18} also support the broad use of structural imaging protocols (including MRIs) in such patients. Lack of neuroimaging evidence for overwhelming neuronal injury in persistently comatose patients should prompt a vigorous attempt to promote brain activation and aggressive treatment of ongoing seizures or other varying persistent functional abnormalities seen after cardiac arrest.

The generalizability of our findings is unknown; however, the consistency of physiological profiles supports further investigation of common underlying mechanisms as proposed here. In addition, the role of early withdrawal of therapy is unknown. At a minimum, our observations underscore the recommendations of current clinical guidelines to wait and periodically reassess patients with discordant prognostic factors who remain in prolonged coma after a cardiac arrest^{5-8,10}. However, our results strongly argue that favorable recoveries are possible even after several weeks of coma in a subset of patients. Better understanding of mechanisms of cellular functional recovery after exposure to anoxic conditions⁷¹ will aid further uncovering of mechanisms of intrinsic neuronal

protection strategies²⁴ and allow design of future clinical trials⁷² that will identify more reliable biomarkers of recovery in patients with prolonged post-cardiac arrest coma.

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Author contributions:

"PBF, NDS and OD contributed to the conception and design of the study; PBF, NDS and OD contributed to the acquisition and analysis of data; PBF and NDS contributed to drafting the text and preparing the figures and tables."

Potential Conflict of Interest:

Nothing to report.

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Table and Figure legends:

Table 1: Overview of relevant baseline clinical variables and hospital evaluations for each patient with prolonged post-cardiac arrest coma and independent functional recovery. (CA: cardiac arrest, ROSC: return of spontaneous circulation, OHCA: out-of-hospital cardiac arrest, PEA: pulseless electrical activity, TTM: targeted temperature management, SSEP: somatosensory evoked potential.)

Table 2: Overview of clinical milestones related to recovery of consciousness, functional outcomes and goals of care discussions for each patient with prolonged post-cardiac arrest coma.

Table 3: Overview of the baseline clinical variables, clinical examination, hospital evaluations and outcomes in a cohort of post-cardiac arrest (n=53) grouped based on presence of BSP on EEG and outcomes within the group of patients with BSP. Data presented as average (IQR) or N/N(%) based on all available data points. (CA: cardiac arrest, OHCA: out-of-hospital cardiac arrest, ROSC: return of spontaneous circulation, TTM: targeted temperature management,

SSEP: somatosensory evoked potential, NSE: neuron specific enolase, WLST: withdrawal of life sustaining therapy, CPC: cerebral performance categories).

Table 4: Maximum frequency of intra-burst spectral peaks and presence of EEG continuity for all patients with BSP. ~~Of note, in this table~~ Patients marked as #1-3 ~~are the~~ correspond to patients with independent functional outcomes following prolonged post-cardiac arrest coma (~~see also~~ shown in Figure 2); patients #4-6 ~~are~~ correspond to the patients in from the prospective cohort with BSP on EEG ~~and~~ demonstrating favorable outcomes (see also Figure 3, patients A1, A2 and A3); patients #7-20 ~~are~~ correspond to the remaining patients in the prospective cohort with BSP on EEG ~~and~~ demonstrating unfavorable outcomes (~~for~~ within this group, patients #7-9, ~~see also~~ Figure 3, correspond to patients B1, B2 and B3 in Figure 3).

Figure 1: Timeline of recovery of three patients with independent functional outcomes following prolonged post-cardiac arrest coma (patient 1: light grey, patient 2: medium gray, patient 3: dark gray), in relation to relevant clinical examination findings (six upper panels of the figure) and relevant electroencephalographic (EEG) features (four lower panels of the figure). For reference, timeline of use of sedative drips is indicated in the middle panel. Cutoff times for anticipated poor prognosis for each feature based on current guidelines⁶ are indicated with vertical lines in each panel of the timeline. Black vertical lines indicate that the feature is regarded to be a strong predictor of poor

outcome (with low False Positive Rate (FPR and narrow Confidence Interval (CI)), while gray vertical lines indicate relatively strong but not universal predictors of poor outcome (with high FPR (5% or above), or wide CI). Large light grey box indicates the typical time-frame when withdrawal of life sustaining therapy (WLST) occurs in comatose patients who do not show signs of clinical recovery of consciousness. Dashed brackets in lower panels indicate when EEG recording was not available (if the feature presented continued to be present or absent on subsequent EEG recording; otherwise, no brackets were drawn regardless of the availability of further EEG recordings). (SIRPIDS: stimulus induced rhythmic, periodic or ictal discharges)

Figure 2: Spectral features of resting EEG patterns for each of the 3 patients with independent functional recovery after prolonged post-cardiac arrest coma. Spectral EEG features on representative days of recordings are presented vertically for each patient. On each diagram, spectral power of the resting EEG is visualized between 0-24 Hz from a single midline channel (Cz). If burst suppression pattern (BSP) was present on EEG on a given day, 'bursting' and 'suppression' periods were analyzed separately and cut from the same EEG segment (see Methods). In these diagrams, red lines represent spectra during 'bursting', blue lines represent spectra during 'suppression' periods. If the EEG showed a continuous background pattern (with or without epileptiform activity), contiguous EEG segments were used to calculate a single spectrum (diagrams with a single green spectra plotted). Blue columns highlight presence of theta

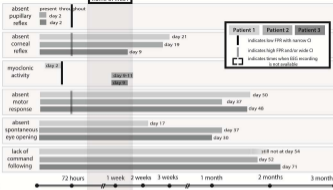
dominant spectral features within the bursts (Patient 1: Day 1 [7.6Hz], Day 7 [7.0Hz], Day 14 [7.74Hz]; Patient 2: Day 10 [7.6Hz]; Patient 3 Day 3 [5.3Hz], Day 6 [7.0Hz]); green column indicates alpha dominant spectral feature within the bursts (Patient 2, Day 14 [8.3Hz]). (VS: vegetative state)

Figure 3: Spectral features in representative comatose post-cardiac arrest patients with burst-suppression pattern (BSP) on acute EEG in the prospective cohort. Plotting and color conventions used in this figure are same as in Figure 2. Spectral EEG features on representative days of recordings are presented horizontally in each row for each patient presented. Panel A shows patterns of recovery in all three patients from the cohort of post-cardiac arrest patients who had BSP on EEG and had favorable outcomes (patients A1, A2 and A3). In these patients, prominent theta (~4-7 Hz) intra-burst and increasing bursting frequency over time is evident. Panel B shows representative examples of non-recovery bursting patterns in representative three patients with BSP (selected from 14 patients) who had unfavorable outcomes. In these patients, if a spectral feature was present (including theta) on multiple days, the frequency of bursting activity decreased with time (e.g. patient B1), or the spectral feature was present briefly (at only one time-point, but not before or after; e.g. patient B2) or there were no intra-burst features present at any time-point (e.g. patient B3). [Maximum frequency of intra-burst spectral peaks and presence of EEG continuity for all patients are detailed in Table 4.](#)

Figure 4: Time evolution of burst-structure in representative comatose post-cardiac arrest patients with burst-suppression pattern (BSP) on acute EEG in the prospective cohort. Each plot represent a single patient with intra-burst spectral features over time (orange, light red and dark red spectra). In all patients with BSP and favorable outcome bursting frequency increased with time (right side of the inverted U shape). In all patients with BSP and unfavorable outcomes, there were either no features present during bursting, or if any feature was present (including theta), it was present briefly and/or the frequency of bursting activity decreased with time (examples of all of these patterns are shown over the left side of the inverted U shape).

Typical time-frame of WJLST

Clinical exam



Sedatives

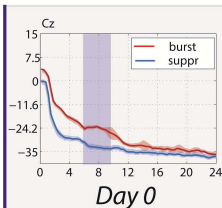


EEG findings

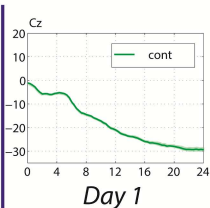


Resting EEG spectra for patients with prolonged post-cardiac arrest coma

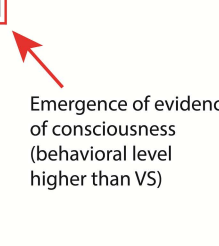
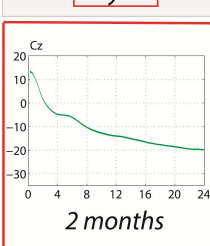
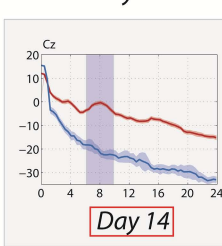
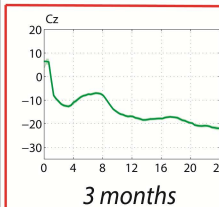
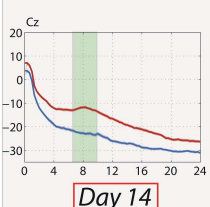
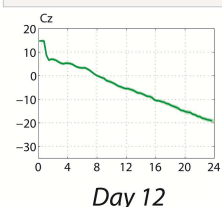
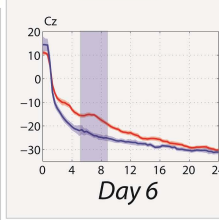
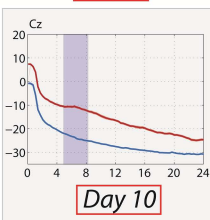
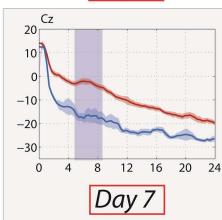
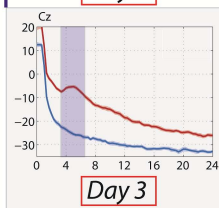
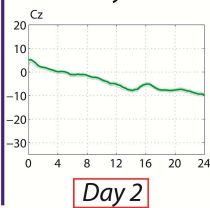
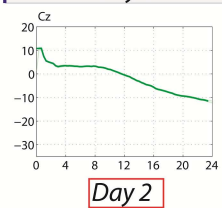
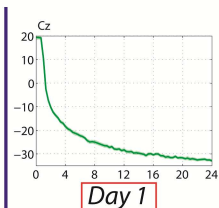
Patient 1



Patient 2



Patient 3



Emergence of evidence of consciousness (behavioral level higher than VS)

Legend

Day 1 Day(s) since cardiac arrest

Red box Sedative drips used

Blue box Therapeutic hypothermia

Grey box Burst suppression pattern (BSP)

EEG spectra (all power vs. frequency):

Red line Bursts during BSP

Blue line Suppression during BSP

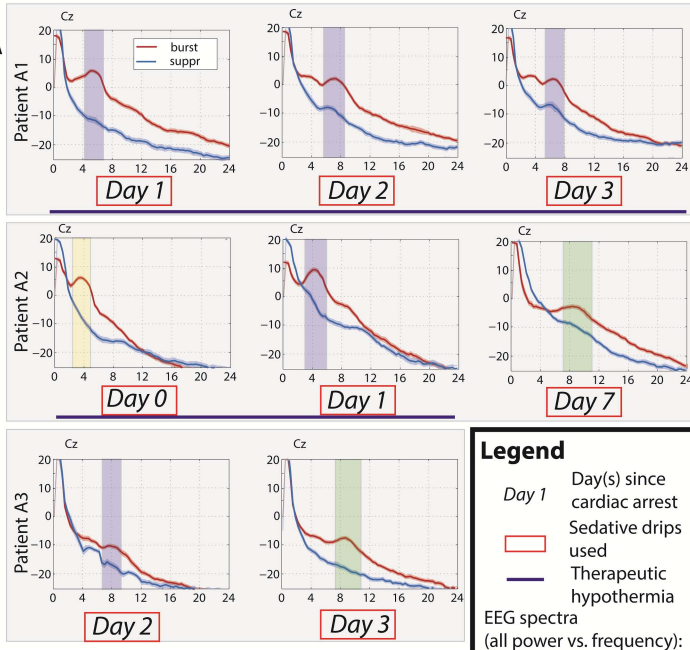
Green line Continuous EEG

Purple box Theta (5-7 Hz)

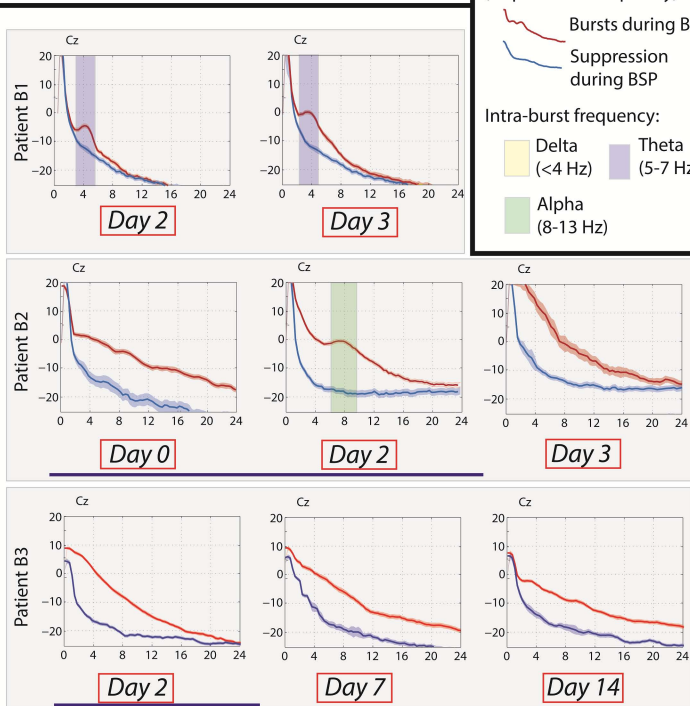
Green box Alpha (8-13 Hz)

A

Recovery patterns

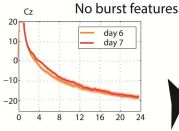
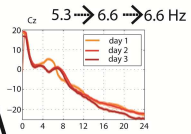
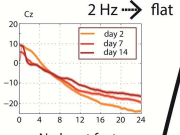
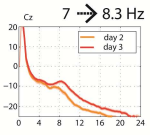
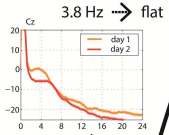
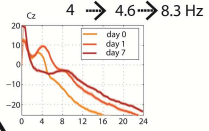
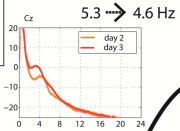
**B**

Non-recovery patterns



Evolution of burst structure

Intra-burst EEG spectra over time



decreasing burst frequency/
no burst features

increasing burst frequency

Patients remained in coma or died

Patients with recovery of consciousness

	Patient 1	Patient 2	Patient 3
age (at the time of CA)	51	71	50
sex	female	male	female
setting; initial rhythm	OHCA; PEA	OCA; V-tach/V-fib	OHCA; V-fib
ROSC (minutes)	12	10	20
TTM protocol (target temp, length)	33 C, 24 hr cooling with 24 hr rewarming	33 C, 24 hr cooling with 24 hr rewarming	33 C, 24 hr cooling with 24 hr rewarming
SSEP	N20 present b/l (day 13)	not available	N20 present b/l (day 10)
neuron specific enolase (NSE)	not available	not available	peaked at 23.8 ug/L on day 3
acute head CT	unremarkable	minimal diffuse loss of grey-white differentiation	unremarkable
brain MRI(s)	Multiple lacunar infarcts in the cerebellum, but no evidence of hypoxic injury above the tentorium (day 13)	No evidence of acute infarction; small chronic subcortical ischemic changes in the left parietal lobe; mild microvascular white matter ischemic disease (day 17)	MRI #1: Evidence of mild hypoxic injury in bilateral caudate heads and putamina (day 9); MRI #2: Resolution of signal abnormalities previously seen; new mild generalized parenchymal volume loss (day 72)

	Patient 1	Patient 2	Patient 3
tracheostomy and feeding tube placed	day 19	day 16	day 14
recovery from coma[^]	day 17	day 37	day 30
recovery of conscious awareness[*]	after day 54	day 52	day 71
disposition and functional state at hospital discharge	day 92; acute rehabilitation Able to speak in full sentences with severe dysarthria; transfers to chair; unable to stand or walk.	day 79; acute rehabilitation Described as “very awake, alert” and having a “good conversation flow”.	day 126; acute rehabilitation Oriented to self, date and time; able to hold a conversation; transfers to chair, able to stand with moderate assistance.
best known functional state	Able to perform activities of daily living independently, but unable to go back full employment because of instability upon standing and walking. Able to travel with family.	Independent in activities of daily living. Recurrent seizures precluded the ability to return to work. Some impairment in short and long-term memory, attention and executive function but able to hold public speeches.	Living at home abroad; video segments several months after return to home demonstrated significant recovery of cognitive and motor capacities (walking, dancing alone, singing and social engagement with friends and family).
goals of care discussions during acute hospital stay	Family decided to continue active care after consultation with author NDS who advised them based on the similarities in clinical profiles and known outcomes of patient 2 and 3 presented here.	Family decided to continue active care despite multiple experts from various academic centers (including author NDS and OD) who agreed that according to the guidelines the chance for neurological recovery above vegetative state was considered negligible.	Family decided to continue care as they lived abroad and were not able to visit the patient in person.

[^] defined as evidence for spontaneous eye opening (transition from coma to vegetative state)

^{*} defined as evidence of intermittent command following (transition from vegetative state to minimally conscious state)

	Total n=53	Patients without BSP (n=36)	Patients with BSP		
			All (n=17)	Unfavorable Outcome (n=14)	Favorable outcome (n=3)
Baseline characteristics	age (at the time of CA)	57.3 (47.25-68)	62.82 (53-78)	65.36 (53-79.5)	51 (45-60.5)
	sex, male	24/36 (67%)	13/17 (76%)	10/14 (71%)	3/3 (100%)
	setting, OHCA	19/36 (53%)	13/17 (76%)	10/14 (71%)	3/3 (100%)
	initial rhythm, shockable [^]	13/29 (45%)	7/14 (50%)	4/11 (36%)	3/3 (100%)
	Witnessed [^]	34/36 (94%)	14/16 (87.5%)	11/13 (85%)	3/3 (100%)
	ROSC (minutes) [^]	23.8 (9-35)	22.75 (13.75-34.25)	24.64 (15.25-34.75)	9.5 (6.75-12.25)
	TTM, target temp	5 (not cooled), 3 (33C), 1 (35.5C), 26 (36C), 1 (n/a)	6 (33C), 1 (34.5C), 9 (36C), 1 (n/a)	5 (33C), 1 (34.5C), 7 (36C), 1 (n/a)	1 (33C), 2 (36C)
	length of ICU stay (days)	23.5 (11.75-25.5)	12.7 (7-19)	11.29 (4.75-15.5)	19.3 (18.5-20)
Exam after rewarming/at 72 hours	pupillary reflex (present) [^]	31/35 (88%)	12/17 (70%)	9/12 (65%)	3/3 (100%)
	corneal reflex (present) [^]	6/12 (50%)	11/14 (78%)	8/12 (66%)	3/3 (100%)
	motor response to pain (better than reflexive)	19/36 (53%)	3/17 (18%)	1/14 (7%)	2/3 (67%)
Prognostic tests	SSEP, N20 absent [^]	2/13 (15%)	3/8 (38%)	3/7 (43%)	0/1 (0%)
	NSE > 33 ug/L [^]	6/23 (26%)	7/13 (54%)	7/12 (58%)	0/1 (0%)
	MRI, abnormal [^]	10/25 (40%)	4/7 (57%)	4/5 (80%)	0/2 (0%)
outcomes	Died	18/36 (50%)	13/17 (76%)	13/17 (76%)	n/a
	Died after WLST	13/18 (72%)	11/13 (85%)	11/13 (85%)	n/a
	Neurological reason for WLST	10/13 (77%)	9/11 (82%)	9/11 (82%)	n/a
	Favorable outcome (CPC 1-2)	7/36 (19%)	3/17 (18%)	n/a	3/3 (100%)

[^]Data not available for all patients.

	Patient	Maximal intra-burst peak frequency	EEG ever continuous
Patients with prolonged coma	#1	7.6 Hz	Yes
	#2	8.3 Hz	Yes
	#3	7 Hz	Yes
Patients in cohort with BSP and favorable outcome	#4	6.6 Hz	Yes
	#5	8.3 Hz	Yes
	#6	8.3 Hz	Yes
Patients in cohort with BSP and unfavorable outcome	#7	5.3 Hz	Yes
	#8	8.3 Hz	Yes
	#9	No peak	No
	#10	No peak	No
	#11	No peak	No
	#12	No peak	Yes
	#13	3.8 Hz	No
	#14	5.3 Hz	Yes
	#15	7 HZ	Yes
	#16	7 Hz	No
	#17	No peak	Yes
	#18	No peak	Yes
#19	3.8 Hz	No	
#20	No peak	Yes	