ORIGINAL RESEARCH

Spectral Content of Electroencephalographic Burst-Suppression Patterns May Reflect Neuronal Recovery in Comatose Post-Cardiac Arrest Patients

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Purpose: To assess the potential biologic significance of variations in burst-suppression patterns (BSPs) after cardiac arrest in relation to recovery of consciousness. In the context of recent theoretical models of BSP, bursting frequency may be representative of underlying network dynamics; discontinuous activation of membrane potential during impaired cellular energetics may promote neuronal rescue.

Methods: We reviewed a database of 73 comatose post-cardiac arrest patients who underwent therapeutic hypothermia to assess for the presence of BSP and clinical outcomes. In a subsample of patients with BSP ($n = 14$), spectral content of burst and suppression periods were quantified using multitaper method.

Results: Burst-suppression pattern was seen in 45/73 (61%) patients. Comparable numbers of patients with (31.1%) and without (35.7%) BSP regained consciousness by the time of hospital discharge. In addition, in two unique cases, BSP initially resolved and then spontaneously reemerged after completion of therapeutic hypothermia and cessation of sedative medications. Both patients recovered consciousness. Spectral analysis of bursts in all patients regaining consciousness ($n = 6$) showed a prominent theta frequency (5–7 Hz) feature, but not in age-matched patients with induced BSP who did not recover consciousness ($n = 8$).

Conclusions: The prognostic implications of BSP after hypoxic brain injury may vary based on the intrinsic properties of the underlying brain state itself. The presence of theta activity within bursts may index potential viability of neuronal networks underlying recovery of consciousness; emergence of spontaneous BSP in some cases may indicate an innate neuroprotective mechanism. This study highlights the need for better characterization of various BSP patterns after cardiac arrest.

Key Words: Cardiac arrest, EEG, Burst-suppression, Recovery of consciousness, Coma.

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Burst-suppression pattern (BSP) observed on EEG refers to quasiperiodic, higher-amplitude ("bursting") activity alternating with low-amplitude, electrical quiescence ("suppression").[1–3] This pattern can be observed under a range of conditions including during deep anesthesia[3,4] or hypothermia,[5] during neonatal development (trace alternant[6]), or in childhood epileptic encephalopathies.[7] At times, it is reversibly induced as a means of cerebral protection during surgery[5,8] and management of status epilepticus.[9] However, when associated with certain pathologic conditions including postanoxic coma after a cardiac arrest,[4,10,11] BSP is generally thought to signal an agonal state, particularly when generated spontaneously by the brain in the absence of sedation or hypothermia.

Burst-suppression pattern can be seen within 48 hours in up to 50% of patients after cardiac arrest undergoing therapeutic hypothermia (TH).[12] Current literature typically describes this pattern as "highly malignant" and it is often reported to have 0% false-positive rate for prediction of poor outcome in these patients.[11,13–15] A recent article[16] used a model based on quantitative measures of EEG background discontinuity and achieved 100% specificity (sensitivity of 50%) for poor outcome as early as 24 hours after cardiac arrest and 90% specificity (sensitivity of 57%) for a good outcome at 12 hours. According to current clinical guidelines, the combination of a BSP on EEG at any time with at least one other variable associated with low false-positive rate is a reasonable consideration for withdrawal of life-sustaining therapy (WLST) at 72 hours after a cardiac arrest.[17–19]

However, several observations raise questions whether the above findings and recommendations can be invariably generalized to all post-cardiac arrest patients. For example, one study showed that the presence of identical bursts during BSP—as opposed to variable bursting patterns—was strongly correlated with unfavorable outcomes after cardiac arrest.[12] In addition, recent case reports describe remarkable recovery of consciousness after days to even weeks of persistent BSP on EEG in the setting of prolonged postanoxic coma.[20,21]

A proposed mechanism underlying the energy dependence of burst suppression[22] supports the inference that quasiperiodic activation of neurons at the threshold of survival may be preserved for longer times in the setting of energy deficit, contributing to their eventual recovery.[20,23] In addition, the spectral content of the

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background EEG is predicted to be reflected within the "bursts" during BSP as measured in healthy volunteers in reversible anesthetic coma.[5,22] In earlier studies of post-cardiac arrest patients, we have shown that regional variations in spontaneous EEG background frequencies correlate with recovery of consciousness and likely reflect functional preservation of corticothalamic integrity when theta (5–7 Hz) activity is present.[24] In this context, we postulated that in the setting of BSP during anoxic coma, spectral features within bursts (e.g., presence of a theta feature) may help to identify and characterize variations in the functional integrity of underlying neuronal networks that may be potentially recoverable, such as large-scale corticothalamic connections.[24]

Here, we study a cohort of patients with cardiac arrest treated with TH and characterize the evolution of spectral features during BSP in a subset of patients ($n = 14$). We examine the potential prognostic implications of variable BSP patterns and investigate whether the characteristics of bursting during BSP may help delineate network dynamics pertinent to restoration of consciousness, such as recovery of functional corticothalamic integrity.[24,25]

METHODS

Patient Cohort, Clinical Data Collection, and Definition of Outcomes

Seventy-three patients with in-, or out-of-hospital cardiac arrest who underwent TH at NewYork-Presbyterian/Weill Cornell Medical Center (NYP/WCMC) between 2010 and 2013 were enrolled into the study under the WCMC Cardiac Arrest/Hypothermia Database Protocol. The study was approved by the institutional review board of NYP/WCMC. All patients underwent total body cooling with target temperature to 33°C for 24 hours after a cardiac arrest and were subsequently rewarmed over 24 to 48 hours. During hypothermia, sedative drips, narcotics, and paralytic medications, or a combination of these were used as dictated by clinical care. Retrospective chart review was performed to collect information about all sedative medication doses and major metabolic derangements during hospitalization. Routine and standardized (i.e., FOUR score[26]) neurologic examinations were used to track neurologic recovery, including recovery of conscious awareness.

Patients were divided into two groups based on clinical outcomes: (1) patients who regained consciousness (defined as the ability to reliably follow commands, speak, and move purposefully) during any time of the hospital course had favorable outcomes, and (2) patients who did not recover consciousness by the time of hospital discharge had unfavorable outcomes.

EEG Recordings

As part of the TH protocol, continuous video EEG monitoring was performed in all patients using a standard video-EEG recording system and reviewing software, both products of Natus-XLTEK (Natus Medical Inc, San Carlos, CA). Collodion-pasted electrodes were placed by certified technicians according to the international 10 to 20 system, and typically included a 19-channel "double banana" montage. Continuous video EEG recordings were visually screened, reviewed, and evaluated at least daily by a board-certified clinical neurophysiologist as part of the routine clinical standard of care.

Quantitative EEG Analysis

For each patient selected, quantitative EEG analysis was performed on each day when EEG recordings were available. For detailed description of quantitative EEG methods, please see Fig. 1. Briefly, as a novel approach, on days when BSP was present, we characterized spectral content of "bursting" and "suppression" periods from the same EEG segments separately. On days when EEG background was continuous, artifact-free segments were selected and used for further analysis. Frequency power spectra of each data set was visually assessed over midline and parasagittal centroparietal electrodes because specific spectral features related to corticothalamic integrity are expected to be best seen over these channels.[24] Spectral features of bursts and suppression periods during BSP and during continuous EEG were compared both among patients and within each patient over time.

Patient Selection

Selection of Patients With and Without BSP

Daily continuous video EEG reports for all 73 patients were reviewed and included in the cohort analysis. Patients were included in the BSP group if charted reports described background EEG as "burst suppression," "suppression burst," or "discontinuous with periods of generalized attenuation" lasting at least 1 second (in agreement with accepted descriptions of burst suppression[27]) at any time during continuous video EEG.

In addition, BSP pattern was considered to be "induced," if at least partial contribution of sedative medications or hypothermia to the appearance of BSP could not be ruled out, and "spontaneous," if the possible residual effects of these interventions were no longer considerable.

Selection of Patients for Quantitative EEG Analysis

All EEG records of patients with BSP were screened and those with sufficiently long, uncorrupt, and artifact-free EEG recordings allowing for accurate quantitative analyses were further assessed. Six patients with favorable outcomes and eight patients with unfavorable outcomes (age and sex matched to patients with favorable outcomes) were identified. Two patients with favorable outcomes had a unique evolution of various BSP patterns with an unanticipated reemergence of prominent, spontaneous BSP after resolution of induced BSP observed during TH protocol. The other four patients with favorable outcomes and all eight patients with unfavorable outcomes had induced BSP only emerging during TH protocol.

RESULTS

Baseline Cohort Characteristics and Clinical Outcomes Based on Presence of BSP

A total of 73 patients (48 men) who remained comatose after a cardiac arrest were evaluated (Table 1). Twenty-four patients in the entire cohort (32.9%) recovered consciousness during the

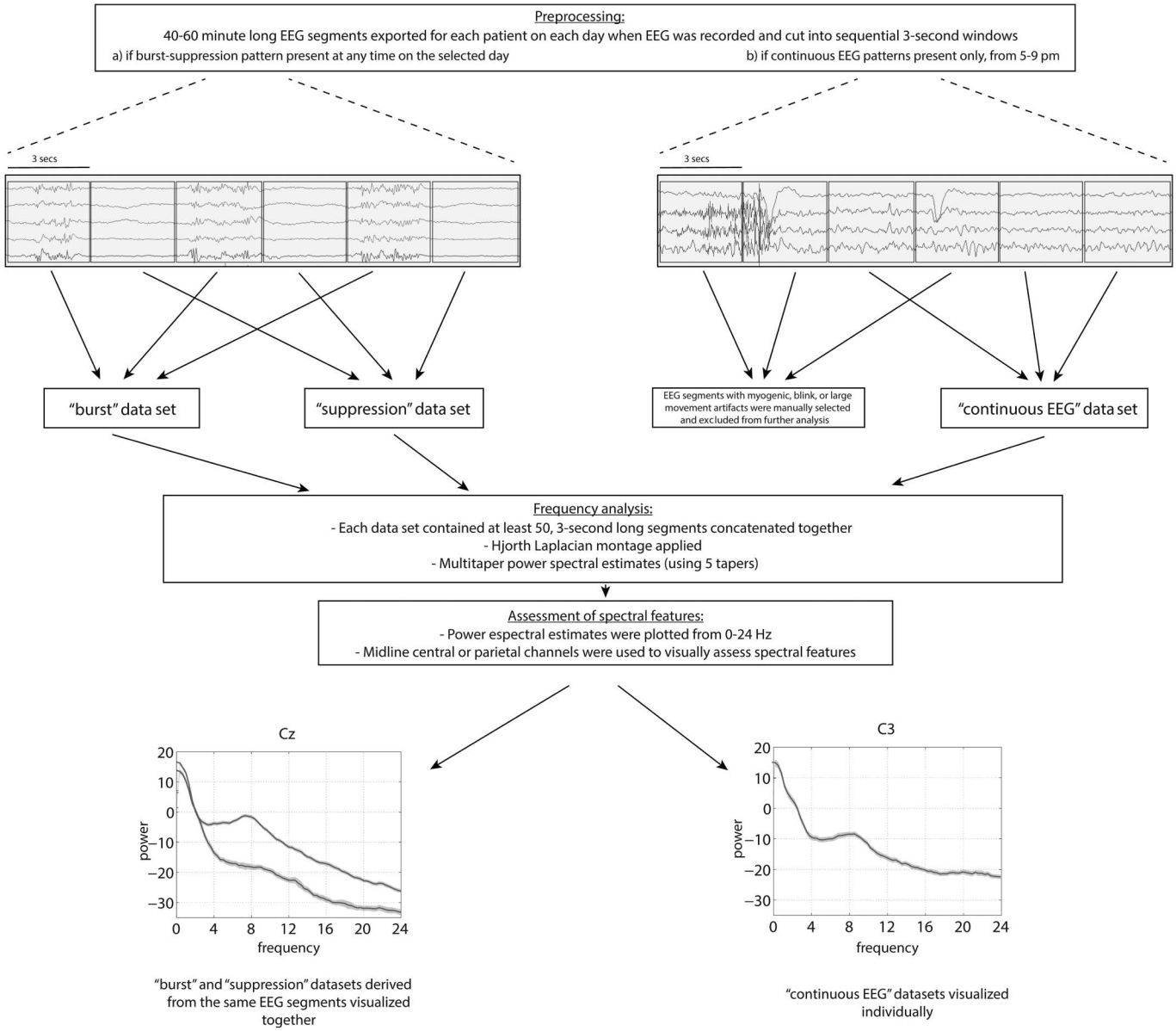

FIG. 1. EEG data selection and quantitative analysis. For each patient selected for quantitative EEG analysis, 40- to 60-minute segments of EEG data were exported each day of recording. These EEG segments were imported into Matlab (MathWorks Inc, Natick, MA) and cut into three-second long periods. If BSP was present, at least 50, artifact-free, three-second long periods of bursts and suppression from the same exported segment were concatenated together, respectively, to create "burst" and "suppression" data sets for that day. If suppression periods were shorter than 3 seconds or if the EEG background was continuous, at least 50 three-second periods were concatenated together to make a "continuous" data set for that day. Each concatenated data set underwent frequency analysis using the multitaper method,[38,39] as implemented by the code mtspectrumc in the Chronux toolbox.[40] Power spectra (0–24 Hz) were plotted for each selected patient for each day of recording over midline and parasagittal centroparietal electrodes because specific spectral features related to corticothalamic integrity are expected to be best seen over these channels.[24] In addition, these channels typically contain the least amount of myogenic and movement artifacts. Power spectra were then visually assessed and spectral features were compared both among patients and within each patient over time. BSP, burst-suppression pattern.

hospital course (Table 2). Of these patients, five later died (due to rearrest, systemic complications, or WLST) and 19 were discharged home or to a rehabilitation facility. Of the 49 patients (67.1%) who had unfavorable outcomes, nine remained in coma, vegetative state, or minimally conscious state and were discharged to a long-term care facility. Of the 40 patients who died before regaining consciousness, 22 (30.1% of total cohort) died after a WLST decision was made.

TABLE 1. Cohort Demographics and Baseline Variables

All Patients ($n = 73$)	Patients With Burst-Suppression Pattern on EEG ($n = 45$; 61.6%)	Patients Without Burst-Suppression Pattern on EEG ($n = 28$; 38.3%)
Male	29	9
Mean age (years)	61.1	68
In-/out-of-hospital arrest	18/27	15/13
PEA/asystole/VFibVTach arrest	21/4/15	10/8/10

PEA, pulseless electrical activity; VFib, ventricular fibrillation; VTach, ventricular tachycardia.

Burst-suppression pattern was seen in 45/73 (61.6%) patients. Importantly, similar proportions of patients with and without BSP on EEG eventually recovered consciousness (14/47 [31.3%] and 10/28 [35.7%], respectively, Table 2). In patients who died, WLST was the most common reason for death in both groups and occurred at comparable times after arrest (mean of 9.75 and 8.6 days, respectively). Burst-suppression pattern was seen only in the setting of sedative use in most patients who recovered consciousness ($n = 12$); however, we found two patients with spontaneous, reemergence of BSP who also recovered consciousness (see below). None of the patients who remained unconscious or died at the time of hospital discharge showed similar reemergence of spontaneous BSP based on review of clinical EEG reports of all patients.

Characterization of Patients Selected for Quantitative EEG Analysis

Patients With Induced and Spontaneous BSP

In the two patients with reemergent spontaneous BPS, initially, induced BSP was seen during active cooling phase of TH. During rewarming, EEG background in both patients became more continuous, i.e., the suppression periods became shorter, consistent with the parametric sensitivity typically associated with BSP during rewarming/weaning of sedatives.[5,22] However, BSP subsequently reemerged (on day 3 and day 5 for patient 1 and 2, respectively) after sedation was stopped and rewarming was complete; periods of suppression became longer and bursts became more prominent, at odds with what is typically expected in this setting. For both patients, EEG became continuous on day 6. Both patients began to reliably follow commands on day 11, recovered ability to speak (day 16 and day 31, respectively), and were discharged to acute rehabilitation facility (day 30 and day 35, respectively).

Spectral analysis (Fig. 2, panel a) of bursts in both patients during induced BSP was dominated by a delta frequency (maximal at 3–4 Hz) feature (patient 1, day 1 and patient 2, days 2–3). During rewarming and immediately after rewarming, the spectra became mostly featureless (patient 1, day 2 and patient 2, day 4). During ensuing spontaneous BSP, bursting spectra showed a prominent theta feature (maximal around 7 Hz), which became more pronounced over time (patient 1, days 3–4 and patient 2, day 5). After EEG in both patients became continuous by day 6, the spectra were mostly dominated by low frequencies only. However, in patient 1, emergence of a normal alpha frequency background (maximal around 10 Hz) was observed on day 9.

Patients With Induced BSP and Favorable Outcome

In all four patients who underwent quantitative EEG analyses, BSP emerged during the TH initially. Subsequently, the record either rapidly became continuous at the end of the cooling phase or remained in BSP throughout TH with gradual emergence of continuous EEG during or shortly after rewarming/weaning of sedatives. Of note, two of the four patients were already able to follow commands by day 3 and the other two patients recovered consciousness by day 9.

Spectral analysis (for representative examples, Fig. 2, panel b) in all four patients showed an early theta peak within the bursts during BSP (e.g., patient 3 on Fig. 2.) or an early delta peak transitioning to theta feature during the initial 24 to 72 hours after the arrest (patient 4). In three of four patients with prolonged EEGs available after resolution of BSP, spectra of the continuous EEG remained initially flat, and then a theta feature emerged first (e.g., patient 3) as patients were recovering consciousness. In one patient, dominant frequency further improved to alpha range before EEG was discontinued (patient 4).

TABLE 2. Clinical Outcomes in the Overall Cohort ($n = 73$)

Patients With Burst-Suppression Pattern on EEG		Patients Without Burst-Suppression Pattern on EEG	
Recovered Consciousness	**Did Not Recover Consciousness**	**Recovered Consciousness**	**Did Not Recover Consciousness**
14 (31.1%) Mean time to recovery of consciousness = 7.6 days (median = 6.5 days).	31 (68.9%) VS/MCS/coma = 9; rearrest = 7; brain death = 3; WLST = 12; mean time to WLST = 9.75 days (median = 8.5 days)	10 (35.7%) Mean time to recovery of consciousness = 7.5 days (median = 7.0 days)	18 (64.3%) VS/MCS/coma = 0; rearrest = 8; brain death = 0; WLST = 10; mean time to WLST = 8.6 days (median = 9 days)

MCS, minimally conscious state; VS, vegetative state; WLST, withdrawal of life-sustaining therapy.

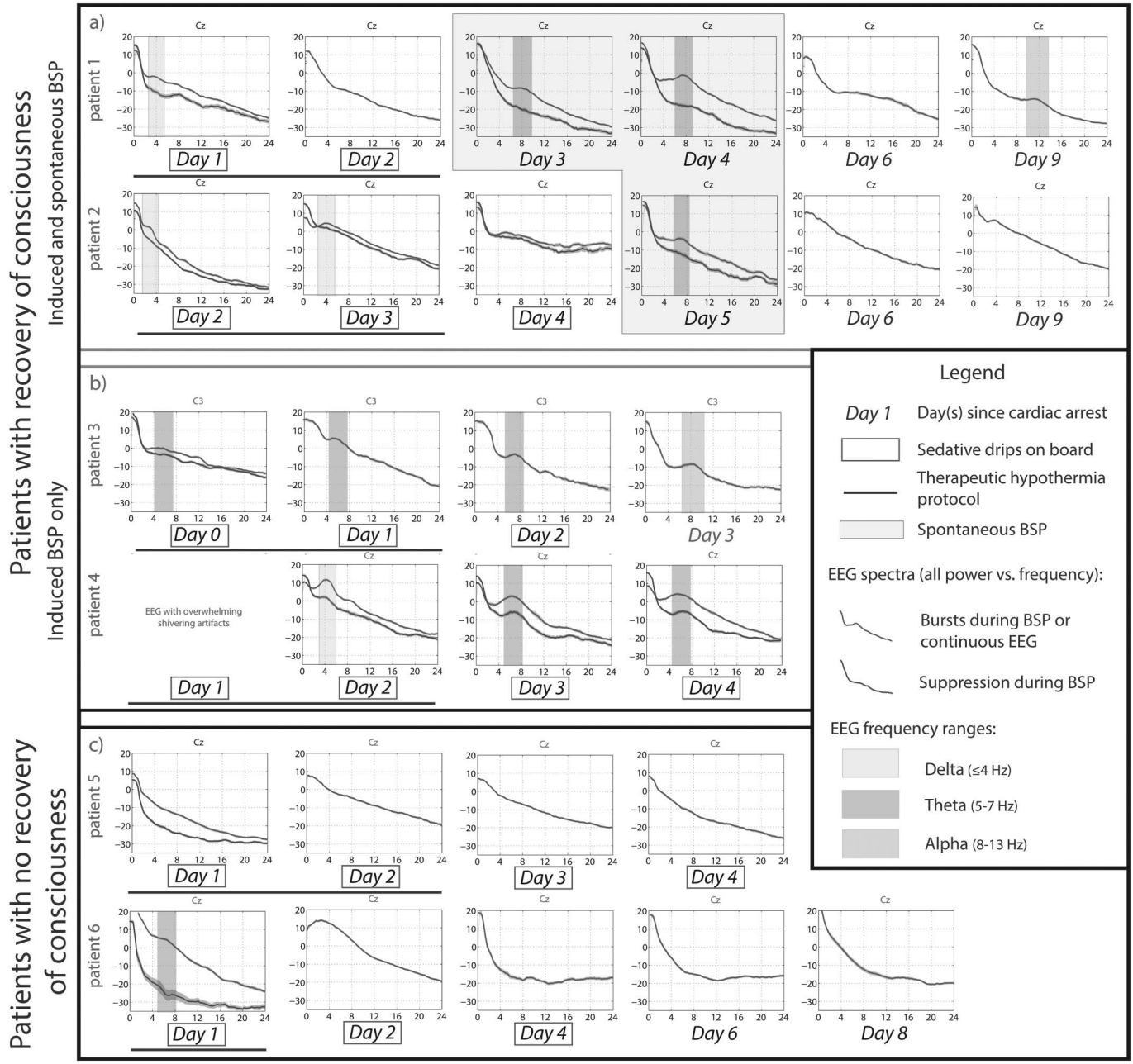

FIG. 2. Examples of power spectral features for representative patients with (1) spontaneous BSP with favorable outcome, (2) induced BSP with favorable outcome, and (3) induced BSP with unfavorable outcome. BSP, burst-suppression pattern.

Patients With Induced BSP and Unfavorable Outcome

In all eight patients, BSP or diffuse suppression was seen initially during TH. After completion of TH, the EEG background either transitioned from BSP to continuous EEG patterns with or without intermixed epileptiform discharges and at times evolution into status epilepticus; remained in BSP in the setting of increasing sedation; or remained in BSP even after rewarming/weaning of sedatives. None of these patients regained consciousness throughout the hospital course.

Spectral analysis (for representative examples, Fig. 2, panel c) revealed no prominent features within bursts nor within the suppression periods in two of eight patients analyzed (e.g., patient five on Fig. 2). In these patients, after resolution of BSP, spectra either remained flat or contained a delta frequency peak only. In four patients, power spectra of "bursts" showed a low-amplitude theta feature within the first 1 to 2 days after cardiac arrest (e.g., patient 6) that was subsequently lost and never recovered. In the remaining two patients (not shown), a very late faint theta feature

was first observed within the bursts only as sedation was weaned (on days 11 and 8, respectively). However, in both cases, further clinical course was limited by a sudden deterioration leading to brain death in one patient and by a terminal extubation in the other.

DISCUSSION

Our results are consistent with the idea that BSP itself may not have intrinsic, universal prognostic value in the setting of anoxic coma after cardiac arrest. Instead, BSP may represent a dynamic brain state assumed during periods of metabolic disequilibrium. In patients undergoing TH after cardiac arrest, BSP often arises in relation to heterogeneous physiologic or pathologic processes contributing to varying degrees. Thus, the clinical significance and potential prognostic implications of BSP could vary according to the mix of underlying conditions giving rise to BSP (i.e., neuronal dysfunction and inefficient energy metabolism due to global hypoxic injury in the setting of concurrent hypothermia and sedative use[4,5,9,12,28]) and may be related to the spatiotemporal characteristics of bursts.

Spectral Content of Bursts During BSP May Help to Identify Viable Neuronal Networks

Quantitative analysis of BSP in all selected patients who regained consciousness revealed the emergence of a theta frequency (5–7 Hz) feature during bursting before clinical signs of recovery of consciousness were evident. We hypothesize that increasing intraburst frequency content during BSP may serve as a possible marker of graded, cortical functional reafferentation after hypoxic brain injury.[24] An earlier study of EEG spectral content in a separate cohort of patients after cardiac arrest[23] also supports this central idea. By contrast, in matched, selected patients who remained unconscious, spectral features of bursts either remained featureless perhaps due to severe injury precluding successful cortical reafferentation (e.g., Fig. 2, patient 5), or initially contained a faint theta feature within 48 hours of arrest that subsequently disappeared and never recovered (e.g., Fig. 2, patient 6). We conjecture that in these patients, an early attempt to reactivate basal networks involved in arousal and consciousness could not be sustained due to progressively worsening metabolic disarray and neuronal injury.

Theta Frequency Activity in the Context of Large Scale, Neuronal Deafferentation After Severe Global Anoxic Brain Injury

In the setting of depressed background synaptic activity, such as after a cardiac arrest, variable degrees of deafferentation may exist between the neocortex, central thalamus, and the striatum (i.e., the mesocircuit hypothesis[25,29]). When deafferentation is complete, the concentration of spectral power generated by functioning neurons lies within the delta frequency (<4 Hz) range and the spectra seem featureless—as described above for patients who did not recover consciousness. This finding has been correlated with poor neurologic outcome and such patients typically remain in coma or persistent vegetative state.[24] By contrast, when there is sufficient afferent cortical input, spectra may initially shift to the theta frequency range as a result of spontaneous, passive oscillations of layer V cortical pyramidal cells.[30,31] This finding has been associated with some preservation of consciousness as observed in patients in minimally conscious state.[32] With higher levels of background activity, thalamocortical connectivity is restored and spectral content shifts to higher frequencies (8–12 Hz). In this context, early theta frequency oscillations within bursts may represent spontaneous activity of intact, isolated cortical networks[24] that are necessary for later recovery of awareness as thalamocortical connectivity is gradually restored.

Spontaneous BSP as a Potential Neuroprotective Mechanism

We hypothesize that emergence of spontaneous BSP may contribute to neuronal rescue in some cases in the setting of hypoxic brain injury after cardiac arrest. A recent model[22] based on measurements from healthy volunteers undergoing anesthesia postulated that an ATP-gated potassium channel present in both cortical and subcortical structures stabilizes the membrane potential during periods of metabolic disequilibrium and ensuing energy deficit by inducing burst suppression. Reports of isolated cortical cell preparations from the cat brain remaining in spontaneous BSP for up to 3 hours before activity ceases altogether[33,34] support this idea. Therefore, spontaneous transition to a state of discontinuous neuronal activation in the setting of metabolic deficit after severe hypoxic injury may serve as an adaptive mechanism to conserve energy and allow for rescue of neurons at the threshold of survival.[35,36]

In our study, both patients with spontaneous reemergence of BSP had favorable outcomes. Although this evolution of BSPs was only observed in two patients who had a mix of positive (preserved cortical responses on somatosensory evoked potential, no evidence of acute hypoxic injury on MRI) and negative predictors for recovery (lack of pupillary reflex at 72 hours in one patient, prolonged BSP on EEG and delayed recovery of consciousness in both patients [9 and 8 days after sedatives were stopped, respectively]), such a pattern was not observed in any of the patients who did not recover consciousness. Furthermore, the evolution of spectral features in both patients suggests that a different physiologic mechanism took over during spontaneous BSP compared with the initial induced BSP. Contrary to expectations of typical evolution of BSP, suppression periods became longer and bursts became more prominent after sedation/cooling were removed. In addition, the spectral content of spontaneous BSP was dominated by theta as opposed to delta frequency activity during induced BSP (Fig. 2). Of note, other processes, such as inefficient clearance of pharmacologic agents due to hepatorenal dysfunction similarly could not explain the observed evolution of variable BSP characteristics. We argue that the reversal of relatively favorable energetics during TH/sedation (i.e., depressed cerebral metabolism[28,37]) after weaning of sedatives and rewarming may have led to increased cerebral metabolic demands and precipitated an innate emergence of spontaneous BSP in the injured cells after hypoxia as an effort to optimize neuronal survival. In other patients who regained consciousness but did not have similar reemergence of BSP,

the degree of energy mismatch may have remained sufficiently low during reversal of cooling/sedation, allowing for gradual transition to continuous neuronal activation without endangering cellular survival. Conversely, for those who did not regain consciousness, energy mismatch and neuronal death may have surpassed the ability of innate cellular mechanisms to rectify.

Study Limitations/Conclusions

Although our findings emphasize some new and unconventional aspects of BSP in patients with post-cardiac arrest coma after TH, several important limitations must be also mentioned. First, because data were gathered retrospectively, EEGs were only available early in the clinical course for many patients and therefore evolution of EEG spectra could not be studied longitudinally in most cases as patients were recovering. In addition, due to file corruption and damage to archived data, sufficient EEG data were not available to perform quantitative analyses in many of the patients. Furthermore, due to the high proportion of patients who underwent WLST, we cannot rule out the possibility that more patients could have regained consciousness if more time is allowed for recovery and the possibility of a "self-fulfilling prophesy" may represent a bias in our results. Finally, in conjunction with the relatively small overall sample size in our database, our quantitative EEG results do not have sufficient power to allow for rigorous statistical analyses and thus the possible general implications of these findings are limited; future prospective studies should include larger samples and examine the possible role of clinical features identified in our small cohort as well as track metabolic and functional cellular markers (e.g., neuron-specific enolase[11]). Nonetheless, our findings demonstrate new insights into the possible significance of BSP in the setting of severe hypoxic brain injury after cardiac arrest and emphasize the need for further investigation into the physiology and functional significance underlying BSP, particularly in relation to prognosis of comatose post-cardiac arrest patients.

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