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Presence of electroencephalogram burst suppression in sedated, critically ill patients is associated with increased mortality

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Abstract

Objectives—This study investigates the possibility of a relationship between oversedation and mortality in mechanically ventilated patients. The presence of burst suppression, a pattern of severely decreased brain wave activity on the electroencephalogram, may be unintentionally induced by heavy doses of sedatives. Burst suppression has never been studied as a potential risk factor for death in patients without a known neurologic disorder or injury.

Design: Post hoc—analysis of a prospectively observational cohort study.

Setting—Medical intensive care units of a tertiary care, university-based medical center.

Patients—A total of 125 mechanically ventilated, adult, critically ill patients.

Measurements and Main Results—A validated arousal scale (Richmond Agitation-Sedation Scale) was used to measure sedation level, and the bispectral index monitor was used to capture electroencephalogram data. Burst suppression occurred in 49 of 125 patients (39%). For analysis, the patients were divided into those with burst suppression (49 of 125, 39%) and those without burst suppression (76 of 125, 61%). All baseline variables were similar between the two groups, with the overall cohort demonstrating a high severity of illness (Acute Physiology and Chronic Health Evaluation II scores of 27.4 ± 8.2) and 98% receiving sedation. Of those with burst suppression, 29 of 49 (59%) died within 6 months compared with 25 of 76 (33%) who did not demonstrate burst suppression. Using time-dependent Cox regression to adjust for clinically important covariates (age, Charlson comorbidity score, baseline dementia, Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, coma, and delirium), patients who experienced burst suppression were found to have a statistically significant higher 6-month mortality [Hazard's ratio = 2.04, 95% confidence interval, 1.12–3.70, $p = 0.02$].

Conclusion—The presence of burst suppression, which was unexpectedly high in this medical intensive care unit population, was an independent predictor of increased risk of death at 6 months. This association should be studied prospectively on a larger scale in mechanically ventilated, critically ill patients.

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Keywords

intensive care; mechanical ventilation; burst suppression; bispectral index; processed encephalogram; sedation; analgesia; delirium

Critically ill, mechanically ventilated patients nearly universally receive large doses of sedative and analgesic medications that frequently lead to deep sedation. Little is known regarding the mortality risks of deep sedation (1, 2). In a controversial study, Monk et al. (2) reported that cumulative intraoperative deep hypnotic time was an independent risk factor for increased mortality during the first year after surgery. Sedation management has been shown to affect various clinical outcome variables such as duration of mechanical ventilation, length of intensive care unit (ICU) and hospital stays, and healthcare cost (3, 4). Current sedation guidelines recommend titration of sedation to a goal level using a valid and reliable clinical assessment tool (5). However, once a patient is sedated to the point of being unresponsive it is not possible to recognize further increase in depth of sedation or suppression of brain activity without the use of electroencephalogram (EEG) or processed EEG data. Because objective EEG monitoring is not usually conducted, patients' depth of sedation could be much deeper than is detectable by clinically validated bedside arousal/ sedation scales.

EEG monitoring to determine depth of sedation in ICU patients is difficult to perform routinely because it is expensive, cumbersome, and requires trained staff to interpret. Processed EEG monitors may prove to be a useful alternative as complementary aids for clinical management, but this remains to be determined. These devices are frequently used to measure depth of sedation during surgery but not routinely for management of ICU patients. The bispectral index (BIS) monitor is one example of a processed EEG device. This monitor uses an easy to apply sensor to collect frontal temporal EEG data and uses a proprietary algorithm to convert this raw EEG data to an easily readable scale of 0–100. A value of 0 is seen with extremely deep sedation (isoelectric EEG activity) and a value of >90 is generally present in awake individuals (6). The BIS also detects the presence of burst suppression, which is severely decreased brain wave activity on EEG recordings. These three types of data (raw EEG data, numerical BIS values, and the burst suppression ratio) can be visualized on the BIS monitor.

In very deep sedation associated with anesthetics, a burst suppression EEG pattern can be seen. Such burst suppression is characterized by periods of suppressed EEG activity alternating with periods of higher amplitude EEG activity (Fig. 1). This pattern, when induced by sedatives, is considered to be a reliable indicator of very deep drug-induced coma (7, 8). With deepening sedation, the proportion of isoelectric (flat) periods to "bursts" increases until eventually the EEG becomes completely isoelectric (7). In some clinical settings such as the presence of intracranial hypertension associated with cerebral injury or persistent status epilepticus, deep sedation is clinically beneficial and sedatives are intentionally titrated to achieve EEG burst suppression (8). Burst suppression may also be seen as a result of anoxic brain injury. Other than these profound and easy-to-detect clinical states, however, burst suppression would generally result as an unintended consequence of unnecessarily high cumulative doses of sedative and analgesic medications. Previous studies have noted that the presence of burst suppression in patients following cardiopulmonary resuscitation (9) and also in neonates with potential neurologic problems (10) is associated with poor outcomes. However, the prognostic value of sedative induced burst suppression in critically ill patients in the absence of seizure, neurotrauma, or anoxic injury is unknown.

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Recent investigations have revealed adverse clinical consequences associated with excessive exposure to sedatives and analgesics (3, 4). In considering this important area of study, we realized that data collected in a cohort study that we had published several years ago (11) might be of assistance in addressing the possible relationship between oversedation, as marked by unintentional burst suppression, and increased death in critically ill, mechanically ventilated patients who had no known history of structural or hypoxic brain injury. Therefore, we conducted this *post hoc* analysis of our previously published observational cohort study, and used the raw EEG and burst suppression data obtained in 125 patients to conduct a pilot investigation through multivariable analysis adjusting for time-varying covariates.

PATIENTS AND METHODS

Study Design

We conducted an observational, cohort study investigating the use of BIS to monitor consciousness in critically ill patients. Some details of this patient population have been previously published (11). All of the data and analyses related to burst suppression and its association with clinical outcomes are entirely original to this manuscript. This *post hoc* analysis was investigator initiated and designed. The statistical analysis and interpretation of data were performed by our academic team completely independent from industry involvement. All of the BIS monitoring, data collection, and data processing were conducted by Vanderbilt University faculty and critical care research nurses without the presence or input of Aspect Medical Systems personnel. Aspect did provide the BIS monitors and an unrestricted research grant used in 2000–2001 to help us with personnel costs incurred during the original prospective cohort data collection. The institutional review board at Vanderbilt University Medical Center reviewed and approved the study protocol. Informed consent was obtained from each patient or his/her surrogate decision maker.

Patients

All patients admitted to the medical ICU during the study period (July 7, 2000–March 5, 2001) were screened for enrollment. Study inclusion criteria were adult medical ICU patients expected to require greater than 24 hr of mechanical ventilation. Exclusion criteria were admission to the ICU after a predefined study cap of six study patients per day had been reached because of study staffing limitations, a history of psychosis or neurologic disease, death or extubation before study nurse assessment, patient or family refusal to participate, previous enrollment in the study, inability to communicate secondary to language barrier or deafness.

Patients received sedation as directed by the patient care team using a Ramsay Scale targeted approach as per standard practice at our institution at the time of the original cohort study. Sedatives and analgesics were administered either by bolus dosing or through a continuous infusion. Sedatives used during the study period included lorazepam, midazolam, diazepam, and propofol. The analgesics administered included fentanyl and morphine. The daily doses of these medications were recorded prospectively for this cohort study.

EEG Data Collection

EEG data were collected using the BIS monitor and the following methods: a brief skin preparation using a dry gauze and isopropyl alcohol was performed and the BIS sensor was applied to the patient's forehead. The BIS sensor provided a two-channel ipsilateral frontal–temporal montage. The sensor was connected to the portable BIS A1050 EEG monitor (Aspect Medical Systems, Norwood, MA). Impedances were measured to ensure that they were 5 K[Omega] or less. Raw EEG data were captured through the BIS at 128 samples per

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second and recorded continuously in real time; processed variables were downloaded live and recorded to the computer every 5 sec. One research nurse recorded events and marked the timing of the clinical assessments while managing a laptop computer to collect the raw EEG and the processed BIS data coming from the BIS monitor. Another research nurse, who was blinded to BIS data throughout the complete study procedures on each patient, performed the clinical assessments of consciousness. All BIS data were reviewed and analyzed off-line and not shared with the study team until the completion of patient enrollment.

BIS monitoring and data collection were conducted daily. Once the BIS sensor had been applied, the patient was observed until the BIS acclimated to a stable value before data collection. Data were then collected for 2 min before initiating clinical assessment of consciousness, throughout the period of clinical assessment, and for the 5 min immediately after the completion of the clinical assessment. Clinical assessment of consciousness included the measurement of the Richmond Agitation-Sedation Scale (12, 13) and the Confusion Assessment Method for the ICU (14, 15). Between 10 and 20 min of raw EEG data were collected per measurement.

In addition, BIS values and burst suppression ratios were recorded. The burst suppression ratio, as calculated by the BIS A1050 standard algorithm, is the percentage of the previous 63-sec epoch of EEG that is recognized as being isoelectric by the processed EEG algorithm. For the purpose of this study, a burst suppression ratio >0 was noted as positive for burst suppression and analyzed as such. Electromyogram and signal quality index, which BIS monitors use to calculate and categorize the quality of individual BIS values, were also recorded. The BIS 3.4 and BIS-XP (also called BIS 4.0) algorithms were used to analyze the raw EEG data. A three electrode EEG sensor was used for patients 1 to 74, and the Quatro XP sensor that provided a second EEG channel using a fourth (above-eye) electrode was used for patients 75 to 125.

Statistical Analysis

Patients' baseline demographic and clinical variables were assessed using Wilcoxon Rank Sum tests for continuous variables, and Pearson chi-square test was used for comparing proportions. Patients were followed from time of enrollment until hospital discharge. All survivors were then followed using the hospital's electronic record system, monthly phone calls, and in-person visits for survival status. For outcome of ICU, hospital, and 6-month mortality, time to death were compared between patients with or without burst suppression. For ICU and hospital mortality analysis, patients were censored at the time of ICU or hospital discharge if they were alive. For 6-month mortality analyses, patients were censored at the time of last contact alive or at 6 months from enrollment, whichever was first. For ICU, total hospital, and post-ICU length of stay and duration of first mechanical ventilation, time to event analysis were used to compare time to discharge or time of first successful extubation. Censoring occurred at time of hospital death. Cox proportional Hazard regression models with time-dependent covariates (16–18) were used for all the analyses to obtain Hazard ratios of ICU, hospital, or 6-month mortality. For time to ICU, hospital, post-ICU discharge, hazard ratios were used to indicate remaining in ICU or hospital. For time to first successful extubation, hazard ratios indicate risk of being on ventilator. The main exposure variable, burst suppression, was included in the Cox regression model as a time-dependent incidence variable, which was coded 0 for the days before the first burst suppression event, and coded 1 thereafter. The time-dependent coma and delirium incidence variables were coded similarly. The seven covariates in the multivariable Cox regression models included time-dependent coma and delirium variables, and five additional baseline covariates that were chosen *a priori* based on clinical relevance (patient age at enrollment, Charlson Comorbidity Index [19], modified Blessed Dementia Rating Scale [20], Acute

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Physiology and Chronic Health Evaluation II score [21], Sequential Organ Failure Assessment score [22–24]). Patients' neurologic status (normal, delirium, comatose) was updated daily in the ICU, and time-dependent variables were used for delirium and coma separately (14, 25). Dummy coding was used for missing observations with modified Blessed Dementia Rating Scale. Because coma was already being handled as a covariate in the model, the Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores were calculated without inclusion of the Glasgow Coma Scale. Collinearity among all independent variables was evaluated by examining the variance inflation factor (26). Assumptions of proportional hazard for the final models were evaluated by examining interactions between time and each variable in the model. Analysis of the association between sedative drugs and burst suppression were performed using generalized estimating equation using repeatedly measured data for daily assessments of burst suppression and sedative dosage with outcome variable being presence and absence of burst suppression. Drug variables were log-transformed to improve model fit. The set of covariates stated above were adjusted in the generalized estimating equation model. All data analyses were performed using R2.3.0 (www.r-project.org) and SAS 8.02, SAS Institute, Cary, NC and significance level of 0.05 was used for statistical inferences.

RESULTS

The details of the study population have been previously described (11). In brief, 125 medical ICU patients were enrolled in the study. Patient baseline demographic data are illustrated in Table 1 separately for those with and without exposure to burst suppression during the ICU stay. The two groups were similar at baseline in regard to age, sex, ethnicity, severity of illness, and admission diagnoses. The mean age of the patients was 56 yr and they were severely ill with APACHE II scores of 27.4 ± 8.2 at time of enrollment. The most common admission diagnosis in each group was sepsis/pneumonia (33 [67%] in patients with burst suppression and 45 [59%] in patients without burst suppression, $p = 0.36$). There were no patients receiving neuromuscular blocking agents at the time of BIS assessment.

There were a total of 501 daily assessments consisting of Confusion Assessment Method for the ICU, Richmond Agitation Sedation Scale, BIS values, and burst suppression ratio made in 125 total patients. Representative raw EEG tracings obtained from study patients using the BIS monitor and BIS-XP software are shown in Figure 2. Burst suppression was noted in 49 of 125 (39%) patients. Nearly half (46 of 93 [49%]) of comatose patients had burst suppression. Of the total of 74 incidences of recorded burst suppression in our patients, 54% occurred during the first 72 hrs of their ICU stay.

Sedative and/or analgesic medications were given to 98% of patients within the 24 hrs before BIS monitoring/assessment. Sedative exposure in patients experiencing burst suppression and those who did not have burst suppression were compared. The mean dose of sedatives and analgesics received in the 24 hr before each measurement of burst suppression was calculated. The mean daily lorazepam dose before the occurrence of burst suppression was 27.75 mg (±58.96) vs. 7.51 mg (±24.57), $p = 0.004$ when burst suppression was not observed. There was no significant differences in the mean daily propofol dose associated with the occurrence of burst suppression vs. the absence of burst suppression [303.95 mg (±1394) vs. 163.91 (±951.40), $p = 0.28$], the mean daily morphine dose [19.59 mg (±49.21) vs. 62.52 (±609.10), $p = 0.75$], nor in the mean daily fentanyl dose [2.08 mg (±7.30) vs. 1.04 (±3.42), $p = 0.51$]. None of these agents was significantly different between groups by dose when adjusted for patient weight (e.g., mg/kg rather than total cumulative dose).

Because patients with chronic substance abuse may receive higher doses of sedative medication putting them at risk for burst suppression, we analyzed a subgroup of patients

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who had a documented history of substance abuse during the 30 days before ICU admission. Only 4 of 17 patients (23.5%) with a history of chronic substance abuse developed burst suppression vs. 45 of 108 (42%) in those without substance abuse. In the group that developed burst suppression, patients with a history of substance abuse (n = 4) received greater amounts of lorazepam (mean lorazepam 0.50 ± 0.51 mg/kg vs. 0.07 ± 0.26, $p = 0.07$) in the 8 hrs before BIS assessment than those without (n = 45) a history of substance abuse. This small sample of only four patients precludes further statistical evaluation within the context of this investigation.

The ICU, hospital, and 6-month mortality outcome data are summarized in Table 2. The mortality rate for the entire cohort was 26% (32 of 125 patients). The ICU mortality of patients with burst suppression was double that of patients without burst suppression. Similarly, the total hospital mortality was nearly twice as high in the group with burst suppression. Of patients with burst suppression, 29 of 49 (59%) died within 6 months compared with 25 of 76 (33%) without burst suppression. After adjustment for clinically important covariates, patients who experienced burst suppression were found to have a statistically significant higher 6-month mortality (hazard ratio [HR] = 2.04, 95% confidence interval [CI], 1.12–3.70, $p = 0.02$).

Additional clinical outcome data are summarized in Table 3. The post-ICU, hospital length of stay was significantly longer in patients who experienced burst suppression (HR 1.84, 95% CI, 1.08–3.16, $p = 0.03$) when compared with those who did not experience burst suppression. The total hospital length of stay was longer in patients who experienced burst suppression. This increase was marginally significant (HR 1.70, 95% CI, 0.98–2.82, $p = 0.06$).

DISCUSSION

This investigation explored the possibility that burst suppression, an independent variable used as a marker of oversedation, may be a risk factor for increased mortality in mechanically ventilated, critically ill patients. For this pilot, hypothesis-generating study, we used a processed EEG marker of deep sedation that could be easily used by bedside clinicians without technical expertise in EEG monitoring. The main observation of this investigation was that burst suppression, an EEG marker of very deep sedation, was independently associated with increased 6-month mortality in critically ill, mechanically ventilated, adult ICU patients. This observation is perhaps even more striking considering that the baseline characteristics between the two groups were similar, with no indication on the front-end that they would have different outcomes. To bolster the strength of this study, we used appropriate statistical methods including time-dependent covariate analysis.

An important secondary finding of this investigation was the unexpectedly high incidence of burst suppression (39%) in the cohort. There was no indication in the plans outlined in these patients medical records that there was any intent or clinical necessity to achieve burst suppression in these patients as a brain protective strategy. A widely recognized but not previously “valued” limitation of sedation scales is that once a patient is comatose, there is no mechanism by which to clinically track a “deeper” level of consciousness or sedation. This high incidence of unintended burst suppression will be of even greater interest if future studies replicate this finding and again show that such burst suppression is associated with increased mortality or with other clinically relevant outcomes.

Despite the increased use of validated sedation scales across ICU settings, in the absence of other objective monitoring, patients remain at risk to become much more deeply sedated than physicians and nurses may intend. If either the depth or the duration of time patients

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spend so heavily sedated could be decreased by monitoring for inadvertent burst suppression when coma is required for safe delivery of mechanical ventilation in severe hypoxemia, or more simply by keeping patients awake or lightly sedated during mechanical ventilation, it is possible that clinical outcomes could be improved. Indeed recent data from sedation studies have guided management of this important aspect of critical care. Target-based (27), protocolized sedation (28), with the incorporation of daily wake up trials (3, 29) have been shown to be associated with lower exposure to sedatives and analgesics and with improved outcomes and thus have been recommended as the "new standard of care" in sepsis management guidelines (30). Despite data being available for over 5 yr, recent large-scale sedation surveys from the United States (Ely EW, unpublished observations), Canada (31), and Europe (32) continue to show modest adherence at best to these standards and have shown that many ICU patients continue to be deeply sedated. These surveys further emphasize how the data in this investigation may lay the groundwork for better awareness about the detrimental effects of high levels of sedation in critically ill patients.

Sedation monitoring has been promoted as the sixth vital sign for patients receiving sedatives or analgesics (33). Given the above-mentioned limitations of clinical assessment tools to determine the true depth of sedation specifically when used to assess patients who are deeply sedated, additional measures of level of sedation should be evaluated in the critical care setting. Although standard EEG is expensive, cumbersome, and requires trained personnel to interpret, our study makes use of an EEG marker of deep sedation, burst suppression, which can be easily obtained in routine clinical practice with the aid of a processed EEG monitor. Processed EEG monitoring, such as the BIS or SEDline (Hospira, Lake Forest, IL), should therefore be evaluated in conjunction with clinical sedation scales and delirium instruments currently used to measure arousal and delirium in critically ill patients. Several factors frequently present in the critically ill (e.g., hepatic or renal failure with associated encephalopathy, EMG artifact from movement) may affect the reliability of the numerical BIS scale when used to monitor these patients (11, 34–36). Electromyogram activity may cause EEG artifact with a fast frequency that can resemble the EEG finding of wakefulness thus leading to spuriously high BIS values in ICU patients (37). Conversely, hepatic and renal encephalopathies are commonly associated with a slowing of the EEG frequency and an increase in its amplitude (38–40), which resemble the EEG findings of sedation leading to a falsely low BIS value. Burst suppression, a flattening of the EEG, should be less likely to occur secondary to these comorbidities, and thus it may prove to be a more reliable indicator of oversedation (in patients requiring deep sedation) than the use of the BIS value alone.

As a *post hoc* analysis of an observational cohort study, there are inherent limitations in our design and methodology. A prospective study on a larger scale should be designed to incorporate a larger number of potential covariates. In addition, the next study should measure BIS over a longer duration of time to avoid under-estimation of burst suppression. Such a study should also categorize patients by the amount of time burst suppression was present rather than dichotomously as ever or never burst suppressed. BIS sensor application just before data collection may have caused stimulation that was reflected in the BIS data collected, another means by which we may have underestimated the amount of burst suppression. We tried to mitigate this by allowing the BIS to acclimate back to a stable baseline before data collection, but there was no assurance that each patient reached their prestimulation EEG pattern. Future studies such as that suggested above should also entertain questions as to the nature of the independent relationship between burst suppression and death at 6 months. It is possible that patients who experience this depth of sedation are more prone to long-term cognitive impairment or other post-ICU recovery complications that jeopardize survival. There might be other unmeasured variables such as

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metabolic, structural, or neurohormonal/neurotransmitter derangements that future studies could elucidate.

CONCLUSIONS

This investigation represents the first attempt to determine the relationship between burst suppression, an unintended and avoidable result of sedative and analgesic use, and survival. We used appropriate statistical design including time-dependent covariates and *a priori* chosen covariates, and the multivariable analyses showed an independent relationship between the presence of burst suppression and increased 6-month mortality. The robust nature of our study's end point (mortality), occurring in association with burst suppression, raises the possibility of a currently unmonitored safety indicator that could help guide management of ventilated ICU patients. However, we caution against firm conclusions in this regard and insist that this report is from a pilot, hypothesis-generating investigation that must be confirmed. To address these questions and the limitations noted above, a prospective investigation using continuous BIS monitoring that includes sedative drug exposure data and long-term neurocognitive data must be considered.

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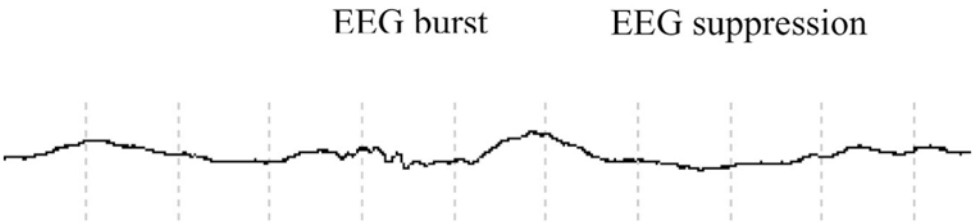

Figure 1. Electroencephalogram

(*EEG*) tracing obtained from pattern of sedation-induced burst suppression.

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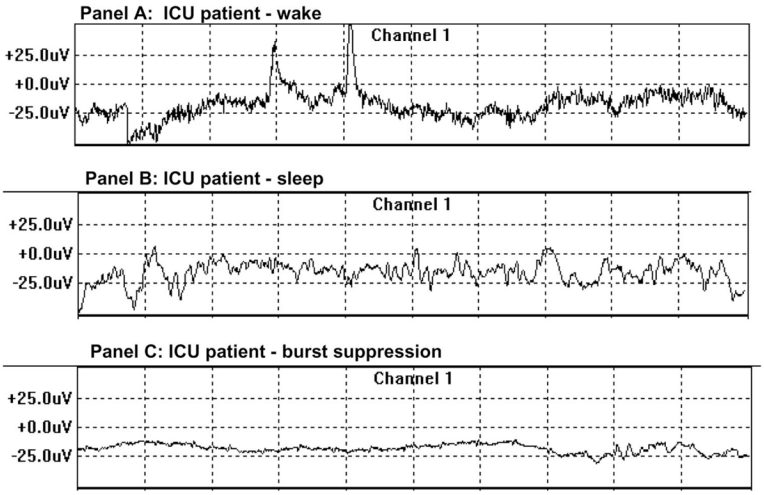

Figure 2. Raw electroencephalogram (EEG) examples. The representative EEG tracings shown above were obtained from our study patients using the bispectral index monitor

A, Demonstrates the low amplitude, high frequency pattern typically seen in the wake state. *B*, Demonstrates the higher amplitude, slower frequency pattern seen with sleep and which can also occur secondary to some sedative and narcotic medications. *C*, Demonstrates the presence of burst suppression, which can occur secondary to very heavy sedation. The amplitude of the EEG is extremely low during the majority of this tracing with a burst of increased EEG activity noted at the end of the tracing. *ICU*, intensive care unit.

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Table 1

Characteristics of patients with and without burst suppression

	Patients with Burst Suppression (n = 49)	Patients without Burst Suppression (n = 76)	*p*
Age (yr), mean ± SD	56 ± 17	56 ± 15	0.99
Female, n (%)	21 (43)	39 (51)	0.36
Non-white, n (%)	8 (16)	11 (14)	0.78
APACHE II, mean ± SD[a]	28 ± 9	27 ± 8	0.66
SOFA[b]	11 ± 3	10 ± 4	0.31
Admission diagnosis[c]			
Sepsis/pneumonia	33 (67)	45 (59)	0.36
MI/CHF	4 (8)	8 (11)	0.66
Renal	3 (6)	2 (3)	0.33
COPD	2 (4)	10 (13)	0.09
Drug overdose	2 (4)	7 (9)	0.28
Gastrointestinal	2 (4)	10 (13)	0.09
Malignancy	1 (2)	3 (4)	0.55
Other	11 (22)	16 (21)	0.85

MI, myocardial infarction; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

[a]APACHE II—Acute Physiology and Chronic Health Evaluation II (21)—is a severity of illness scoring system, and these data were calculated using the most abnormal parameters during the first 24 hours following admission to the intensive care unit. APACHE II scores range from 0 (best) to 71 (worst).

[b]SOFA—Sequential Organ Failure Assessment (23, 24)—is an organ failure scoring system which was also calculated using the most abnormal parameters during the first 24 hrs following admission to the intensive care unit. SOFA scores range from 0 (best) to 24 (worst);

[c]The admission diagnoses were recorded by the patients' medical team as the diagnoses most representative of the reason for intensive care unit admission. Patients were sometimes given more than one admission diagnosis by the medical team resulting in column totals over 100%.

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Table 2

Effect of burst suppression on patient mortality

	Patients with Burst Suppression (n = 49)	Patients without Burst Suppression (n = 76)	HR (95% CI)	*p*
ICU mortality, n (%)	18 (37)	14 (18)	1.78 (0.80–3.96)	0.16
Total hospital mortality, n (%)	24 (49)	18 (24)	1.96 (0.98–3.94)	0.06
Total 6-mo mortality, n (%)	29 (59)	25 (33)	2.04 (1.12–3.70)	0.02[a]

HR, hazard ratio; CI, confidence interval; ICU, intensive care unit.

[a]Multivariable time-dependent Cox proportional hazards regression model were used to compute *p* values incorporating baseline covariates including patient age at enrollment, Charlson Comorbidity Index (19), modified Blessed Dementia Rating Scale (20), Acute Physiology and Chronic Health Evaluation II score (21), Sequential Organ Failure Assessment score (23, 24), admitting diagnoses of sepsis or acute respiratory distress syndrome, and time varying covariates for coma and delirium.

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Table 3

Effect of burst suppression on length of stay (LOS)

	HR (95% CI)	*p*
ICU LOS	1.04 (0.63–1.73)	0.87[a]
LOS, 1st vent	0.80 (0.48–1.32)	0.40
Hospital LOS	1.70 (0.98–2.82)	0.06
Post-ICU, hospital LOS[b]	1.84 (1.08–3.16)	0.03

ICU, intensive care unit; HR, hazard ratio; CI, confidence interval.

[a]Multivariable time-dependent Cox proportional hazards regression model were used to compute *p* values incorporating baseline covariates including patient age at enrollment, Charlson Comorbidity Index (19), modified Blessed Dementia Rating Scale (20), Acute and Chronic Health Evaluation II score (21), Sequential Organ Failure Assessment score (23, 24), admitting diagnoses of sepsis or acute respiratory distress syndrome, and time varying covariates for coma and delirium (daily yes/no);

[b]patients who died in the ICU were not included in the post-ICU (ward) length of stay analysis.