Therapeutically induced EEG burst-suppression pattern to treat refractory status epilepticus—what is the evidence?

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Abstract

Current guidelines advocate to treat refractory status epilepticus (RSE) with continuously administered anesthetics to induce an artificial coma if first- and second-line antiseizure drugs have failed to stop seizure activity. A common surrogate for monitoring the depth of the artificial coma is the appearance of a burst-suppression pattern (BS) in the EEG. This review summarizes the current knowledge on the origin and neurophysiology of the BS phenomenon as well as the evidence from the literature for the presumed benefit of BS as therapy in adult patients with RSE.

Keywords

EEG · Treatment · Anesthetic drug · Monitoring · Outcome

In this article

- Origin and neurophysiology of the burst-suppression phenomenon
- Evidence for burst-suppression to treat refractory status epilepticus
- Depths of artificial coma until burst-suppression
- Morphology of bursts in burst-suppression
- The struggle to maintain a burst-suppression pattern
- Conclusion

Status epilepticus (SE) bears a high risk of significant morbidity and mortality [1]. With an annual frequency of 10–40 per 100,000 it represents the second most frequent neurological emergency following stroke [1, 2]. Status epilepticus becomes refractory (RSE) if it persists after the sufficient administration of benzodiazepines as first-line and one or more second-line antiseizure drugs (ASDs). Current guidelines recommend aggressive treatment for RSE with convulsions or impaired consciousness using continuously administered anesthetic drugs to induce a deep coma with the aim of terminating RSE [2–4]. In addition, a recent two-center study revealed that early administration of anesthetics immediately after first-line treatment may bring more benefits than risks in specific subgroups [5].

To treat RSE with anesthetics, experts suggested close monitoring of anesthetized patients with EEG, either aiming for the cessation of electrographic seizures, the emergence of a BS pattern, or isolectricity-specific EEG patterns that can be established with increasing doses [10–14]. Monitoring with EEG also helps to avoid a too-deep anesthesia, especially in the context of barbiturate coma. Consequently, national and international guidelines adopted this approach for maintaining such artificial coma for at least 24h, followed by gradual withdrawal, concurrently acknowledging the
lack of evidence for the ideal titration goal [3, 4, 15]. Based on similar weak evidence regarding BS, experts consider achieving an inter-burst interval of about 10 s for 24 h to be reasonable [2]. An international survey from 2003 among epileptologists and critical care neurologists in Austria, Germany, and Switzerland revealed that two thirds of physicians considered a BS pattern as the suitable titration target for proper treatment of RSE [16]. However, larger prospective studies concerning the achievement of such a goal and its effect on outcome are lacking. Further, concerns regarding the adverse effects and complications that can accompany prolonged and deep anesthesia, including prolonged postictal mechanical ventilation, infections, and severe arterial hypotension, propofol infusion syndrome, and cardiotoxicity or paralytic ileus from barbiturates raise doubts about this therapeutic step [7, 17–22].

This narrative review is based on a literature search of PubMed and in the references lists of selected studies. It summarizes the current knowledge on the origin and neurophysiology of the EEG BS phenomenon and aims to compile and revise the evidence from the literature for the benefit of BS as therapy in adult patients with RSE.

**Origin and neurophysiology of the burst-suppression phenomenon**

The BS phenomenon describes an EEG pattern consisting of alternating epochs of high-voltage broad-spectrum oscillations (bursts) and electrical suppression. According to the current American Clinical Neurophysiology Society’s (ACNS) Standardized Critical Care EEG Terminology, bursts must average ≥ 0.5 s and have at least four phases and may last up to 30 s, whereas suppression is either < 10 μV or ≥ 10 μV and < 50% of the higher voltage background activity (while the latter is formally an attenuation, the principle of the BS pattern remains). Finally, the proportion of suppression must comprise of 50–99% of the recording [23].

The BS phenomenon was first described in 1936 in the cat cortex [24], whereas the term itself was first introduced in 1949 by Swank and Watson [25].

In humans, BS is physiologically present during sleep in preterm babies and neonates in form of the so-called tracé discontinu and tracé alternant and might most likely represent immature brain structures, unstable neuronal circuits, and hypofunctional neurotransmitter receptors and ion channels [26]. Beyond the perinatal period, BS is mainly encountered in several pathological conditions, such as infantile epilepsy syndromes including Ohtahara syndrome, early myoclonic encephalopathy, and Aicardi syndrome [27, 28], as well as comatose states due to various pathological states, including space-occupying lesions, toxic or metabolic causes, infection, trauma, stroke, or hy-
poxic–ischemic brain injury [8, 9, 29, 30]. Furthermore, iatrogenic hypothermia [31] and deep general anesthesia may also elicit a BS pattern [32].

Surface EEG suggested a synchronous onset of BS [33]. Further, the EEG appearance of BS in functionally or anatomically disconnected cortex supported deafferented cortical neurons as its source [34–36]. However, both observations were recently challenged. Intracranial EEG recordings from patients under propofol anesthesia as well as calcium imaging in rat cortices revealed a substantial asynchrony of cortical bursts that are spatially inhomogeneously distributed [37, 38]. In addition, animal experiments suggested a subcortical source for BS modulation by observing persisting hippocampal neuronal oscillations in the presence of cortical isoelectric EEG and identifying thalamic activity as a modulator of the cortical suppression-to-burst transition [38, 39].

Currently, there are mainly two hypotheses discussed regarding the neurophysiological mechanisms underlying BS. The first is the cortical hypersensitivity hypothesis that is based on observations from isoflurane-anesthetized cats in BS, where mechanical stimuli triggered bursts, followed by a stimulus-refractory suppression caused by depletion of extracellular calcium levels [40]. Further studies suggested concurrent suppression of inhibitory cortical signals [41]; thus, hypersensitivity during BS may be the result of reduced inhibition rather than increased cortical excitation. The second proposition is the metabolic hypothesis that explains the occurrence of suppression by relative intracellular depletion of adenosine triphosphate (ATP), which enhances opening of ATP-regulated potassium channels until intracellular ATP levels are restored and bursts may re-emerge, which in turn rapidly deplete ATP [29].

**Evidence for burst-suppression to treat refractory status epilepticus**

The most prominent challenge in treating SE is the time-dependent development of pharmacoresistance against ASDs and anesthetics [42]. In vitro and in vivo animal experiments indicate that ongoing neuronal discharges result in an internalization of the postsynaptic GABA<sub>A</sub> receptors as early as 1 h after the onset of epileptic seizures [43–45] as well as alterations in GABA<sub>A</sub> receptor-associated scaffold proteins [46]. More recently, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor plasticity [47] and intracellular accumulation of chloride ions [48] were suggested to contribute to SE perpetuation. Consequently, early seizure control appears to be key in preventing these molecular modifications. It is conceivable that once these molecular modifications have already taken place, a supersaturated therapy with continuously administered anesthetics may be needed to break the self-sustaining vicious cycle of BS.

To reach a BS pattern is a common EEG surrogate for adequate seizure-terminating anesthetic dosage [2–4]. However, this approach and the known risks of adverse events and clinical complications that may emerge during such prolonged and deep artificial coma raise further questions, such as whether the achievement of BS is truly beneficial or whether seizure suppression following a more superficial artificial coma might be equivocal, and whether the morphology of BS may contain relevant information about the success of the treatment per se.

**Depths of artificial coma until burst-suppression**

The first study that specifically analyzed the depth of artificial coma on outcome in adult patients with RSE included 35 patients on continuously administered barbiturates [49]. The proportion of surviving patients varied among subgroups showing different EEG patterns. While among 20 patients with an isoelectric EEG curve 12 survived, three of 12 with a BS pattern and three of three patients with seizure suppression only survived. From these results, the authors concluded that a deeper suppression was associated with better outcome [49]. However, multivariable models adjusting for other important confounders regarding mortality were not performed. This study was followed by a systematic review of 28 studies between 1980 and 2001 with a total of 193 adult patients with RSE treated by midazolam, propofol, or pentobarbital [6]. Compared to seizure suppression, patients treated with the aim of generalized EEG background suppression (i.e., BS or isoelectric curve) had a lower frequency of breakthrough epileptic seizures but also a higher need for continuously administered vasopressor treatment due to severe arterial hypotension. These findings are limited by the fact that most patients with the goal of EEG background suppression were treated with pentobarbital but none with midazolam. However, mortality was not associated with any specified titration goals. A retrospective analysis including 49 episodes with RSE in adults could not demonstrate a benefit in outcome by achievement of BS [50]. As a limitation, the presence of BS was retrospectively identified from EEG reports and, thus, the duration of BS was not quantified and multivariable models adjusting for potential confounders in this context were lacking. Another retrospective study of 53 patients with RSE not following hypoxic–ischemic encephalopathy with almost 90% qualifying as super-RSE and a high mortality of nearly 1 in 3 found worse outcome correlated with BS or isoelectric EEG. On the other hand, seizure suppression alone was significantly associated with good outcome [51]. By contrast, further retrospective RSE studies excluding hypoxic–ischemic encephalopathy could not reproduce any association between BS and poor outcome [52, 53].

How long a BS pattern should be maintained remains unknown. While guidelines advocate to keep a BS pattern for at least 24 h [3, 4, 15], a shorter duration might be equally sufficient in selected cases [54].

Unfortunately, only few studies regarding RSE treatment have quantified BS in any way. A recent investigation computationally calculated the burst suppression ratio (QBSR) in EEG recordings of 17 patients with RSE. On adjusted multivariable analysis, there was no association between QBSR and outcome, thus depth or duration of BS ratio were not associated with outcome [55].

**Morphology of bursts in burst-suppression**

Overall, data on burst morphology and outcome on RSE are scarce. The ACNS Termi-
nalogy of Critical Care EEG defined “highly epileptiform bursts” if two or more epileptiform discharges are seen within most (>50%) bursts and occur at an average of ≥ 1 Hz within a single burst, or if a rhythmic, potentially ictal-appearing pattern occurs within >50% bursts [23]. A retrospective single-center study identified a BS pattern with “identical bursts,” characterized by identical first 0.5 s of each burst, in 20% of adult patients with diffuse hypoxic–ischemic encephalopathy, all with a fatal course. Such identical bursts were absent in patients who had an artificial BS pattern due to isoflurane or propofol anesthesia, although the indication for the anesthesia was not further specified [56]. In addition, it remains unclear whether nonsurvivors died of uncontrolled RSE or from an underlying potentially fatal etiology. A study of 19 adult patients with RSE not caused by hypoxic–ischemic encephalopathy studied whether burst characteristics within the 12 h of continuous EEG monitoring prior to a weaning attempt could predict successful weaning. Predictors for successful weaning were bursts with absence of monomorphic sharp waves within the bursts, amplitudes of < 125 μV, and containing < 50% epileptiform activity. However, the results did not indicate any benefit of inter-bursts intervals of ≥10 s or any role of the lengths of bursts [57]. Another study with 24 adult patients with a BS not caused by hypoxic–ischemic encephalopathy showed that highly epileptiform discharges within the bursts were associated with subsequent emergence of epileptic seizures [58]. A novel approach was recently demonstrated by the analysis of functional connectivity measures that revealed successful anesthetic weaning in association with larger, more densely connected, and more highly clustered spatial functional networks [59].

The struggle to maintain a burst-suppression pattern

As a general limitation, the methods to assess BS in all the aforementioned studies were heterogeneous, limiting the generalizability of the discussed findings and urgently calling for studies applying more systematic and standardized assessments.

There is a discrepancy between the common recommendation to achieve a BS with inter-burst suppression of about 10 s [2], and the daily struggles mirrored by the fact that such BS in retrospective studies was only achieved in approximately 40–60% of cases but the overall duration of BS remained unspecified [6, 50]. A study that quantitatively assessed BS in 35 adult RSE patients revealed a remarkable inter-patient and intra-patient variability of suppression proportions despite an uninterrupted and constant administration rate of intravenous anesthetics [60].

Our own preliminary retrospective EEG analysis of 147 patients with RSE treated with anesthetics between 2011 and 2019 in a Swiss tertiary medical care center underscores this issue by revealing a low number of achieved EEG BS pattern (Table 1) despite having continuous EEG monitoring units and the same consulting neurologists and epileptologists during the entire study period. As a limitation to this overview, the titration target might not have been specified as a BS in all 147 patients (preliminary results).

**Conclusion**

In summary, the limited data and small evidence from the literature suggests that EEG burst-suppression (BS) might be a useful surrogate for the titration of anesthetics to achieve deep artificial coma in patients suffering from refractory status epilepticus (RSE).

Despite the importance of optimal RSE treatment in clinical practice, prospective clinical trials in this context are lacking and the evidence for EEG BS pattern as a surrogate for sufficient anesthesia and persistent seizure suppression are anecdotal case reports or retrospective studies describing heterogeneous patient populations and a variety of different methods to quantify and qualify the EEG BS. The difficulty to maintain BS in daily practice, even in tertiary care centers, is in contrast with the current guidelines and represent a further limitation of the evidence supporting BS for the treatment of RSE.

Aside from several early studies raising concerns regarding the risks and complica-

### Table 1: Overview of 147 patients with RSE between 2011 and 2019 treated with anesthetics at the University Hospital Basel, a Swiss tertiary medical care center

| RSE etiology (n, %) | n | median | %/IQR |
|---------------------|---|--------|-------|
| Female (n, %) | 65 | 42.2 |
| Age (years; median, IQR) | 63 | 53–74 |
| RSE etiology (n, %) | 62 | 42.2 |
| Presumed fatal etiologies<sup>a</sup> | 85 | 57.8 |
| Presumed non-fatal etiology | 36 | 24.5 |
| Focal NCSE without coma | 28 | 19.1 |
| SE with motor symptoms (convulsive or myoclonic) | 83 | 56.5 |
| NCSE with coma | 34 | 23.1 |
| Incomplete burst-suppression (with < 50% suppression; n, %) | 25 | 17.0 |
| No burst-suppression (n, %) | 88 | 59.9 |

**RSE** refractory status epilepticus, IQR interquartile range, NCSE nonconvulsive status epilepticus, SE status epilepticus, EEG electroencephalography

<sup>a</sup>Fatal etiologies (not mutually exclusive) included hypoxic–ischemic encephalopathy (following resuscitation; none with spontaneous burst-suppression), acute intracranial hemorrhage, infectious (meningo-)encephalitis, acute ischemic stroke, fast-growing brain tumors, and acute autoimmune encephalitis.

<sup>b</sup>Burst-suppression pattern was assessed by two examiners for all available EEGs during RSE treatment by evaluating the percentage of suppression in a 2-min epoch for every 1 h of EEG recording. The overall level of EEG suppression was defined as the maximal level of suppression reached during an episode of RSE.
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tions associated with continuously administered antiepileptics to induce deep coma, recent studies provide limited evidence that such artificial coma may probably not markedly increase the overall complication rate especially in RSE patients with underlying potentially life-threatening conditions. By contrast, limited data further suggest that patients with rather benign etiologies of SE are at risk of adverse events and complications that may alter their outcome. Thus, until better data are available, clinicians are urged to tailor antiseizure treatment to the different patients’ conditions and to carefully balance the potential risks against the benefits of artificial coma with EEG BS when managing patients in RSE.

References
1. Sutter R, Kaplan PW, Ruegg S (2013) Outcome predictors for status epilepticus—what really counts. Nat Rev Neurol 9:525–534
2. Rossetti AO, Lowenstein DH (2011) Management of refractory status epilepticus in adults: still more questions than answers. Lancet Neurol 10:922–930
3. Brophy GM, Bell R, Claassen J, Aldredge B, Bleek TP, Glauser T et al (2012) Guidelines for the evaluation and management of status epilepticus. Neuroradiol J 17:361–370
4. Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tuniper P et al (2010) EFNS guideline on the management of status epilepticus in adults. Eur J Neurol 17:348–355
5. De Stefano P, Baumann SM, Semmlack S, Ruegg S, Marsch S, Seck M et al (2021) Safety and efficacy of coma induction following first-line treatment in status epilepticus: a two-center study. Neurology 97:e564–e576
6. Claassen J, Hirsch LJ, Emerson RG, Mayer SA (2002) Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia 43:146–153
7. Sutter R, Marsch S, Fuhr P, Kaplan PW, Ruegg S (2014) Anesthetic drugs in status epilepticus—risk or rescue? A six-year cohort study. Neurology 82:656–664
8. Shanker A, Abel JH, Schamberg G, Brown EN (2021) Electrolyte of burst suppression EEG patterns. Front Psychol 12:673529
9. Sutter R, Kaplan PW (2012) Electroencephalographic criteria for nonconvulsive status epilepticus: synopsis and comprehensive survey. Epilepsia 53(Suppl 1):S1–S5
10. Kaplan PW (2003) Nonconvulsive status epilepti-

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Declarations

Conflict of interest. U. Fisch, A.L. Jünger, L. Hert, S. Ruegg and R. Sutter declare that they have no competing interests.

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Therapeutisch induziertes Burst-Suppression-Muster im EEG zur Behandlung des refraktären Status epilepticus – wie ist die Evidenz?

In aktuellen Leitlinien wird empfohlen, einen refraktären Status epilepticus (RSE) mit kontinuierlich verabreichten Anästhetika zu behandeln, um ein künstliches Koma herbeizuführen, sofern durch Erst- und Zweitlinien-Antiepileptika die Anfallsaktivität nicht gestoppt werden konnte. Ein gängiges Surrogat zur Überwachung der Tiefe des künstlichen Komas ist das Auftreten eines Burst-Suppressions-Musters (BS) im Elektroenzephalogramm (EEG). In der vorliegenden Übersichtsarbeit werden sowohl die aktuelle Wissensstand über den Ursprung und die Neurophysiologie des BS-Phänomens als auch die Belege aus der Literatur für den vermuteten Nutzen der BS als Therapie bei erwachsenen Patienten mit RSE zusammengefasst.

Schlüsselwörter
EEG · Behandlung · Anästhetika · Überwachung · Outcome

Zusammenfassung

(1) 

Das AS, Lee JW, Izzy S, Vaitkevicius H (2019) Ultra-short burst suppression as a “reset switch” for refractory status epilepticus. Seizure 64:41–44

(2) 

Peedical J, Mehdiratta N, Zhu S, Njadrasul P, Ng MC (2021) Quantitative burst suppression on serial intermittent EEG in refractory status epilepticus. Clin Neurophysiol Pract 6:275–280

(3) 

Hofmeijer J, Tjepkema-Cloostermans MC, van Putten MJAM (2014) Burst-suppression with identical bursts: a distinct EEG pattern with poor outcome in postanoxic coma. Clin Neurophysiol 125:947–954

(4) 

Johnson EL, Martinez NC, Ritze EE (2016) EEG characteristics of successful burst suppression for refractory status epilepticus. Neurocrit Care 25:407–414

(5) 

Thompson SA, Hantus S (2016) Highly epileptiform bursts are associated with seizure recurrence. J Clin Neurophysiol 33:66–71

(6) 

Rubin DB, Angelini B, Shoukat M, Chu CJ, Zafar SF, Westover MB et al (2020) Electrophysiologic predictors of successful weaning from anesthetics in refractory status epilepticus. Brain 143:1143–1157

(7) 

An J, Jonnalagadda D, Moura V, Purdon PL, Brown EN, Westover MB (2018) Variability in pharmacologically-induced coma for treatment of refractory status epilepticus. PLoS ONE 13:e205789 (Hahn CD, editor)