



# To Wean or Not to Wean: Machine Learning to the Rescue

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## Electrographic Predictors of Successful Weaning From Anaesthetics in Refractory Status Epilepticus

Rubin DB, Angelini B, Shoukat M, Chu CJ, Zafar SF, Westover MB, Cash SS, Rosenthal ES. *Brain*. 2020;143(4):1143-1157. doi:10.1093/brain/awaa069

Intravenous third-line anesthetic agents are typically titrated in refractory status epilepticus to achieve either seizure suppression or burst suppression on continuous EEG. However, the optimum treatment paradigm is unknown and little data exist to guide the withdrawal of anesthetics in refractory status epilepticus. Premature withdrawal of anesthetics risks the recurrence of seizures, whereas the prolonged use of anesthetics increases the risk of treatment-associated adverse effects. This study sought to measure the accuracy of features of EEG activity during anesthetic weaning in refractory status epilepticus as predictors of successful weaning from intravenous anesthetics. We prespecified a successful anesthetic wean as the discontinuation of intravenous anesthesia without developing recurrent status epilepticus, and a wean failure as either recurrent status epilepticus or the resumption of anesthesia for the purpose of treating an EEG pattern concerning for incipient status epilepticus. We evaluated 2 types of features as predictors of successful weaning: spectral components of the EEG signal and spatial-correlation-based measures of functional connectivity. The results of these analyses were used to train a classifier to predict wean outcome. Forty-seven consecutive anesthetic weans (23 successes, 24 failures) were identified from a single-center cohort of patients admitted with refractory status epilepticus from 2016 to 2019. Spectral components of the EEG revealed no significant differences between successful and unsuccessful weans. Analysis of functional connectivity measures revealed that successful anesthetic weans were characterized by the emergence of larger, more densely connected, and more highly clustered spatial functional networks, yielding 75.5% (95% CI: 73.1%-77.8%) testing accuracy in a bootstrap analysis using a holdout sample of 20% of data for testing and 74.6% (95% CI: 73.2%-75.9%) testing accuracy in a secondary external validation cohort, with an area under the curve of 83.3%. Distinct signatures in the spatial networks of functional connectivity emerge during successful anesthetic liberation in status epilepticus; these findings are absent in patients with anesthetic wean failure. Identifying features that emerge during successful anesthetic weaning may allow faster and more successful anesthetic liberation after refractory status epilepticus.

## Commentary

Status epilepticus (SE) is a condition in which abnormally prolonged seizures occur that can lead to long-term neurologic consequences. The annual incidence of SE is 12.6 per 100 000 person-years, and the case fatality rate is 14.9%.<sup>1</sup> Most cases of SE need to be treated emergently, and based on treatment, SE is often divided into 4 stages.<sup>2</sup> First-line anti-seizure medications (ASM) are used to treat “early SE”; usually, these are benzodiazepines. If first-line medications fail to control the SE, it is referred to as “established SE.” Several nonsedating ASM are used as second-line agents, and a recently published study showed comparable effectiveness of fosphenytoin, levetiracetam, and valproic acid.<sup>3</sup> Failure of second-line agent(s) results in “refractory SE (RSE),” and treatment will often require therapeutic coma (TC) with intravenous anesthetic drugs (IVAD).

If upon weaning IVAD, the patient continues to be in SE, the term “super refractory SE” is used.

Refractory SE occurs in 29% to 43% of all cases of SE.<sup>4</sup> By this stage of SE, convulsions, if they occurred, have generally stopped, and the patient is in a state of “electromechanical dissociation.” To accurately diagnose and treat RSE, continuous electroencephalographic (cEEG) monitoring is necessary.<sup>5</sup> Therapeutic coma induced with IVAD is often used in this stage of RSE, and in order to determine adequacy of treatment and sustainability of effectiveness after IVAD withdrawal, cEEG monitoring is particularly helpful.<sup>6</sup> Once a TC has been instituted, most often with midazolam or propofol, the dose of the IVAD is gradually increased until a burst suppression (BS) pattern is reached. Traditionally, bursts of 3 to 4 seconds with periods of suppression of about 10 seconds is the target, and



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this pattern is continued for about 24 hours.<sup>7</sup> Thereafter, the IVAD is weaned, with the hope that the SE does not recur. There are many unknowns in this process, including the degree of EEG suppression that needs to be achieved, the duration for which the BS pattern should be continued, and the rate of withdrawal of the IVAD, to name a few. Evaluation of the EEG BS pattern has been used to predict which patients might successfully wean off the IVAD. In 2017, *Epilepsy Currents* published a summary of a paper that evaluated EEG characteristics that predicted a successful withdrawal of IVAD.<sup>8,9</sup>

A recent paper by Rubin and colleagues returns to the question of whether features of the BS pattern in patients in TC with IVAD for treatment of RSE can be used to predict who can successfully wean off the IVAD.<sup>10</sup> These authors take a unique and contemporary approach to evaluation of the bursts. Instead of evaluating just the raw EEG features, they applied quantitative measure and machine learning tools to the EEG patterns to see whether these tools would yield information previously hidden to the naked eye. Specifically, Rubin and colleagues evaluated the EEGs in 23 wean successes and 24 wean failures using spectral components of the EEG signal and spatial correlation-based measures of functional connectivity. While the spectral components did not differentiate between successful and unsuccessful weans, functional connectivity measures did. Functional networks that were larger, more densely connected, and more highly clustered yielded at 75.5% testing accuracy for a successful wean (95% CI: 73.2-75.9). These findings were confirmed in an external validation cohort as well.

The quantitative EEG features that Rubin and colleagues used were changes in relative  $\alpha$  power,  $\alpha$ - $\delta$  ratio, and several frequency-specific measures such as  $\theta$  and  $\delta$  power.<sup>10</sup> Functional connectivity measures included network density and a standard series of graph-theoretical parameters describing the topology of the network. While the quantitative measures can be obtained with standard analysis tools, sophisticated machine learning algorithms were needed to for the functional connectivity analysis.

An important finding in this study was how early the functional connectivity measures could differentiate a successful from an unsuccessful wean. Six hours before IVAD discontinuation, network density, clustering coefficient, and size of the largest component of the network are greater in the wean success group than the wean failure group. In fact, models constructed by the authors begin to diverge in these analyses as early as about 16 hours prior to the wean, and by 12 hours, the test model outperforms the control model. Thus, with these models, soon after instituting TC with IVAD, it may be possible to determine which patients may be successfully weaned from the IVAD within 12 to 16 hours. This could greatly shorten the time patients are exposed to IVAD.

Therapeutic coma induced with IVAD is widely considered a standard of care in the treatment of certain types of RSE.<sup>11-13</sup> However, complications associated with IVAD in the treatment of RSE are also well recognized. Several studies have noted the increased risk of morbidity and mortality associated with TC induced by IVAD used to treat RSE.<sup>14-16</sup> Thus, there has been great interest in optimizing the use of the “necessarily evil”

IVAD, including determining the optimal duration of TC as well as favorable prognostic EEG indicators that would allow weaning of IVAD.

An early study evaluating pentobarbital in the treatment of RSE found that if the EEG reached a “flat” state, 85% of the patients had persistent control of SE, while only 50% of patients who had a BS pattern achieved persistent control.<sup>17</sup> The morphology of the burst pattern has also been evaluated to see whether that could be used to predict if a wean would be successful. A study of 24 patients found that presence of “highly epileptiform bursts” (bursts containing epileptiform morphologic features) were more likely to be associated with a wean failure.<sup>18</sup> Similar findings were noted in another study of 17 successful and 20 unsuccessful wean attempts.<sup>8</sup> Presence of epileptiform activity in the bursts corrected with failure of wean attempts, while absence of such feature were more likely associated with a successful wean. In this study, the inter-burst interval, BS ratio, and the length of bursts did not differentiate between successful and unsuccessful wean attempts.<sup>8</sup>

While studies have suggested that epileptiform activity in the bursts of a BS EEG may suggest that the IVAD wean attempt may be unsuccessful, occasional spikes, and sharp waves noted during weaning may be compatible with a successful wean. Electroencephalographic features typically considered to be on the ictal-interictal continuum may be seen during weaning and do not necessarily imply wean failure.<sup>19</sup> These features include lateralized and generalized periodic discharges. Appearance of these features should not necessarily result in abandoning the wean attempt.


The optimal duration of TC with IVAD for RSE has also been investigated. A study of 182 patients somewhat surprisingly found that longer duration of TC (27.2 vs 15.6 hours) was more often associated with seizure recurrence.<sup>20</sup> This study also noted that higher IVAD doses during the first trial of TC were more likely to have fewer complications and shorter duration of mechanical ventilation. These authors advocated for a deeper but shorter duration (less than the commonly used 24-48 hours) TC with IVAD.

It is important to appreciate that while TC is often “prescribed” as bursts of 3 to 4 seconds and suppression of 10 seconds, as noted above, in reality that may not always occur. A study evaluated the variability of the BS pattern in 35 RSE patients in TC, with the reference BS ratio being  $0.8 \pm 0.15$ .<sup>21</sup> Only 8% (median, IQR 0%-29%) of total time was spent at the reference BS range. This study highlighted the remarkable variability of the amount of BS within patients.


The study by Rubin and colleagues nicely supplements the currently available literature on how to evaluate the EEG during BS of TC for RSE. Not only it is important to evaluate the morphology of the activity in the bursts and the degree of suppression, functional connectivity analyses using machine learning may further help predict which patients can be successfully weaned from IVAD. Moreover, these analyses may help identify which patients can be successfully weaned early after instituting TC, thus limiting exposure to IVAD and reducing complications.

This study does leave a few questions unanswered, however. Most patients in this study were treated with propofol. Will other IVAD such as midazolam, pentobarbital, or ketamine have similar results? Can functional connectivity analysis be used repeatedly to determine when to start weaning? If a patient has unfavorable results initially, would prolonging the TC result in improvement of functional connectivity? If so, repeat analyses could help precisely time when to start weaning IVAD. Finally, the sophisticated machine learning algorithms used by Rubin and colleagues are not yet widely available and not practical to do instantaneously at the bedside. With improvement in technology, this may become possible, making this technique more clinically useful and widespread.

Refractory SE is a high morbidity disease state. Treatment with TC using IVAD, while important to implement, is not without its complications. Rubin and colleagues have identified a valuable clue that may facilitate treatment of these patients and help reduce complication.

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