Can Processed Electroencephalographic Indices Be Used to Estimate Postoperative Delirium Risk?

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See Article, page 32

Postoperative delirium (POD) is a common neurocognitive disturbance after surgery and anesthesia, affecting up to half of hospitalized surgical patients over age 70.[1] The sequelae of POD are not self-limited: POD confers a significant increase in patient morbidity and mortality,[2] and is an independent risk factor for accelerated cognitive decline that can persist for several years.[3] While POD prevention could have a significant impact on preserving cognitive function, especially among vulnerable patient populations, at present we lack reliable biomarkers to identify at-risk patients and evaluate the efficacy of potential treatments.

The importance of intraoperative electroencephalography (EEG) as a modality for POD detection has been underscored by differences in several EEG metrics observed during delirious episodes; however, such metrics are not available in commonly used processed EEG (pEEG) monitors, limiting their clinical utility. Human experimental studies have identified several EEG features in patients with delirium, including loss of alpha (~8–13 Hz) oscillations,[4,5] loss of alpha band functional connectivity,[4] variations in aperiodic EEG activity,[6] presence and duration of burst-suppression,[7] and EEG emergence trajectory.[8] Moreover, these EEG features have been shown to be independent risk factors for POD development. By contrast, the major intraoperative pEEG monitors (BIS, SedLine, Entropy Module, CONOX Monitor) provide proprietary measures of "anesthetic depth" on a dimensionless scale between 0 and 100 (pEEG indices), each with a different range of values commensurate with anesthetic-induced unconsciousness during general anesthesia. Though the individual pEEG indices have been demonstrated to be largely influenced by the spectral composition of the EEG,[9] these indices can be discordant with raw EEG waveforms[10] and inconsistent across monitors.[11] Thus, it is not surprising that large randomized clinical trials using pEEG indices to assess the utility of EEG-guided anesthesia have failed to demonstrate a consistent association with POD development,[12,13] with the most recent trial, Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes-Canada (ENGAGES-Canada), concluding that EEG-guided anesthesia is not a useful strategy to mitigate POD risk.

The landscape of the available literature begs the question—is there any utility of pEEG monitors in our clinical practice in preventing perioperative neurocognitive disorders? In the current issue of *Anesthesia & Analgesia*, Obert et al[14] argue that pEEG indices during anesthetic emergence can be used to estimate the risk of POD. This work relies on previous findings of Hesse et al, which demonstrated that the trajectory of EEG patterns during anesthetic emergence is associated with variable odds of developing POD.[8] For example in Hesse et al, a reference emergence trajectory was established (*Traj Ref*) whereby the EEG shifted from being first delta-dominant, then spindle-dominant, then nonslow-wave before wake. In contrast, Hesse et al also noted an abrupt emergence trajectory (*Traj Abrupt*) that moved directly from delta-dominant EEG to wake; this trajectory was associated with a 4x odds of developing POD. Lastly, an emergence trajectory that lacked delta-dominant EEG activity entirely before awakening (*Traj High*) was associated with an 8x odds of developing POD (Figure). Obert et al hypothesized that the pEEG indices themselves could be used to differentiate the various emergence trajectories associated with POD. To test this hypothesis, they used a previously validated "EEG player"[15] which can input raw EEG into several pEEG monitors and obtain the resulting pEEG indices (along with other pEEG metrics) from the sample EEG trace. As part of the study, the authors input identical EEG traces to BIS, SedLine, Entropy, and CONOX pEEG

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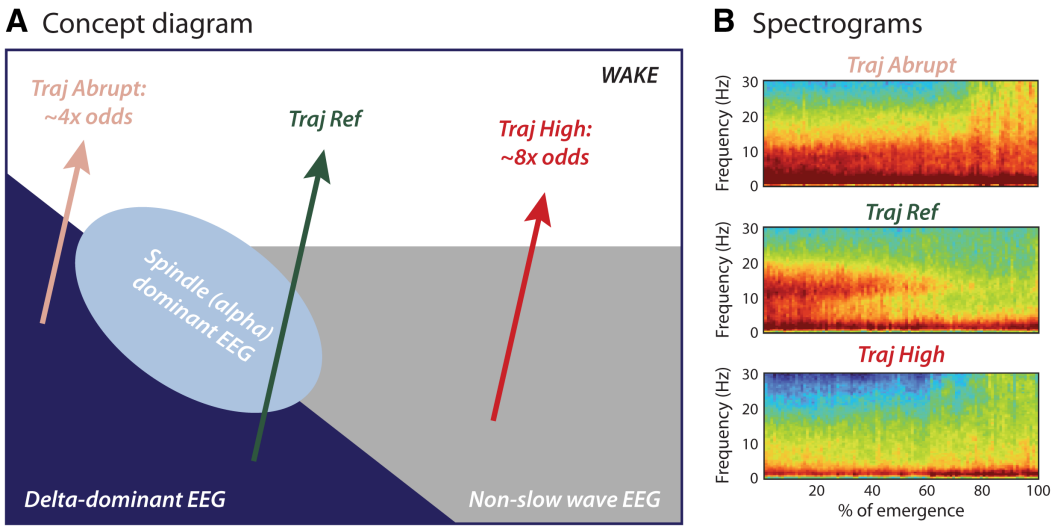

Figure. Emergence EEG trajectories identified in Hesse et al and evaluated in Obert et al. A, Conceptual diagram modified from Hesse et al compared to the reference trajectory (*Traj Ref*—green arrow), moving directly from delta-dominant EEG to wake (*Traj Abrupt*—pink arrow) is associated with a ~4x odds of developing POD, and moving from nonslow wave EEG to wake (*Traj High*—red arrow) is associated with an ~8x odds of developing POD. B, Corresponding spectrograms for emergence EEG trajectories evaluated in Obert et al.

monitors, evaluating and comparing the performance of each monitor in identifying specific emergence trajectories. The authors restricted their analyses to data obtained from patients in the Hesse et al study who underwent maintenance anesthesia with sevoflurane and EEG monitoring *via* a SedLine monitor. Using only SedLine-collected EEG was necessary because 4-channel EEG data were needed for the EEG player to generate SedLine pEEG outputs. These restrictions yielded 19 patients in the Hesse et al dataset with the reference emergence trajectory (*Traj Ref*), which were compared with 20 patients each with *Traj Abrupt* and *Traj High* trajectories for a total of 59 patients. The period of emergence was defined as the period beginning from inspired sevoflurane concentration of 0.0% ("gas off") to the first Observer's Assessment of Alertness/Sedation Scale (OAA/S) score of 2 or greater, which was assessed every minute. Emergence trajectories were normalized from 0% to 100% of the total emergence time.

Here, Obert et al demonstrated that the emergence trajectories of the pEEG indices reflected the differential emergence trajectories as quantified by the raw EEG traces. First, they showed that *Traj Ref*, which was previously associated with a nominal risk of developing POD, exhibited a smooth and linear increase of all pEEG indices—BIS index, SedLine Patient Safety Index (PSI), GE spectral entropy (SE), and CONOX qCON index—throughout emergence. Moreover, 3 of the 4 pEEG indices (BIS, PSI, and SE) could identify and differentiate *Traj Abrupt* (4x odds of developing POD) from *Traj Ref*; compared to *Traj Ref*, *Traj Abrupt* yielded low pEEG index values for the majority of emergence before abruptly rising. Regarding *Traj High* (8x odds of developing POD), BIS, PSI, and qCON indices were significantly different from *Traj Ref*, displaying higher index values from the beginning of emergence and remaining high. Finally, the authors compared the relative performance of all the indices tested, showing the highest correlations across indices for *Traj Ref*, and more modest and variable correlations across indices for *Traj Abrupt* and *Traj High*.

By extending observations made from raw EEG patterns to those that can be interpreted from pEEG indices, the results of this study offer 2 substantial clinical implications. First, these results can help clinicians estimate POD risk for their patients in real time without the need for spectral interpretation of EEG. Indeed, for a significant proportion of anesthesia providers, the pEEG index remains the primary EEG metric for estimating brain state intraoperatively. These results also broaden the clinical utility of identifying emergence trajectories to single-channel pEEG systems that do not provide spectrograms for interpretation. Secondly, if differences in pEEG index trajectories are associated with differential odds of developing POD, then pEEG indices may represent a feasible, actionable, and scalable metric for identifying POD risk in future large-scale randomized controlled trials.

There are important limitations in this study, primarily with regard to validation and generalizability of results, that warrant further consideration. First, the "raw EEG" inputs to the 4 pEEG monitors were previously collected via a SedLine monitor; thus by definition, these EEG data have been preprocessed (ie, grounded, referenced, filtered) using proprietary algorithms potentially unique to SedLine, raising concern for bias toward the performance of the PSI. While it is reassuring that PSI did not demonstrate superior

performance to BIS, SE, or qCON indices in the study, ideally the study could be performed using conventional scalp EEG with specified preprocessing as the EEG player input. Secondly, the authors limited their analysis to patients undergoing general anesthesia with sevoflurane maintenance. Sevoflurane anesthesia is known to exhibit a classic alpha-delta EEG pattern during maintenance[16] which is likely to influence the pEEG indices. While these results would likely be generalized to propofol anesthesia based on its maintenance EEG signature, it is unclear whether these results could extend to agents that antagonize N-methyl-D-aspartate (NMDA) receptors such as ketamine and/or N_2O (though many clinical spaces are actively decommissioning N_2O supply systems due to its high environmental cost). Third, the patients in the *Traj Ref* group were significantly younger than the patients in the *Traj Abrupt* and *Traj High* groups. Age is one of the most salient risk factors for POD, and it is possible that the differences seen across groups are more reflective of age-related EEG changes[17] as opposed to POD risk. Thus the current study will be strengthened if the results were validated in an age-matched cohort.

Despite these limitations, the results of Obert et al provide a framework for future studies in the context of the current literature. For example, it is known that pEEG indices are not faithfully correlated to the level of consciousness during serial awakenings from sedation;[18] indeed, Obert et al showed a large range of pEEG indices depending on emergence trajectory without consciousness (as assessed by the OAA/S). Moreover, the recovery of consciousness from anesthesia is marked by a series of transitions through a reduced set of metastable intermediate states.[19] Taken together, it is possible that the dynamics of the pEEG indices during transitional states may have neurophysiological significance, which would augment the clinical utility of pEEG indices beyond their periodic assessment during anesthetic maintenance, though this remains to be tested. Conversely, Obert et al noted that during anesthetic maintenance, patients in the *Traj Ref* group exhibited significantly more alpha power, which is protective with respect to POD risk.[20] This observation raises the question of whether maintenance EEG features alone could be used to evaluate POD risk, and whether such features could be differentiated via pEEG indices. Lastly, this study was agnostic to the potential contribution of burst-suppression to POD development. Burst-suppression incidence and duration have both been associated with increased POD risk in human experimental studies,[7] and burst-suppression can have a large impact on qEEG indices.[9] A detailed analysis of the effects of burst suppression on emergence trajectory and the corresponding pEEG indices could prove quite useful in understanding the conflicting results of the effects of burst-suppression on POD in large-scale randomized controlled trials,[12,13] and could help refine experimental protocols and/or analyses for future prospective clinical trials. ■

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