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INVITED COMMENTARY

Dynamic Variables of Electroencephalography may be a Window into Brain Responsiveness

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Extracorporeal cardiopulmonary support in the form of venoarterial or venovenous extracorporeal membrane oxygenation (ECMO) has become increasingly important and increasingly used in critical care in the last few years [1]. ECMO can be life-saving and has transformed the landscape of critical illness in a variety of conditions, including acute respiratory distress syndrome, cardiac failure, cardiac arrest, and SARS-CoV-2 infections, to name just a few. The neurocritical care of the comatose ECMO patient remains understudied and has not been the subject of prospective randomized studies, but a number of publications have demonstrated the occurrence of a variety of acute brain injuries (ABIs) during ECMO, such as ischemic stroke, brain hemorrhage, seizures, cerebral air embolism, delirium, and anoxic brain injury. ABIs occur in 7–20% of adults and neonates on ECMO [2–4] and in around 5.9% of patients with COVID-19 on ECMO [5]. Detection of these ABIs remains challenging, but a number of studies have suggested that the use of noninvasive brain monitoring techniques, such as continuous electroencephalography (EEG), may be useful in detecting ABIs [6].

The neurocritical care consultant is frequently called to evaluate and advise on the care of the ECMO patient. The clinical frequently center around whether an ABI has

occurred and prognosis. The consultation is often challenging because the patient is in a coma, and it is not clear if a neurologic insult has occurred, and imaging is unavailable or unrevealing. The assessment is typically further complicated by the presence of sedative-hypnotic medication, which blunts the neurologic examination and affects neurophysiologic monitoring, such as EEG [7]. The assessment is often crucial to overall goals of care decision-making and may have profound implications for the patient and society. It is against this backdrop of uncertainty that the consultant seeks additional objective information on which to refine the assessment.

In this issue of *Neurocritical Care*, Dr. Hwang and colleagues [8] address this important clinical scenario by providing data on their experience with continuous EEG in a cohort of 40 ECMO patients. The authors report that selected continuous EEG variables, such as spontaneous variability of the EEG, state changes on the EEG, and reactivity of the EEG, are suggestive and predictive of survival to discharge. This most recent work adds to considerable literature about the usefulness of these dynamic variables of EEG and good outcome [9]. The presence of one of more of these dynamic variables has been correlated with good outcomes in multiple prior studies. Why is that? What do these dynamic variables indicate about brain function? Some suggest that reactivity and variability of EEG are indicators of brain responsiveness either to internal or external stimuli. In a highly sophisticated study, Claassen and colleagues [10] related EEG responsiveness to verbal instructions as a sign of covert consciousness in patients with cognitive motor dissociation using a structured paradigm. In the Claassen article, a highly rigorous stimulation-task oriented protocol requesting the patient to move their hand was coupled

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with advanced signal analysis to determine EEG response to stimulation. In contrast, the Hwang article uses measures of unstructured EEG responsiveness to nonspecific stimuli or spontaneous variability during ECMO. However, both of these studies feature the unique abilities of EEG to study brain responsiveness in the obtunded patient. The spontaneous variability and reactivity to stimulation that was studied in the Hwang et al. article adds to the body of science suggesting that EEG can in fact be an indicator of responsiveness during ECMO and this responsiveness correlates with outcome.

The Hwang et al. article does acknowledge limitations, including small sample size, potential for withdrawal of life support (WOLST) to influence findings, and the influence of sedation. The authors avoided studying sedated periods, with the exception of including data from patients on dexmedetomidine and fentanyl. However, dexmedetomidine does influence EEG and can produce sleeplike findings, so in part these findings, especially state changes, may be affected by medication. What remains poorly explored in the literature is the ability use healthy EEG responses to sedation and sedation holidays as another component of EEG evaluation of the comatose patient. A recent study suggests that EEG findings during sedation may correlate with outcome after traumatic brain injury [11]. It is curious that decisions about WOLST were not influenced by the EEG findings per se but that the WOLST subgroup had absent or poor findings in two of the three variables studied. This suggests that other clinical factors leading to the decision for WOLST correlate with the EEG parameters. Finally, the authors did not correlate the presence of the three EEG variables with specific neuroimaging findings or incidence of ABI. Such cross-correlation in future studies may be helpful to understand the how ABI may negatively influence the EEG variables of reactivity, variability, and state change.

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