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INVITED EDITORIAL COMMENTARY

Brain Oxygen Monitoring and the Potential for Precision Medicine for Acutely Brain-Injured Patients

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The management of acutely brain-injured patients is transitioning from treatment supported by guidelines that are mostly founded in anecdotal "practitioner experience" to one supported by randomized clinical trials. After years of "hypothesis generating" research, the neurocritical care community is increasingly engaged in research focused on hypothesis testing. The nature of these research endeavors is diverse and includes classic randomized controlled clinical trials, carefully designed bench-to-bedside and bedside-to-bench experiments, and large international prospective observational cohort studies such as the International Initiative for Traumatic Brain Injury Research (https://intbir.nih.gov/). This change of direction for research in acute brain injury is a testament to the maturation of the Neurocritical Care field and will move our specialty to the next level.

The study by Rass and colleagues, in this issue of Neurocritical Care, provides an example of a small but crucial step in this direction. At its heart, the authors investigate the real-world applicability of a multimodality monitoring-based protocol using invasive brain oxygen and pressure measurements in patients with subarachnoid hemorrhage. The impact of a management approach guided by such a multimodality monitoring protocol on outcome was not the subject of this study. Instead, the authors wanted to determine the ability to adhere to a prescribed protocol. The potential to improve outcomes using a brain oxygen guided management approach is currently under investigation for patients with traumatic brain injury in the Brain Oxygen Optimization in Severe TBI Phase 3 (BOOST-3) trial (https://siren.network/clinical-trials/boost-3). This study builds on the successful completion of BOOST-2, which demonstrated a reduction in brain tissue hypoxia in traumatic brain injury patients using a brain tissue oxygen monitoring-guided management protocol [1].

While the patient population between the BOOST studies and that presented here differs, they all aim to determine whether the management of acutely brain-injured patients should or can be guided by invasive monitoring of brain physiology. Rass and colleagues investigate this question in a two-center study involving intensive care units in Austria and Switzerland. There are some noteworthy limitations to their study such as overall sample size and the small number of centers involved. There were also striking enrolling center differences in multimodality monitoring protocols, the number of contributed patients, the rate of complications such as delayed cerebral ischemia, and the critical care management of the patients.

However, Rass and colleagues importantly demonstrated that even in the context of neurocritical care teams that are highly apt at utilizing multimodality monitoring, brain tissue hypoxia was a frequent occurrence despite the implementation of a brain oxygen targeted therapy. The BOOST-3 study, if positive, will provide evidence that patients with acute brain injury may have a better outcome if treated with a multimodality, informed management protocol. The kind of implementation science outlined by Rass and colleagues here requires attention and commendation as translating clinical trial results to the real world is notoriously challenging, and even more so if it concerns technically complex diagnostic techniques such as multimodality monitoring.

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Additionally, precision medicine is increasingly gaining traction in many healthcare specialties. Fundamental to this approach is an adequate phenotypical characterization of the patient and the pathology that afflicts the patient. Treatment plans for cancer patients now increasingly are informed by measures that capture the endophenotype of the individual [2]. For the longest time, measurements of brain function were either crude, non-standardized, or nonexistent. Over the last decade, many brain physiology biomarkers have been developed and standardized including behavioral measures (FOUR score) [3], electroencephalography (EEG terminology) [4], and multimodality monitoring (MMM guidelines) [5]. The most fundamental difference for the management of the critically ill patient compared to other disease processes is that these measures require a high temporal resolution and necessitate immediately availability at the bedside. Noninvasive (EEG) and invasive (MMM) monitoring show great promise for harnessing these requirements for the future of managing patients with acute brain injury.

The most established of the invasive brain monitoring parameters is the measurement of intracranial pressures. It has come of age since its introduction half a century ago. However, intracranial pressure has limitations as its elevation may be caused by a number of factors and these need to be identified in order to be treated appropriately. This shortcoming was illustrated well in Randy Chestnut's clinical trial that failed to demonstrate the benefits of intracranial pressure monitoring [6] most likely due to the fact that pressure measures alone cannot guide the best intervention [7]. Brain swelling, a hemorrhage, and hydrocephalus all elevate the pressure in the brain but require entirely different interventions. Measurements of oxygen may provide additional insight at what the underlying cause for the elevated intracranial pressure is. Additional measures of brain physiology such as ICP waveform analysis, microdialysis, blood flow, and intracortical EEG may further elucidate the etiology of elevated intracranial pressure in real time at the bedside. This concept of invasive measurements of brain physiology may allow the physician to gain insights into the endophenotype in real time at the bedside to guide therapy [8].

To accomplish fundamental improvements in patient outcomes using such technology, collaborations between institutions across continents will be necessary. However, it will be crucial that traditional concepts of data ownership be discussed as well as exploring new avenues to assure that investigators and centers that perform the arduous task of collecting annotated datasets will be acknowledged for their efforts.

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