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INVITED COMMENTARY

Advanced Bio-signal Analytics for Continuous Bedside Monitoring of Aneurysmal Subarachnoid Hemorrhage: The Future

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Over the past two decades, there has been a dramatic expansion of cerebral physiologic monitoring devices in neurocritical care [1–4]. This type of monitoring can take many forms, including, but not limited to, intracranial pressure (ICP), cerebral perfusion pressure (CPP), brain tissue oxygen ($PbtO_2$), near-infrared spectroscopy (NIRS) regional cerebral oxygen saturations, transcranial Doppler (TCD) cerebral blood flow velocity assessments, thermal diffusion-based cerebral blood flow (CBF), and cerebral microdialysis. Such devices have seen a large uptake in the multimodal monitoring (MMM) of cerebral physiology in adult traumatic brain injury (TBI), with support from international experts [1, 3], adoption within recent renditions of guideline-based therapeutic strategies [5–7], and sparking ongoing randomized control trials on therapeutic targets based on the raw data provided from such devices [8, 9].

Aside from the raw cerebral physiologic information provided from these data, advances in offline and bedside bio-signal analytic platforms and techniques have led to derivation of additional indices of cerebral physiologic function. Again, the majority of the literature in this area pertains to adult TBI populations, with derived measures including those related to cerebrovascular reactivity (i.e., cerebral autoregulation) [10, 11], cerebral compensatory reserve [12, 13], signal complexity (i.e., entropy) [14, 15], and autonomic function [16, 17], to name a few. Cerebrovascular reactivity monitoring, taking the form of continuously updating Pearson correlation coefficients, derived from the relationship between slow-wave vasogenic fluctuations in a driving pressure for CBF and a surrogate measure of pulsatile cerebral blood volume/CBF, has seen increasing adoption within MMM of the TBI patient [11, 18]. The pressure reactivity index (PRx) is one such example, and the most commonly recognized cerebrovascular reactivity metric, derived from the relationship between ICP and mean arterial pressure (MAP) [10].

PRx has a strong independent association with 6-month outcome in TBI, beyond that of ICP, when adjusting for baseline admission characteristics [19–23]. In addition, PRx has received some validation in experimental models as a measure of the Lassen autoregulatory curve [24–26], with defined thresholds associated with outcome in the adult TBI populations [20, 27]. Further, recent analysis suggests that during the current era of guideline-based therapeutics in TBI, the majority of cerebral physiologic derangement is related to impaired cerebrovascular reactivity [28, 29], which remains independent to current therapeutic interventions [30]. In corollary, such cerebrovascular reactivity metrics can be used to derive other personalized physiologic targets in TBI care, with optimal CPP (CPPopt) being the exemplar [31, 32], with time spent away from CPPopt demonstrating a stronger association with outcome, compared to Brain Trauma Foundation (BTF)-based CPP thresholds [33]. This has sparked ongoing phase II studies on CPPopt vs BTF-based CPP

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targets in adult TBI [9]. Finally, dosing or exposure time to certain cerebral physiologic derangements is emerging as an increasingly important factor dictating outcome in TBI care [34–36].

Despite all of these promising advances in MMM, it is clear that the main focus has been in adult TBI populations. This leaves one uncertain as to its applicability in other neurological conditions requiring critical care management. In particular, one other patient population typically requiring invasive monitoring during their acute neurocritical care phase is the aneurysmal subarachnoid hemorrhage (aSAH) population. The main reason for the knowledge gap in advanced MMM/bio-signal analytics in aSAH patients is related to the need for proper patient volumes, high-frequency physiologic data capture, and expertise in biomedical engineering and data science. The previous literature had suggested a role for MMM and cerebrovascular reactivity monitoring in aSAH populations [37–41]. This work had documented the link between impaired PRx values and poor 6-month outcome in aSAH. Similarly, this early work had suggested the potential for continuous PRx monitoring to detect cerebral vasospasm and subsequent clinical deterioration [38]. The main limitation of the previous work has been limited patient numbers and the questionable ability to extrapolate the findings of these important initial works to other aSAH populations.

The recent publication by Svedung Wettervik et al. in Neurocrit Care [42] is a major step forward in our understanding of integrated MMM and bio-signal analytic approaches in aSAH patients, and should be considered a seminal work in the field. To date, this is the largest population of aSAH patients with high-frequency digital physiologic recordings described. In addition to this, there has been a thoughtful analysis of ICP, CPP, PRx, and CPPopt during the acute phase of their intensive care unit (ICU) stay, providing some of the first cerebral physiologic dysfunction dosing/exposure assessments. As with the TBI population [34–36], Svedung Wettervik et al. have been able to correlate time spent with ICP above 20 mmHg, CPP below various thresholds, and PRx above + 0.05 (a threshold defined in TBI populations) [20], to be associated with worse outcome in aSAH. PRx was seen, as with the preliminary smaller works [37, 38], to be much more deranged in those developing symptomatic cerebral vasospasm. Further to this, they provide some of the first CPPopt derivations in aSAH patients [39], extending upon the prior aSAH and extensive TBI work in the field [33]. These findings provide validation of the utilization of MMM and derived metrics for prognostication and monitoring in aSAH, while also bolstering support of the potential role of cerebrovascular reactivity metrics for vasospasm detection/monitoring.

The analysis outlined in the work by Svedung Wettervik et al. provides a platform for moving forward in the field of advanced monitoring in aSAH. However, it must be emphasized that the results highlighted should not be taken as absolute, nor adopted for routine monitoring in aSAH populations at this time. Much further work is required, which will necessitate more complex analytic strategies and expanding to multicenter collaborative efforts. Natural starting points could focus on existing data sets, exploring dose/time burden in more detail, similar to recent works in the TBI populations, using contour analysis [34–36]. Further, establishing critical thresholds associated with outcome in aSAH is required, as has been conducted in the TBI cohort [20, 27], while also exploring CPPopt in more detail, perhaps using alternative ICP-derived cerebrovascular reactivity measures, such as those derived in the TBI populations from pulse waveform analysis of ICP [43, 44].

Expanding beyond existing data sets, clearly there is need for multicenter collaboration to collect expansive larger data sets and provide further validation to the results from this current study. Aside from validation, such data collection strategies could benefit from linking high-fidelity cerebral physiologic information from MMM platforms, with protein biomarker information from cerebrospinal fluid (CSF), microdialysate, and serum. Such proteome information linked with MMM physiologic data could provide insight into cellular/molecular pathways involved in secondary insult after aSAH. Furthermore, the addition of genomic data from genome-wide association studies, and epigenomic information related to biological aging, may improve our understanding of the impact of genetic variation and biological age on cerebral physiologic response post-aSAH. Such omics approaches, integrating physiome, proteome, and genome/epigenome data, would require multi-disciplinary teams consisting of: clinicians, physiologists, biomedical engineers, biologists, geneticists, epidemiologists, and data scientists. Further, such work would necessitate the use of big data strategies, time series approaches for temporally resolved data, and application of machine learning/artificial intelligence techniques in order to understand such complex data sets.

Despite the complexity of the above potential approach, this could help us better understand pathways involved in cerebral physiologic dysfunction post-aSAH, improve prognostication models, and lead to the development of personalized therapeutic approaches, including individual physiologic thresholds and pharmacologic targets, focused on reduction/elimination of secondary brain injury. The basis of such approaches is routed in high-resolution MMM and cerebral physiologic signal analytics. The work from Svedung Wettervik et al. in the aSAH

population provides that crucial platform for us to move forward in the development of personalized medicine in aSAH care, and they should be applauded for their contribution to science.

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