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Editorial

Arresting edema: Important after anoxic brain injury?

The quest for "*mens sana in corpore sano*" (Juvenal) is a priority in resuscitationresearch. Development of cerebral edema and intracranial hypertension after cardiac arrest has been recognized since the 1940s,[1] yet a nuanced understanding of these complex processes remains elusive. Cerebral edema and intracranial hypertension are distinct (albeit related) entities and can result from many pathophysiological processes. In some cases, cytotoxic edema is an epiphenomenon of severe injury, energetic failure and neuronal swelling. Here, detection of edema is prognostic, but may not alter clinical care unless early therapies specifically targeting the underlying pathways are discovered. In others, vasogenic edema predominates and results from blood-brain-barrier dysfunction and hydrostatic forces. This may benefit from osmolar therapy. Unfortunately, it is challenging with current methods to differentiate these phenotypes at the bedside. Moreover, whether edema results in intracranial hypertension depends on intracranial compliance, making intracranial pressure a potentially insensitive proxy measurement of edema formation. Regardless of this complexity, whether deployed as a component of multimodality prognostication or used as a serial measure to guide clinical care, validated bedside measures of intracranial pressure and edema formation are needed.

In this issue of *Resuscitation*, Cardim et al.,[2] assess correlations between invasive versus non-invasive measures of intracranial pressure (ICP) in 11 post-arrest patients [editor to add cite when published]. Invasive ICP was measured directly via intraparenchymal monitor, an established reference standard in other brain-injured populations. Non-invasive alternatives included optic nerve sheath diameter ($nICP_{ONSD}$), transcranial doppler (TCD) based diastolic flow-velocities ($nICP_{FVd}$), and jugular venous pressure (JVP). Their main finding was that all 3 non-invasive measures were correlated with invasive ICP. In this small sample size, correlations with invasive ICP were weak to moderate ($r = 0.30–0.58$). Nevertheless, both $nICP_{ONSD}$ and $nICP_{FVd}$ were strongly predictive of intracranial hypertension with areas under the receiver operating characteristic curve >0.9. A strength of this work is the assessment of multiple modalities of non-invasive measures. Although invasive ICP monitoring is common in tertiary care hospitals, it is not widely available at many centers that care for patients after cardiac arrest. Moreover, post-arrest patients may have contraindications to invasive monitoring, such as pharmacological anticoagulation.

Beyond simple detecting intracranial hypertension, each of the non-invasive tools selected by Cardim can offer insights into individual patients' physiology and may thus guide precision care. For example, although TCD-based ICP estimation has limitations, it provides valuable information about intracranial compliance, critical closing pressures, cerebrovascular reactivity and autoregulation.[3,4] These parameters may guide not only management of intracranial hypertension but also allow systemic hemodynamics to be manipulated to preserve cerebral perfusion.

Unlike use of TCDs, which is a relatively recent technology, the concept of ONSD to approximate cerebrospinal-fluid (CSF) pressure has been explored since the 1800s by scholars like Quincke and Tenon, who identified the optic nerve sheath to be continuous with the dura and the enclosed spaces within the sheath to be continuous with cranial spaces.[5–7] Early studies of intrathecal infusion of crystalloid in humans demonstrated predictable anterior ONSD widening, but varying pressure-diameter response relationships between individuals.[7] Although several recent studies in other types of acute brain injury identified ONSD as a promising proxy for ICP, no universal thresholds have been established.[8,9] Proposed cutoffs for intracranial hypertension range from 4.8 mm to >5.7 mm,[7–9] and Cardim, et al.'s threshold of 5.95 mm to predict ICP >20 mmHg is consistent with these. Importantly, individual ONSD thresholds corresponding to intracranial hypertension may vary, the relationship is not always linear, inter-rater reliability is only moderate (0.6 in this study), and responsiveness over time is uncertain. Further exploration of ONSD expansion rate as a dynamic measure of evolving cerebral edema after cardiac arrest may be needed. While some studies indicate that ONSD can rapidly reflect acute ICP changes,[10,11] the differences may be in the range of 0.1 mm making detection challenges.[10] Despite its limitations, ONSD has the potential to provide meaningful insights into ICP and cerebral edema after cardiac arrest.

Unfortunately, neither ONSD nor TCD-velocities (nor invasive ICP monitoring) reveal the underlying mechanisms of an individual patient's cerebral edema, or detect edema in a compliant brain. To this end, neuroimaging may be a valuable adjunct to ICP measures in categorizing edema subtypes.[12] Diffusion restriction on magnetic resonance imaging (MRI), thought to reflect cellular-swelling/cytotoxic edema, has been associated with unfavorable outcome, though does not always indicate irreversible injury. Patients with cellular swelling could benefit from early targeted neuroprotective therapy, since symptomatic reduction in intracranial water content with osmolar therapies would not address causative pathways of energy failure or neuronal toxicity driving the edema and potential cell death. Conversely, those with primarily vasogenic edema, indicated by MRI fluid-attenuated inversion recovery hyperintensity, may have relatively

preserved neuronal function but rapid accumulation of brain water and ICP elevation. Such cases may benefit from acute osmotic therapies to protect against imminent herniation or molecularly guided strategies.

These are not theoretical issues. Drug therapies molecularly targeting cytotoxic and/or vasogenic cerebral edema have shown promising results in preclinical models. Two exciting targets have emerged as key contributors to vasogenic edema after anoxic brain injury: aquaporin-4 and Sur1-Trpm4.[13–17] Inhibition of aquaporin-4 in animal models of asphyxial cardiac arrest with predominantly cellular swelling reduces cerebral edema, increases neuronal survival and improves functional outcome.[14] Inhibition of Sur1-Trpm4 with glibenclamide results in improvement in both neuronal survival/functional outcome, as well as BBB integrity and vasogenic edema.[15–17] Given the encouraging results of glibenclamide in early clinical trials of ischemic stroke and TBI,[18,19] it may be an exciting avenue to explore in the CA population.

Unfortunately, we still lack the ability to identify post-arrest patients likely to benefit from these therapies. Recent advances identifying molecular contributions to edema are beginning to uncover answers, and suggest that a 'one-size-fits-all' approach is unlikely to be effective. Discriminating between patient phenotypes and identifying pathophysiologic mechanism will likely be key to effectively targeting treatments. In the interim, continued development of accurate non-invasive bedside measures of ICP is expected to yield valuable risk-stratification and prognostic tools, and may guide future scientific advances by enriching future trials for patients likely to derive benefit from novel treatments.

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Ruchira M. Jha*

Department of Critical Care Medicine, Neurology and Neurological Surgery, Safar Center for Resuscitation Research and Clinical and Translational Science Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Jonathan Elmer

Department of Emergency Medicine, Critical Care Medicine and Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

* Corresponding author at: 646A Scaife Hall, 3550 Terrace Street, University of Pittsburgh, Pittsburgh, PA 15261, USA.
E-mail address: jharm3@upmc.edu (R. Jha).

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