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INVITED EDITORIAL COMMENTARY

"Take a Number"—Precision Monitoring Directs Precision Therapy

Patrick M. Kochanek[1,2*], Ruchira M. Jha[1,3,4,5] and Robert S. B. Clark[1,2]

Over the years, defining the "optimal" intracranial pressure (ICP) threshold to intervene with a single number has served to help guide the field of neurocritical care to manage complex disorders, such as severe traumatic brain injury (TBI), in a "heuristic" or practical manner. However, in a disease as complex and heterogeneous as severe TBI, simple may be less than optimal and in some cases, even misleading. ICP targets to optimize cerebral blood flow (CBF), prevent herniation, and impact other more nuanced effects may be regional, temporal, and/or vary depending on the therapy used to affect them.

In this issue of *Neurocritical Care*, Lazaridis et al. [1] present a timely and provocative "View Point" that addresses the heuristic nature of ICP thresholds. They raise appropriate concern about "unidimensional excursions," the fact that an association between an ICP threshold and outcome does not imply that a therapy targeting values about that threshold will improve outcome, and suggest that heuristic thresholds may simply exist because of the association between ICP and injury severity. The somewhat capricious nature of a singular heuristic ICP threshold was further brought to light by the move from a threshold of 20 to 22 mmHg in the most recent severe TBI guidelines published by the Brain Trauma Foundation (BTF) [2]. Indeed, from our perspective, that change in the guidelines in part served as a springboard for the authors to raise a number of key concerns and question the "fast and frugal" nature of using a single ICP threshold.

We have great respect for the challenges faced by the BTF committees in working to define the best evidence-based ICP threshold—including first-hand experience by the first author of this editorial as the lead author on the pediatric severe TBI guidelines for over a decade [3–5]. This concern, as one might imagine, is magnified in pediatrics, where obligate age-related changes in mean arterial blood pressure imply the need for age-related differences in optimal ICP and cerebral perfusion pressure (CPP), yet the available evidence does not quite meet the bar to generate strong evidence-based recommendations—despite some support [6, 7]. Many factors magnify the complexity in defining a single threshold in both adults and children. Issues of timing, duration, and dose are challenging to address with a single threshold and have multiple implications. For example, a duration of 5 min that ICP must be above the threshold is often used to direct intervention. But to the bedside clinician, that often depends on the level of increase. Indeed, some evidence suggests that any brief increases are importantly deleterious [8]. Similarly, the optimal ICP threshold in a given patient may vary at different times after the injury—i.e., that even a perfectly derived threshold in a patient may represent a moving target.

Looking back across the decades, it was always somewhat perplexing that therapies that reduce CBF, and not coupled to a metabolic reduction, such as hyperventilation, were recommended to reduce ICP—and shown to be associated with some of the best outcome data [9]. To recognize the potential pitfalls and/or unrecognized complexity of a heuristic view of ICP thresholds in the setting of hyperventilation, one only needs to review that early work of Darby et al. [10] with interrogation of the complex effects of hyperventilation on CBF in patients assessed using stable Xenon-computed

*Correspondence: kochanekpm@pitt.edu
[1] Department of Critical Care Medicine, Safar Center for Resuscitation Research, John G. Rangos Research Center, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, 6th Floor, 4401 Penn Avenue, Pittsburgh, PA 15224, USA
Full list of author information is available at the end of the article

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tomography—where a reduction in ICP appeared to result from an overall reduction in CBF and cerebral blood volume (CBV), but was accompanied by marked increases in perfusion in contused and/or injured brain regions where blood pressure autoregulation and CO_2 reactivity were lost.

Beyond preventing herniation, that ICP-directed therapy improves CBF and prevents brain tissue hypoxia [11] has long been a tenant for the need to define a threshold—however, there has been a longstanding controversy as to the role of ischemia in TBI—particularly outside of the initial hours after injury [12, 13]. The fact that both BTF-generated ICP-directed therapy and strategies suggested by the Lund protocol, given their substantive differences in management, are both associated with favorable outcomes reveals the complexities here [2, 14]. But beyond any putative relationship between ICP and CBF, provocative, pre-clinical work by Lafrenaye et al. [15] has suggested that ICP values below the threshold for effects on CBF may have cellular effects independent of effects on perfusion—resulting in neuronal membrane damage and neuronal injury. Similarly, effects of ICP and ICP-directed therapy on the recently recognized glymphatic pathway add further nuance to the picture [16].

Recently, elegant studies and descriptive data generated by Launey et al. [17] along with other studies from the Clinical Neurosciences group in Cambridge have expanded our knowledge of the relationship between ICP and ischemia, versus the role of coupled reductions in CBF and metabolism, after severe TBI using ^{15}Oxygen positron emission tomography. In severe TBI, ischemia was common early after injury, consistent with classic reports [18, 19], but ischemic brain volumes were elevated even in the absence of raised ICP, and CBV was increased versus normal despite lower $PaCO_2$ used in ICP management. Thus, the expected impact of targeting a simplistic ICP threshold value on the perfusion remains unclear at best.

We have also been interested in these issues with the goal to prevent rather than react to the development of cerebral edema. We seek to define the patients most likely to swell, and those who may benefit most from specific therapies targeting brain edema. We have been interested in augmenting conventional monitoring with specific edema-linked CSF biomarkers [20], along with edema-relevant genotyping [21–23]. We also recently explored the use of trajectory analysis of ICP with the hope of ultimately rapidly defining those who may benefit most from specific targeted interventions to block brain swelling [24]. The application of "precision monitoring" will likely be essential to that goal.

In the current era, all facets of TBI management are being challenged. As mentioned, Lazaridis et al. [1] suggest that the association between raised ICP and both mortality and unfavorable outcome may simply reflect its association with severity of injury. That may, in some cases be true. However, many moderate TBI patients that "talk and die," including after fairly long lucid intervals are obvious examples that in TBI, optimal management of ICP can directly and profoundly impact outcome. Further complicating the picture, as mentioned, using trajectory analysis, we recently identified groups of adults with severe TBI that have poorer outcome than other trajectory-generated groups, despite little evidence of intracranial hypertension [24]. The generalizability of those trajectory groups remains to be demonstrated, but that study sheds additional light on the challenges of defining a threshold (and its utility) along with implications for trial design in studies of ICP-directed therapy.

It is unfortunate and surprising that decompressive craniectomy—taking ICP concerns out of the secondary injury equation—although life-saving in some cases, appears to have some unwanted effects possibly related to issues such as brain deformation, alterations in CBF regulation, disturbed glymphatic flux, persistent alterations in brain compliance, spreading depression, rapid de-escalation of otherwise protective facets of neurocritical care, or others yet to be characterized [25, 26] that may blunt its efficacy. And, as pointed out by Lazaridis et al. [1], how data from patients with decompression should influence ICP or CPP thresholds remains a conundrum, given that data from them are often included in studies addressing these issues, but they are clearly a group distinct from patients with an intact skull.

The concept of managing severe TBI without ICP monitoring—i.e., relying on clinical exam and serial imaging, has garnered some momentum [27, 28]. However, any therapeutic regimen developed to target brain swelling in TBI relies largely on the vast experience obtained from ICP-directed therapy [4, 29]. In agreement with Lazaridis et al. [1], rather than take steps backward, and abandon ICP monitoring, we believe that it is important to build on the information that ICP monitoring provides—even with decades of heuristic data. Also, greater integration of advanced imaging into clinical decision making is further supported given the fact that in the Best Trip study, more rather than less therapy, in general, was used in the group managed without ICP monitoring [27]. The potential benefits of "more therapy" versus "more monitoring," however, remain undefined since in that study, there did not appear to be a functional difference in composite endpoint. Precision medicine to improve TBI outcomes will likely require "precision monitoring." An ICP threshold represents a heuristic starting point in the management of severe TBI—and across other relevant diseases in neurocritical care—while recognizing the need for

integrating multi-modal monitoring in a temporal, potentially regional, more nuanced, and cybernetic manner to guide therapy. Lazaridis et al. [1] also suggest that in some patients it may be very difficult to generate an optimal ICP threshold.

The authors of the pediatric severe TBI guidelines published last year, a long overdue algorithm [4], attempted to address the many nuances that were unable to be addressed in an evidence-based manner. Issues were raised such as the overall dose of raised ICP or fact that the thresholds defined in the guidelines may reflect minimum targets that should not be breached—whether discussing an ICP of 20 mmHg, or a given value for CPP, Hgb, or other parameter thresholds, for that matter. An approach to integrating multi-modal monitoring of ICP, CPP, and PbO_2 along with other information was presented—although at this stage in our understanding, one could argue that any discussion of integrating multimodal monitoring to guide decision making is also quite heuristic. An algorithm based on the adult guidelines was also just published [30].

Many nuanced tools for precision monitoring of ICP and brain swelling have been developed including pressure reactivity index, pressure amplitude index, and compensatory-reserve-weighted ICP, among others, and as discussed in the Viewpoint, it is exciting to see some of these additional tools show promise in providing complementary insight into studies from CENTER-TBI [31, 32] and with an ultimate goal that these, and other data, might be able to be integrated by machine learning to generate a brain management artificial intelligence paradigm [1]. Such an approach should also be developed to leverage the recently completed ADAPT trial in 1000 pediatric severe TBI cases with ICP-directed therapy [33]. Such paradigms might also likely benefit from biomarker and genetic data, and germane to ICP-directed therapy, specifically from biomarkers and genetics-linked to brain edema [20–23]. Studies such as "BOOST III" inquiring whether adding therapies targeting additional "thresholds," such as for PbO_2 [34], or more recent approaches in development to continuously assess brain compliance, refining the classic vision and approach of Anthony Marmarou [35–37], are also welcome steps forward. Precision monitoring of TBI, of course, will need to be integrated with conventional parameters, such as injury mechanism, and imaging, among other factors.

Finally, we must recognize that few studies have directly and prospectively addressed the issue of ICP threshold—in TBI or other relevant neurocritical care diseases. Robertson et al. [38] revealed the challenges and complexities related to comparing ICP or CPP targets in severe TBI. Those challenges include not only the ability to achieve the desired target, and the need to monitor the impact of that intervention on CBF and metabolism, but also the need to recognize and optimally manage the extra-cerebral consequences of the therapies. These consequences vary depending on the choice of therapy [39]. It thus is clear that "more" therapy is not always the answer. To that end, defining the optimal multi-modal "precision monitoring" approach, integrating the richest possible dataset generated with injury type, comorbidities, imaging endophenotype, biomarkers, and genetics, remains a vital goal for severe TBI. With that information we believe that it is likely that "more of a targeted therapy at the optimal time, in the right patient, and in the appropriate brain region" will be achievable across neurocritical care. Until that time, our guess is that we just need to "take a number."

Author details
[1] Department of Critical Care Medicine, Safar Center for Resuscitation Research, John G. Rangos Research Center, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, 6th Floor, 4401 Penn Avenue, Pittsburgh, PA 15224, USA. [2] Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, 4401 Penn Avenue, Pittsburgh, PA, USA. [3] Department of Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. [4] Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. [5] Clinical and Translational Science Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

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