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EDITORIAL

Intracranial pressure thresholds in severe traumatic brain injury: Con

The injured brain is not aware of ICP thresholds!

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The Brain Trauma Foundation (BTF) has recently updated its protocol-based management guidelines for the care of hospitalized patients with acute traumatic brain injury (TBI) [1]. In comparison with the previous 2007 guidelines [2], several recommendations have been changed, and a more stringent approach to adhere to high-quality studies was used. In view of the descriptive nature of the underlying studies included in the previous guidelines, the updated guidelines no longer provide recommendations for specific indications for ICP monitoring. However, on the basis of low-quality evidence (level IIB), the use of information from ICP monitoring to reduce in-hospital and 2-week post-injury mortality is still recommended [1]. In that respect, one of the more remarkable changes in the 2016 guidelines is the higher threshold for the treatment of raised intracranial pressure (ICP): from 20 to 22 mmHg.

Treating physicians who are well aware of the multifaceted intracranial pathologies seen in severe TBI patients and the complexity of secondary brain injury mechanisms after primary trauma will find this revision difficult to understand. Even though the association between raised ICP and worse clinical outcomes is well established [3], this does not translate into a single treatment threshold. A single number to define intracranial hypertension in all patients and all settings is physiologically implausible.

The new level IIB recommendation to treat ICP at a threshold of 22 mmHg is based on one (one!) single-center retrospective study of 459 severe TBI patients, treated over 12 years [4]. This study aimed to identify the thresholds for ICP and other related brain monitoring variables that showed the highest statistical association with outcome. The univariate association between ICP (average value for the whole monitoring period) and outcome was examined using a method of sequential chi-squares, testing ICP values in steps of 1 mmHg increment. At an ICP of 22 mmHg, the highest chi-square was obtained and was designated as the "ICP threshold for outcome".

The BTF decision to amend the ICP threshold on the basis of this study can be challenged with many arguments. First, in this study raised ICP was treated, so the association found might represent treatment failure rather than a treatment threshold. Second, the ICP over the whole hospital stay of each individual patient was averaged. From a conceptual point of view, this is entirely different compared to the clinical situation with time-dependent variations of ICP values above or below a given threshold. Moreover, as ICP is a continuous physiologic variable, it is important to use the variable

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as it is and to apply adequate statistics accounting for repeated measures within patients [5]. Third, the identified "threshold" was applied to the overall cohort, predominantly male (77.5%) and young patients (average 34 years). In the subgroups of female or elderly patients, a different "threshold" of 18 mmHg was identified, already suggesting that a "one-size-fits-all recommendation" is questionable. Fourth, the change of 2 mmHg falls within the measurement errors of ICP [6]. Finally, when suggesting a treatment threshold of 22 mmHg, it is unclear how clinicians should respond. Should we apply aggressive treatments when ICP is 23 mmHg, but not when it is 21 mmHg? Knowing that the evidence is low for most if not all of the therapeutic interventions to treat elevated ICP, it is unclear to which level of therapeutic intensity the threshold of 22 mmHg refers.

Simplifying brain physiology after severe TBI to a threshold-based management strategy is arbitrary in the complex interaction of ICP, cerebral blood flow, and brain metabolism, considering feedback mechanisms of neurovascular (un)coupling, cerebral autoregulation, and CO_2 reactivity (Fig. 1). Moreover, routine ICP measurement in the supratentorial compartment lacks the sensitivity to detect infratentorial pressure changes which obviously relate to outcome. Furthermore, supratentorial ICP is influenced by regional heterogeneity and the extent of midline shift.

Defining secondary brain injury associated with increased ICP is an issue that cannot be reduced to a simple quantifiable variable, without taking into account the context of time. This new concept is often referred to as the "ICP dose", which can be expressed as a proportion of measurements or the area under the curve above (or below) a certain threshold [7–9]. Indeed, recent studies have demonstrated the association of insults of elevated ICP, defined as episodes above a certain threshold for a certain time, and worse clinical outcomes [7–10]. While brief episodic increases of ICP may not necessarily result in downstream metabolic derangement, a sustained high ICP is commonly associated with deleterious effects on brain tissue [10].

In addition, Guiza et al. [7] demonstrated that even ICP episodes < 20 (or 22) mmHg could be relevant, depending on the duration of these insults. These findings imply that the oversimplified understanding of threshold pathology (e.g., ICP > 22 mmHg) leads to the current misconception that "normality" (e.g., ICP < 22 mmHg) guarantees absence of pathologic processes. In other words, a "normal ICP" does not necessarily guarantee sufficient cerebral perfusion and oxygen delivery. For example, ICP-dependent changes in CPP are dynamic, therefore requiring therapeutic flexibility of intensification and de-escalation, a fact which is regularly overlooked [11].

If therapy should not be driven by thresholds, what should clinicians use instead? In many studies (older and more recent), an ICP below 15 mmHg was not associated with poor outcomes, whereas an ICP above 25–30 mmHg almost always was [3, 10]. In between lies

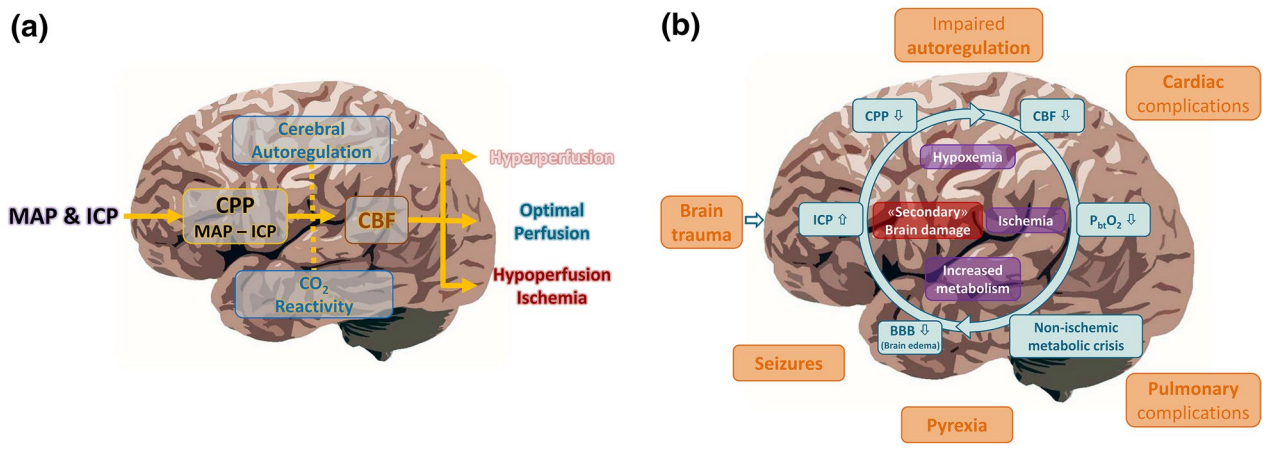

Fig. 1 Complex interaction of the blood pressure and cerebral perfusion. **a** Illustrates the complexity of cerebral blood flow (CBF) regulation by determinants of cerebral autoregulation status, CO_2 reactivity (hypocapnia-associated vasoconstriction and hypercapnia-associated vasodilation of the brain vessels), and the metabolic demand (neurovascular coupling). The conventional view on the "pressure drives flow" concept is based on impaired cerebral autoregulation and loss of CO_2 reactivity with changes in mean arterial pressure (MAP) directly influencing cerebral perfusion pressure (CPP) and CBF. **b** Cerebral and systemic causes of primary and secondary brain injury after trauma. The blue circle indicates the "vicious cycle" of raised intracranial pressure (ICP) resulting in a decreased cerebral perfusion pressure (CPP), decrease in brain tissue oxygen tension ($P_{bt}O_2$), metabolic distress, and disruption of the blood–brain barrier (BBB). Orange boxes indicate cerebral and extracerebral contributors aggravating secondary brain injury

a broad range, where additional information is needed to decide on therapeutic aggressiveness. A first and important source of information is brain imaging, to define the nature, extent, and cause of intracranial hypertension, and to exclude surgically removable mass lesions. Second, additional multimodal neuromonitoring, including brain tissue oximetry, microdialysis, or blood flow measurements, could allow for a more personalized treatment strategy (Fig. 1). As such, a titrated approach to manage borderline values of ICP can be stratified on the presence or absence of associated brain tissue hypoxia (brain tissue oxygen tension, $P_{bt}O_2 < 20$ mmHg), cerebral hypoperfusion (CBF < 17 ml/100 g/min), or metabolic distress (lactate-to-pyruvate ratio > 40), indicating a mismatch between substrate delivery to the brain and the metabolic demand. This would enable clinicians to individualize cerebral resuscitation after TBI. A recent phase II trial was able to demonstrate that, using a protocolized approach, it is possible to reduce the time of brain tissue hypoxia with a trend towards a more favorable outcome [12]. In the near future, bedside monitors or software with pressure–time–dose calculation in real time, and early warning systems, can alert the treating physician to present or imminent critical episodes of increased ICP. Several algorithms have been published which are able to predict ICP increases as early as 30 min in advance, a performance that would be perfectly acceptable for clinical use [13–15].

In summary, a single ICP threshold for all severe TBI patients is an oversimplification of a complex pathophysiological process. In clinical practice, titrating the level of therapeutic intensity is never easy or straightforward. In the vision to provide personalized medicine in severe TBI, ICP should be understood in a multidimensional way (dose–time–covariates) and interpreted in the context of factors determining energy delivery and consumption of the injured brain. With that purpose, monitoring of cerebral metabolism and oxygenation in addition to ICP monitoring and neuroimaging should be considered.

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