Time-burden insults of neuromonitoring signals: practical implications for the management of acute brain injury

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Purpose of review
To explore recent insights into measures of time-burden insults in intracranial pressure (ICP) monitoring, and potential implications for clinical management.

Recent findings
The ICP is an important therapeutic target in patients with traumatic brain injury (TBI) and some other brain injuries. Current clinical guidelines in TBI recommend starting treatment above a fixed ICP threshold of 22 mmHg. The concept of ICP burden was introduced recently, which takes both intensity and duration of an episode of elevated ICP into account. This burden of ICP is visualized in a colour-coded plot. In different cohorts of brain injured patients, prolonged ICP elevations, even at values below 20 or 22 mmHg, are associated with worse outcomes, and higher ICPs can only be tolerated briefly. The ICP burden plots are influenced by age, cerebral perfusion pressure, and cerebrovascular autoregulation, illustrating the complexity and dynamic aspect of secondary insults of elevated ICP events, and the need for personalization. Two clinical trials are currently investigating the impact of presenting this information at the bedside to clinicians.

Summary
The implementation of information on ICP burden at the patient's bedside could assist clinicians in recognizing secondary brain injury and result in more personalized ICP management.

Keywords
acute brain injury, clinical decision making, critical care, intracranial pressure, intracranial pressure dose

INTRODUCTION

Continuous invasive monitoring of patients suffering from acute life-threatening traumatic, ischemic, or haemorrhagic brain injuries has become the cornerstone of neurocritical care, to optimize demand and perfusion of the injured brain, or to detect impending herniation [1▪]. This includes invasive monitoring of arterial blood pressure, intracranial pressure (ICP), and their derivative cerebral perfusion pressure (CPP). In a number of centres, additional monitoring such as continuous electroencephalography, invasive brain tissue oxygen, or cerebral microdialysis are used [2–4]. Even while significant variation exists between centres and countries in the use and indications for ICP monitoring, its use to detect secondary brain injury and guide patient management is associated with more aggressive treatment. This approach, especially in patients with clinical signs of intracranial hypertension, is associated with lower 6-month mortality [5], in particular in patients with traumatic brain injury (TBI) [6▪]. The Brain Trauma Foundation guidelines suggest to start treatment for the management of intracranial hypertension in patients with TBI when the ICP exceeds a threshold of 22 mmHg, previously 20 mmHg [7–9]. These thresholds are based on retrospective epidemiological studies, investigating the association between ICP values and outcome. The long-upheld 20 mmHg threshold was based on one study by Marmarou *et al.* [10] from 1991, which found that a cutoff of 20 mmHg was most indicative of outcome in a cohort of

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KEY POINTS

- Current treatment of intracranial pressure is threshold-based, which might not be representative for the secondary brain injury in individual patients with acute brain injury.
- Visualizations of the relationship between ICP dose (combining intensity and duration) and neurological outcome are clear representations of the tolerance of increased ICP in different types of brain injury.
- Cohort or patient-specific factors can influence the brain's tolerance of intracranial hypertension. This should be taken into account in the interpretation of the ICP burden curves.
- Implementing information on ICP burden at the patient bedside could assist clinicians in identifying secondary brain injury; however, it is currently unknown how clinicians will integrate this information in their clinical decision making.

430 patients from the Traumatic Coma Data Bank. In more recent guidelines, this threshold was changed to 22 mmHg, based on a single-centre retrospective study in 459 TBI patients by Sorrentino *et al.* [11], who calculated Pearson's chi-square values of different ICP values and their association with outcome, and found that ICP values above 22 mmHg showed the highest chi-square and thus were most discriminative for outcome. However, neither of these studies were designed to investigate or suggest treatment thresholds. More recently, Riparbelli *et al.* [12] were unable to reproduce the findings by Sorrentino *et al.* [11] using the same methods and closely comparable cohorts. In the often-cited BEST-TRIP trial, two regimens of ICP treatment were compared, and the treatment arm where ICP was monitored and treated at a threshold of 20 mmHg did not lead to better outcomes compared with ICP treatment based only on clinical evaluation and imaging [3]. Even while higher ICP values are clearly harmful in TBI patients, the epidemiological thresholds of 20 or 22 mmHg do not equal therapeutic thresholds. Moreover, they are not individualized and might be too sensitive or not sensitive enough to detect secondary brain injury depending on the patient and the brain injury. This is why the complex interaction between ICP, cerebral blood flow, cerebrovascular autoregulation, and brain metabolism in these patients should also be considered [13]. More recently, it has been proposed that the cumulative burden of elevated ICP over time may provide a more representative assessment of the impact of intracranial hypertension and its relationship with patient outcomes. In what follows, we will describe the insights gained into the ICP burden to date. In addition, we will discuss how the ICP burden can be visualized and possible implications for clinical management.

INTRACRANIAL PRESSURE BURDEN

Factoring in both the intensity and duration of an ICP insult, burden of ICP measures is considered more informative parameters than the mean, minimum, maximum, and percentage above and below a threshold of ICP when describing secondary brain damage [14,15]. In literature, different terms, such as ICP dose, pressure time dose (PTD) and pressure time index (PTI) are used interchangeably as measures of the ICP burden. For consistency, we will use the term 'ICP dose' throughout this review. The ICP dose is defined as the area under the curve (AUC) of ICP episodes above a certain value for at least a given duration [14,16,17,18], shown in Fig. 1a. Multiple studies have investigated the ICP dose above the previously recommended treatment threshold of 20 mmHg, in single-centre or multicentre cohorts of severe TBI patients. A higher ICP dose above 20 mmHg was associated with increased mortality rates [14,15,19,20], decreased functional outcome [15,19,20], increased length of stay [15], and worse Marshall CT classification [14]. Also, in patients with aneurysmal subarachnoid haemorrhage (aSAH), the dose of ICP may better reflect the elevated ICP insults that the brain suffers after rupture. In a single-centre aSAH patient cohort ($n = 55$), exposure to ICP doses at thresholds of 25–30 mmHg was associated with increased early mortality and an ICP dose with a threshold of 30 mmHg was identified as a significant prognostic indicator for 6-month unfavourable outcomes [21].

Unlike the abovementioned studies, where the ICP dose above a single threshold was calculated, Shaw *et al.* [22] considered the relationship between ICP dose above various thresholds (1–40 mmHg) and length of stay, measured in hours, in a small cohort of severe TBI patients ($n = 10$). Findings demonstrated that prolonged elevated ICP during the early monitoring period is associated with prolonged length of stay [22].

To further explore the impact of ICP doses of different duration and intensities on neurological outcomes, Güiza *et al.* [18] introduced the concept of a visualization showing the relationship between episodes of elevated ICP and the 6-month Glasgow Outcome Scale (GOS) scores. First, the ICP dose was identified for a whole range of ICP thresholds between 10 and 40 mmHg. Next, the Pearson correlation between the average number of doses per

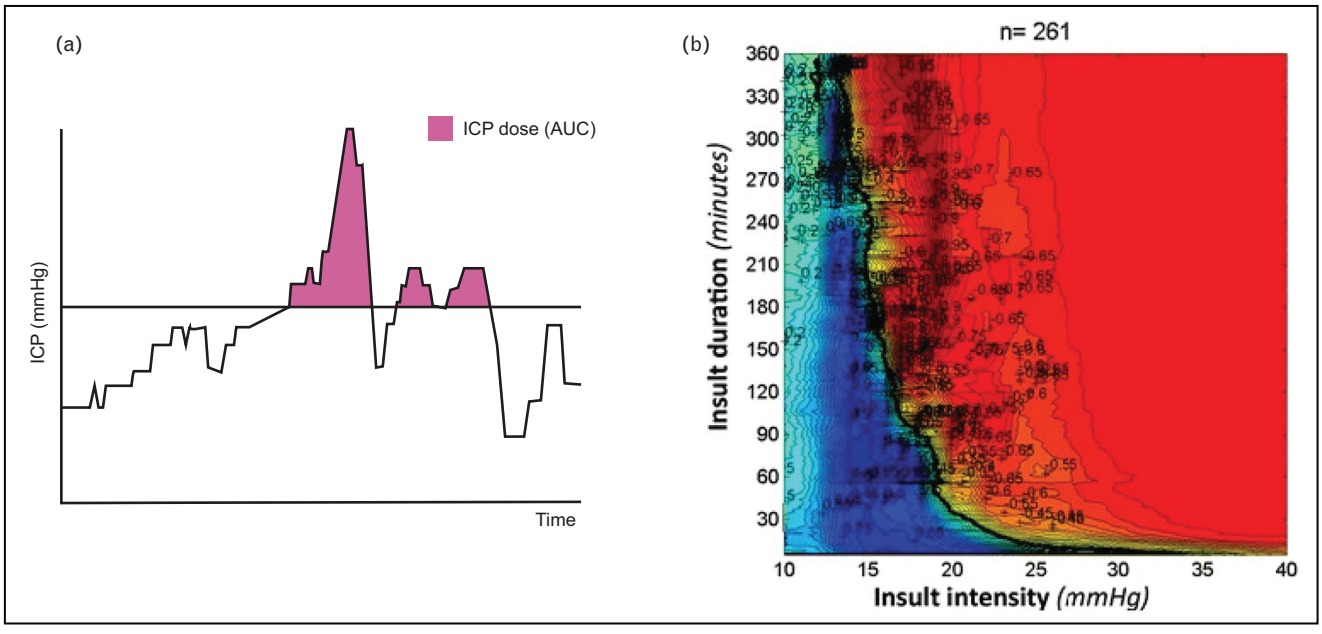

FIGURE 1. Concepts of (a) ICP dose, which factors in both the intensity and duration of an intracranial pressure (ICP) insult, defined as the area under the curve (AUC) of ICP episodes above a certain value for at least a given duration; (b) Visualization plot in which the correlation between Glasgow Outcome Scale (GOS) and average number of ICP insults per GOS category is plotted for the adult cohort ($n = 261$). Each colour-coded point in the graph represents the univariate correlation between, an ICP insult [defined by a threshold of ICP intensity (X-axis), and a certain duration (Y-axis)] with outcome. Dark red points represent ICP events associated with worse outcome (low GOS), dark blue points represent ICP events associated with better outcome (high GOS). The transition curve, or the contour of zero correlation is outlined in black. Reproduced with permission from [18]. Figure is best seen in colour in the online version.

patient and the GOS score was visualized in a colour-coded plot [18], shown in Fig. 1b. Within this plot, the transition curve marks the contour for zero correlation and represents the transition between the two regions of insult types that are observed more frequently either in patients with lower or with higher GOS scores [18]. The concept was developed in the BrainIT dataset, a multicentre European adult ($n = 261$) cohort where it demonstrated the predictive nature of ICP doses for worse outcomes at 6 months and confirmed the intuitive understanding that higher ICP levels are less tolerable at a longer duration [18]. Furthermore, the transition curve shows that prolonged insults of even moderate ICP levels, between 15 and 20 mmHg, can result in worse outcomes [18].

When the same methodology was applied to a paediatric cohort ($n = 99$), episodes of lower intensity and shorter duration than those observed in adults were associated with worse outcomes. In this cohort, the transition curve showed that prolonged insults of ICP above 10 mmHg (and 20 mmHg for more than 8 min) are associated with worse outcomes [18]. A more recent study in an independent, international, multicentre, paediatric TBI cohort ($n = 104$) confirmed these findings [23].

In four other independent patient cohorts, the robustness of the methodology for visualizing the relationship between ICP dose and neurological outcome was demonstrated [24–26], further supporting the importance of the intensity burden of ICP insults in patients with acute brain injury. Similar transition curves were found in an independent patient cohort of severe TBI patients from Cambridge ($n = 1112$) [24], as well as in the high-resolution subset of the Center-TBI study ($n = 277$) [25], even while the transition occurred at slightly different intensity-duration combinations. For instance, compared to the BrainIT dataset where insults above 20 mmHg for at least 37 min (and 25 mmHg for more than 12 min) were associated with worse outcomes [18]; in Cambridge, this transition was set at 20 mmHg for at least 13 min [24], and in Center-TBI, the transition occurred at 22 mmHg for more than 5 min (and 16 mmHg for more than 60 min) [25]. These differences in identified thresholds may be accounted for by differences in cohort characteristics and by the quantification of the burden of ICP insults with lower temporal resolution, which can potentially lead to an overestimation of the burden of elevated ICP. One study confirmed that a more accurate quantification of the burden of

elevated ICP can be acquired by using the beat-to-beat analysis of the AUC [27]. In two cohorts of patients with aSAH, ICP doses at lower thresholds were associated with worse outcome, indicating a worse tolerance to even moderate elevated ICP insults. In the Innsbruck cohort insults ranging from 10 mmHg for 350 min to 15 mmHg for 10 mmHg were harmful. In the Monza cohort, harmful thresholds ranged from 5 mmHg for 160 min to 15 mmHg for 5 min [26].

When replotting the exponential transition curve for a multicentre European cohort of patients with severe TBI, results showed that the curve was not influenced by the change of guidelines for CPP management before ($n = 166$) and after ($n = 95$) 2007 [28]. However, this post-2007 cohort was too small to investigate whether an CPP target of 60 mmHg represents better tolerance for elevated ICP insults. In the larger adult and paediatric cohorts, when CPP was critically low (below 50 mmHg), ICP no longer was a univariate predictor for outcome [18,23].

Three studies visualizing the relationship between ICP dose and outcome demonstrated that autoregulation has a major effect on the transition curves in both the adult and paediatric cohorts [18,23,25]. Furthermore, when analysing the pressure reactivity index (PRx $> +0.20$) in relation to the ICP, an individual ICP threshold beyond which cerebrovascular reactivity consistently becomes impaired can be determined [29]. In a small cohort, the ICP doses above an individual PRx threshold in comparison to the ICP doses above the treatment thresholds of 20 and 25 mmHg, showed a stronger association with mortality [29]. These findings were confirmed in a European cohort ($n = 128$) [30], providing further evidence that the tolerability of ICP is dependent on the autoregulatory status of the brain. These individualized thresholds might enable the potential implementation of individualized treatment which also takes cerebrovascular reactivity into account [29].

Ding *et al.* [31▪] introduced a variation on the method to visualize the relationship between intensity and duration of ICP insults utilizing odds ratios instead of Pearson's correlation. Consistent with earlier observations, their results showed an association between intensity and duration of ICP exposure and that even moderate ICP levels can result in worse outcomes [31▪].

Overall, there is uncertainty on how long elevated ICP must persist to cause harm and there is no predefined consensus on which ICP doses should lead to treatment. Whilst colour-coded plots have given us insights into the relationship between ICP insults and GOS, some aspects of these plots remain unclear. First, the visualizations cannot differentiate whether there is a causation or only an association between ICP doses and worse outcome [25]. Second, for thresholds associated with a longer duration of elevated ICP, other confounders might influence long-term outcomes, making it difficult to determine if reducing ICP would directly improve outcomes [25]. Third, these analyses were conducted on retrospective data of patients managed according to treatment guidelines to prevent secondary injury; therefore, it is difficult to determine the effects of medical interventions on the clinical outcome [18]. Furthermore, current identified ICP doses above a threshold associated with an unfavourable outcome, or mortality, are population based and may not represent the impact of ICP doses for individual patients [25]. Moreover, patients' individual ability to tolerate an elevated ICP may change over time through disease progression [25]. Factors, such as age, CPP and autoregulation, should be taken into account when translating these results to other patient cohorts or individual patients.

CURRENT BEDSIDE IMPLEMENTATION OF INTRACRANIAL PRESSURE BURDEN CONCEPTS

Even while retrospective analysis on different cohorts have shown a clear association between ICP dose and outcome in acute brain injury patients, elegantly illustrated by graphical visualisations of this important relationship between ICP dose and neurological outcome, this information is currently not available in our standard clinical monitors. To understand the potential impact of providing clinicians with the additional information of ICP dose, this information needs to be provided at the patient bedside.

Currently, two studies are being conducted in which information on the ICP burden is provided at the bedside. First, The Intracranial PrEssure Time dOse (ImPETO) is a prospective, observational, international cohort study [32], which uses the Integra CereLink ICP monitor to display the PTD continuously. The ImPETO study is aimed to clinically assess if continuously recorded PTD is associated with the patients' outcomes and to identify a threshold of PTD associated with the transition from good to negative outcomes. The researchers hypothesize that a high PTD will be associated with worse outcome. Furthermore, the study results will provide insights into a possible threshold for PTD associated with good outcomes and better documentation and understanding of the PTD and its association with long-term patients' outcomes.

Second, in the MONTE (Monitor for iNTracranial hypErtension) pilot trial, clinicians are provided with additional information on the neurological status

of patients with TBI, including the information on the ICP burden, cerebrovascular autoregulation, and prediction of harmful ICP doses with a 30-min forewarning. The machine learning model predicting the probability that the patient will have an ICP dose associated with worse outcome demonstrated good discrimination and calibration when externally validated (AUC: 0.94, accuracy: 0.89, precision: 0.87, sensitivity: 0.78, specificity: 0.94, calibration-in-the-large: 0.03, calibration slope: 0.93) [33▪]. In the MONTE monitor, the ICP burden will be displayed as the percentage of time in which the patient has experienced a harmful ICP dose and an ICP above a predefined threshold in the past 4 h, 24 h, or the entire length of monitoring. The MONTE pilot study is a multicentre randomized trial aimed to evaluate the feasibility of the methodology to assess safety and effectiveness of the MONTE software. The main hypothesis of this pilot study is that the protocol is feasible and can be utilized in a future larger clinical trial powered to demonstrate an impact on outcome and patient management [34]. In this trial, the treating physician is asked to perform a clinical reassessment of the patient every 4 h and to complete a questionnaire to gain insight into the use of the additional information provided on the neurological status of the patient. With respect to ICP burden implementation, this pilot study will provide insights into the potential impact of the display of ICP dose and percentage of ICP above a threshold on the clinical decision-making process of physicians.

CONCLUSION

ICP is an important monitoring tool in the management of acute brain injury patients, however, current treatment is based on a fixed threshold approach. Retrospective analysis on different cohorts has shown an association between ICP dose and mortality and functional outcome in acute brain injury patients. To further improve personalization of thresholds, factors such as age, CPP, and autoregulation should be taken into account. Two clinical trials are currently ongoing in which information on the ICP burden is implemented at the bedside. Bedside implementation will provide insights into the impact of ICP burden information on clinical decision making and patient outcomes.

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Conflicts of interest

There are no conflicts of interest.

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