Visualizing the pressure-time burden of elevated intracranial pressure after severe TBI – a retrospective confirmatory study

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Elevated intracranial pressure (ICP) after severe traumatic brain injury (TBI) is an important cause of secondary brain injury, either by hypoperfusion because of decreased cerebral perfusion pressure (CPP), or by mechanical distortion leading to brain herniation [1]. The thresholds to treat elevated ICP in severe TBI (20 or 22 mmHg) are based on epidemiological studies [2, 3], however, the early application of aggressive measures to treat brief episodes of ICP elevations above 20 mmHg have demonstrated harm [4]. Moreover, the association between elevated ICP and outcome is not merely due to crossing a threshold but will depend upon the magnitude as well as the duration of intracranial hypertension. This has been elegantly demonstrated in a multicentre prospective European dataset (n= 261), by Güiza and colleagues [5]. Using a 3-dimensional visualisation technique, they demonstrated that worse outcomes (taken at 6 months) could be explained by the interaction between the level of ICP elevation and the duration of the hypertensive episode, confirming a concept that clinicians intuitively relate to. For instance, insults of high ICP, over 30 mmHg, seemed to be only tolerated for a short time (<8 minutes), whereas ICP elevations over 20 mmHg lead, on average, to a poor outcome if sustained over 37 minutes. The ability to tolerate elevated ICP was decreased in children, when cerebrovascular autoregulation was absent, and when CPP was inadequate. To date, this visualisation technique has not been replicated outside of the prospective European dataset [5]

We sought to confirm these findings by applying the same visualisation method on an independent patient cohort of 1112 severe TBI patients from Addenbrooke's Hospital (Cambridge, United Kingdom), collected between 1991 and 2017. Patient demographics and management protocols have been previously described [6]. Since all data were extracted from the hospital records and fully anonymized, no data on patient identifiers were available, and therefore formal patient or proxy consent and institutional ethics approval were not required.
From minute-by-minute resolution data (time-averaged), ICP hypertensive episodes were defined as being above a given intensity threshold I, for at least a given duration D. For each pair of intensity and duration thresholds <I,D>, the average number of corresponding episodes per patient was calculated, separately in each 6-month Glasgow outcome score (GOS) group [5]. Thereafter, the Pearson correlation between the average number of ICP episodes and GOS was calculated for each <I,D>, and colour-coded according to a predefined colour map (Figure 1). In this way, a single time point with elevated ICP can contribute to multiple insults on the colour contour-plot. For example, an ICP of 12.5 mm Hg for 5.5 minutes will contribute to the episode-outcome Pearson correlation for the ICP greater than 10, 11 and 12 mm Hg intensity category, and for the greater than 1,2,3,4 and 5 minute duration category. Multivariable logistic regression was used to study the effect of the amount of time in the red-zone of these plots, with patient outcome (mortality and unfavourable outcome) with adjustment for age and initial Glasgow coma scale

From the 1112 patients, 33 million ICP insults were identified. By plotting the relationship between the insult count for each <I,D> pair and the outcome, a 3-dimensional colour coded contour-plot was obtained, similar to that of Güiza and colleagues (Fig 1). The contour of zero correlation, i.e. the transition curve between the good and bad outcome associations, occurred at similar, but not identical values. For example, the current data indicate that a an ICP insult

of at least 20 mm Hg starts to be associated with poor outcome when they last longer than 13 minutes, compared with 37 minutes from the previous paper from the multicentre European cohort. Differences in patient population or patient management likely contribute to these quantitative differences in the transition curve and should be investigated in appropriately designed studies that include detailed patient descriptors. Unfortunately, a detailed description of patient ICP therapies is not available in the current cohort. Nevertheless, the striking qualitative similarity of contour plots indicates that the concept of the intensity duration burden of ICP insults is important after traumatic brain injury. On multivariable analysis, after adjusting for age and initial Glasgow coma scale, the fraction of time spent in the red-zone was significantly related to mortality (odds ratio 6.87, confidence interval 4.2-11.3, $p<0.001$) and unfavourable outcome (odds ratio 2.85, confidence interval 1.9-4.3, $p<0.001$).

Prospective studies of this visualisation technique at the bedside can begin, taking into account information on therapeutic intensity and other important prognostic variables. This will require international concerted efforts in high fidelity brain monitoring data coupled with detailed clinical contextual information. With increasing size of datasets, important sub analyses may be performed to answer questions such as: are males more sensitive to increases in ICP; are ICP increases more harmful in diffuse injuries; or should ICP management in older patients be different to younger patients? After elucidation of aformentioned issues, overlaying of a particular patients current ICP over the colour coded ICP burden plot could assist in ICP interpretation and therefore patient management.

Whilst elevated ICP after traumatic brain injury is an intuitive example of physiologic insult burden visualisation, it is likely that this technique could be applied to other secondary injuries such as autonomic dysfunction, hyperthermia, brain hypoxia, or neuro-metabolic dysfunction. Furthermore, the technique could be applied to monitoring physiologic insults in anaesthetic or intensive care contexts outside of traumatic brain injury.

Despite modern ICP and multimodal brain monitoring over the past 25 years, patient mortality seems to be remaining relatively static [6]. This underlines an urgent need for innovative and reproducible techniques to allow meaningful interpretation of bedside signals. While unlikely to be a panacea, the intensity – duration contour plots that have now been replicated are a promising tool that may allow more nuanced interpretation of secondary brain injury.

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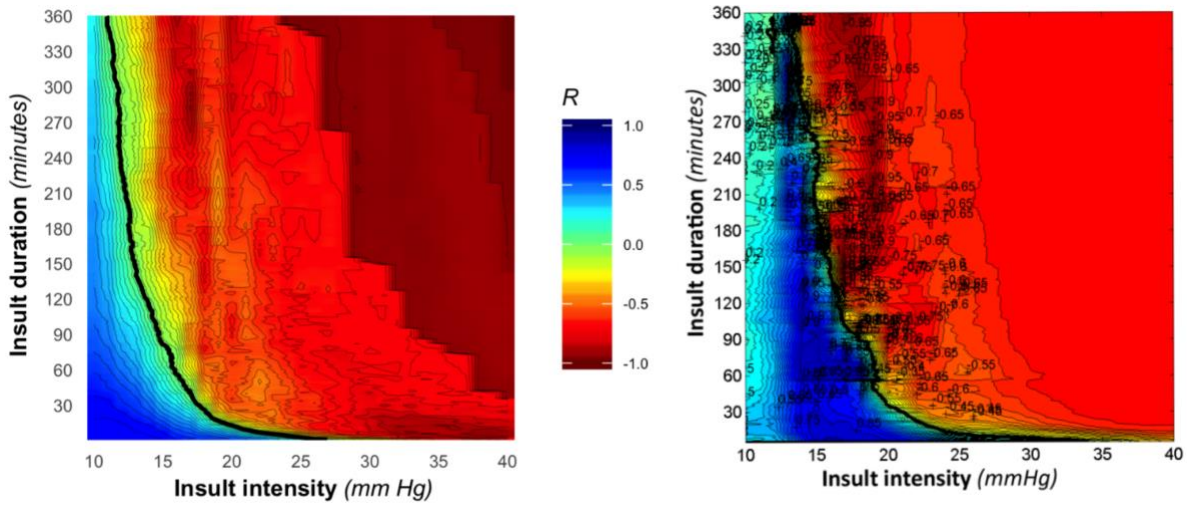
References

1. Stocchetti N, Carbonara M, Citerio G, et al (2017) Severe traumatic brain injury: targeted management in the intensive care unit. Lancet Neurol 16:452–464. https://doi.org/10.1016/S1474-4422(17)30118-7
2. Marmarou A, Anderson RL, Ward JD, et al (1991) Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg 75:S59–

S66. https://doi.org/10.3171/sup.1991.75.1s.0s59
3. Sorrentino E, Diedler J, Kasprowicz M, et al (2012) Critical thresholds for cerebrovascular reactivity after traumatic brain injury. Neurocrit Care 16:258–66. https://doi.org/10.1007/s12028-011-9630-8
4. Cooper DJ, Rosenfeld J V, Murray L, et al (2011) Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med 364:1493–502. https://doi.org/10.1056/NEJMoa1102077
5. Güiza F, Depreitere B, Piper I, et al (2015) Visualizing the pressure and time burden of intracranial hypertension in adult and paediatric traumatic brain injury. Intensive Care Med. https://doi.org/10.1007/s00134-015-3806-1
6. Donnelly J, Czosnyka M, Adams H, et al Twenty-Five Years of Intracranial Pressure Monitoring After Severe Traumatic Brain Injury: A Retrospective, Single-Center Analysis. https://doi.org/10.1093/neuros/nyy468

Figure legend



Visualizing the relationship between the number of ICP insults and GOS across different intensities and durations from Addenbrooke's cohort (left, n=1112, 33 million episodes), and previously published multicentre European cohort (right, n= 261, 8 million episodes, figure reproduced from Güiza and colleagues, 2015 [5]).

Each coordinate <I,D> in the figure refers to a hypertensive ICP episode of at least a certain intensity (magnitude) I (x-axis), for at least a certain duration D (y-axis). The colour coding indicates the univariate correlation between the average number of episodes <I,D> per patient and GOS; a blue colour indicates association with better outcome whereas a red colour indicates association with worse outcome (i.e. more ICP insults related to worse outcome). The black like marks the transition zone between a positive and negative correlation. The current data (left) are qualitatively AND quantitatively similar to those previously published (right)

ICP intracranial pressure; *GOS* Glasgow outcome scale; *R* Pearson correlation coefficient.