Patient-Specific ICP Epidemiologic Thresholds in Adult Traumatic Brain Injury: A CENTER-TBI Validation Study

Frederick A. Zeiler,[1-4] Ari Ercole,[1] Manuel Cabeleira,[4] Erta Beqiri,[4,6] Tommaso Zoerle,[5] Marco Carbonara,[5] Nino Stocchetti,[5,6] David K. Menon[1], Christos Lazaridis,[7] *Peter Smielewski,[4] *Marek Czosnyka,[4,8]; CENTER-TBI High Resolution ICU Sub-Study Participants and Investigators[#]

1. Division of Anaesthesia, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
2. Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
3. Clinician Investigator Program, Rady Faculty of Health Science, University of Manitoba, Winnipeg, Canada
4. Brain Physics Laboratory, Division of Neurosurgery, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
5. Neuro ICU Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
6. Department of Physiopathology and Transplantation, Milan University, Italy
7. Departments of Neurology and Neurosurgery, Section of Neurocritical Care, University of Chicago, Chicago, IL, USA
8. Institute of Electronic Systems, Warsaw University of Technology, Warsaw, Poland

***P Smielewski and M Czosnyka are joint senior authors.**

 # The CENTER-TBI High Resolution Sub-Study Participants and Investigators are listed at the end of the manuscript before the references.

Corresponding Author:

Frederick A. Zeiler BSc MD PhD FRCSC (Neurosurgery)
Assistant Professor
Department of Surgery
Rady Faculty of Health Sciences
University of Manitoba
Winnipeg, MB, Canada
R3A 1R9

Email: umzeiler@myumanitoba.ca

Contributing Authors:

Ari Ercole MD PhD FRCA FFICM
Consultant in Intensive Care Medicine
Division of Anaesthesia
University of Cambridge
Email: ae105@cam.ac.uk

Manuel Cabeleira BSc

Brain Physics Laboratory
Division of Neurosurgery
Dept of Clinical Neurosciences
University of Cambridge
Email: mc916@cam.ac.uk

Erta Beqiri MD
Brain Physics Laboratory
Division of Neurosurgery
Dept of Clinical Neurosciences
University of Cambridge
Email: erta.beqiri@gmail.com

Tommaso Zoerle MD
Neuro ICU Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico
Milan
Email: tommaso.zoerle@policlinico.mi.it

Marco Carbonara MD
Neuro ICU Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico
Milan
Email: marco.carbonara@gmail.com

Nino Stocchetti MD
Department of physiopathology and transplantation, Milan University
Neuro ICU Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milan
ORCID unique identifier: 0000-0003-3250-6834
Email: nino.stocchetti@policlinico.mi.it

David K. Menon MD PhD FRCP FRCA FFICM FMedSci
Head, Division of Anaesthesia, University of Cambridge
Honorary Consultant, Neurosciences Critical Care Unit, Addenbrooke's Hospital
Professorial Fellow, Queens' College, Cambridge
Senior Investigator, National Institute for Health Research, UK
Email: dkm13@cam.ac.uk

Christos Lazaridis MD EDIC
Associate Professor
Departments of Neurology and Neurosurgery
University of Chicago
Email : lazaridis@uchicago.edu

Peter Smielewski PhD
Senior Research Associate
Laboratory of Brain Physics
Division of Neurosurgery
University of Cambridge
Email: ps10011@cam.ac.uk

Marek Czosnyka PhD
Professor of Brain Physics
Brain Physics Laboratory, Division of Neurosurgery
University of Cambridge
Cambride, UK
CB2 0QQ
Email: mc141@medschl.cam.ac.uk

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Conflicts of Interest:

PS and MC receive part of licensing fees for the software ICM+ (Cambridge Enterprise Ltd, UK) used for data collection and analysis in this study.

Previous Presentation of Work: None

Abstract:

Background: Patient-specific epidemiologic ICP thresholds in adult TBI have emerged, using the relationship between pressure reactivity index (PRx) and ICP, displaying stronger association with outcome over existing guideline thresholds. The goal of this study was to explore this relationship in a multi-center cohort in order to confirm the previous finding.

Methods: Using the Collaborative European Neuro Trauma Effectiveness Research in TBI (CENTER-TBI) high-resolution intensive care unit (ICU) cohort, we derived individualized epidemiologic ICP thresholds for each patient using the relationship between PRx and ICP. Mean hourly dose of ICP was calculated for every patient for the following thresholds: 20 mm Hg, 22 mm Hg and the patient's individual ICP threshold. Univariate logistic regression models were created comparing mean hourly dose of ICP above thresholds to dichotomized outcome at 6 to 12-months, based on Glasgow Outcome Score – Extended (GOSE) (alive/dead - GOSE >=2/GOSE=1; favourable/unfavourable – GOSE 5 to 8/GOSE 1 to 4, respectively).

Results: Individual threshold were identified in 65.3% of patients (n=128), in keeping with previous results (23.0 +/- 11.8 mm Hg (IQR: 14.9 to 29.8 mm Hg)). Mean hourly dose of ICP above individual threshold provides superior discrimination (AUC 0.678, p=0.029), over mean hourly dose above 20 mm Hg (AUC = 0.509, p=0.03) or above 22 mm Hg (AUC = 0.492, p=0.035) on univariate analysis for alive/dead outcome at 6 to 12 months. The AUC for mean hourly dose above individual threshold trends to higher values for favourable/unfavourable outcome, but fails to reach significance (AUC = 0.610, p=0.060). This was maintained when controlling for baseline admission characteristics.

Conclusions: Mean hourly dose of ICP above individual epidemiologic ICP threshold has stronger associations with mortality compared to the dose above BTF defined thresholds of 20 or 22 mm Hg, confirming prior findings. Further studies on patient specific epidemiologic ICP thresholds are required.

Keywords: ICP threshold, individual ICP threshold, patient-specific thresholds, pressure reactivity, PRx,

Introduction:

Recent analysis of cerebral physiology in adult TBI has suggested a potential role of individualized treatment regimens based on advanced monitoring of cerebrovascular reactivity and the derivation of individualized cerebral perfusion pressure (CPP) targets, termed optimal CPP (CPPopt).[1,2] This represents a shift towards more individualized medicine in the care for moderate/severe TBI patients. Data from initial studies suggests stronger outcome associations with individualized CPP targets, compared to applying the same target range applied to all patients.[1–3]

Aside from individualized CPP targets, individualized epidemiologic intracranial pressure (ICP) thresholds have been suggested based on a single center retrospective study in adult TBI.[4–6] Using the relationship between continuously monitored cerebrovascular reactivity, using the pressure reactivity index (PRx), and ICP, one can find the ICP threshold where all subsequent higher ICP values yield PRx measures consistently above +0.20,[4] a threshold value for PRx known to be associated with impaired cerebrovascular reactivity and global outcome in adult TBI.[7–10] This has been termed the patient-specific or individualized ICP threshold, identifiable in approximately 68% of patients.[4] Prior retrospective analysis supports a potentially stronger association between the dose of ICP above individual epidemiologic thresholds, compared to the Brain Trauma Foundation (BTF) guideline defined

threshold of 20 mm Hg, with global outcome in TBI.[4] However, this has not been replicated in any other group of patients or outside of this single center.

The goal of this study is to utilize the multi-center Collaborative European Neuro Trauma Effectiveness Research in TBI (CENTER-TBI) study[11] high-resolution intensive care unit (ICU) cohort data set, to evaluate the ability to derive individualized ICP epidemiological thresholds using a semi-automated algorithm and compare the association between dose above individual threshold and BTF guideline ICP thresholds (ie. 20 mmHg and 22 mmHg) with global patient outcome.

Methods:

Patient Population:

All patients from the multi-center CENTER-TBI high resolution ICU cohort were included in this study. These patients were prospectively recruited during the periods of January 2015 to December 2017. A total of 21 centers in the European Union (EU) contributed. All patients were admitted to ICU for their TBI during the course of the study, with high frequency digital signals recorded from their ICU monitors during the course of their ICU stay. All patients suffered predominantly from moderate to severe TBI (moderate = Glasgow Coma Score (GCS) 9 to 12, and severe = GCS of 8 or less). A minority of patients suffered from mild TBI (GCS13-15), with subsequent early deterioration leading to ICU admission for care and monitoring. All patients in this cohort had invasive ICP monitoring conducted in accordance with the BTF guidelines.[12]

Ethics: Data used in these analyses were collected as part of the CENTER-TBI study which had individual national or local regulatory approval; the UK Ethics approval is provided as an exemplar: IRAS No:

150943; REC 14/SC/1370). The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws of the country where the Recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects". Informed Consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF.

Data Collection:

As part of recruitment to the multi-center high resolution ICU cohort of CENTER-TBI,[11] all patients had demographics prospectively recorded. Similarly, all patients had high frequency digital signals from ICU monitoring recorded throughout their ICU stay, with the goal of initiating recording within 24 hours of ICU admission. All digital ICU signals were further processed (see Signal Acquisition/Signal Processing). For the purpose of this study, the following admission demographic variables were collected: age, sex, admission Glasgow Coma Scale (GCS – total and motor) and admission pupillary response (bilaterally reactive, unilateral reactive, bilateral unreactive). We focused on the use of entirely non-imputed raw data, as final imputation of the entire CENTER-TBI dataset is an ongoing process and will be part of subsequent publications and analysis. CENTER-TBI data was accessed/extracted using Opal database software[13], accessed on Sept 16th, 2018.

Signal Acquisition and Processing:

Signal acquisition and processing was conducted in an identical manner to previous CENTER-TBI high resolution ICU sub-study publications. Details can be found in Appendix A and the previous publications from this cohort.[14,15] PRx was derived via the moving correlation coefficient between 30 consecutive 10 second mean windows of the parent signals (ICP and mean arterial pressure (MAP)), updated every minute.[16]

Individual Patient Specific ICP Threshold Determination

For each patient, the relationship between PRx and ICP for the entire recording period was utilized to determine their individual ICP epidemiologic threshold. Based on the methodology outlined in the previous publications on the topic,[4] the ICP value where PRx is +0.20, and all higher ICP values have PRx values persistently above +0.20 was considered the individual ICP threshold. Previous publications employed manual direct observation of the relationship between PRx and ICP, via error bar plotting, to determine the individual ICP threshold.[4,5] It must be acknowledged that these individual thresholds for ICP do not represent therapeutic targets, but an individualized epidemiological thresholds, derived from the relationship between cerebrovascular reactivity values associated with global long-term outcome. Thus the derived individual thresholds quoted within the manuscript should not be considered as therapeutic in nature, and purely preliminary exploratory work into personalized ICP thresholds in TBI. Further, the method for determination requires the use of the entire recording period, limiting this current technique to purely retrospective analysis.

In this study, we developed a semi-automated algorithmic method using R statistical computing software (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). First, for every patient an error bar plot of PRx vs. ICP, using 2.5 mm Hg bins of ICP, was constructed for each patient. This was

smoothed using locally weighted scatterplot smoothing (LOESS) functions for each patient. Second, using these LOESS fitted values, we subsequently identified the lowest ICP value for which PRx was between +0.19 and +0.21 (ie. the lowest ICP values for intersection between the fitted LOESS function and the line "y" = +0.20 (ie. PRx = +0.20). This ICP value was selected as the patient's individual ICP threshold. These thresholds were then assessed for validity by manual inspection of each patient's error bar and LOESS function plots of PRx versus ICP. Any discrepancies between the algorithm-derived individual ICP threshold and the manually inspected ICP threshold were then corrected by hand, if present (hence "semi-automated"). Figure 1 displays two patient examples of the error bar and LOESS function plots, with the individual ICP threshold identification.

***Figure 1 here**

Data Processing:

Grand mean values of all physiologic variables were calculated per patient. In addition, post-ICM+ processing of physiologic data occurred in R. Dose above ICP threshold was determined for the BTF defined ICP thresholds of 20 mm Hg and 22 mm Hg, as well as for the patient's individual ICP threshold. Dose was calculated in the following manner for each min-by-min observation: if ICP > ICP Threshold, then Dose = ICP – ICP Threshold, otherwise generate no value. We then summated the dose over the entire recording period, and subsequently divided this value by the total duration of recording (in hours) to generate the mean hourly dose above threshold for thresholds of: 20 mm Hg, 22 mm Hg and the patient's individual ICP threshold.

Statistics:

All statistical analysis was conducted using R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and XLSTAT (Addinsoft, New York, NY; https://www.xlstat.com/en/) add-on package to Microsoft Excel (Microsoft Office 15, Version 16.0.7369.1323). Normality of continuous variables was assessed via Shapiro-Wilks test. For all testing described within, the alpha was set at 0.05 for significance. All continuous variables were found to be non-parametrically distributed.

Despite GOSE being collected at both 6- and 12-months post-injury in this cohort of patients, there was missing data present in both categories of outcome, as described in previous publications from the CENTER-TBI high-resolution ICU cohort. Thus, we combined GOSE scores from both 6 and 12 months in order to provide a "6 to 12 Month" GOSE. For patients where GOSE was reported for both 6 and 12 months, the last (ie. latest or 12 month) GOSE score was selected for analysis.

GOSE was then dichotomized into the following categories: A. Alive (GOSE 2 to 8) vs. Dead (GOSE 1); and B. Favourable (GOSE 5 to 8) vs. Unfavourable (GOSE 4 or less). Demographics and physiologic variables were compared between each dichotomized group using: Mann-Whitney U and chi-square testing where appropriate. Box plots were created for variables of interest comparing between dichotomized groups.

Univariate logistic regression (ULR) and bivariate logistic regression was conducted, comparing variables to both dichotomized GOSE outcomes, assessing superiority via AUC, Akaike Information Criterion (AIC) and Delong's Test. Only ULR and bivariate logistic regression was conducted as this is only the second set of data for which individual ICP thresholds have been assessed, and we were only interested in

testing a new algorithm for detection and validate the previous single-center results. Bivariate models composed of hourly dose above ICP of 20 mm Hg and mean PRx, and hourly dose above ICP of 22 mm Hg and mean PRx, were both created to assess association with both dichotomized outcomes. These models were compare to the univariate models which assessed the association between hourly dose above individual ICP threshold and the dichotomized outcomes.

Finally, the results from the univariate logistic regression analysis were confirmed through multi-variable logistic regression, by controlling for standard International Mission for Prognosis and Analysis of Clinical Trials in TBI Core (IMPACT-Core) admission variables: age, GCS motor sub-score and pupillary response (as measured through an ordinal scale: bilaterally reactive, unilateral reactive, bilateral unreactive).[17] Note, not all patients had a complete data set for this analysis, and so we focused only on those with complete IMPACT-Core variables and identifiable individual ICP thresholds (ie. n=127).

Results:

Patient Demographics

There were 196 patients from the CENTER-TBI high-resolution ICU cohort, with high-frequency physiologic signals and demographic variables, which were included in this study. This particular cohort has been described in detail within previous publications.[14] The mean age was 46.6 +/- 19.7 years, with 150 being male. Median admission GCS was 8 (IQR: 5 to 13), and mean duration of physiologic monitoring was 159.3 +/- 115.1 hours.

Using the semi-automated algorithm described to determine individual ICP thresholds, a total of 128 out of 196 (65.3%) had an identifiable individual ICP epidemiologic threshold, in keeping with previous single center literature on the topic,[4] with mean individual ICP threshold of 23.0 +/- 11.8 mm Hg (IQR: 14.9 to

29.8 mm Hg), and 73 of the 128 patients with an identifiable individual ICP threshold displaying individual thresholds above BTF defined 20 mm Hg. Our semi-automated algorithm correctly identified the presence or absence of a patient's individual ICP threshold in 162 out of 196 (83.2%). Thirty-four patients had either an incorrectly identified individual ICP threshold when there wasn't one present (n=20), or no individual ICP threshold identified when there was one present (n=14). These 34 discrepancies were identified through manual inspection of both the error bar and LOESS function plots of PRx versus ICP, and subsequently corrected.

Patient demographics for those patients with an individual ICP threshold and those without an identifiable individual ICP threshold can be seen in Table 1, with comparison of demographic and physiologic factors between the two groups of patients. Of note is the higher mean ICP ($p=0.041$) and PRx ($p<0.0001$) in the patients without an identifiable individual ICP threshold, as identified via Mann-Whitney U testing, with a sustained higher PRx value in keeping without being able to identify an ICP threshold using the described methodology.

***Table 1 here**

Comparing demographics and physiologic variables between dichotomized outcome groups for the patents with an identifiable individual ICP threshold, we find that only mean PRx ($p<0.001$ for alive/dead, and $p=0.005$ for favourable/unfavourable outcomes) and mean hourly dose above the patient's individual ICP threshold ($p=0.010$ for alive/dead, and $p=0.020$ for favourable/unfavourable outcomes) are significantly different (ie. higher), via Mann-Whitney U testing, in those who died or demonstrated unfavourable outcome at 6 to 12-months. Mean hourly dose of ICP above 20 and 22 mm Hg failed to display any significant difference between the dichotomized groups. Appendix B provides a

tabulated summary of this information. Figure 2 displays box plots of the mean hourly dose above each ICP threshold across both dichotomized outcomes.

***Figure 2 here**

Mean Hourly Dose of ICP Above Threshold and Outcome – Univariate Analysis

Univariate logistic regression was performed for each demographic and mean hourly dose of ICP above threshold with both 6 to 12-month dichotomized outcomes. Table 2 displays the results of the ULR analysis with AUC's, AIC and p-values tabulated for each variable. Age was noted to be statistically associated with both alive/dead (AUC = 0.820; 95% CI 0.736-0.904; p<0.0001) and favourable/unfavourable (AUC = 0.708; 95% CI 0.618-0.799; p<0.0001) outcomes. Higher mean PRx was also noted to be associated with mortality and unfavorable outcome, in keeping with the previous larger single-center studies on cerebrovascular reactivity in adult TBI.[7,10,16]

The mean hourly dose of ICP above the patient's individual threshold displayed the highest AUC's and lowest AIC values for association with both dichotomized outcomes (AUC = 0.678, p=0.029 for alive/dead, and AUC = 0.610, p=0.060 for favourable/unfavourable), with higher dose associated with mortality and unfavourable 6 to 12-month outcome. This was in comparison to the mean hourly dose of

ICP above the BTF based treatment thresholds of 20 and 22 mm Hg,[12] as well as bivariate models including mean hourly ICP dose above 20/22 mm Hg and mean PRx. The association with mortality was statistically much stronger than unfavourable outcome, also in keeping with previous studies assessing the association between ICP and global outcome in adult TBI.[7,12]

***Table 2 here**

Comparing AUC's via Delong's test indicated that there was a significant difference between the AUC for mean hourly dose of ICP above individual threshold and both mean hourly dose of ICP above 20 and 22 mm Hg for alive/dead outcome (p=0.047 and p=0.044, respectively). However, no significant difference was noted between the AUC's of the three hourly dosing variables when outcomes where dichotomized as favourable/unfavourable.

Finally, Comparing the bivariate models with mean hourly dose of ICP above 20/22 mm Hg and mean PRx, to the univariate model with mean hourly dose of ICP above individual threshold, for alive/dead outcome, the univariate models with mean hourly dose of ICP above individual threshold displayed statistically significant higher AUC's compared to the bivariate models ($p<0.05$ for all; Delong's test). There was no difference in AUC when comparing the bivariate models to the univariate individual threshold model for favorable/unfavourable outcome. Figure 3 displays the univariate receiver operating curves for mean hourly dose of ICP above 20 mm Hg, above 22 mm Hg, and above individual ICP threshold.

***Figure 3 here**

Controlling for Admission IMPACT-Core Variables

Only 127 of the 128 patients with identifiable individual ICP thresholds had complete IMPACT-Core admission variables. Controlling for these admission characteristics in multi-variable logistic regression, it was found that comparing models with baseline characteristics and mean hourly dose of ICP above 20 mmHg or 22 mmHg, to those with mean hourly dose above individual ICP threshold, that the models with mean hourly dose above individual threshold trended toward higher statistically significant AUC's, for both dichotomized outcomes. This confirms that the mean hourly dose above individual ICP threshold maintains significance, when controlling for IMPACT-Core covariates. Appendix C provides a table summarizing the findings for the multi-variable logistic regression analysis.

Discussion:

This validation study provides multi-center confirmation of the presence of individual epidemiologic ICP thresholds, and replicates the strong association between time spent above this threshold and global outcome in adult TBI. There are some important aspects which deserve highlighting.

First, we have been able to display that individual ICP thresholds in moderate/severe TBI can be detected in 65.3% of patients from this cohort. This is in keeping with prior retrospective single center results on the topic.[4] This is an important finding because not only does it validate previous results, but it also suggests that future studies will need to take this into account in order to be powered appropriately. Failure to detect individual threshold may be attributed to low ICP (never disturbing autoregulation) or too high ICP, when autoregulation is continuously disturbed. The wide distribution of individualized thresholds (interquartile range) from 14.9 to 29.8 mm Hg underlines the importance of

such approaches to examining the individually defined burden of intracranial hypertension, as opposed to accepting fixed thresholds that are identical across patients. The individual thresholds identified for ICP below the BTF guideline ICP thresholds of 20 or 22 mm Hg are at this point still unclear in significance. This methodology is still very much nascent, with this current work only being the second in the literature, and requires substantial validation and exploration in other TBI populations as well as controlled experimental models. Thus, these ICP thresholds below 20 mm Hg require further investigation, and we in no way suggest that ICP targets would be changed to target such low values. There needs to be a substantial subpopulation analysis in those patients who display low individual ICP thresholds, in order to explain why such values may exist. This will be the focus of future studies on the topic. As mentioned, the goal of this study was to only provide a multi-center validation of the previously published single-center retrospective results from Cambridge.[4]

Second, we have, for the first time, created a semi-automated algorithm for the detection of individual ICP thresholds, an improvement over prior completely manual determination from plots of PRx and ICP. Though a first attempt, the accuracy rate in this study was 83.2%. It must be acknowledged that the notion of using an abnormal ICP compliance curve doesn't require a computer to determine, and can in fact be determined by inspection of the plotted physiology at the bedside by the treating clinician. Thus, our semi-automated algorithmic process would benefit from refinement and optimization, which will be the focus of future analyses in this area. Further to this, there are other potential options for assessing individual patient ICP thresholds, employing cerebral compliance indices, such as RAP (correlation between pulse amplitude of ICP and ICP),[18,19] or using ICP waveform analytic techniques.[20,21] Exploration into these techniques as means to derive individual ICP thresholds is required, but may prove fruitful.

Third, we have been able to confirm the strong association between and dose of ICP above individual ICP threshold, which was shown in the original publication describing this relationship,(6) and done so in

a multi-center data set. These results validate the presence and detectability of individual ICP thresholds, and provide a conceptual framework for developing these as treatment targets in the future targets, as we move towards individualized medicine. Support for such an approach is justified in the stronger association between mean hourly dose of ICP above individual threshold and both dichotomized 6 to 12-month outcomes, using ULR and multi-variable logistic regression controlling for standard IMPACT-Core admission characteristics. ICP (time x intensity) dose calculated above individual thresholds were much more strongly associated with outcome compared to the dose above BTF defined thresholds of 20 and 22 mm Hg.[12]. The current analysis focuses on confirmation of past findings, but subsequent work will examine the impact of individual ICP thresholds in more complex multi-variable models which include co-variates beyond those used in the IMPACT-Core prediction model.

Thus, there is still limited data to support the adoption of individual ICP thresholds as a clinically utilized measure at this time.

Fourth, an important finding re-iterated by the results of this work is that ICP and burden of ICP suffered after TBI is linked to outcome in TBI. Particularly the dose of ICP spent above BTF thresholds, as well as individual ICP threshold, was statistically significantly associated with outcome. This is important to emphasize as recent literature has led to questions regarding the utility of ICP monitoring in adult TBI,[22,23] leading to confusion in some providers as to the need for such monitoring devices. However, the results within this work added to the existing large body of evidence supporting the link between ICP and patient outcome in TBI.[7,12,24]

One shortcoming of the approach implemented in this manuscript is that individualized thresholds were calculated based on all of the ICP values across the patient stay. This approach clearly does not lend itself to providing a management target early in the course of the patient's stay, which is when it is needed. However, the we hypothesize that individual thresholds of ICP may be detectable on-line (on

the basis of recent ICP monitoring data points), and provide decision support for individualized management across all tiers of ICP therapy- starting from hypertonic solutions and finishing with better targeted decompressive craniectomy. Such a concept is still experimental and would require the use of sliding windows of data over time, to calculate the intersect between the PRx versus ICP function and PRx of +0.20. We envision such methodology to be similar to current CPP optimum sliding window determinations employed in real-time.[1–3] However, it should be acknowledged that the feasibility of this has not been tested, and the concept is only a theory requiring much further investigation. If proven feasible, this would allow for a continuously updating individual ICP threshold value which could then account for changes in individual thresholds over time, where the current described methodology is incapable of accomplishing.

Limitations

Important limitations deserve highlighting. First, as mentioned in other studies published from this cohort,[14] despite the data from the CENTER-TBI high-resolution cohort being collected in a prospective manner, the treatments and therapies received by patients remain heterogeneous. Such heterogeneity may have impacted the individual ICP threshold determination, and it is currently unclear whether individual therapeutic measures directed at ICP differentially impact the derivation of individualized thresholds. Such analysis, including the impact of injury and patient heterogeneity, will require even larger prospectively collected high-resolution data sets.

Second, our methodology for identification of individual ICP thresholds relies on the use of PRx, as previously described.[4] This current study was conduct as a simple validation of this previous retrospective single-center work. However, given the methodology of individual ICP thresholds is still new, there is the potential that other methods for estimating such thresholds may prove equivalent or superior. There is the potential that thresholding ICP based on autoregulation may be too simplistic,

and other measures, such as compensatory reserve metrics,[18,19] may provide more information regarding stratifying critical values of ICP. The concept of individual ICP thresholds using PRx is still in its experimental. This concept is based on individual ICP thresholds derived through impairment in cerebrovascular reactivity, through epidemiologically defined critical values from previous retrospective studies,[7] not compensatory reserve. It still remains unclear if using a pure compliance/compensatory reserve index such as RAP,[18,19] would provide different information for the determination of individual ICP thresholds. Cerebrovascular reactivity can be impaired in both settings of normal and elevated ICP in adult TBI, where compensatory reserve indices tend to remain normal until extreme ICP elevations. Hence, we decided to employ a method of individual ICP threshold determination using vascular reactivity. It is unclear if these calculated thresholds occurring at lower ICP values represent normal brain or just dysautoregulation and pressure-passivity at low ICP. Further work is required to correlate these findings with other continuously derived cerebral physiologic metrics (such as blood flow velocity, PbtO2, CBF, or near-infrared based measures) and neuroimaging biomarkers, in order to determine is the brain is in a "normal" state when individual ICP thresholds are determined to be below 20 mm Hg. As such, the current methodology should be considered an experimental starting point for such analysis, and not employed in the treatment of patients. There are plans for much further analysis of other physiologic metrics for the derivation of individual ICP thresholds, and these will for the focus of various other studies on both the Cambridge retrospective TBI database and the CENTER-TBI high resolution ICU cohort.

Third, the overall patient numbers with an identifiable individual ICP threshold was low, at 128 and only 127 with full IMPACT-Core admission variables and an identifiable individual ICP threshold. Though based on the initial population size with a documented outcome and presence of baseline characteristics (n=196), a yield of 65.3% for individual ICP threshold is in keeping with prior larger retrospective studies on the topic.[4] This relatively small population effect may be exemplified by the

low AUC values on univariate analysis, and during correction for baseline IMPACT-Core co-variates, despite reaching statistical significance. As such, future investigations into individualized ICP thresholds will definitely require larger cohorts. At the moment, we are unable to make definitive comments on the characteristics related to not being able to derive an individual ICP threshold. It is possible that patient admission demographics and both extra- and intra-cranial injury burden characteristics will be predictive of those patients in whom an individual ICP is not identifiable. Such analysis was not the focus of this study, and will form the basis for a much larger analysis conducted on an amalgamated cohort from the large retrospective Cambridge TBI database and the CENTER-TBI high resolution ICU cohort. The hope is with such larger patient cohorts, we will be able to shed some light on the topic.

Fourth, despite the automated portion of the algorithm for detection of individualized ICP thresholds demonstrating an acceptable accuracy rate of 83.2%, there still existing substantial room for improvement. As this was the first attempt at producing an semi-automated approach for individual ICP threshold determination, we feel encouraged about being able to improve upon this, as previous methods required a completely manual inspection of plots.[4] This will be the focus of future work.

Fifth, despite our results indicating that those patients with no discernable individual ICP threshold displayed higher mean PRx and ICP values, our understanding as to the characteristics of such patients is limited. Future analysis of individual ICP thresholds will not only need to focus on those with an identifiable threshold, but also on those without, so we can better understand what contributes to a lack of a patient-specific threshold.

Finally, despite the finding that ICP doses derived from individualized ICP thresholds display potentially stronger associations with outcome compared to BTF defined thresholds, the concept of individualized threshold should still be considered experimental. Currently, individual ICP thresholds should not

replace the BTF defined thresholds in monitoring and care of moderate and severe TBI patients. Much further evidence is required to validate these individualized targets as clinically valuable in TBI.

Conclusions:

Individual epidemiologic ICP thresholds are present in two thirds of the adult TBI population. Mean hourly dose of ICP above a patient's individual epidemiologic ICP threshold demonstrates a stronger association with mortality compared to the dose above BTF defined thresholds of 20 or 22 mm Hg, confirming prior single center findings. Further studies on individual patient specific epidemiologic ICP thresholds are warranted.

Disclosures:

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CENTER-TBI High Resolution Sub-Study Participants and Investigators:

Anke Audny [1], Beer Ronny [2], Bellander Bo-Michael [3], Buki Andras [4], Chevallard Giorgio [5], Chieregato Arturo [5], Citerio Giuseppe [6, 7], Czeiter Endre [8], Depreitere Bart [9], Eapen George†, Frisvold Shirin [10], Helbok Raimund [2], Jankowski Stefan [11], Kondziella Daniel [12], Koskinen Lars-Owe [13], Meyfroidt Geert[14], Moeller Kirsten[15], Nelson David [3], Piippo-Karjalainen Anna [16], Radoi Andreea [17], Ragauskas Arminas [18], Raj Rahul [16], Rhodes Jonathan [19], Rocka Saulius [18], Rossaint Rolf [20], Sahuquillo Juan [17], Sakowitz Oliver [21, 22], Stevanovic Ana [20], Sundström Nina [23], Takala Riikka [24], Tamosuitis Tomas[25], Tenovuo Olli [26], Vajkoczy Peter [27], Vargiolu Alessia [6], Vilcinis Rimantas [28], Wolf Stefan [29], Younsi Alexander [22],

[1] Department of Physical Medicine and Rehabilitation, University hospital Northern Norway
[2] Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria
[3] Department of Neurosurgery & Anesthesia & intensive care medicine, Karolinska University Hospital, Stockholm, Sweden
[4] Department of Neurosurgery, University of Pecs and MTA-PTE Clinical Neuroscience MR Research Group and Janos Szentagothai Research Centre, University of Pecs, Hungarian Brain Research Program, Pecs, Hungary
[5] NeuroIntensive Care, Niguarda Hospital, Milan, Italy
[6] NeuroIntensive Care Unit, Department of Anesthesia & Intensive Care, ASST di Monza, Monza, Italy
[7] School of Medicine and Surgery, Università Milano Bicocca, Milano, Italy
[8] Department of Neurosurgery, University of Pecs and MTA-PTE Clinical Neuroscience MR Research Group and Janos Szentagothai Research Centre, University of Pecs, Hungarian Brain Research Program (Grant No. KTIA 13 NAP-A-II/8), Pecs, Hungary
[9] Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium
[10] Department of Anesthesiology and Intensive care, University Hospital Northern Norway, Tromso, Norway
[11] Neurointensive Care, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

[12] Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark
[13] Department of Clinical Neuroscience, Neurosurgery, Umea University Hospital, Umea, Sweden
[14] Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium
[15] Department Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark
[16] Helsinki University Central Hospital, Helsinki, Finland
[17] Department of Neurosurgery, Vall d'Hebron University Hospital, Barcelona, Spain
[18] Department of Neurosurgery, Kaunas University of technology and Vilnius University, Vilnius, Lithuania
[19] Department of Anaesthesia, Critical Care & Pain Medicine NHS Lothian & University of Edinburg, Edinburgh, UK
[20] Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany
[21] Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany
[22] Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany
[23] Department of Radiation Sciences, Biomedical Engineering, Umea University Hospital, Umea, Sweden
[24] Perioperative Services, Intensive Care Medicine, and Pain Management , Turku University Central Hospital and University of Turku, Turku, Finland
[25] Neuro-intensive Care Unit, Kaunas University of Health Sciences, Kaunas, Lithuania
[26] Rehabilitation and Brain Trauma, Turku University Central Hospital and University of Turku, Turku, Finland
[27] Neurologie, Neurochirurgie und Psychiatrie, Charité – Universitätsmedizin Berlin, Berlin, Germany
[28] Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania
[29] Interdisciplinary Neuro Intensive Care Unit , Charité – Universitätsmedizin Berlin, Berlin, Germany

References:

1. Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit Care Med. 2002;30:733–8.

2. Aries MJH, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias AG, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med. 2012;40:2456–63.

3. Needham E, McFadyen C, Newcombe V, Synnot AJ, Czosnyka M, Menon D. Cerebral Perfusion Pressure Targets Individualized to Pressure-Reactivity Index in Moderate to Severe Traumatic Brain Injury: A Systematic Review. J Neurotrauma. 2017;34:963–70.

4. Lazaridis C, DeSantis SM, Smielewski P, Menon DK, Hutchinson P, Pickard JD, et al. Patient-specific thresholds of intracranial pressure in severe traumatic brain injury. J Neurosurg. 2014;120:893–900.

606 5. Lazaridis C, Smielewski P, Menon DK, Hutchinson P, Pickard JD, Czosnyka M. Patient-Specific
607 Thresholds and Doses of Intracranial Hypertension in Severe Traumatic Brain Injury. Acta Neurochir
608 Suppl. 2016;122:117–20.

609 6. Lazaridis C, Czosnyka M. Patient-specific intracranial pressure. Response. J Neurosurg. 2014;120:892.

610 7. Sorrentino E, Diedler J, Kasprowicz M, Budohoski KP, Haubrich C, Smielewski P, et al. Critical
611 thresholds for cerebrovascular reactivity after traumatic brain injury. Neurocrit Care. 2012;16:258–66.

612 8. Brady KM, Lee JK, Kibler KK, Easley RB, Koehler RC, Shaffner DH. Continuous measurement of
613 autoregulation by spontaneous fluctuations in cerebral perfusion pressure: comparison of 3 methods.
614 Stroke. 2008;39:2531–7.

615 9. Zeiler FA, Donnelly J, Calviello L, Lee JK, Smielewski P, Brady K, et al. Validation of pressure reactivity
616 and pulse amplitude indices against the lower limit of autoregulation, Part I: experimental intra-cranial
617 hypertension. J Neurotrauma. 2018;In Press.

618 10. Zeiler FA, Donnelly J, Smieleweski P, Menon D, Hutchinson PJ, Czosnyka M. Critical Thresholds of ICP
619 Derived Continuous Cerebrovascular Reactivity Indices for outcome prediction in Non-Craniectomized
620 TBI Patients: PRx, PAx and RAC. J Neurotrauma. 2018;35:1107–15.

621 11. Maas AIR, Menon DK, Steyerberg EW, Citerio G, Lecky F, Manley GT, et al. Collaborative European
622 NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal
623 observational study. Neurosurgery. 2015;76:67–80.

624 12. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the
625 Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2017;80:6–15.

626 13. Doiron D, Marcon Y, Fortier I, Burton P, Ferretti V. Software Application Profile: Opal and Mica:
627 open-source software solutions for epidemiological data management, harmonization and
628 dissemination. Int J Epidemiol. 2017;46:1372–8.

629 14. Zeiler FA, Ercole A, Cabeleira M, Carbonara M, Stocchetti N, Menon DK, et al. Comparison of
630 Performance of Different Optimal Cerebral Perfusion Pressure Parameters for Outcome Prediction in
631 Adult TBI: A CENTER-TBI Study. J Neurotrauma. 2018;Epub Ahead of Print.

632 15. Zeiler FA, Ercole A, Cabeleira M, Zoerle T, Stocchetti N N, Menon DK, et al. Univariate comparison of
633 performance of different cerebrovascular reactivity indices for outcome association in adult TBI: a
634 CENTER-TBI study. Acta Neurochir (Wien). 2019;

635 16. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of
636 the cerebral vasomotor reactivity in head injury. Neurosurgery. 1997;41:11–7; discussion 17-19.

637 17. Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, et al. Predicting outcome after
638 traumatic brain injury: development and international validation of prognostic scores based on
639 admission characteristics. PLoS Med. 2008;5:e165; discussion e165.

18. Calviello L, Donnelly J, Cardim D, Robba C, Zeiler FA, Smielewski P, et al. Compensatory-Reserve-Weighted Intracranial Pressure and Its Association with Outcome After Traumatic Brain Injury. Neurocrit Care. 2017;

19. Zeiler FA, Kim D-J, Cabeleira M, Calviello L, Smielewski P, Czosnyka M. Impaired cerebral compensatory reserve is associated with admission imaging characteristics of diffuse insult in traumatic brain injury. Acta Neurochir (Wien). 2018;

20. Nucci CG, De Bonis P, Mangiola A, Santini P, Sciandrone M, Risi A, et al. Intracranial pressure wave morphological classification: automated analysis and clinical validation. Acta Neurochir (Wien). 2016;158:581–8; discussion 588.

21. Fan J-Y, Kirkness C, Vicini P, Burr R, Mitchell P. Intracranial pressure waveform morphology and intracranial adaptive capacity. Am J Crit Care Off Publ Am Assoc Crit-Care Nurses. 2008;17:545–54.

22. Chesnut RM, Temkin N, Carney N, Dikmen S, Rondina C, Videtta W, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med. 2012;367:2471–81.

23. Ropper AE, Chi JH. Treatment of traumatic brain injury without direct intracranial pressure monitoring. Neurosurgery. 2013;72:N19-20.

24. Adams H, Donnelly J, Czosnyka M, Kolias AG, Helmy A, Menon DK, et al. Temporal profile of intracranial pressure and cerebrovascular reactivity in severe traumatic brain injury and association with fatal outcome: An observational study. PLoS Med. 2017;14:e1002353.

Figure Legends:

Figure 1: Two Patient Examples of Individual ICP Threshold Determination via Semi-Automated Method

a.u. = arbitrary units, ICP = intracranial pressure, LOESS = locally weighted scatterplot smoothing, mm Hg = millimeters of Mercury, MAP = mean arterial blood pressure, PRx = pressure reactivity index (correlation between ICP and MAP). Panel A and B = patient 1, Panel C and D = patient 2. Panel A – error bar plot of PRx vs. ICP, dotted line displays PRx threshold of +0.20, Panel B – LOESS function plot with 95% confidence intervals, intersection between PRx = +0.20 line (dotted) and the LOESS function yields the patients individual ICP threshold. Panels C and D display similar finding for a second patient.

Figure 2: Box Plots of Mean Hourly Dose Above ICP Threshold for Dichotomized 6 to 12-Month Outcome Groups

*GOSE = Glasgow Outcome Score – Extended, ICP = intracranial pressure, mm Hg = millimeters of Mercury. Panel A – Mean hourly hose of ICP above 20 mm Hg for alive and dead (A/D) outcome, Panel B – Mean hourly hose of ICP above 20 mm Hg for favourable and unfavourable (F/U) outcome, Panel C – Mean hourly hose of ICP above 22 mm Hg for alive and dead (A/D) outcome, Panel D – Mean hourly hose of ICP above 22 mm Hg for favourable and unfavourable (F/U) outcome, Panel E – Mean hourly dose of ICP above patient's individual ICP threshold for alive/dead (A/D) outcome, Panel F – Mean hourly dose of ICP above patient's individual ICP threshold for favourable/unfavourable (F/U) outcome. Alive/Dead (A/D) Dichotomization (Alive = GOSE >=2, Dead = GOSE 1). Favourable/Unfavourable (F/U) Dichotomization (Favourable = GOSE 5 to 8, Unfavourable = GOSE 1 to 4). *p-values reported are for Mann-Whitney-U test, comparing mean values between dichotomized groupings.*

Figure 3: Univariate Logistic Regression – Mean Hourly Dose of ICP Above 20, 22 and Individual Thresholds

*GOSE = Glasgow Outcome Scale Extended, ICP = intracranial pressure, ULR = Univariate Logistic Regression. Panel A = Mean Hourly Dose of ICP Above 20 mm Hg ULR for Alive/Dead (A/D) Outcome, Panel B = Mean Hourly Dose of ICP Above 20 mm Hg ULR for Favourable/Unfavourable (F/U) Outcome, Panel C = Mean Hourly Dose of ICP Above 22 mm Hg ULR for Alive/Dead (A/D) Outcome, Panel D = Mean Hourly Dose of ICP Above 22 mm Hg for Favourable/Unfavourable (F/U) Outcome, Panel E = Mean Hourly Dose of ICP Above Individual Threshold ULR for Alive/Dead (A/D) Outcome, Panel F = Mean Hourly ICP Dose Above Individual Threshold ULR for Favourable/Unfavourable (F/U) Outcome. Alive/Dead (A/D) Dichotomization (Alive = GOSE >=2, Dead = GOSE 1). Favourable/Unfavourable (F/U) Dichotomization (Favourable = GOSE 5 to 8, Unfavourable = GOSE 1 to 4). *Indicates AUC reported failed to reach statistical significance in the ULR model.*