Intra- and Extra-Cranial Injury Burden as Drivers of Impaired Cerebrovascular Reactivity in Traumatic Brain Injury

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Abstract:

Impaired cerebrovascular reactivity has been associated with outcome following traumatic brain injury (TBI), but it is unknown how it is affected by trauma severity. Thus, we aimed to explore the relationship between intra-cranial (IC) and extra-cranial (EC) injury burden and cerebrovascular reactivity in TBI patients. We retrospectively included critically ill TBI patients. IC injury burden included detailed lesion and computerized tomography (CT) scoring (ie. Marshall, Rotterdam, Helsinki and Stockholm Scores) on admission. EC injury burden were characterized using the injury severity score (ISS) and APACHE II score. Pressure reactivity index (PRx), pulse amplitude index (PAx) and RAC were used to assess autoregulation/cerebrovascular reactivity. We used univariate and multi-variate logistic regression techniques to explore relationships between IC and EC injury burden and autoregulation indices. A total of 358 patients were assessed. ISS and all IC CT scoring systems were poor predictors of impaired cerebrovascular reactivity. Only subdural hematomas and thickness of SAH ($p<0.05$, respectively) were consistently associated with dysfunctional cerebrovascular reactivity. High age ($p<0.01$ for all) and admission APACHE II scores ($p<0.05$ for all) were the two variables strongest associated with abnormal cerebrovascular reactivity. In summary, diffuse IC injury markers (thickness of SAH and the presence of a SDH) and APACHE II were most associated with dysfunction in cerebrovascular reactivity after TBI. Standard CT scoring systems and evidence of macroscopic parenchymal damage are poor predictors, implicating potentially both microscopic injury patterns and host response as drivers of dysfunctional cerebrovascular reactivity. Age remains a major variable associated with cerebrovascular reactivity. Keywords: dysautoregulation, imaging, biomarkers, injury burden, TBI

Introduction:

Impaired cerebral autoregulation and cerebrovascular reactivity are major contributors to poor functional outcome and mortality after traumatic brain injury (TBI).[1-3] The pressure reactivity index (PRx) is the most widely described index to define affected cerebral autoregulation, derived from intra-cranial pressure (ICP) and mean arterial pressure (MAP),[4] and has been validated against the autoregulation curve of Lassen in animal models.[5] Two other ICP derived indices, PAx (correlation between pulse amplitude of ICP (AMP) and MAP))[6] and RAC (correlation between AMP and CPP),[7,8] also represent aspects of cerebrovascular reactivity, and have also been shown to have outcome associations in TBI. We recently identified critical thresholds for PRx, PAx and RAC associated with mortality and poor functional outcome in a TBI population who had not undergone decompressive craniectomy(non-DC),[8,9] with the most robust outcome associations observed for RAC.[8]

These thresholds may therefore characterize critical points in the loss of autoregulatory capacity/cerebrovascular reactivity, beyond which the burden of abnormal physiology impacts outcome. However, despite a growing body of literature on these continuous ICP derived indices of cerebrovascular reactivity, very little is understood with regards to what drives impaired vascular reactivity after TBI. Potential drivers of such a relationship include the severity and type of intra-cranial (IC) injury, the severity of extracranial (EC) injury, and/or the physiological response to injury.

One past study from our center evaluated the association between intracranial injury burden and autoregulatory function in 126 patients post-TBI,[10] and showed that PRx was more commonly abnormal in patients with Diffuse Injury Grade III, as compared to other diffuse and focal injury classifications, on the Marshall Scale .[10,11] However, the Marshall grading system is just one of many available, and its summary descriptions do not provide a full characterization of the type, extent and severity of intracranial injury. Further, the PRx outcome threshold of >0 used in this analysis may have been non-optimal, since a recent re-analysis suggests that its derivation may have been heavily confounded by inclusion of patients with decompressive craniectomy where different intracranial conditions apply.[8,9] Consequently, we have an imperfect understanding of how intracranial injury impacts on autoregulation following TBI, and there are no publications relating the severity of extracranial injury or post-injury physiology to the incidence of abnormal cerebral autoregulation.

Understanding such relationships is important, since their elucidations could allow early patient stratification, and potentially reveal mechanistic targets for therapy. We therefore decided to undertake a detailed exploration of these relationships in a large non-DC TBI patient population with archived high frequency digital ICU signals. There were two main goals of this study:

1. Determine the association between admission IC injury burden (assessed by recognized CT scoring systems in TBI and an extensive CT based IC lesion database) and impaired cerebrovascular reactivity.
2. Determine how the burden of extracranial injury and abnormal physiology relates to impaired cerebrovascular reactivity.

Methods:

This study was conducted as a retrospective analysis of a prospectively maintained database cohort, in which high frequency clinical neuromonitoring data had been archived. Monitoring of brain modalities was conducted as a part of standard NCCU patient care using an anonymized database of physiological monitoring variables in neurocritical care. Data on age, injury severity, and clinical status at hospital discharge were recorded at the time of monitoring on this database, and no attempt was made to re-access clinical records for additional information. Since all data was extracted from the hospital records and fully anonymized, no data on patient identifiers were available, and need for formal patient or proxy consent was waived. This TBI patient population has previously been described in our work on critical autoregulation thresholds for outcome.[8]

Patient Population and Demographic Data Acquisition

All patients (n=358) were admitted to the Neurosciences and Trauma Critical Care Unit (NCCU) at Cambridge University Hospitals NHS Foundation Trust (CUH), during the period of March 2005 to December 2016. Patients with primary or secondary decompressive craniectomy were excluded. In addition, only patients with at least 6 hours of recorded signals were included in this study. Patients suffered either moderate to severe TBI, or mild TBI and subsequently deteriorated to a point where they required intracranial monitoring, sedation and mechanical ventilation. Treatment received during the recording periods included standard ICP-directed therapy, with an ICP goal of less than 20 mmHg and CPP goal of

greater than 60 mmHg. Demographic data (sex, age, admission GCS and pupillary response) were prospectively recorded, and therefore available to the study.

Intra-Cranial (IC) Injury Burden Data Acquisition

All admission CT-head scans were accessed and archived retrospectively. These scans were assessed by a qualified specialist neurosurgeon for a variety of injury characteristics. First, the Marshall,[11] Rotterdam,[12] Helsinki[13] and Stockholm[14] CT (tally) scores were determined for each patient. The Stockholm score was also assessed as an ordinal score using the following system: 0 to 1 = 1; 1.1 to 2 = 2; 2.1 to 3 = 3; 3.1 to 4 = 4; 4.1 to 5 = 5; 5.1 to 6 = 6, which displayed a strong correlation with the continuous Stockholm CT score (r=0.947,). Next, a comprehensive CT lesion/characteristic database was constructed for each admission CT scan. A list of the lesions assessed/measured can be found in Appendix A of the supplementary materials.

Extra-Cranial (EC) Injury Burden Data Acquisition

As part of standard trauma and NCCU care, the admission total Injury Severity Score (ISS)[16] and Acute Physiology And Chronic Health Evaluation II (APACHE II)[17] score were determined for each patient as part of national audit requirements and were retrospectively available for this study.

Physiological Signal Acquisition

Arterial blood pressure (ABP) was obtained through either radial or femoral arterial lines connected to pressure transducers (Baxter Healthcare Corp. CardioVascular Group, Irvine, CA). ICP was acquired via an intra-parenchymal strain gauge probe (Codman ICP MicroSensor; Codman & Shurtleff Inc., Raynham, MA). All signals were recorded using digital data transfer or digitized via an A/D converter (DT9801; Data Translation, Marlboro, MA), where appropriate, sampled at frequency of 50 Hertz (Hz) or higher, using the ICM+ software (Cambridge Enterprise Ltd, Cambridge, UK,

http://www.neurosurg.cam.ac.uk/icmplus). Signal artifacts were removed manually prior to further processing or analysis.

Signal Processing

Post-acquisition processing of the above signals was conducted using ICM+. CPP was determined as CPP = MAP – ICP. AMP was determined by calculating the fundamental Fourier amplitude of the ICP pulse waveforms over a 10 second window, updated every 10 seconds. Ten second moving averages (updated every 10 seconds to avoid data overlap) were calculated for all recorded signals: ICP, ABP (which produced MAP), AMP and CPP.

PRx, PAx and RAC were derived for every patient as follows: a moving Pearson correlation coefficient was calculated between ICP and MAP (for PRx), or AMP and MAP (for PAx), or AMP and CPP (for RAC), using 30 consecutive 10 second windows (ie. five minutes of data), updated every minute.

Finally, data for this analysis were provided in the form of a minute by minute time trends of the parameters of interest for each patient. From this, data was extracted for; entire recording period for each patient (n=358), 1st 24 hours of recording (n= 340), and 1st 72 hours of recording (n=277) were produced in order to assess the association between IC and EC injury burden and cerebrovascular reactivity, across various durations of recording. Within these separate datasets, a grand mean was calculated per patient for each index across the duration of that recording period and subsequently utilized for the final statistical analysis. Furthermore, in each of these sheets we evaluated the following binary thresholds for PRx, PAx and RAC: A. PRx: >0, >0.25, >0.35; B. PAx: >0, >0.25; and C. RAC: > -0.05, > -0.10. These are the critical thresholds associated with patient outcome previously defined.[8,9] Finally, for the entire recording dataset, we calculated the percentage of recording time (% time) spent above each threshold for every patient.

Statistics

Statistics were performed utilizing XLSTAT (Addinsoft, New York, United States; https://www.xlstat.com/en/) add-on package to Microsoft Excel (Microsoft Office 15, Version 16.0.7369.1323) and R statistical 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/). For all statistical tests described, alpha was set at 0.05 for significance, with correction for multiple comparisons.

General Statistics

Simple descriptive statistics were utilized to summarize the patient demographics (Appendix A). Box plots were also employed to summarize the cerebrovascular reactivity indices, with respect to IC and EC injury scoring systems. A Shapiro Wilks test found significant non-normality in the distributions of all continuous variables of interest and non-parametric tests were used.

Initially, we were interested in whether the burden of IC and EC injury, quantified using widely accepted scoring systems, were related to differences in PRx, PAx and RAC based on category of injury burden. Using the entire recording period datasets, we first examined correlations between ICP derived indices (PRx, PAx and RAC) and the IC and EC injury scores using Spearman's test. Similarly, the % time spent above index threshold was correlated with IC and EC injury scores. Finally, we compared the mean PRx, PAx and RAC values across each category of IC injury scoring system for: Marshall, Rotterdam, Helsinki and ordinal Stockholm scores; using the Kruskal-Wallis (KW) test for the Marshall CT grade, and a one-way Jonckheere-Terpstra (JT) test for the ordinal Rotterdam, Helsinki and Stockholm (converted from continuous) scores. This was repeated for % time above thresholds of PRx, PAx and RAC. We chose the KW test for the Marshall system, given this system is not an ordinally arranged grading system. The JT test was chosen for the Rotterdam, Helsinki and ordinal Stockholm graded, given these systems are ordinal in nature and we wished to test if there was statistically significant increase in mean values as the ordinal IC CT score increased. The JT test was performed in a one-way method, testing for increasing mean values, running 1000 permutations, yielding a p-value.

Next, we evaluated the difference between individual patient demographics and injury characteristics for those patients above and below various thresholds in PRx, PAx and RAC (using above defined thresholds). Using the entire recording

period data sheet, continuous variables were compared using the Mann-Whitney U test, while categorical variables were compared via chi-square testing.

Injury Burden Association with Impaired Cerebrovascular Reactivity

We defined impaired cerebrovascular reactivity using the above mentioned critical thresholds for PRx, PAx, and RAC. Each threshold was tested, for every demographic and injury variable.

First, a univariate binary logistic regression (ULR) analysis was performed utilizing the three datasets; evaluating all patient demographics and injury characteristics, comparing to the following binary outcomes of interest: A. PRx Above 0, B. PRx above +0.24, C. PRx above +0.35, D. PAx above 0, E. PAx above +0.25, F. RAC above -0.05, and G. RAC above -0.10.

Second, multivariable binary logistic regression (MLR) was performed using the above thresholds for PRx, PAx and RAC as binary outcomes. Any variables reaching statistical significance (or close to it: p-values <=0.100) in the ULR were entered into the initial MLR model, yielding unique multivariable models for each index threshold tested. Running sequential multivariable models, we then employed a backward elimination method, deleting those variables which were grossly insignificant (ie. p>0.100), until we reached the best potential model (based on highest AUC, statistical significance p<0.05, and individual component variables reaching p<0.100 within the model). This was conducted for each index threshold tested.

Both of ULR and MLR techniques described above were performed for each recording period: entire recording, 1st 24 hours, and 1st 72 hours. We only report the results of the entire recording period, given the other two periods displayed confirmatory results. Strength of relationship to the outcomes of interest were reported via area under the receiver operating curve (AUC), with bold AUC's reaching a p<0.05.

Results:

Patient Demographics

Patient demographics for each of the 3 data sheets are summarized in Appendix B of the Supplementary materials. A total of 358 patients were included in the entire recording period cohort, with a mean recording period length of 189.1 +/- 151.1 hour (range: 8.5 to 1033.0 hours duration). There were 340 and 277 patients in the 1st 24 hours of recording and 1st 72 hours of recording cohorts, respectively. Injury data are summarized in Appendix C of the supplementary material for the entire recording period cohort.

IC Injury Scores and Cerebrovascular Reactivity

No significant correlation was detected between any of the ICP indices (PRx, PAx and RAC) and any of the IC injury burden scores (Spearman's correlation). Comparing the indices to the IC injury scores, all coefficients were positive, however failed to reach r-values greater than 0.250 (however with most reaching $p<0.05$). When comparing the % time spent above threshold for PRx, PAx and RAC with the IC injury scores, we found identical trends. All Spearman tables can be seen in Appendix D of the Supplementary materials.

Given the non-ordinal nature of the Marshall CT grading system, Kruskal Wallis (KW) test was used to compare the mean PRx, PAx and RAC values across individual IC score categories. For the Rotterdam, Helsinki and ordinal Stockholm score we compared the mean PRx, PAx and RAC values across each ordinal category using a one-way Joncheere-Terpstra (JT) test. Marshall CT grade[11] displayed no statistically significant association with the mean PRx, PAx or RAC on KW testing. Similarly, the Marshall CT grade was not significantly associated with % time above thresholds for PRx, PAx and RAC, with the only exception being the percentage of time spent with a PRx threshold above 0

The Rotterdam CT score displayed some statistically significant association with mean PRx ($p=0.001$), PAx ($p=0.001$) and RAC ($p=0.001$). Similar results were seen for the % time spent above threshold, with most PRx and RAC % times above threshold reaching significance. The JT testing confirmed a statistically significant increase in the mean values of the indices and % time above threshold, with increasing Rotterdam score.

The Helsinki CT score[13] displayed the most significant association, comparing mean index values and % time above threshold across score categories using the JT test. All mean index values and % times above threshold were significantly different between ordinal Helsinki score categories (all $p<0.002$), with increasing mean values seen with increasing Helsinki score values. The mean PRx, PAx, and RAC vs Helsinki CT score can be seen in Figure 1.

***Figure 1 here**

Finally, the ordinally arranged Stockholm score[14] seemed to display significant association between mean index values and % time above thresholds for RAC only. The JT testing confirmed a statistically significant increase in the mean values of RAC with increasing ordinal Stockholm score value. All mean values for indices and % time above thresholds, for each IC scoring system category can be seen in Appendix E of the Supplementary Materials.

EC Injury Scores and Cerebrovascular Reactivity

We evaluated the EC injury scores (ISS[16] and APACHE[17]) in a similar manner. As with the majority of the IC injury scores, the ISS EC injury score failed to reach any statistically significant relationship with any of the ICP indices of cerebrovascular reactivity. Out of all IC and EC injury scores, the APACHE score displayed the strongest correlation with PRx ($p = 0.016$), PAx ($p=0.001$) and RAC ($p=0.001$), with r-values up to 0.285. Similar trends were found when comparing the % time spent above threshold for PRx, PAx and RAC with the IC and EC injury scores. All Spearman tables can be seen in Appendix C of the Supplementary materials. Figure 2 displays box plots of the PRx, PAx and RAC values compared to ISS[15] and APACHE[16] scores.

****Figure 2 here***

Patient Demographics and Injury Characteristics – Across Binary Index Thresholds

Table 1 displays the results of the Mann-Whitney U testing for across the various binary outcome thresholds for RAC, with similar results found for PRx and PAx (Appendix F). Various variables displayed statistical significance between those below versus above threshold. Of note, age and APACHE[17] scores were the two variables consistently different between those patients below and above the index thresholds, with higher age and APACHE[17] scores seen in those above the thresholds.

The ISS[16] and IC scoring systems[11-14] were rarely statistically different between those patients below and above threshold. Those patients with PRx, PAx, and RAC values above threshold were most likely to display significantly higher Helsinki CT score values.

Patients with PRx values above 0 displayed more contusions, higher largest lesion volume, higher total contusion volume and more midline shift. A similar pattern was seen for patients with PAx values above 0. The other index thresholds tested rarely displayed a statistically significant difference in the continuous variable IC injury characteristics.

***Table 1 here**

Univariate Logistic Regression (ULR) Analysis – Prediction of Impaired Cerebrovascular Reactivity

We further evaluated the association between all patient demographics, EC injury and IC injury characteristics with the development of impaired cerebrovascular reactivity. Using the defined thresholds for PRx, PAx and RAC for impaired cerebrovascular reactivity,[8,9] we employed ULR techniques to evaluate each variable in relation to its ability to predict impairment in the entire recording period dataset. Each threshold was evaluated against each variable. Table 2 displays the ULR AUC's and p-values for the patient demographic data and both the IC and EC scoring systems tested, while Appendix G displays the ULR AUC's and p-values for the individual IC injury characteristics tested. Similar results were seen for the 1st 24 hours and 1st 72 hours recording datasets (Appendix H and I of the Supplementary materials).

Various patterns of statistically significant relationships with impaired cerebrovascular reactivity were seen. Of note, the most commonly seen statistically significant association (with the highest AUC's and lowest p-values) with impaired cerebrovascular reactivity was patient age (AUC = 0.606 to 0.783; $p<0.025$ for all) and the APACHE[17] score (AUC = 0.619 to 0.704; $p<0.032$ in all except the PRx >0 threshold). IC CT scores were mostly not significantly associated with impaired cerebrovascular reactivity, although some evidence for association was detected for the Stockholm CT score[14] being the most significant scoring system for PAx >0.25, RAC > -0.10 and RAC > -0.05 thresholds. Of note, for most thresholds tested, admission GCS, sex, ISS[16] and pupillary reactivity were not related to impaired cerebrovascular reactivity.

There were some noteworthy patterns from the evaluation of the individual IC CT-based lesions. Associations depended on the threshold chosen, but in general, across all index thresholds tested, the most commonly seen associations were between markers of diffuse IC injury, rather than macroscopic parenchymal damage. The following injury characteristics were most commonly statistically associated with impaired cerebrovascular reactivity: presence of convexity SDH, presence of falcine SDH, presence of bilateral SDH, thickness of tSAH and the presence of SC DAI lesions. Some important characteristics rarely associated with impaired cerebrovascular reactivity: MLS, largest lesion volume, # of contusions, total contusion volume, basal cistern compression, lateral ventricle compression, 4th ventricle compression and gyral compression.

***Table 2 here**

Multivariable Logistic Regression (MLR) Analysis

Based on the results of the ULR analysis, we created individualized multivariable models for each binary threshold outcome, performing a sequential "elimination method" of MLR analysis in order to arrive at the best predictive model for each index threshold (see methods section). For each model, we included only those variables reaching statistical significance (or close to it: $p<=0.100$) in ULR, as highlighted in Tables 2 and Appendix G. Similar results were seen for the 1st 24 hours and 1st 72 hours recording data sheets.

The MLR models for the binary PRx threshold outcomes displayed similar trends to those mentioned in the ULR section, markers of systemic injury and diffuse IC injury seem to predominate over those of IC parenchymal damage. For the binary threshold outcome of PRx above 0, the best model was that composed of age (p=0.093), presence of bilateral SDH (0.009), convexity tSAH thickness over 5mm (p=0.049) and the presence of SC DAI lesions (p=0.001); with an AUC for the model of 0.670 (p<0.0001). For the binary threshold outcome of PRx above +0.25, the best model was composed of sex (p=0.015), APACHE II score (p=0.032), presence of convexity SDH (p=0.016), presence of falcine SDH (p=0.051) and the presence of bilateral convexity SDH (p=0.023); with an AUC for the model of 0.758 (p=<0.0001). Finally, for the binary threshold outcome of PRx above +0.35, the best model was composed of APACHE II score (p=0.003), presence of convexity SDH (p=0.072), presence of bilateral convexity SDH (p=0.062) and complete filling of the basal cisterns with tSAH (p=0.025); with an AUC for the model of 0.791 (p<0.0001).

For the binary threshold outcome of PAx above 0, the best model contained age (p<0.0001), presence of any basal cistern compression (p=0.011), presence of bilateral contusions (p=0.062) and the presence of SC DAI lesions (p=0.019); with an AUC for the model of 0.752 (0<0.0001). For the binary threshold outcome of PAx above +0.25, the best model contained age (p=0.001), presence of convexity SDH (p=0.099), presence of falcine SDH (p=0.067) and the presence of bilateral SDH (p=0.015); with an AUC for the model of 0.871 (p<0.0001).

Finally, the multi-variate models for the binary RAC threshold outcomes displayed similar results to those of PRx and PAx. For the binary threshold outcome of RAC above -0.05, the best model contained age (p=0.016), APACHE II (0.092), presence of tentorial SDH (p=0.048), presence of tSAH filling the basal cisterns (p=0.028) and the presence of SC DAI lesions (p=0.051); with an AUC for the model of 0.744 (p<0.0001). Similarly, for the model with RAC above -0.10 as an outcome, the best model contained age (p=0.027), Stockholm Score (0.062), APACHE II score (p=0.032), any gyral compression (p=0.017), tSAH amount in the basal cisterns (p=0.087) and the presence of SC DAI lesions (p=0.009); with an AUC for the model of 0.756 (p<0.0001).

Discussion:

Through a detailed analysis of both admission IC and EC injury burden, as it relates to cerebrovascular reactivity during the ICU phase of TBI care, we have identified some interesting and important trends.

First, whilst the admission IC CT scores (Marshall,[11] Rotterdam,[12] Helsinki,[13] Stockholm[14]) are well validated as predictors of outcome, overall they appear to show little association with impaired cerebrovascular reactivity after TBI. We saw some statistically significant differences between categories of the IC scoring systems for both: A. raw mean values of PRx, PAx and RAC; and B. mean % time spent above index threshold; using KW and JT testing. The Helsinki and Rotterdam scoring systems appear to display the strongest relationship to some of the indices of cerebrovascular reactivity. Similarly, through JT testing, it appears that the various scoring categories for the Helsinki score display statistically different mean values for the indices and % time above threshold, with increasing values seen as the ordinal score increases. Among the CT scoring systems, Helsinki provides the greatest role for large mass lesions as both basal cistern compression and mass lesions >25 cm^3 greatly increase the score, suggesting that these space occupying lesions may affect cerebral autoregulation. However, when evaluating the ability of the Helsinki score to predict "impairment" of cerebrovascular reactivity, ULR and MLR analysis display that the Helsinki score falls out of statistical significance. This was also seen with the Marshall, Rotterdam and Stockholm score in ULR and MLR analysis. The Stockholm CT score had the strongest correlations to RAC and PAx. The tSAH burden is the main outcome predictor in the Stockholm CT score, as recently shown in comparison to the other CT scoring systems. This could indicate that RAC and PAx are more strongly associated with more wide spread tSAH which presumably is a potential driver for several secondary injury cascades following TBI.

Secondly, the EC injury scores (ISS[16] and APACHE[17]) displayed interesting trends. The ISS failed to be associated with either the indices or impaired cerebrovascular reactivity. Thus, the combined IC and EC trauma burden, as assessed by the ISS does not appear to be associated with impairment of autoregulation/cerebrovascular reactivity. In contrast, the APACHE[17] score was the most strongly, out of both the IC and EC scoring systems, associated with both raw index values and % time spent above thresholds. Furthermore, the APACHE reaches statistical significance in ULR for its association with all thresholds of ICP indices of cerebrovascular reactivity (except for the PRx >0 threshold). This predictive value for impaired reactivity is even maintained in some the multi-variate models tested for the thresholds of: PRx > +0.35 and RAC > -0.10. Examining the differences between the ISS and APACHE, it can be seen that the APACHE[16]

provides a much more robust assessment of the patient's systemic response to injury, including accounting for: A. age, B. hemodynamic response, C. core temperature, and D. laboratory values. Thus, the patient's individual "host response" to injury, appears to be most associated with impaired cerebrovascular reactivity, not the tallied gross injury burden. This raises the question of systemic host response to injury, not cumulative injury burden, as a potential driver of autoregulatory failure/cerebrovascular dysfunction post-TBI. This requires investigation. It is possible that diffuse IC injury patterns, which were more associated with impaired cerebrovascular reactivity, are also more likely to be associated with severe systemic multi-system trauma, and hence worse APACHE scores. Thus, the association between APACHE and impaired autoregulation/cerebrovascular reactivity may be reflective of this relationship, and not necessarily the host systemic biochemical/metabolic or inflammatory response, driving impaired vascular reactivity. Much further work is required to explore this relationship.

Thirdly, diffuse IC injury patterns, not gross macroscopic parenchymal injury, appear to be most associated with impaired cerebrovascular reactivity. This was seen in both the ULR and MLR analysis of the detailed admission IC injury characteristics. The presence of a convexity SDH, falcine SDH, bilateral convexity SDH, thickness of convexity tSAH, amount of tSAH in the basal cisterns and presence of SC DAI lesions, appear to be the most significant predictors of impaired cerebrovascular reactivity, regardless of the ICP index threshold tested. All of these markers are those of diffuse injury, implicating a mechanism of high energy, with both acceleration/deceleration and angular acceleration/shearing forces applied to the parenchyma. This implies that "diffuse" injury, other than what is captured by the CT scoring systems, is more predictive of impaired reactivity. Furthermore, all markers of gross macroscopic parenchymal injury failed to be associated. In aggregate, this could explain the lack of significance of IC CT scoring systems in predicting impaired cerebrovascular reactivity. Given these results, diffuse microscopic injury burden, not visible on admission CT scans, may be a driver of impaired cerebrovascular reactivity. Magnetic resonance imaging (MRI) based assessment of IC injury in the acute phase may shed light on this injury pattern, and requires further investigation.

Finally, age appears to be robustly associated with both the raw indices and % time spent above index thresholds. In addition, age was a strong predictor of impaired cerebrovascular reactivity in both ULR and MLR analysis. This relationship between advancing age and impairment of autoregulatory capacity has been described in part before,[18]

our analysis in this non-DC cohort confirms this variable as a key player in an individual patient's cerebrovascular reactivity post-TBI. Age is also included within the APACHE score calculation, and thus may play a role in why the APACHE scores were statistically significant in their associations with impaired cerebrovascular reactivity. From our data set, we were unable to determine if this was that case given the amalgamated single score that was stored within the NCCU database. Age may play a role in the baseline ability of the cerebrovascular tree to autoregulate, and/or the host response to injury. Further investigation into local and global biochemical/metabolic response and inflammatory response to TBI is required, in order to fully understand how age impacts autoregulatory function/cerebrovascular reactivity post-TBI.

Limitations

Despite the interesting results, there are some important limitations to highlight. First, this is a retrospective cohort of non-DC patients. The treatments received during the patient's ICU phase directly influenced the physiologic variables and signals recorded. Furthermore, this treatment may not have been homogenous throughout all patients included in this study. We were unable to take this into account within the analysis, given the lack of information available on treatments received.

Second, this cohort is a non-DC cohort only. This was chosen specifically to avoid the confounding introduced post-DC, during which ICP and ICP derived indices of cerebrovascular reactivity are impacted.[19,20] Thus, the results of this analysis only apply to non-DC patients. Similar analysis is required for DC patients, analyzing the associations while taking into account the influence of craniectomy on the physiologic variables measured.

Thirdly, the ISS included in this study is the total ISS, thus including injury to the body as well as the head and brain, not making it an exclusive score for the EC injury burden. Head ISS is based on anatomical localization of lesions on admission head CT scans, similar to many of the CT scoring systems included and, depending on the presence of polytrauma, will contribute significantly to the total ISS variable used in this study. Moreover, APACHE II contains admission GCS which is commonly used to assess the severity of brain injury, similar to the IC CT scoring systems. Thus,

the EC injury variables used in this study will do different degrees be influenced by the IC injury burden. Future studies may avoid this by only using non-head ISS components, unfortunately not available for the current cohort.

Fourth, this is a single center study and thus requires further validation. We plan to repeat this analysis for validation purposes in a larger moderate to severe TBI cohort from the prospective CENTER-TBI study,[21] once recruitment ends. In addition, TRACK-TBI[22] may also provide valuable data sets to explore these relationships between IC and EC injury burden.

Finally, our goal was to determine if there was an association between admission IC and EC injury characteristics and the development of impaired cerebrovascular reactivity during their ICU stay, as defined by the continuous indices: PRx, PAx and RAC. We did not assess the association between IC CT imaging findings from images other than the admission CT. Lesions identified on admission CT do tend to progress over time, and thus the link between this progression and cerebral autoregulation cannot be commented on at this time. This is however another important avenue which requires exploration in future studies, assessing the association between lesion progression/change (or new lesion development on subsequent follow-up imaging) and cerebrovascular reactivity. This again, is something that is potentially best answered by the data curated within CENTER-TBI[21] and TRACK-TBI[22], where regular follow-up imaging is to be conducted and archived, along with high frequency physiologic signals for assessment of cerebral autoregulation.

Future Directions

Given these interesting results, there is room for further investigation regarding the drivers of impaired autoregulation/cerebrovascular reactivity. First, this is a single study, and requires prospective validation. As mentioned, we plan to conduct a validation study on the "high-resolution" moderate to severe TBI cohort from the CENTER-TBI study.[21] Second, repeating this analysis within a DC cohort of TBI patients is required to see if these relationships hold true in the setting of DC. Third, exploration of the "host response" to injury and its links to impaired cerebrovascular reactivity is required. This would require the use of both IC and systemic analysis of: biochemistry/metabolism and inflammatory response to injury, with their links to cerebrovascular reactivity. In addition,

more refined variables of extracranial polytrauma could be used. Finally, the link between diffuse microscopic injury and impaired cerebrovascular reactivity requires exploration. As CT is insufficient to evaluate this type of injury burden, the application of MRI within the acute phase post-TBI may shed light on this potential association. It is only through a truly "multi-faceted" approach, will we be able to understand the drivers of impaired autoregulation/cerebrovascular reactivity.

Conclusions:

Diffuse IC injury markers (such as thickness of SAH, presence of sub-cortical DAI lesions, and the presence of a SDH) and systemic injury response (as assessed via APACHE II) are most associated with dysfunction in cerebrovascular reactivity after TBI. Standard IC CT scoring systems and evidence of macroscopic parenchymal damage are poor predictors, implicating potentially both microscopic injury patterns and host response as drivers of dysfunctional cerebrovascular reactivity. Age remains a major variable associated with cerebrovascular reactivity.

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EPT has received salary support from Swedish Society for Medical Research and Swedish Society of Medicine.

DKM has consultancy agreements and/or research collaborations with GlaxoSmithKline Ltd; Ornim Medical; Shire Medical Ltd; Calico Inc.; Pfizer Ltd; Pressura Ltd; Glide Pharma Ltd; and NeuroTraumaSciences LLC.

MC and PS have financial interest in a part of licensing fee for ICM+ software (Cambridge Enterprise Ltd, UK).

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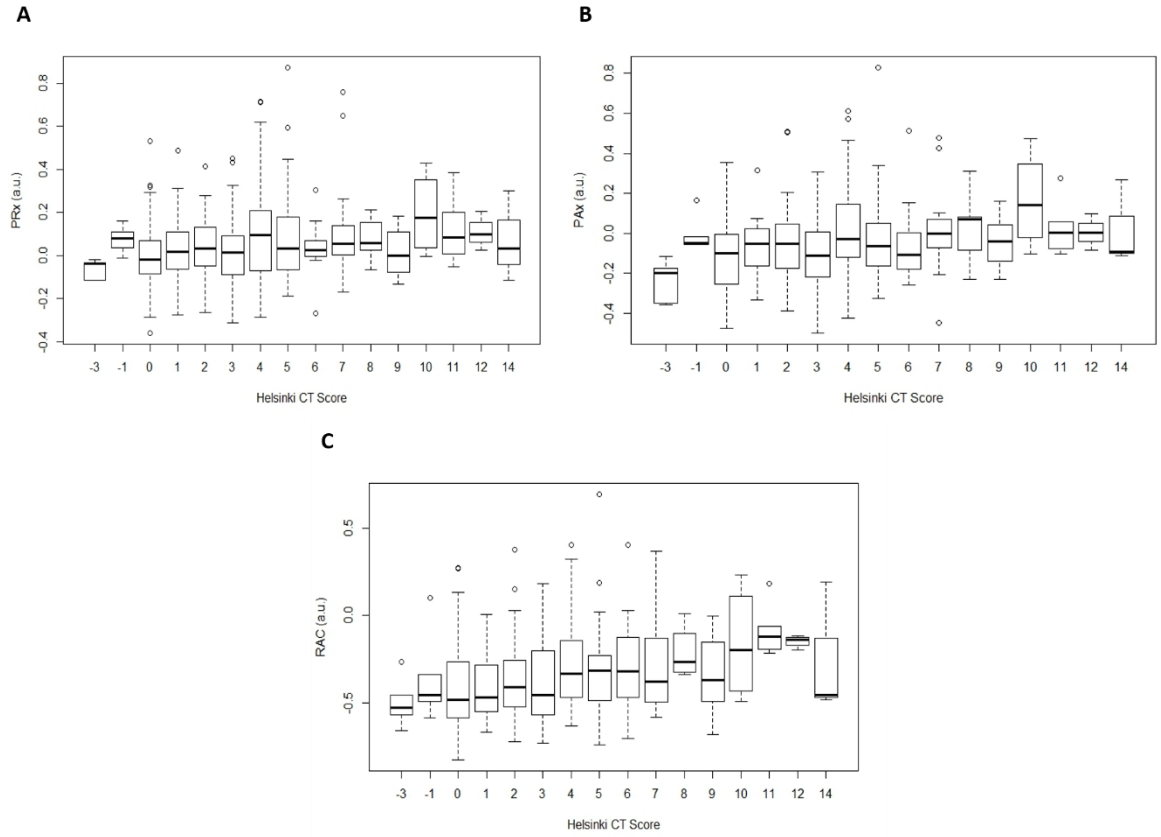
Figure Legends:

Figure 1: Box Plots of PRx, PAx and RAC versus Helsinki CT Score

a.u. = arbitrary units, CT = computed tomography, PAx = pulse amplitude index (correlation between pulse amplitude of ICP (AMP) and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP. Panel A: PRx vs. Helsinki Score (p=0.01 on JT testing), Panel B: PAx vs. Helsinki Score (p=0.001 on JT testing), Panel C: RAC vs. Helsinki Score (p=0.001 on JT testing).

Figure 2: Box Plots of PRx, PAx and RAC versus APACHE and ISS Scores

APACHE = APACHE injury score, a.u. = arbitrary units, ISS = injury severity score, PAx = pulse amplitude index (correlation between pulse amplitude of ICP (AMP) and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP. Panel A: PRx vs. APACHE (r=0.130; p=0.016), Panel B: PRx vs. ISS (r=0.-0.018; p= 0.762), Panel C: PAx vs. APACHE (r=0.257; p=0.001), Panel D: PAx vs. ISS (r=-0.064; p=0.264), Panel E: RAC vs. APACHE (r=0.285; p=0.001), Panel F: RAC vs. ISS (r=0.027; p=0.644).


A
PRx (a.u.)
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
-3 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 14
Helsinki CT Score
B
PAx (a.u.)
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
-3 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 14
Helsinki CT Score
C
RAC (a.u.)
-0.5
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0.5
-3 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 14
Helsinki CT Score

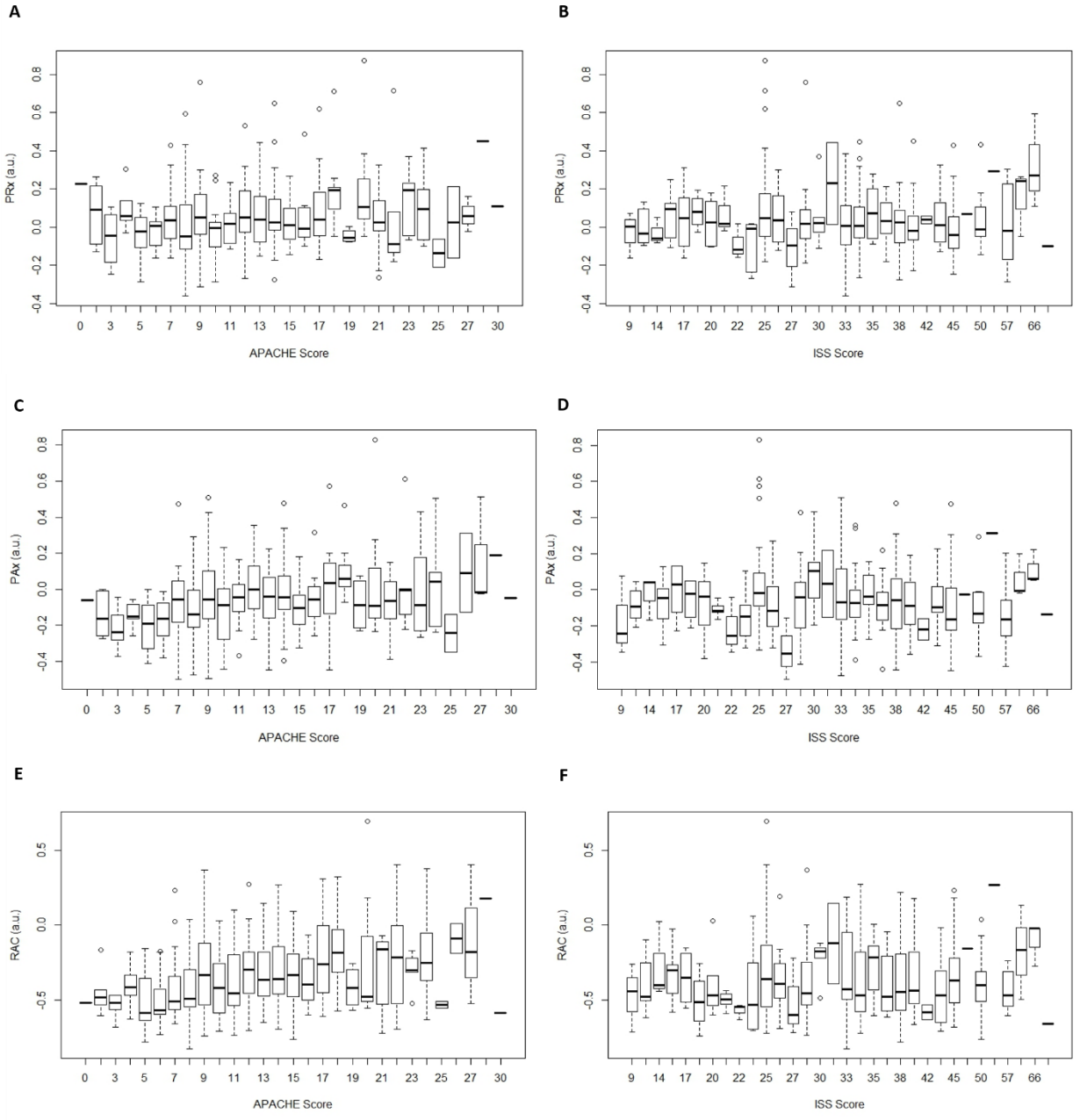
A
PRx (a.u.)
APACHE Score
B
PRx (a.u.)
ISS Score
C
PAx (a.u.)
APACHE Score
D
PAx (a.u.)
ISS Score
E
RAC (a.u.)
APACHE Score
F
RAC (a.u.)
ISS Score

Table 1: RAC Thresholds – Non-Binary Demographics and Injury Characteristics

Demo (Mean and Medians with Std Dev/IQR)	RAC		p-value	RAC		p-value
	<-0.05	**≥-0.05**		**<-0.10**	**≥-0.10**	
N	312	44	-	300	56	-
Age	39.2 (16.7)	50.6 (17.5)	**<0.0001**	38.9 (16.7)	49.7 (17.0)	**<0.0001**
GCS	7 (4-10)	5 (3-8.25)	0.078	7 (4-10)	6 (3-8.25)	0.143
Marshall	2 (2-3)	3 (2-4)	0.433	2 (2-3)	3 (2-3.25)	0.455
Rotterdam	2 (2-3)	2 (2-4)	0.252	2 (2-3)	2 (2-4)	0.135
Helsinki	2 (0-4.75)	4 (2-6.25)	**0.016**	2 (0-4.75)	4 (2-6)	**0.005**
Stockholm	2.06 (0.89)	2.35 (0.95)	0.055	2.05 (0.89)	2.32 (0.91)	**0.034**
Stockholm Range	2 (2-3)	3(2-3)	0.088	2 (2-3)	3 (2-3)	**0.041**
ISS	32.6 (11.2)	35.2 (12.3)	0.384	32.8 (11.2)	33.9 (12.2)	0.829
APACHE II	11.7 (5.5)	14.4 (5.7)	**0.006**	11.6 (5.5)	14.6 (5.6)	**0.001**
MLS (mm)	1.6 (3.4)	3.0 (5.2)	0.051	1.6 (3.4)	2.6 (4.7)	0.166
Largest Lesion Volume	12.3 (22.1)	18.7 (32.1)	0.055	12.4 (22.4)	17.0 (29.2)	0.091
# Contusions	0.44 (0.87)	0.43 (0.73)	0.684	0.42 (0.85)	0.52 (0.83)	0.204
# DAI Lesions	1.1 (2.8)	0.5 (1.6)	**0.021**	1.2 (2.9)	0.43(1.4)	**0.005**
Total Contusion Volume	4.0 (8.7)	6.3 (17.2)	0.797	5.9 (17.0)	6.1 (13.3)	0.257

 # = number, N = number of patients, CPP = cerebral perfusion pressure, DAI = diffuse axonal injury, MLS = midline shift, mm = millimeters, ISS = injury severity score, GCS = Glasgow Coma Scale, RAC = correlation between pulse amplitude of ICP (AMP) and cerebral perfusion pressure (CPP).

Table 2: Univariate Logistic Regression of Admission Demographics and Scores with ICP Index – Grand Mean Data

	PRx >0		**PRx >0.25**		**PRx >0.35**		**PAx >0**		**PAx >0.25**		**RAC >-0.05**		**RAC>-0.10**	
	AUC	**P**	**AUC**	**P**	**AUC**	**P**	**AUC**	**P**	**AUC**	**P**	**AUC**	**P**	**AUC**	**P**
Age	**0.606**	**0.001**	**0.637**	**0.007**	**0.655**	**0.025**	**0.720**	**<0.0001**	**0.783**	**<0.0001**	**0.685**	**<0.0001**	**0.679**	**<0.0001**
Sex	0.495	0.850	**0.640**	**0.040**	0.663	0.204	0.555	0.526	0.699	0.073	0.586	0.335	0.534	0.621
Admission GCS	0.592	0.551	0.633	0.983	0.722	0.977	0.621	0.374	0.620	0.994	0.651	0.723	0.625	0.773
Admission Pupil Reactivity	0.564	0.241	**0.628**	**0.012**	**0.675**	**0.003**	0.558	0.648	**0.695**	**0.013**	0.600	0.050	0.577	0.098
Admission Marshall CT Grade	**0.584**	**0.029**	0.596	0.537	0.656	0.361	0.581	0.392	0.665	0.192	0.562	0.748	0.531	0.905
Admission Rotterdam CT Grade	0.562	0.157	**0.656**	**0.032**	0.689	0.107	0.569	0.443	0.689	0.140	0.628	0.149	0.570	0.332
Admission Helsinki CT Score	0.634	0.335	0.685	0.540	0.773	0.488	0.644	0.213	0.709	0.577	0.661	0.525	0.656	0.396
Admission Stockholm CT Score	0.544	0.072	0.519	0.601	0.650	0.063	0.550	0.147	**0.640**	**0.022**	**0.594**	**0.045**	**0.585**	**0.030**
Admission Stockholm CT "Range"	0.556	0.473	0.578	0.754	0.675	0.324	0.557	0.875	**0.670**	**<0.0001**	0.642	0.152	0.612	0.192
ISS	0.518	0.734	**0.598**	**0.027**	0.560	0.375	0.545	0.393	0.565	0.521	0.553	0.192	0.514	0.545
APACHE II	0.526	0.406	**0.619**	**0.032**	**0.702**	**0.002**	**0.652**	**<0.001**	**0.704**	**0.001**	**0.633**	**0.004**	**0.651**	**0.001**

*AUC = area under the receiver operative curve, p = p-value, GCS = Glasgow Coma Scale, CT = computed tomography, ISS = injury severity score, PRx = pressure reactivity index (correlation between ICP and MAP), PAx = pulse amplitude index (correlation between pulse amplitude of ICP (AMP) and MAP), RAC = correlation between AMP and CPP. *NOTE: bolded values are those which have reached statistical significance (p<0.05).*