Association Between Physiologic Signal Complexity and Outcomes in Moderate and Severe Traumatic Brain Injury: A CENTER-TBI Exploratory Analysis of Multiscale Entropy

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Abstract:

In traumatic brain injury (TBI), preliminary retrospective work on signal entropy suggests an association with global outcome. The goal of this study was to provide multi-center validation of the association between multi-scale entropy (MSE) of cardiovascular and cerebral physiologic signals, with 6-month outcome. Using the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) high-resolution intensive care unit (ICU) cohort, we selected patients with a minimum of 72 hours of physiologic recordings, and a documented 6-month Glasgow Outcome Scale Extended (GOSE) score. 10- second summary data for heart rate (HR), mean arterial pressure (MAP), intracranial pressure (ICP) and pulse amplitude of ICP (AMP), were derived across the first 72 hours of data. MSE complexity index (MSE-Ci) was determined for HR, MAP, ICP and AMP, with the association between MSE and dichotomized 6-month outcomes assessed using Mann-Whitney-U testing and logistic regression analysis. A total of 160 patients had a minimum of 72 hours of recording and a documented outcome. Decreased HR MSE-Ci (7.3 (IQR 5.4 to 10.2) vs. 5.1 (IQR 3.1 to 7.0); p=0.002), lower ICP MSE-Ci (11.2 (IQR 7.5 to 14.2) vs. 7.3 (IQR 6.1 to 11.0); p=0.009) and lower AMP MSE-Ci (10.9 (IQR 8.0 to 13.7) vs. 8.7 (IQR 6.6 to 11.0); p=0.022), were associated with death. Similarly, lower HR MSE-Ci (8.0 (IQR 6.2 to 10.9) vs. 6.2 (IQR 3.9 to 8.7); p=0.003) and lower ICP MSE-Ci (11.4 (IQR 8.6 to 14.4) vs. 9.2 (IQR 6.0 to 13.5)), were associated with unfavourable outcome. Logistic regression analysis confirmed that lower HR MSE-Ci and ICP MSE-Ci were associated with death and unfavourable outcome at 6-months. These findings suggest that a reduction in cardiovascular and cerebrovascular system entropy is associated with worse outcomes. Further work in the field of signal complexity in TBI multi-modal monitoring is required.

Keywords: autoregulation, cerebral physiology, complexity, multiscale entropy, outcome

Introduction:

Signal complexity, which is quantifiable using various entropy surrogate measures, has been explored as a means to estimate a systems ability to accommodate future change.[1] Within biological systems, physiologic signal complexity relates to integrative homeostatic status and has been shown to be associated with global outcomes, across a range of pathologies.[1–7] In particular, reduced complexity or entropy in heart rate (HR) or arterial blood pressure (ABP), has been shown to be associated with worse outcomes in cardiac and critical care literature.[6,8–11] It is believed that reduced complexity reflects a more rigid biological system, less capable of accommodating perturbations or new insults.

In the traumatic brain injury literature, some preliminary work has been conducted exploring both heart rate variability (HRV) and approximate entropy, in association with 6-month outcomes.[3,12–15] These preliminary studies, though based on retrospective data sets, have demonstrated strong associations between reduced signal complexity, and poor outcome in TBI. In particular, a reduction in HRV, approximate entropy of HR, intracranial pressure (ICP), and mean arterial pressure (MAP), have all displayed some association with 6-month outcome in TBI.[14] These findings, support that potentially a multi-system approach to entropy be considered, where a decreased ability to compensate in both the cerebral (ICP) and cardiovascular (HR and MAP) biological systems, may contribute to poor outcome in moderate/severe TBI.

The main limitation of these previous works is that they are primarily retrospective, single center studies. Similarly, adopting new multi-scale entropy (MSE) techniques, has yet to be fully explored in a multi-center adult TBI data set in association with outcome. MSE provides a comprehensive assessment of signal entropy over various time scales for a given physiologic variable. Furthermore, the relationship between MSE and other multi-modal monitoring aspects of cerebral physiology associated with 6-month outcome, such as continuously assessed cerebrovascular reactivity or cerebral compensatory reserve, has only been preliminarily explored.[3,16–18] Using the prospective multi-center high-resolution data set from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI), we aim to explore MSE of raw physiologic signals, their relationship to 6-month outcome and association with impaired cerebral physiology in moderate/severe TBI patients.

Methods:

Patient Population:

All patients from the multi-site CENTER-TBI high resolution intensive care unit (ICU) monitoring cohort with a minimum of 72 hours of high-frequency physiologic data and with a 6-month Glasgow Outcome Scale – Extended (GOSE) score, were included in this analysis. Patients with EVD based ICP data only i.e. no parenchymal sensor were excluded given the interrupted nature of their recordings (i.e. reliable ICP can be recorded only when the drainage is closed). These patients were prospectively recruited between January 2015 and December 2017 from 21 centers in the European Union (EU). 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. As part of the inclusion criteria into the high- resolution cohort of CENTER-TBI, all patients had invasive ICP monitoring in place, with data recording within 24 hours of their injury to ensure early capture of data. 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 were categorised at the time of admission as suffering from less severe TBI, but experienced 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 Brain Trauma Foundation guidelines.[19] Including targeting an ICP threshold of 20 mmHg, and CPP range of 60 to 70 mmHg. PRx was not used to direct management of patients.

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, all patients had demographics, injury and imaging data 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, basic admission demographics and centrally reported computed tomography (CT) variables for the first available CT of each patient were extracted.[20] They included: age, admission best GCS motor score and pupillary reactivity (bilaterally reactive, unilateral reactive, bilateral unreactive), Marshall CT Classification,[21] Rotterdam CT score,[22] Helsinki CT score,[23] presence or absence of traumatic subarachnoid haemorrhage (tSAH), extradural hematoma (EDH), pre-hospital hypotension (defined as a recorded systolic blood pressure <90 mmHg) and pre-hospital hypoxia (defined as a recorded oxygen saturation of <= 92%). Glasgow Outcome Scale Extended (GOSE) scores at 6-months were also obtained from the database where available. CENTER-TBI data version 2.1 was accessed for the purpose of this study, via Opal database software.[24]

Signal Acquisition:

Arterial blood pressure (ABP) was obtained through arterial lines connected to pressure transducers. ICP was acquired from an intra-parenchymal strain gauge probe (Codman ICP MicroSensor; Codman & Shurtleff Inc., Raynham, MA), parenchymal fibre optic pressure sensor (Camino ICP Monitor, Integra Life Sciences, Plainsboro, NJ, United States; https://www.integralife.com/). All signals were recorded using digital data transfer or digitized via an A/D converter (DT9803; Data Translation, Marlboro, MA), where appropriate; sampled at frequency of 100 Hertz (Hz) or higher, using the ICM+ software (Cambridge Enterprise Ltd, Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk) or Moberg CNS Monitor (Moberg Research Inc, Ambler, PA, USA, https://www.moberg.com) or a combination of both. Signal artefacts were removed using both manual and automated methods prior to further processing or analysis. Similar data acquisition procedures have occurred in other CENTER-TBI studies.[25–30]

Signal Processing:

Post-acquisition processing of the above signals was conducted using ICM+ (Cambridge Enterprise Ltd, Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk). Similar processing has occurred in other CENTER- TBI studies.[25–30] All signal data were filtered to only include the first 72 hours of recording, in order to focus on the acute phase of physiology during the ICU stay. This 72 hour time period of data was chosen for two reasons. First, it represents the period post-TBI where we would expect the greatest degree of physiology change/response to injury during active treatment. Second, many patients in the high- resolution cohort for CENTER-TBI only had ~3 days of physiologic data capture.

CPP was determined as MAP – ICP. Pulse amplitude of ICP (AMP) was determined by calculating the fundamental Fourier amplitude of the ICP pulse waveform 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: heart rate (HR), ICP, ABP (which produced MAP), AMP, and CPP. This 10-second by 10-second data was utilized for the determination of MSE (see MSE determination section below), as we were interested in the complexity of slow fluctuations in recorded physiology.

In addition, we desired to compare MSE of various raw physiologic measures with cerebrovascular reactivity and compensatory reserve, using the first 72 hours of data. As such, we derived PRx as the moving correlation coefficient between 30 consecutive 10 second mean windows of ICP and MAP, updated every minute. Similarly, RAP (correlation (R) between AMP (A) and ICP (P)) was determined as the moving correlation coefficient between 30 consecutive 10 secondary mean windows of AMP and ICP, updated every minute. Minute-by-minute data was then derived for these indices and the raw physiology (ICP, MAP, AMP, and CPP). Grand mean values of all physiologic variables were calculated per patient, across the first 72 hours of data. In addition, the following post-processing of this physiologic data occurred in R (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/):

a. % Time Spent with ICP Above 20 mmHg and 22 mmHg.[19]
b. % Time with CPP below 60 mmHg, and above 70 mmHg.[19]
c. % Time Spent with PRx Above Threshold: For each patient the % of time spent above the following clinically defined thresholds were calculated: 0, +0.25, +0.35.[31,32] All of these thresholds for PRx have been defined in previous published literature as statistically significant for association with 6-month global outcome in adult TBI patients.
d. Given the difficulty in interpretation of RAP, we derived the area under the curve (RAP- AUC) over time for the first 72 hours, integrating the signal via linear interpolation methodology – as described in our previous work on RAP.[33–35]

MultiScale Entropy (MSE) Determination:

MSE calculations were conducted for each patient over the 72-hour period of monitoring, deriving the summary complexity index (MSE-Ci) for each raw physiologic parameter: HR, MAP, ICP and AMP. A full description of MSE background and theory is beyond the scope of this manuscript, and has been covered in detail in other works in neurocritical care.[3,4,18,36] The referenced literature should serve as a source for those interested in the details of sample entropy (SampEn) and MSE.[1,3,36] However, in short, MSE serves as a method to estimate the complexity/non-linear dynamic properties of a signal or time- series variable, based on more than one scale of time. It accomplishes this through the determination of SampEn for over various time scales for a given signal, with different time scales derived through application of non-overlapping averaging of data. In particular, a scale of 1 represents the native signal (ie. in our case 10-second by 10-second data), where a scale of τ ($\tau > 1$) represents a coarse-grained time series obtained by averaging of every τ consecutive samples from the native signal. For our SampEn calculations, we used a tolerance (r) of 0.15 and an embedding dimension (m) of 2, in keeping with previous literature on the topic.[3,4,36] For the purpose of our analysis we determined MSE over 20 scales, which has previously been conducted using physiologic signals in neurocritical care populations.[3,4] Detailed description on the scaling process can be found in the referenced literature.

Once SampEn has been determined for each scale, across the 72-hour period of physiology, then the MSE-Ci was determined as a summary measure output for MSE. This was accomplished through deriving the area under the MSE curve (ie. SampEn vs. Scale curve) for each patient through numerical

integration of SampEn in the range of scales from 1 to 20. This subsequently led to the derivation of HR MSE-Ci, MAP MSE-Ci, ICP MSE-Ci and AMP MSE-Ci, for each patient.

Statistics:

All statistical analysis was conducted using R. Normality of continuous variables was assessed via Shapiro-Wilks test, where all variables displayed non-parametric characteristics, and are hence presented as median (range) or median (IQR). Error bars for SampEn over the various scales were produced for the entire population dichotomized by outcome. The alpha for all statistical tests performed was set at 0.05, with no specific correction for multiple comparisons, given the exploratory nature of this work.

MSE-Ci values and physiologic measures were compared using Pearson correlation coefficients. MSE-Ci, other physiologic measures and demographic data were compared between dichotomized 6-month outcome groups, using Mann-Whitney-U and chi-square testing, where appropriate. GOSE was dichotomized into: Alive/Dead, and Favourable/Unfavourable (with less than or equal to 4 denoting unfavourable outcome). To assess the association between MSE-Ci values and outcome, univariate logistic regression (ULR) was conducted for both dichotomized GOSE defined outcomes. ULR was also performed for admission patient demographics and the cerebral physiologic metrics highlighted above in th "Signal Processing" portion of the methods. Area under the receiver operating curve (AUC), 95%
confidence intervals (CI's) and p-values for the univariate models are reported. All AUC's and 95% CI's for ULR were determined using bootstrapping techniques with 2000 iterations, with only the statistically significant results reported. Further assessment between MSE-Ci values and dichotomized outcomes was conducted using multi-variable logistic regression (MLR) models, adjusting for baseline admission

characteristics. Finally, MLR models assessing MSE-Ci and outcomes were created adjusting for admission characteristics as well as ICP and PRx.

Results:

Patient Population

A total of 160 patients met the inclusion criteria of having at least 72 hours of high-resolution physiology and a recorded 6 month GOSE. The median age was 49 years (IQR: 29 to 62), with 128 (80.0%) being male. The median admission GCS total and motor sub-scores were 6 (IQR: 3 to 9) and 4 (IQR: 1 to 5), respectively. The median admission Marshall CT grade was 4 (IQR: 2 to 6), with 27 (16.9%) and 23 (14.4%) patients have a history of pre-hospital hypoxia and hypotension, respectively. Twenty-eight (17.5%) and 15 (9.4%) patients presented with bilaterally fixed and unilaterally fixed pupils, respectively. Appendix A outlines the patient demographics and physiologic characteristics between dichotomized outcome groups: Alive/Dead and Favourable/Unfavourable.

Entropy Differences Between Outcome Groups – Mann-Whitney-U/Chi-Square Testing

SampEn was determined for scales 1 through 20 for each patient. In order to determine if there was a difference between SampEn for dichotomized outcome groups, we generated population based descriptive error bar plots for: HR, MAP, ICP and AMP. Figure 1 provides the error bar plots for SampEn vs. Scale for Alive versus Dead patient cohorts, whereas Figure 2 provides these error bar plots for Favourable vs. Unfavourable patient cohorts. In general, across the population, those falling into dead or unfavourable categories at 6 months post-injury displayed lower SampEn compared to alive and

favourable outcome patients, regardless of the scale used. This suggests that more rigid cardiovascular (ie. HR and MAP) and cerebral (ie. ICP and AMP) systems are associated with worse outcomes in adult TBI.

*Figure 1 here

*Figure 2 here

To explore this relationship between signal complexity and dichotomized outcomes further, we analyzed differences in MSE-Ci using Mann-Whitney-U. Table 1 provides the comparison of physiologic variables between dichotomized outcome groups, with p-values for Mann-Whitney-U testing reported.

Differences between admission demographic variables can be seen in Appendix A of the supplementary materials. In keeping with other studies from the CENTER-TBI high-resolution data set, elevated mean ICP ($p<0.0001$), AMP ($p=0.002$) and PRx ($p=0.002$), were associated with death at 6 months.[25,30] Similar relationships were not found for association with unfavourable 6-month outcomes. Evaluating MSE-Ci in association with mortality at 6-months, lower HR MSE-Ci (7.3 (IQR 5.4 to 10.2) vs. 5.1 (IQR 3.1 to 7.0); $p=0.002$), lower ICP MSE-Ci (11.2 (IQR 7.5 to 14.2) vs. 7.3 (IQR 6.1 to 11.0); $p=0.009$) and lower AMP MSE-Ci (10.9 (IQR 8.0 to 13.7) vs. 8.7 (IQR 6.6 to 11.0); $p=0.022$), were associated with death. Similarly, lower HR MSE-Ci (8.0 (IQR 6.2 to 10.9) vs. 6.2 (IQR 3.9 to 8.7); $p=0.003$) and lower ICP MSE-Ci (11.4 (IQR 8.6 to 14.4) vs. 9.2 (IQR 6.0 to 13.5)), were associate with unfavourable outcome.

*Table 1

Association of MSE with Dichotomized Outcomes – Logistic Regression Analysis

Employing logistic regression techniques, we then further evaluated the association between MSE-Ci values and 6-month dichotomized outcomes. Table 2 provides the results of univariate logistic regression analysis for MSE-Ci variables, in association with both dichotomized outcomes.

Supplementary Appendix B provides the univariate logistic regression analysis results for the admission demographics and cerebral physiologic metics. In keeping with the Mann-Whitney-U testing, HR MSE-Ci and ICP MSE-Ci were found to be statistically associated with both 6-month dichotomized outcomes.

Creating MLR models, adjusting for admission age, pupillary status and GCS motor score, only HR MSE-Ci variables remained statistically significant in association with 6-month dichotomized outcomes (AUC 0.674, 95% CI 0.550-0.786 , p=0.003; AUC 0.607, 95% CI 0.516-0.699, p=0.014; for alive/dead and
favourable/unfavourable outcome respectively). Similarly, evaluating MLR models adjusting for admission characteristics and both mean ICP and PRx, only HR MSE-Ci remained statistically significant in association with favourable/unfavourable outcome at 6-months (AUC 0.630, 95% CI 0.541-0.7171, p=0.034).

*Table 2 here

Correlations Between MSE and Cerebral Physiology

Using the first 72 hours of recorded data, we compared MSE-Ci variables to cerebral physiologic variables over that time period using Pearson linear correlation coefficients. HR MSE-Ci displayed a weak negative correlation with % time with ICP above 20 mmHg (r= -0.284, p=0.0003) and ICP above 22 mmHg (r= -0.262, p=0.0008). MAP MSE-Ci displayed weak negative correlations with: % time with ICP above 20 mmHg (r= -0.167, p=0.03), ICP above 22 mmHg (r= -0.184, p=0.02), PRx above 0 (r= -0.226, p=0.004), PRx above +0.25 (r= -0.170, p=0.03), and PRx above +0.35 (r= -0.166, p=0.04). ICP MSE-Ci displayed weak negative correlations with: % time with PRx above 0 (r= -0.178, p=0.02), PRx above +0.25 (r= -0.161, p=0.04), and PRx above +0.35 (r= -0.161, =0.04). Finally, AMP MSE-Ci displayed weak negative correlations with: % time with ICP above 20 mmHg (r= -0.168, p=0.03) and % time with ICP above 22 mmHg (r= -0.198, p=0.01). No statistically significant correlation was identified between RAP or RAP AUC measures and MSE-Ci metrics.

Discussion:

Through exploration of the CENTER-TBI high-resolution ICU cohort, we have provided some confirmatory multi-center findings regarding signal complexity and outcome. Such findings are some of the worlds first in a multi-center prospectively collected high-resolution data set in TBI. With our cohort considered one of the largest currently available. First, in keeping with some of the retrospective literature on the topic, a decrease in entropy seen in HR and ICP, was associated with both mortality and unfavourable 6-month outcomes.[3,14,16] This was confirmed through Mann-Whitney-U testing and logistic regression analysis. These differences in entropy between alive/dead and favourable/unfavourable outcome groups was also seen in the descriptive error bar plots of SampEn vs. Scale. The association

with decreased entropy and outcome was preserved for HR MSE-Ci, when adjusting for baseline admission characteristics. These findings provide multi-center confirmation that decreased entropy, signifying increased system rigidity, in both the cardiovascular system (ie. HR) and cerebrovascular system (ie. ICP – a surrogate of pulsatile cerebral blood volume), is linked with poor outcome. This likely reflects both the cardiovascular and cerebrovascular systems inability to compensate for further perturbation or insult. We must acknowledge, this concept of different organ/homeostatic systems
becoming more "rigid", lacking compensatory capacity, and this being linked with global outcome is theoretical at this point. The existing literature on systemic physiology and signal complexity points to worse outcomes with lower entropy values in individual measures.[1,4,7–11,36] This suggests that as signal complexity decreases, signifying a more rigid system mathematically, that this is associated with worse outcome. The cardiovascular literature is robust in this area, where metrics such as HR or pulse pressure variance/complexity are strong predictors of outcome in many pathologies.[8,10,11] Similarly, some preliminary results in TBI literature suggest the same regarding HR and ICP data.[4,7,14,18] Our findings
suggest that both HR and ICP signal complexity may be important in prognostication in moderate/severe TBI. The exact relationship between the two is still unclear and remains speculative. They could represent separate distinct systems, whose signal complexity are independently related to global outcome in TBI. Yet, more likely is that they are closely inter-linked, with intra-cranial changes impacting cardiovascular changes, as a function on ongoing secondary insult after-TBI.[14] Autonomic dysfunction in TBI as a result of primary and secondary injuries, may be an example of such a driving mechanism linking intra-cranial and cardiovascular signal complexities.[2,12,13] Much further work in this area is required, and we merely pose the theory of a multi-system aspect to signal complexity and outcome association.

Second, decreased AMP MSE-Ci was also found to be associated with death on Mann-Whitney-U testing. These findings, however, were not supported through logistic regression analysis. This association suggests the decreased complexity in a signal known to be associated with cerebral compensatory

reserve, is associated with mortality. AMP is known to reflect aspects of cerebral compensatory reserve, and is utilized in the derivation of indices which measure aspects of compensatory reserve, such as RAP.[17,33,34,37] Thus, decreased entropy of AMP, which may reflect increased rigidity in the compensatory reserve system, appears to be associated with mortality. This preliminary finding is in parallel to the association seen between worse RAP and compensatory reserve weighted ICP values, and outcome in TBI.[33,34] Though it must be emphasized, these results for AMP MSE-Ci do require substantial validation, and reducing such complex systems into single entropy measures may be too simplistic.

Third, comparing the strength of association between MSE-Ci variables and the dichotomized outcomes via logistic regression analysis, the overall AUC and 95% CI's for the MSE-Ci variables were quite similar to the individual standard IMPACT and CT variables (see Appendix B). Furthermore, compared to the raw physiologic metrics, the AUC and 95 CI's were also of similar magnitude to known outcome associates in TBI, such as ICP and PRx. Though it must be acknowledged, that they were not statistically different on comparison. Thus, the role for MSE-Ci variables in the development of more complex prognostic models in moderate/severe TBI remains unclear, as the benefit above and beyond standard TBI demographic and physiologic metrics has yet to be shown. With that said, much further work is required in the area of physiologic signal complexity and its role in prognostication. As such, the results here should be considered preliminary/exploratory and interpreted with caution.

Fourth, in this particular cohort, MAP entropy was neither associated with outcome or found to be significantly different between outcome groups. This likely reflects the tight MAP control, and active treatment of MAP/CPP throughout the course of the patient's ICU care. These findings are in contradiction to recent descriptions of the association between variability ABP data and both patient outcome, where such prior work suggests a link between decreased variance/complexity in ABP and both worse global outcome.[14,16] Further work on the association between MAP signal complexity and both outcome and physiologic correlates in TBI is required.

Finally, various understandable physiologic correlations were seen with MSE-Ci variables. A correlation between increased % time spent with ICP above 20 and 22 mmHg, and decreased HR MSE-Ci, MAP MSE- Ci and AMP MSE-Ci. This suggests that as ICP becomes progressively higher, signal complexity in both the cardiovascular (ie. HR and MAP) and cerebral compensatory reserve systems (ie. AMP) appear to decrease, reflecting increased rigidity. Similarly, increased PRx values were correlated with decreased HR MSE-Ci, MAP MSE-Ci and ICP MSE-Ci. This suggests that as cerebrovascular reactivity worsens, both the cardiovascular (ie. HR and MAP) and cerebrovascular (ie. ICP – surrogate measure of pulsatile cerebral blood volume) systems become less complex, and more rigid. Such findings are in keeping with previous approximate entropy, MSE and ICP/blood-pressure variability work done in moderate/severe TBI.[3,14,16–18]

Clinically, MSE calculations for various aspects of the cardiovascular and cerebrovascular systems may prove valuable in prognostic modelling. Quantifying objectively individual body systems ability to accommodate perturbations, would serve invaluable both in long-term prognostication, but also in short term outcome an physiologic prediction. It is possible that information gleaned from MSE estimations may allow for more acute prediction and modelling of physiology "state" during the acute phase of ICU stay. Such advanced modelling may allow for the prediction of those more likely to fail medical management and be in need of more aggressive measures, such a decompressive craniectomy or application of therapeutic hypothermia. Much further work in this area is required.

Limitations

Despite the promising findings, there are some important limitations which deserve highlighting. First, our cohort is one of the largest prospectively collected multi-center data sets with high-frequency digital physiology in TBI, making it uniquely positioned to investigate many question in TBI physiology.

However, despite the advantages of our data set, we must acknowledge we have only 160 patients with a minimum of 72 hours of recordings and a recorded 6-month outcome. Thus, the strength of conclusions that can be drawn from this work remains limited. It supports the need for ongoing multi- center collaborative efforts in high-resolution physiological monitoring. Second, patients underwent active treatment during their ICU stay which may all conceivably impact on homeodynamic physiologic integrity. As such, the recorded physiology does not necessarily reflect the natural physiologic history of TBI. Such recordings may have been influenced by therapeutic measures, impacting the derived entropy measures seen. The impact of therapeutic intensity on system entropy in TBI is a field which requires much further investigation. Fourth, the strength of relationships between MSE-Ci and other recorded cerebral physiologic variables, may not represent true weak correlations, but may suggest non-linear relationships between such complex physiology signals. Such non-linear analytics were not performed in this analysis, and do need to considered in future investigations. Future work could benefit from not only non-linear time-series approaches, both uni- and mulit-variate, but also through the application of machine learning classification techniques. This work is planned as part on ongoing European and Canadian collaborative effects in TBI physiology.[38–40] Finally, the results here must be considered preliminary and exploratory in nature. The field of signal entropy in in TBI is in its infancy. The utility of such metrics in the bedside care of moderate/severe TBI patients remains unknown at this time.

Conclusions:

Decreased MSE in HR and ICP is associated with mortality and unfavourable outcome at 6-months in moderate/severe TBI. Decreased AMP MSE may be associated with mortality. Increased ICP correlates with a reduction in HR, MAP and AMP MSE, whereas increased PRx correlates with decreased HR, MAP and ICP MSE. These findings suggest that a reduction in cardiovascular and cerebrovascular system

entropy is associated with worse outcomes. The possible pathophysiological alterations underlying this association deserve to be explored. Further work in the field of signal complexity in TBI multi-modal monitoring is required.

Disclosures:

Data used in preparation of this manuscript were obtained in the context of CENTER-TBI, a large collaborative project with the support of the European Union 7th Framework program (EC grant 602150). Additional funding was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (USA) and from Integra LifeSciences Corporation (USA).

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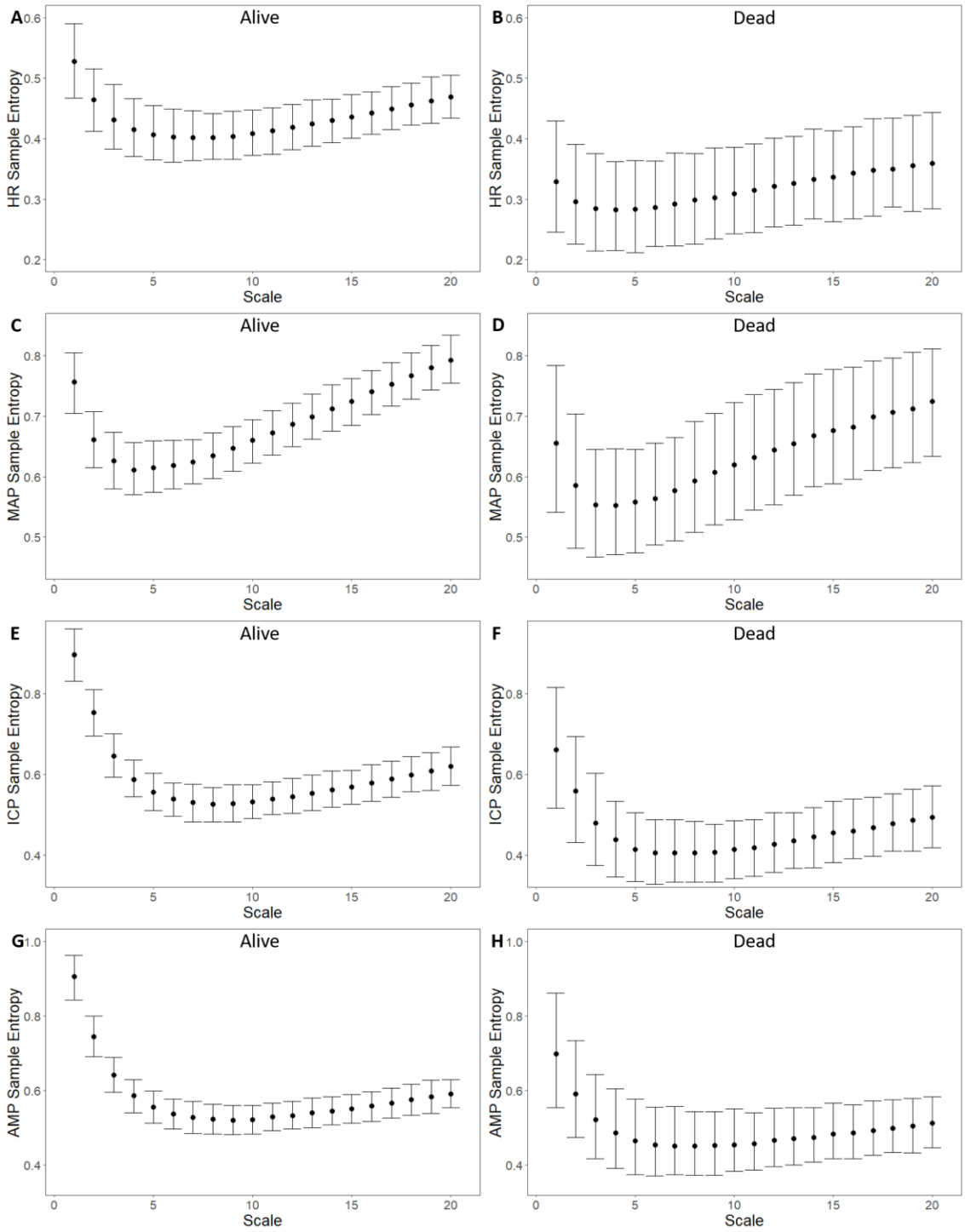
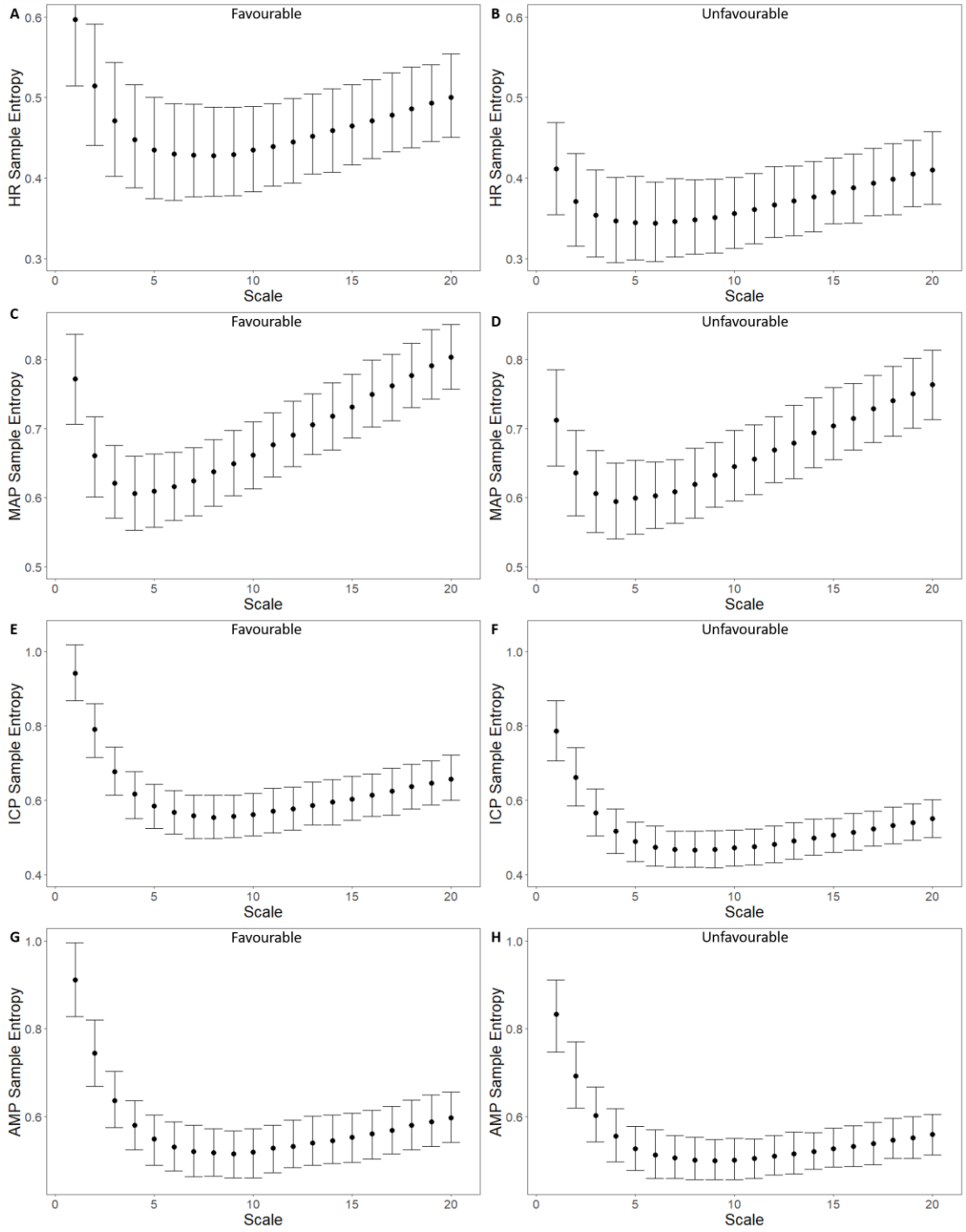
Figure Legends:

Figure 1: Sample Entropy vs. Scale – Population Error Bar Plots for HR, MAP, ICP and AMP – Alive/Dead Cohorts



AMP = pulse amplitude of ICP, HR = heart rate, ICP = intracranial pressure, MAP = mean arterial pressure. Panel A – HR Sample Entropy vs. Scale Alive Cohort, Panel B – HR Sample Entropy vs. Scale Dead Cohort, Panel C – MAP Sample Entropy vs. Scale Alive Cohort, Panel D – MAP Sample Entropy vs. Scale Dead Cohort, Panel E – ICP Sample Entropy vs. Scale Alive Cohort, Panel F – ICP Sample Entropy vs. Scale Dead Cohort, Panel G – AMP Sample Entropy vs. Scale Alive Cohort, Panel H – AMP Sample Entropy vs. Scale Dead Cohort.

Figure 2: Sample Entropy vs. Scale – Population Error Bar Plots for HR, MAP, ICP and AMP – Favourable/Unfavourable Cohorts



AMP = pulse amplitude of ICP, HR = heart rate, ICP = intracranial pressure, MAP = mean arterial pressure. Favourable = Glasgow Outcome Scale Extended score of 5 or higher, Unfavourable = Glasgow Outcome Scale Extended score of 4 or less. Panel A – HR Sample Entropy vs. Scale Favourable Cohort, Panel B – HR Sample Entropy vs. Scale Unfavourable Cohort, Panel C – MAP Sample Entropy vs. Scale Favourable Cohort, Panel D – MAP Sample Entropy vs. Scale Unfavourable Cohort, Panel E – ICP Sample Entropy vs. Scale Favourable Cohort, Panel F – ICP Sample Entropy vs. Scale Unfavourable Cohort, Panel G – AMP Sample Entropy vs. Scale Favourable Cohort, Panel H – AMP Sample Entropy vs. Scale Unfavourable Cohort.

Table 1: Summary of Patient Physiology Based on Alive/Dead or Favourable/Unfavourable Outcome Groups – Mann-Whitney-U Testing

Variable	**Median Value (IQR)**		**p-value**	**Median Value (IQR)**		**p-value**
	Alive (n=129)	**Dead (n=31)**		**Favourable (n=67)**	**Unfavourable (n=93)**	
Mean HR (beats/min)	73.3 (62.4 to 83.8)	71.7 (62.8 to 82.7)	0.914	71.0 (62.0 to 79.9)	73.6 (63.6 to 83.8)	0.328
MAP (mmHg)	81.9 (75.3 to 88.8)	85.1 (81.2 to 90.1)	**0.028**	83.1 (78.0 to 89.8)	83.2 (75.6 to 88.8)	0.597
Mean ICP (mmHg)	12.6 (9.4 to 14.3)	17.3 (12.0 to 22.2)	**<0.0001**	12.6 (9.6 to 14.9)	13.1 (10.4 to 17.60	0.180
Mean AMP (mmHg)	2.0 (1.4 to 2.8)	3.1 (2.0 to 4.9)	**0.002**	1.9 (1.5 to 2.7)	2.3 (1.4 to 3.2)	0.365
Mean CPP (mmHg)	69.5 (64.5 to 75.6)	67.2 (58.7 to 74.4)	0.174	72.5 (64.8 to 76.9)	67.8 (63.3 to 75.0)	0.060
Mean PRx (a.u.)	-0.022 (-0.134 to 0.096)	0.135 (-0.078 to 0.410)	**0.002**	-0.017 (-0.121 to 0.047)	0.020 (-0.150 to 0.189)	0.161
Compensatory Reserve Variables						
Mean RAP (a.u.)	0.749 (0.581 to 0.842)	0.720 (0.512 to 0.802)	0.256	0.787 (0.606 to 0.845)	0.723 (0.533 to 0.829)	0.086
RAP AUC Above 0	3008.6 (2443.0 to 3487.7)	2608.5 (2103.0 to 3219.1)	0.091	3010.2 (2481.1 to 35050.2)	2904.2 (2211.7 to 3315.9)	0.199
RAP AUC Above +0.4	1483.0 (1041.9 to 1838.6)	1184.8 (745.9 to 1658.9)	0.095	1538.8 (1076.7 to 1874.2)	1398.9 (832.6 to 1759.0)	0.104
% Time Above Threshold Variables						
% Time with ICP Above 20 mmHg	3.2 (0.8 to 9.7)	14.4 (3.1 to 61.6)	**0.0002**	2.6 (1.1 to 8.3)	4.4 (0.8 to 20.3)	0.327
% Time with ICP Above 22 mmHg	1.7 (0.4 to 5.0)	7.7 (1.9 to 44.0)	**0.0001**	1.9 (0.6 to 4.0)	2.3 (0.4 to 12.5)	0.318
% Time with CPP Below 60 mmHg	11.1 (3.3 to 34.5)	11.1 (3.8 to 57.2)	0.251	7.1 (3.0 to 30.7)	18.5 (4.4 to 40.3)	0.053
% Time with CPP Above 70 mmHg	47.5 (22.6 to 71.7)	37.0 (12.1 to 71.0)	0.300	57.7 (22.1 to 78.6)	37.0 (20.1 to 67.5)	0.082
% Time with PRx Above 0	44.9 (31.6 to 59.1)	67.2 (39.8 to 85.2)	**0.002**	44.5 (33.7 to 53.2)	49.1 (31.6 to 71.0)	0.157

% Time with PRx Above +0.25	21.9 (13.7 to 32.1)	34.7 (17.8 to 71.2)	**0.002**	22.1 (13.8 to 28.8)	25.0 (13.9 to 44.4)	0.156

% Time with PRx Above +0.35	16.3 (9.0 to 23.6)	25.0 (12.8 to 63.4)	**0.0009**	16.4 (9.2 to 20.8)	17.7 (9.7 to 34.0)	0.125
MSE-Ci Variables						
HR MSE-Ci	7.3 (5.4 to 10.2)	5.1 (3.1 to 7.0)	**0.002**	8.0 (6.2 to 10.9)	6.3 (3.9 to 8.7)	**0.003**
MAP MSE-Ci	12.9 (9.9 to 16.2)	11.7 (8.1 to 14.6)	0.189	13.0 (10.5 to 15.6)	12.0 (9.0 to 16.2)	0.385
ICP MSE-Ci	11.2 (7.5 to 14.2)	7.3 (6.1 to 11.0)	**0.009**	11.4 (8.6 to 14.4)	9.2 (6.0 to 13.5)	**0.017**
AMP MSE-Ci	10.9 (8.0 to 13.7)	8.7 (6.6 to 11.0)	**0.022**	10.2 (8.1 to 13.4)	10.1 (7.2 to 13.0)	0.449

a.u. = arbitrary units, ABP = arterial blood pressure, AMP = pulse amplitude of ICP, RAP AUC = area under RAP over time curve, CPP = cerebral perfusion pressure, HR = heart rate, ICP = intra-cranial pressure, IQR = inter-quartile range, MAP = mean arterial pressure, mmHg = millimeters of Mercury, MSE = multi-scale entropy, MSE-Ci = MSE complexity index, PRx = pressure reactivity index (correlation between ICP and MAP), RAP = correlation between AMP and ICP Note: all bolded p-values are those <0.05 when comparing the variables between Alive/Dead and Favourable/Unfavourable outcome groups. Favourable = Glasgow Outcome Scale of 5 to 8, Unfavourable = Glasgow Outcome Scale of 1 to 4.

Table 2: Univariate Logistic Regression Analysis – Multi--Scale Entropy (MSE) and Dichotomized 6-Month Outcome

Model	**AUC A/D (95% CI)**	**AIC**	**p-value**	**AUC F/U (95% CI)**	**AIC**	**p-value**
HR MSE-Ci	0.679 (0.560-0.783)	154.2	**0.017**	0.636 (0.550-0.720)	215.6	**0.019**
MAP MSE-Ci	0.576 (0.458-0.691)	159.8	0.221	0.540 (0.452-0.630)	221.1	0.500
ICP MSE-Ci	0.652 (0.542-0.749)	154.2	**0.012**	0.611 (0.520-0.697)	215.6	**0.016**
AMP MSE-Ci	0.633 (0.525-0.735)	158.0	0.076	0.535 (0.444-0.623)	221.0	0.471

A/D = alive/dead, AMP = pulse amplitude of ICP, AIC = Akaike Information Criterion, AUC = area under the receiver operating curve, CI = confidence interval, F/U = Favourable/Unfavourable outcome (ie. Favourable = Glasgow Outcome Scale of 5 to 8; Unfavourable = Glasgow Outcome Scale of 1 to 4), HR = heart rate, ICP = intra-cranial pressure, MAP = mean arterial pressure, MSE = multi-scale entropy, MSE-Ci = MSE complexity index.