

Full title: Early asymmetric cardio-cerebral causality and outcome after severe traumatic brain injury

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Running title: Cardio-cerebral causality and TBI outcome

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ABSTRACT

The brain and heart are two vital systems in health and disease, increasingly recognised as a complex, interdependent network with constant information flow in both directions. After severe traumatic brain injury (TBI), the causal, directed interactions between the brain, heart and autonomic nervous system have not been well established. Novel methods are needed to probe unmeasured, potentially prognostic information in complex biological networks that are not revealed via traditional means. In this study, we examine potential bi-directional causality between intracranial pressure (ICP), mean arterial pressure (MAP) and heart rate (HR) and its relationship to mortality in a 24-hour period early after TBI. We applied Granger causality (GC) analysis to cardio-cerebral monitoring data from 171 severe traumatic brain injury patients admitted to a single neurocritical care center over a ten-year period. There was significant bi-directional causality between ICP and MAP, MAP and HR, ICP and HR in the majority of patients ($p < 0.01$ in 86-97%). MAP influenced both ICP and HR to a greater extent (higher GC, $p < 0.00001$), but there was no dominant unidirectional causality between ICP and HR ($p = 0.85$). Those who died had significantly lower GC for ICP causing MAP and HR causing ICP ($p = 0.006$ and $p = 0.004$ respectively) and were predictors of mortality independent of age, sex and traditional intracranial variables (ICP, cerebral perfusion pressure, GCS and PRx). Examining the brain and heart with GC-based features for the first time in severe TBI patients has confirmed strong interdependence, and reveals a significant relationship between select causality pairs and mortality; these results support the notion that impaired causal information flow between the cerebrovascular, autonomic and cardiovascular systems are of central importance in severe TBI.

Keywords: granger causality, traumatic brain injury, outcome, network, complexity

INTRODUCTION

Traumatic brain injury (TBI) continues to be a debilitating, multi-systems disease of the young¹, characterised by a cascade of host responses and physiological perturbations on the cerebral and cardiovascular systems, potentially mediated via the autonomic nervous system², in those that survive the primary insult. Yet, our ability to alter the evolution of secondary injury continues to be restricted by how we interpret the limited information available to us in relation to pathophysiology. There is a growing body of evidence that individual biological systems likely represent a complex network of hidden, unmeasured 'hubs' with dynamic interdependence that ensures homeostasis in health, and stability after acute injury³⁻⁷. Recent work has characterised the functioning of the individual autonomic², cardiovascular and cerebrovascular⁸ systems after acute brain injury, but this may not reveal the full picture regarding disease severity and the health of the system. Increasingly, more attention is being paid to connectivity and information flow between these systems⁹⁻¹¹, yet a multi-systems approach in TBI, where physiological perturbations manifest extra-cranially, has yet to be fully explored.

An understanding of physiology in terms of information exchange within a network is key to understanding the fluctuations and instability we observe in physiological parameters- something that is known to vary with disease. The traditional view of homeostasis sees physiological stability in the face of external perturbation, achieved by an integrative negative feedback system. In such a model, the healthy state should be characterised by stability of measured physiological parameters with any fluctuations resulting from exogenous influence. Conversely, physiological instability would be expected to result from failure of homeostasis. This viewpoint is increasingly recognised as incomplete. In fact, fluctuations in physiological measurements such as heart rate and blood pressure are ubiquitous in health. The loss of variability ("decomplexification") is a characteristic of disease, rather than an indication of healthy physiological stability. Physiological decomplexification

is seen in a number of diseases^{12,13}, in situations of physiological challenge¹⁴ and can be an early predictor of outcome after TBI⁸. Given that such physiological fluctuations are present in health and reduced in disease, they must arise internally by some physiological mechanism rather than through exogenous influence. A more appropriate description may be that of homeokinetics- a concept borrowed from the physics of complex systems which suggests that functional equilibrium is a result of dynamic rather than static processes¹⁵. Spontaneous fluctuations are now famously known to arise spontaneously in complex networks^{16,17} and it is highly plausible that this may be the case in physiological systems, which consist of a large number of interacting biological sub-systems. Temporal self-similarity ('scaling') is characteristic of such networks seen also in physiological fluctuations¹⁸ varying in both chronic disease¹⁹ and under acute physiological or pharmacological perturbation¹⁴. It is the connectivity of such networks that determines their dynamics.

A sufficiently complex network allows sufficient adaptability to 'absorb' external shocks whilst at the same time the fluctuations can allow an agile response to internal changes - exactly as is seen in physiology. Such a systems approach may give new insights into physiological control and illness, but unfortunately the detailed biological subsystems are too numerous to be measured. However, in the setting of TBI, signals such as heart rate (HR), mean arterial pressure (MAP), and intracranial pressure (ICP), are likely superficial surrogates of these hidden subsystems; connectivity in the underlying biological system may be reflected as causal connectivity between the recorded signals.

Granger causality (GC) has been widely used since its introduction by Granger in the 1960s, as a statistical tool for directed, functional connectivity and causal inference, initially in economics²⁰, but now increasingly well-established in neuroscience and neuroimaging primarily within the brain through MEG/EEG or fMRI^{21,22}. With time-series variables, it provides an estimation of information transfer and the 'cause-and-effect' relationship between two variables with minimal assumptions of the underlying physical mechanisms²¹. Some have looked at the cardio-respiratory system causality²³ and cardio-cerebral interactions reflecting central modulation of ANS outflow¹⁰. Studies involving TBI

patients have been limited to EEG/MEG signal analysis showing network connectivity disruption^{24,25}, and after spinal cord injury²⁶ and subarachnoid hemorrhage⁷. This study uses Granger causality analysis to explore evidence of inter-connectivity between the cerebrovascular, cardiovascular and autonomic systems using routinely measured surrogate signals (ICP, MAP, and HR) in a large cohort of 171 severe TBI patients, and evaluate possible biological significance by relating it to outcome as a proxy for disease severity and likely network impairment.

METHOD

Patient selection and data acquisition

Data recordings from patients admitted to the Neurosciences and Trauma Critical Care Unit (NCCU) at Cambridge University Hospitals, Cambridge UK after severe head injury between 2002 and 2012 were examined for retrospective analysis. An intraparenchymal probe was placed as per departmental clinical protocol for the recording of ICP (Codman & Shurtleff Inc., MA, USA). Invasive blood pressure was recorded from an indwelling radial artery catheter and HR was derived from routine cardiac monitoring. All signals were continuously sampled using ICM+ software (Cambridge, UK, <http://www.neurosurg.cam.ac.uk/icmplus>) at a frequency between 30 to 200 Hz. In order to suppress pulse and respiratory waves to focus entirely on the slow fluctuations of ICP, we subsequently re-sampled the signals by averaging over ten second epochs.

Total data recording length varied between patients from <1 hour to 14 days. We were particularly interested in those that had time for the disease process to evolve. As such, only those with at least 72 hours recording of ICP, MAP and HR along with the Glasgow Coma Scale (GCS), and Glasgow Outcome Scale (GOS) were selected. For the time period specified, 198 patient recordings were accessed. Those known to have more than 2-hour gaps (n = 10) and over 24 hours from ictus at the time of admission (n = 17) were excluded. 171 patients entered our analysis. Since recordings in the

first 24 hours tended to be either incomplete due to surgical intervention or confounded by artefacts due to sedation holds in apparently less severely injured patients, we selected the second 24 hours period for our analysis. All were sedated, mechanically ventilated and managed according to a cerebral perfusion pressure (CPP) orientated protocol²⁷ during their stay in critical care. Data collection and analysis was approved by institutional review. The pressure reactivity index (PRx), a moving Pearson correlation between ICP and MAP, was additionally calculated as a measure of cerebral autoregulation.

Conditional Granger Causality Analysis

Assuming that variable X and variable Y are the measured time courses of two physiological signals, bivariate Granger causality quantifies the ability of unique past information in one of the time series in predicting future values of the other. Specifically, if incorporating past values of X improves the prediction of the current value of Y, one says that X Granger-causes Y. The causal information flow between three time-series variables, ICP, MAP, and HR, required a multivariate extension, often referred to as 'conditional' Granger causality analysis (GCCA)²⁸. For example, GCCA could infer a causal relationship from MAP to ICP only if past information in the MAP helped predict future ICP, after taking into account the influence of HR. Mathematical theory behind GC is described extensively elsewhere^{20,29,30}. We used the code published by Seth *et al* implemented in MATLAB^{31,32} (R2014a, MathWorks Inc. Natick, Massachusetts, United States). GC values were derived from a 24-hour recording period with 8640 data points recorded in parallel for ICP, MAP, and HR. Data was scrutinized for covariance stationarity and normalized to zero mean/unit variance by following the Box and Jenkins differentiation approach³³. The optimal model order was obtained during the regression analysis using the Akaike Information Criteria³⁴. With the model residuals, an *F*-statistic was calculated with $p < 0.01$ used as threshold for significance of causal interaction after appropriate Bonferroni correction. 6 output variables were grouped into 3 pairs to reflect extent of bi-directional

causal information flow: Pair 1 (ICP-to-MAP and MAP-to-ICP); Pair 2 (ICP-to-HR and HR-to-ICP); Pair 3 (MAP-to-HR and HR-to-MAP).

Statistical analysis

Statistical analysis was undertaken using IBM SPSS Statistics for Macintosh, Version 21.0. The PRx, mean values for ICP, CPP, MAP, and HR and GC for 171 patients over 24 hours were computed. Outcome was assessed at 6 months after head injury using Glasgow Outcome Scale³⁵. Groups were dichotomised into survival versus death, as well as favourable versus unfavourable outcome (good recovery or moderate disability versus severe disability or death). Interval data are expressed as mean \pm SD or 95% confidence interval, or median with interquartile range, and compared with one-way ANOVA, or Kruskal-Wallis non-parametric testing as appropriate. Categorical data were compared using chi-squared testing. Paired-sample Wilcoxon signed rank test was used to compare the mean GCs between pairs of variables (e.g. Pair 1: ICP-to-MAP vs MAP-to-ICP). The Mann-Whitney *U*-test (2 groups) and Kruskal-Wallis test (for > 2 groups) were used to compare the GC between outcome groups. Pearson's correlation was used to examine correlation between continuous variables. A multivariable logistic regression model was used to identify independent predictors for the dichotomised outcomes. Variables were normalised as appropriate if found not to follow a normal distribution before inclusion in the logistic regression model. $P < 0.05$ was chosen to represent a significant difference. All statistical tests were two-tailed and correction for multiple comparisons was made.

RESULTS

Patient demographics

From Table 1, 171 patients were included in the study; 129 patients were male (75.4%) and 42 were female (24.6%). The average age was 38.1 ± 15 . Based on the initial post-resuscitation Glasgow Coma Scale, 107 (62.6%) sustained severe head injury ($GCS \leq 8$). At six months post injury, 131 (76.6%) survived and 40 (23.4%) died.

Establishing directional causality

Table 2 shows GC values (mean \pm SD). There is significant causality in both directions between variable pairs, where the threshold was set at $p < 0.01$ (no significant change at the $p < 0.05$ level). Over 94% of patients for pairs 1 (ICP and MAP) and 3 (MAP and HR) variables, and 86.5% of patients for pair 2 (ICP and HR) variables; this was significantly lower than other pairs (McNemar's test; $p < 0.05$).

Pairs 1 and 3 showed significant asymmetry in GC magnitude. Figure 1 visually depicts the causal interaction strength and direction between ICP, MAP, and HR using GC-weighted arrows where MAP

was the dominant causal variable between MAP-to-ICP vs ICP-to-MAP ($p < 10^{-12}$) and MAP-to-HR vs HR-to-MAP ($p < 0.00001$). There was no difference between variables in pair 2, ICP-to-HR vs HR-to-ICP ($p = 0.85$).

Correlation of cardio-cerebral causality with outcome

Figure 2 shows mean and 95% confidence intervals for ICP, CPP and PRx separated by GOS outcome groups. PRx was the only traditional intracranial variable in this early monitoring period that showed significant difference across disability groups ($p = 0.039$). Those that died had a significantly more positive PRx than those that had good outcome ($p = 0.013$).

Figure 3 shows mean and 95% confidence intervals for GC variables separated by GOS outcome groups. There were significant differences between groups for ICP-to-MAP ($p = 0.008$), MAP-to-ICP ($p = 0.015$), and HR-to-ICP ($p = 0.039$) using the independent-samples Kruskal-Wallis test with correction for multiple comparisons. Those who had poorer outcome appeared to have lower GC suggesting a less connected network. Figure 4 shows GC for ICP-to-MAP ($p = 0.006$) and HR-to-ICP ($p = 0.004$) causation to also be significantly smaller in those that died compared to those who survived. While patients with 'good outcome' had significantly higher GC than all other groups for MAP-to-ICP (Figure 3), this was not seen when outcome was dichotomised for mortality. ICP-to-HR was also lower in those that died but was not significant ($p = 0.06$). There was no statistical significance found when we compared favourable and unfavourable outcome groups (dichotomisation not shown).

Cardio-cerebral causality as an independent predictor of mortality

Using multivariable logistic regression we identified age and GCS ≤ 8 and PRx as significant predictors of mortality and favourable outcome when Granger causality is excluded from analysis (Table 3, left-hand column). Again in this monitoring period ICP, CPP, MAP and HR were not significant predictors. In a forward-conditional model, we confirmed ICP-to-MAP and HR-to-ICP as independent predictors of mortality (with specificity set at 80%, sensitivity was 60% with GC and 47% without) suggesting

there is distinct information provided by GC data (Table 3, right-hand column). However, no GC variable was found to be significant predictors of favourable outcome (data not shown).

Correlation between causality and the pressure reactivity index

Only the GC for MAP-to-HR was strongly correlated with PRx (Figure 5; $r = -0.322$, $p = 0.0001$) indicating lower connectivity during impaired cerebral autoregulation (high, positive PRx). No correlation was seen between ICP-to-MAP or HR-to-ICP and PRx.

DISCUSSION

To our knowledge, this is the first study that examines how the cerebrovascular, cardiovascular and autonomic nervous systems causally interact as a complex network and its implications to outcome after severe TBI patients. The bidirectional or strong unidirectional interaction dominated by the MAP in the system, as captured by Granger conditional causality analysis, may reflect mechanisms of causal information flow between the three systems. When compared with outcome, GC for ICP-to-MAP and HR-to-ICP were significantly lower in those who died and were independent predictors of mortality unique from age, GCS, and PRx, an example of the biological consequences of disruption in network information flow.

MAP dominates as the main causal driver to ICP and HR in keeping with recent evidence⁷, and may be a reflection of abnormal vaso-reactivity and baroreceptor sensitivity following acute brain injury. When cerebral autoregulation is defective, ICP tends to correlate passively with MAP (positive PRx)³⁹. When patients were separated into those with intact (negative PRx) and those with disrupted cerebral autoregulation (positive PRx), MAP remained the dominant causal influence to ICP. The strong influence of MAP supports evidence that outcome is sensitive to individualised cerebral perfusion pressure (CPP)⁴⁰, the difference between MAP and ICP. While we found significant

differences between all GOS groups for ICP-to-MAP ($p = 0.008$) and MAP-to-ICP ($p = 0.015$), only ICP-to-MAP separated those who survived from those who died ($p = 0.006$). More severely injured patients may have had reduced capacity for cerebral influence of the cardiovascular system. Alternatively, the cardiovascular system was perhaps at the limit of its capacity in terms of trying to maintain homeostasis (either physiologically or due to need for critical care support) where no further influence was possible.

It is no surprise that MAP should influence HR, and vice versa, given the direct relationship between MAP and cardiac output (HR and stroke volume product). In response to changes in MAP, baroreceptor function provides the afferent signals in a negative-feedback circuit in the medulla that maintains MAP at normal levels. Interestingly, MAP is a significantly stronger causal inference to HR when cerebral autoregulation is intact (negative PRX) suggesting overlap in regulatory circuits in the brain for both the autonomic nervous system and the cerebral vasculature. However, no correlation was found between magnitudes of causality (between MAP and HR) with outcome in either direction. Adequate cardiovascular resuscitation in the ICU or preserved peripheral baroreceptor function may have played a role; given that recent studies have been able to show reduced cardiovascular complexity (individually for MAP and HR)⁸ and autonomic impairment² predicting poor outcome in TBI, this may not tell the entire story. While the strong inverse correlation between MAP-to-HR and PRx merits further examination, we know at least from these results that simply examining cardiovascular connectivity alone, at least in an early 24 hour period, is insufficient as a signal for outcome.

The significant bidirectional casual influence for HR and ICP (over 86% of cases), unlike for MAP and ICP did not establish one direction as dominant in terms of causal influence ($p = 0.85$). Rather than peripheral, central baroreceptor function as a mediating mechanism may be involved. There is evidence that pathological ICP after TBI alters baroreceptor function in rodents⁴¹ and humans⁴², with pathologically hemispheric lesions post stroke also impairing this important function⁴³. Extreme ICP

elevations cause severe bradycardia and systolic hypertension, by the well-known Cushing reflex. In the setting of normal pressure hydrocephalus, interdependence has been shown between ICP and the intervals between consecutive normal sinus heart beats (RR interval)³⁸. Certainly, ICP regulation has been linked to common areas such as the brainstem⁴⁴ and hypothalamus⁴⁵, areas thought to be important intracranial centres for autonomic nervous system control. A recent study in healthy volunteers using fMRI, HR and respiratory variation demonstrated a causal role of the amygdala, hypothalamus, brainstem and, among others, medial, middle and superior frontal gyri, superior temporal pole, paracentral lobule and cerebellar regions in modulating the central autonomic network using GCCA¹⁰.

The observation of HR influencing ICP may seem non-intuitive at first but we believe there may be direct and indirect mechanisms. One mechanism could be changes in HR and therefore cardiac output may briefly alter blood carbon dioxide (CO₂) levels in the cerebral vasculature, thereby influencing ICP with a time lag. Furthermore, changes in HR alters time in diastole, and hence subtly changing compartmental blood or CSF volumes. After subarachnoid hemorrhage significant causal influence from HR to ICP was found in the first 96 hours, and bi-directional causality from day 4-7⁷. Autonomic impairment, as measured by heart rate variability and baroreflex sensitivity, was shown to be independently linked to mortality after TBI². In this study, the GC was significantly lower for HR-to-ICP ($p = 0.039$) in those that died and lower for ICP-to-HR although not reaching significance ($p = 0.06$); this either reflects an underpowered study, or simply that severe TBI asymmetrically disrupts information flow such that the complex cerebrovascular system is exquisitely more sensitive to the influence of the autonomic nervous systems than vice versa.

We confirmed in a multivariate logistic regression that GC for ICP-to-MAP and HR-to-ICP were significantly lower in those who died and independent predictors of mortality unique from age, GCS, and PRx. Our findings suggest GC is revealing additional clinically important information through exploring directional information flow in TBI. This could be interpreted as a breakdown of network

behaviour and therefore explains the impaired homeokinesis and reduced fluctuations in the most seriously injured patients⁸. Despite this, a certain degree of caution is necessary when interpreting these results. In reality, one cannot establish the exact underlying mechanisms and future work is being conducted to tease out why only certain disruptions to information flow matters more to others. Moreover, the inability of GC analysis, at least at this sample size, to separate favorable/unfavorable outcome suggests the relationship to outcome may not be continuous. Both a strength and drawback to studies similar to this is the potential to provide insight into pathophysiology when there exists no ground truth regarding what is truly happening at a fundamental anatomic level to confirm one's observations, as the damaged cardio-cerebral system evolves post-ictus.

Whilst technical in nature, the emergence of connectivity analysis in complex networks may be of central importance in a multisystem disease like TBI. Much like our everyday airport systems, there are both regional and hub 'nodes', where a degree of complexity and connectivity ensures efficient flight paths i.e. information transfer. For example, poor weather at a regional node may inconvenience local travellers, but a snowstorm at a hub often leads to widespread, and crippling consequences to the entire network. In the setting of these results, we see the ICP, MAP and HR as perhaps surface-level hubs, emanating from multiple, hidden sub-networks, and only disruption to causal information flow involving the brain-specific ICP hub (ICP-to-MAP and HR-to-ICP) was significantly associated with TBI mortality. The pressure in the system (i.e. MAP) can perhaps be seen as a 'dominant' hub. While this makes physiological sense, it remains to be seen whether this is specific to TBI patients.

Clinical care of TBI patients in the ICU makes available large volume, high density, and routinely measured time-series variables. GC is a well-established methodology in the multivariable environment of quantitative neurosciences^{21,22} and this study shows it is possible to harness such data in TBI patients. However, GC is also one of many connectivity methodologies; different models

may perform better or worse but a full comparison of performance is beyond the scope of this exploratory study. Connectivity in neurosciences has been split into 'functional' and 'effective'. Functional connectivity describes statistical dependencies between variables, whether directed (Granger causality and transfer entropy)^{20,46} or undirected (correlation or coherence), whereas effective connectivity aims to frame observed data in the simplest mechanistic models, as exemplified by Dynamic Casual Modeling (DCM), which uses Bayesian networks assess model performance⁴⁷. Unlike DCM, one of the main strengths to GCCA is the minimal underlying physical assumptions required by existing as a statistical description only of the data presented; this lent itself well in our case to an initial exploration of a network of signal information flow. Certainly future work may involve DCM as a complimentary tool, with its different set of assumptions, to explore interpretations of these initial observations with GCCA⁴⁷.

These observations and clear link to mortality using conditional Granger causality analysis compels us to look further at what is left unmeasured. Longitudinal calculations in real time of the GC, with careful recording of clinical interventions and attention to the timing post-ictus are needed to correlate potential causal information flow changes with deterioration or treatment effects such as fluid resuscitation, vasoactive drugs or surgical decompression. Whether this can be used to direct intervention and improve outcome is unknown; further principled, and multimodal approaches to examine complex physiological networks may shed light on secondary injury after TBI.

LIMITATIONS

Some of the strengths of this study include the large cohort, a uniform and early time period for analysis, selection of patients with known time from ictus, at least 72 hours of monitoring, and removal of large data gaps and frequent interventions within the first 24 hours. We believe this allows potential for early clinical interventions, adds temporal information, allows secondary injuries to manifest and potentially be reflected in our analysis, and removes those with very short data recordings (due to death/futility, withdrawal of care, recovery, de-escalation of care or withdrawal of consent) with extreme values that can skew the group trends.

However, this is a retrospective, observational study where it was not feasible to control for the effects of clinical interventions (e.g. CSF drainage, medication administration, weaning from the ventilator, or the rate of disconnection based on baseline neurological status etc). There is an ongoing effort to align better clinical information in future databases, especially with the advent of electronic healthcare records. For example, a large part of the earlier data collection period was

prior to an electronic record so many patients were limited to initial presenting GCS as a marker of severity. Although all patients were monitored on a single neuro-critical care unit where therapeutic interventions were standardized, variation inevitably occurs.

The lack of a control group is also a limitation to this study. Future studies should compare our results to patients with ICP monitoring without TBI. The feasibility is a challenge since ICP monitoring is removed before the brain is fully 'normal' and ICP is much less frequently measured non-TBI cohorts. Reassuringly, both variables (ICP-to-MAP and HR-to-ICP) predicting TBI mortality involved ICP, whereas causality between MAP and HR (without ICP) had no relation to outcome. This is despite the fact that non-traditional methods examining information content (entropy) within HR and MAP time-series data have found significant correlation to poor outcome in TBI^{8,37}, while other groups have also shown this in non-TBI patients⁴⁸. Given this pattern of findings, we retain some confidence that examining causal information flow, particularly involving ICP, is specific to TBI patients.

Granger causality analysis is based on a statistical concept and is model-free; it sheds light on potential underlying mechanisms of information flow between physiological systems but requires caution when interpreting in the clinical setting. The physiological signals as measured by ICP, MAP or HR most likely reflect an ensemble of regulatory systems; any attempts at causality measurement can only reflect an 'averaging' of these individual subunits where direct and indirect paths contribute. For this reason, proof of causality from one system to another cannot be definitive. Moreover, GC can only describe data that is presented and cannot account for unmeasured variables (whether metabolic e.g. CO₂ or biochemical) that potentially affect our measured variables. This data was not available, certainly not at the same time resolution. Fortunately, Granger looks at causality over smaller timescales than our 24-hour analysis period. While it is unlikely to explain the link to mortality, is hoped that future studies will be able to account CO₂ changes over the same analysis period.

Finally, causal relationships may not be static in time. For example had ICP 'caused' MAP for the first 12 hours and then this direction reversed for the next 12 hours (assuming the same causal magnitude), no causal relationship would have been found. Reassuringly, this does mean any significant causality found in one direction may have been an underestimation. Further studies are needed to identify any transitions in directionality relation to existing treatment protocols, exploring more granular, temporal relationships, and in combination with other non-traditional markers of poor outcome.

CONCLUSION

Early causal information flow disruption between the cerebrovascular, autonomic and cardiovascular systems is selectively associated with increased mortality after severe traumatic brain injury. This was found to be independent of age, presenting Glasgow coma scale, intracranial pressure and autoregulation. Conditional Granger causality analysis for routinely measured intracranial pressure, mean arterial pressure, and heart rate signals may reflect unique unmeasured mechanisms in the setting of secondary brain injury.

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DISCLOSURES

ICM+ software (www.neurosurg.cam.ac.uk/icmplus) is licensed by Cambridge Enterprise Ltd, UK.

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