IEEE Access
Multidisciplinary | Rapid Review | Open Access Journal

Received August 5, 2021, accepted August 23, 2021, date of publication August 30, 2021, date of current version September 8, 2021.

Digital Object Identifier 10.1109/ACCESS.2021.3108636

Variations in Information Flow Patterns Following Intracranial Hypertensive Events in Traumatic Brain Injured Patients

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ABSTRACT Intracranial hypertension is an acute, life-threatening neurological condition that can lead to high risk of mortality. Its prompt identification and timely management are key to functional recovery and resuscitation of the patient. The objective of the present study is to propose quantitative measures for the early assessment of intracranial hypertensive (IH) episodes in traumatic brain injured (TBI) patients and to explore the association between intra-individual variability and IH events. To achieve this, we identified fifty-nine IH events in twelve TBI patients, and analyzed intracranial pressure (ICP), mean arterial pressure (MAP) and heart rate (HR). The notion of Granger causal (GC) analysis was adopted to quantify the bi-directional information flow patterns among ICP, MAP and HR. Additionally, the coefficient of variations of GC values was estimated to quantify intra-individual variations. The present study shows that GC values of ICP-to-MAP, MAP-to-ICP and HR-to-ICP decrease during an IH event while the GC value of HR-to-MAP increases during an IH event. Moreover, it was also observed that TBI patients show more inconsistency during ICP elevations. Our findings suggest that directional communications across cardiovascular (MAP and HR) and cerebrovascular (ICP) mechanisms are associated with the onset of intracranial hypertension. These derived GC measures may also be utilized as functional bio-markers in physiological diagnostics.

INDEX TERMS Heart rate, Granger causality, traumatic brain injury, intracranial hypertension, intracranial pressure, mean arterial pressure.

I. INTRODUCTION

Traumatic Brain Injury (TBI) is responsible for deleterious physiological insults and the worst functional outcomes. TBI is the leading cause of global deaths and disabilities [1]. It is well established that the hostile pressure gradient is the main driver of TBI, and can cause severe damage to the brain. For example, over-elevated cerebral perfusion pressure (CPP) can break down the blood-brain barrier [2]–[4] and increase vulnerability to the development of pathological conditions such as cerebral edema, transient ischemic attack, stroke, eclampsia, heart failure, aortic dissection and renal injury [5], [6]. Similarly, low CPP can result in brain ischemia and the so-called secondary brain injury after TBI [2].

The associate editor coordinating the review of this manuscript and approving it for publication was Rajeeb Dey.

To this, recent guidelines by the Brain Trauma Foundation [7] recommend CPP as a target (to be maintained between 60 and 70 mmHg) to achieve favorable outcomes for the survival of a patient. CPP, which is defined as the pressure gradient between intracranial pressure (ICP) and mean arterial blood pressure (MAP) [8], can be maintained by regulating ICP or MAP. Since MAP cannot be raised indefinitely, the maintenance of ICP at an acceptable level is crucial for TBI patients.

Cumulative evidence suggests that early episodes of intracranial hypertension (elevated ICP) following TBI increase mortality risk [9]–[12]. Therefore, it has been proposed to examine this end of the ICP spectrum while developing TBI management therapies to avoid irreversible brain damage. Having a central role in the human circulatory system, ICP homeostasis is ensured by the

complex interplay of cardiovascular and cerebrovascular control mechanisms. One of these mechanisms is named as cerebral auto-regulation, which maintains blood flow despite of changes in CPP. Under normal physiology, cerebral auto-regulation involves different processes such as metabolic, myogenic and neurogenic mechanisms [13]. For example, α-adrenoreceptors in the brain vessels cause vasoconstriction in response to systemic hypertension to keep the cerebral blood flow stable, and prevent hyperemia [13], [14]. Another control mechanism which effectively buffers acute CPP fluctuations is termed as arterial baroreflex [15]–[17].

Arterial baroreflex is arbitrated by pressure sensitive neurons such as baroreceptors. These neurons are lying in the aortic arch and carotid sinuses. The arterial baroreflex provides input to the cardiovascular centre in the medulla oblongata in response to any blood pressure (BP) swing and adjusts different sympathetic and parasympathetic activities of the central nervous system accordingly [18], [19].

Baroreflex operates as a negative feedback dynamic system. The increase in BP triggers baroreceptors inhibiting sympathetic tone and activates parasympathetic drive, which slow down heart rate for the ultimate buffering of the increase in BP [15], [20], [21]. Conversely, a drop in BP has the opposite effect and results in increasing the heart rate [16], [22], [23]. An established tool for baroreflex assessment is to examine the complex signatures of BP and HR interactions [24]. Due to the closed-loop nature of the physiological mechanisms, recent studies explore information transfer between different modules of the underlying relationships [25]. For example, multivariate autoregressive model-based GC analysis has been extensively employed to examine information transfer patterns between BP, cerebral blood flow and end-tidal CO_2 time series quantifying the human sympathetic cerebrovascular control [26]. A similar approach was adopted to quantify the dynamics of the putative Cushing reflex in cerebral hemodynamics and baroreflex control across spinal cord injured individuals by Saleem *et al.* [27].

A plethora of studies [28]–[30] investigated the physiological derangements after TBI and its neurological outcomes. For example, Doherty *et al.* [31] observed that blood-brain barrier (BBB) permeability changes after TBI, which can trigger multiple pathologic events. The BBB impairment can affect the central nervous system by initiating some adverse processes such as alteration in signaling pathways and immune infiltration [32], [33]. Dysfunction of the autonomic nervous system was also observed in TBI patients [28]. Other systemic complications observed in TBI patients are linked to neurogenic causes including cardiovascular, respiratory, haematological and inflammatory response [29]. Cardiac sequelae after TBI may be in the form of myocardial infarction, arrhythmia or ischemia [30], and respiratory complications may cause pulmonary edema. Similarly, haematological complications may develop coagulopathy and the cascaded inflammatory events after TBI can mediate systemic changes, leading to neutrophilia, fever and muscle breakdown [29].

Many studies have been conducted to examine the association of cardiovascular and cerebrovascular physiological signals with the onset of TBI in humans. However, to the authors' best knowledge, the present study is the first attempt to identify the role of intracranial hypertensive events in the baroreflex control of TBI patients. To achieve this, the notion of multivariate Granger causal analysis was adopted to quantify variations in couplings of physiological variables including BP, HR and ICP. GC values were estimated across the total of fifty-nine IH events, identified in twelve TBI patients. GC analysis provides novel physiological indices that might be adopted along with (real-time) ICP monitors for the predictive modelling of intracranial hypertension management in TBI patients. The hypothesis of the present study is firstly based on the occurrence of an IH event that can affect the relationship between cardiovascular (MAP and HR) and cerebrovascular (ICP) systems which might be explored by using GC analysis, and secondly on the association of intra-individual variability with the ICP elevation that may be measured with the coefficient of variation of GC values. The major contributions of this study are summarized as follows:

- Analyzed the role of intracranial hypertensive events in the baroreflex control of TBI patients,
- Applied GC analysis to measure the variations between physiological parameters (ICP, MAP and HR) and measured coefficient of variation for the intra-individual variability,
- Clinically significant findings to develop physiological monitors for intracranial hypertension management in the TBI patients.

The remainder of this study is divided into multiple sections. Section II describes the methodology used to analyze the data of TBI patients. Section III presents our findings while next section discusses these findings in more detail. Section V highlights clinical significance of the study and paper ends with the conclusion in Section VI.

II. MATERIALS AND METHOD

The data examined in this study were obtained from Physionet (public source) [34]. Data collection was performed in accordance with the rules and regulations of the MIT-MGH General Clinical Research Center and MIT COUHES Committee to consider human beings as experimental subjects. The detailed description of the data collection process can be found in [35]. However, a brief overview is provided here.

A. DATA COLLECTION & PRE-PROCESSING

The data contain multi-channel signal recordings of ICP, electrocardiogram (ECG) and arterial BP (ABP). Hemodynamic monitoring devices by General Electric (TRAM-rac 4A) were installed in multiple surgical intensive

care units of the Robert Wood Johnson Medical Center (RWJMC) at Rutgers State University, USA. These devices continuously record physiological time series at a sampling frequency of 50 Hz from an analog input of ±5V and the resolution of 1.41 mV (1V corresponds to 100 mmHg). An indwelling fluid-filled catheter (Arterial Line, Edwards Life Sciences Inc.) was inserted in the radial artery to monitor continuous ABP. Micro-transducers by Camino Laboratories (Camino Direct Pressure Monitor) were inserted into the frontal cranium for continuous monitoring of ICP and identification of IH regions.

IH event identification is directly associated with ICP. The high ICP value (above 25mmHg) for the consecutive 5 minutes after 60 minutes normal ICP value (below 25mmHg) was identified as an IH event in TBI patients. These IH events were identified by a self-determining event detection process, which consists of two stages. In the first stage, all the data were segmented into multiple windows of one minute each. Mean and variance of ICP signals for each window were calculated. Windows with variance greater than 50mmHg^2 were considered as artifacts and were excluded from further analysis. In the second stage, windows meeting the eligibility criteria of an IH event (ICP > 25mmHg) were selected as IH events [35].

The data were analyzed using our in-house built MATLAB (*Mathworks Inc.*) routines. The detection of IH events was done by using CHARM GUI [35]. HR was calculated from continuous ECG signals by estimating R-R peaks. Raw ABP and ICP were beat-to-beat averaged resulting in non-uniformly sampled MAP and ICP time series. These decimated time series (HR, MAP and ICP) were linearly interpolated before being re-sampled to 0.1 Hz [36].

B. GRANGER CAUSALITY

Different probabilistic and analytical techniques have been proposed to comprehend causal interactions between different physiological time series [26], [27], [37]. The basic idea of Granger causality was introduced by Wiener [38] in 1956. According to him, a time series X is said to be causal to a time series Y if Y can be better predicted by adding previous knowledge of X over and above that of Y.

Granger [39] extended this idea to formulate an autoregressive model. According to him, if the prediction error of time series Y is decreased by adding past knowledge of time series X in an autoregressive model over and above that of time series Y, X is said to have causal (driving) effect on Y.

Mathematical derivation of the above description was developed by Granger [39], and is given as follows: suppose there are two time series X and Y i.e., $X = [X(1)\ X(2)\ \ldots\ X(N)]$ and $Y = [Y(1)\ Y(2)\ \ldots\ Y(N)]$. If we want to predict Y by adding the linear combinations of its past values then we can have the following *reduced* autoregressive model,

$$Y(n) = A_{YY}(1)\,Y(n-1) + A_{YY}(2)\,Y(n-2) + \cdots + A_{YY}(M)\,Y(\text{n-M}) + \epsilon(n) \quad (1)$$

where the residual $\epsilon(n)$ is the prediction error and M is the order of an autoregressive model. If we consider previous values of both time series X and Y (X is an exogenous input), the *full* autoregressive model becomes,

$$Y(n) = A_{YY}(1)\,Y(n-1) + A_{YY}(2)\,Y(n-2) + \cdots + A_{YY}(M)\,Y(\text{n-M}) + A_{XY}(1)\,X(n-1) + A_{XY}(2)\,X(n-2) + \cdots + A_{XY}(M)\,X(\text{n-M}) + \widehat{\epsilon}(n) \quad (2)$$

where the residual $\widehat{\epsilon}(n)$ is the prediction error and M is the order of autoregressive model.

The Akaike information criterion was used for model order estimation. It states that X is said to be Granger causal to Y, denoted as $X \rightarrow Y$, if the full model given in equation 2, represents a better prediction of the data than the reduced model given in equation 1. The strength of Granger causality is determined in terms of GC value, defined as

$$F_{X\rightarrow Y} = \ln\frac{\left|\sum_{\widehat{\epsilon}}\right|}{\left|\sum_{\epsilon}\right|} \quad (3)$$

where $\left|\sum\right|$ is determinant of the residuals co-variance matrix, and $\sum_{\widehat{\epsilon}}$ and $\sum_{\epsilon}$ are co-variance matrices of autoregressive model residuals $\widehat{\epsilon}(n)$ and $\epsilon(n)$, respectively. In this study, GC values are estimated for MAP-to-ICP, ICP-to-MAP, MAP-to-HR, HR-to-MAP, HR-to-ICP and ICP-to-HR combinations.

C. COEFFICIENT OF VARIATION

Intra-subject variation is evaluated by estimating the coefficient of variation (CV), which is defined as the ratio of standard deviation (SD) to the mean of the data [40], [41] i.e.,

$$CV(\%) = \frac{\sigma}{\mu} \times 100\% \quad (4)$$

where σ is the standard deviation, and μ is the mean value of data.

D. STATISTICAL ANALYSIS

All values are reported as mean ± SD, unless otherwise stated. Normality of data was verified using Shapiro-Wilk test. The significance of difference between pre-events vs. IH events was verified using parametric dependent sample t-test. The significance of the differences between GC values of the following comparisons was also evaluated using the parametric dependent sample t-test: MAP-to-ICP vs. ICP-to-MAP, ICP-to-HR vs. HR-to-ICP, MAP-to-HR vs. HR-to-MAP. The smaller the p-value, the stronger the evidence to reject the null hypothesis, i.e. there is less than 5% probability of being correct for the null hypothesis. To stay consistent with the existing literature, the present study also adopted $p < 0.05$ to test the a-priori significance.

III. RESULTS

The data recordings of thirteen TBI patients were processed to identify IH events. These patients stayed approximately

TABLE 1. Number of IH events identified in 12 TBI patients. Subject 9 is not mentioned in the table because it was found to have no IH event.

Subject number	1	2	3	4	5	6	7	8	10	11	12	13
Number of IH events	6	16	1	1	13	3	1	3	3	4	2	6

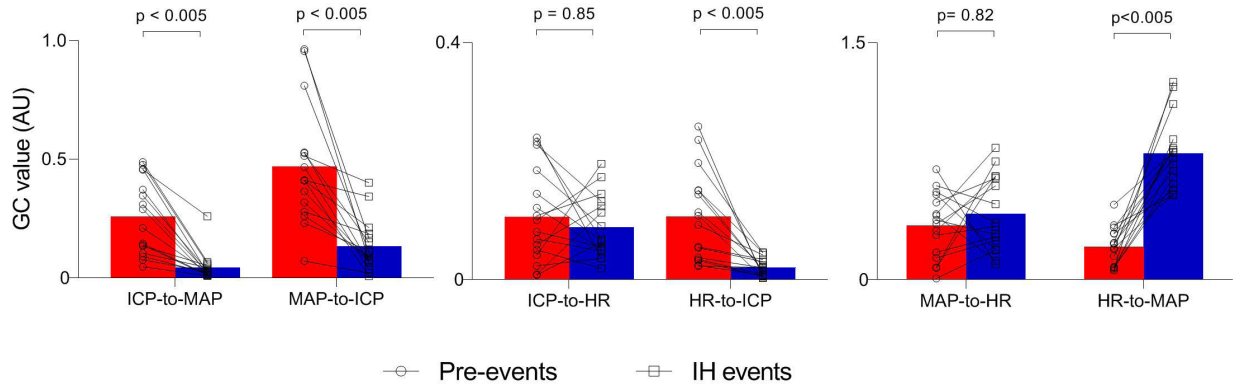

FIGURE 1. GC values estimated from sixteen events of the representative subject (subject 2) for pre-events vs. IH events. GC, Granger causal; IH, intracranial hypertensive.

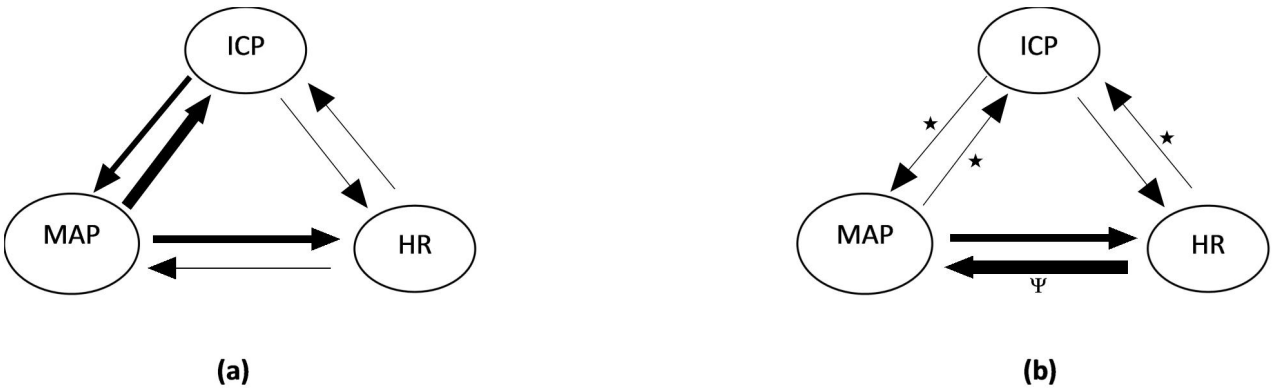

FIGURE 2. Granger causal strengths demonstrated by weighted arrows. ⋆ represents statistically significant decrease and Ψ represents statistically significant increase for (a) pre-events vs. (b) IH events. IH, intracranial hypertensive.

between 42 hours to 512 hours in the hospital. We identified IH events (event criteria defined in materials and method section) ranging from 16 IH events in subject 2 to no IH event in subject 9. The present study analyzed data recordings of only 12 TBI patients because not a single IH event was observed in subject 9. Detail of all identified and selected IH events, after rejecting some artifacts, is given in Table 1.

The data segments of five minutes were extracted before the start of every IH event in order to differentiate dynamics of IH events from that of normotensive regions. These events are named as pre-events. Herein all comparisons are given for IH events vs. pre-events. The data were divided into two groups. A subject with the highest number of IH events (subject 2 with 16 IH events) was considered as a first group that aims to explore the intra-individual variations across IH episodes while all other subjects were pooled in the second group. Group-wise description of the results is provided in the following sections.

A. GROUP 1: REPRESENTATIVE SUBJECT 2

GC values estimated from 16 events of subject 2 for both pre-events and IH events are shown in Figure 1. A significant decrease was observed in GC values for ICP-to-MAP and MAP-to-ICP for IH events as compared to those of pre-events. For ICP and HR relations, a significant decrease was found across HR-to-ICP. However ICP-to-HR remained unaltered for IH events. In contrast, a significant increase was observed for HR-to-MAP, whereas MAP-to-HR remained unchanged for IH events. An illustration of a physiological network derived from GC patterns among MAP, ICP and HR, is shown in Figure 2 for both pre-events and IH events. It is evident that MAP played the role of key driver with strong communication to both ICP and HR. However, information flow decreased for both MAP-to-ICP and ICP-to-MAP during IH events (Figure 2b). Interestingly, the information flow pattern from MAP-to-HR was not significantly altered for pre-events vs. IH events. However, the

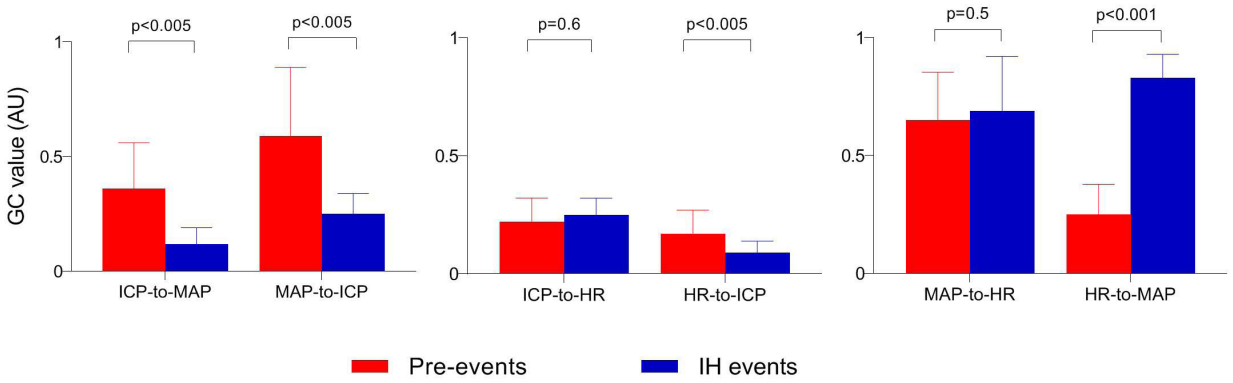

FIGURE 3. GC values estimated for all subjects excluding subject 2 for pre-events vs. IH events. GC, Granger causal; IH, intracranial hypertensive.

other arm (from HR-to-MAP) showed a significant increase during IH events. Average GC values along with percentages of segments having significant causal interactions ($p < 0.05$) for both pre-events and IH events are shown in Tables 2 and 3. It is evident that significant interactions were found across at least 65% of segments for both pre-events and IH events.

TABLE 2. GC values for pre-events of the representative subject (subject 2).

	% of pre-events having significant causal interactions (p<0.05)	GC value (mean±SD)	Significance (p-value)
MAP-to-ICP	89	0.45±0.23	0.0001
ICP-to-MAP	81	0.28±0.16	
ICP-to-HR	86	0.13±0.09	0.85
HR-to-ICP	71	0.11±0.06	
MAP-to-HR	86	0.34±0.19	0.02
HR-to-MAP	81	0.20±0.13	

TABLE 3. GC values for IH events of the representative subject (subject 2).

	% of IH events having significant causal interactions (p<0.05)	GC value (mean±SD)	Significance (p-value)
MAP-to-ICP	94	0.15±0.11	0.05
ICP-to-MAP	71	0.05±0.04	
ICP-to-HR	70	0.10±0.07	0.002
HR-to-ICP	64	0.03±0.02	
MAP-to-HR	91	0.40±0.25	0.0001
HR-to-MAP	84	0.77±0.23	

Intra-individual variations of GC values, in terms of coefficients of variations (%), are given in Table 4. It is evident for pre-events that the highest CV of 69% was found across ICP-to-HR whereas the lowest CV of 51% was found across MAP-to-ICP. IH events were found with the highest CV of 80% for ICP-to-MAP and the lowest CV of 30% for HR-to-MAP. Interestingly, high CVs were observed across all GC values of IH events as compared to pre-events, except HR-to-MAP.

B. GROUP 2: ALL SUBJECTS EXCLUDING SUBJECT 2

Estimated GC values from 43 pre-events and IH events of all subjects (excluding subject 2) are given in Figure 3. It was observed that strength of information transfer decreases for IH events for both arms of ICP-MAP interactions. Similarly, a decrease was observed across HR-to-ICP arm for IH events.

TABLE 4. Coefficients of variation (%) of GC values for a representative subject (i.e., subject 2).

	Pre-events	IH events
MAP-to-ICP	51	73
ICP-to-MAP	57	80
ICP-to-HR	69	70
HR-to-ICP	54	67
MAP-to-HR	55	62
HR-to-MAP	65	30

Whereas the ICP-to-HR arm did not show any significant change for pre-events vs. IH events. For MAP-HR interactions, a significant increase was found in the HR-to-MAP arm for IH events whereas the MAP-to-HR arm did not show any significant change across pre-events vs. IH events. The physiological network resulted in the same pattern as that of the representative subject 2 (not shown here on account of space).

Consistent with the representative case (subject 2), MAP was found playing the role of central entity across ICP-MAP-HR interactions. However, IH events caused a decrease in the coupling strengths of ICP-to-MAP, MAP-to-ICP and HR-to-ICP, and an increase in HR-to-MAP information flow. Average GC values along with percentages of segments having significant causal interactions ($p < 0.05$) for both pre-events and IH events are shown in Tables 5 and 6. At least 69% pre-events and 61% IH events were found having significant causal interactions.

TABLE 5. GC values for pre-events of all subjects excluding subject 2.

	% of IH events having significant causal interactions (p<0.05)	GC value (mean±SD)	Significance (p-value)
MAP-to-ICP	87	0.59±0.30	0.0001
ICP-to-MAP	85	0.36±0.20	
ICP-to-HR	80	0.22±0.10	0.23
HR-to-ICP	69	0.17±0.10	
MAP-to-HR	90	0.65±0.20	0.01
HR-to-MAP	86	0.25±0.13	

IV. DISCUSSION

The study of human physiology for information exchange in a closed-loop network is important for characterization of the instability and variations in monotonous

TABLE 6. GC values for IH events of all subjects excluding subject 2.

	% of pre-events having significant causal interactions (p<0.05)	GC value (mean±SD)	Significance (p-value)
MAP-to-ICP	91	0.25±0.09	0.02
ICP-to-MAP	78	0.12±0.07	
ICP-to-HR	73	0.25±0.07	0.005
HR-to-ICP	61	0.09±0.05	
MAP-to-HR	93	0.69±0.24	0.005
HR-to-MAP	89	0.83±0.10	

physiological parameters. Consistent with the first hypothesis, it was observed that the IH event: 1) reduces the GC value across both arms of ICP-MAP interactions; 2) reduces the GC value only across the HR-to-ICP arm of ICP-HR interactions; and 3) increases the GC value across the HR-to-MAP arm of HR-MAP interactions. The examination of the second hypothesis reveals that IH events, as compared to pre-events, show more inconsistency in TBI patients in terms of increased CV, except the HR-to-MAP interactions where reduced CV was found during IH events.

Variations in physiological parameters including BP and HR, are pervasive in human health [42]–[44]. Stability in these parameters is an indication of stable health while variations can lead to failure of homeostasis, and are considered as a symptom of disease [42], [44], [45]. Complex networks can have the ability to absorb external shocks and the fluctuation can be a subtle response to internal physiological changes. Although the direct monitoring of physiological processes is common these days, the application of a systematic approach (as adopted in the present study) can provide new intuitions in the current clinical practice. To this, MAP, ICP and HR time series encapsulate key information for IH occurrences in TBI patients, and inter-connection of these respective sub-systems can be apprehended by their Granger causal analysis [42], [46].

The effect of intracranial hypertension on TBI patients is complex. It may involve the interaction between ICP, cerebral auto-regulation, cerebral edema and systemic blood pressure. Cerebrovascular auto-regulation maintains the persistent cerebral blood flow in spite of variations in systemic BP in healthy populations [47], [48]. However, in TBI patients, cerebrovascular auto-regulation is weakened, i.e. an increase in systemic BP can lead to the breakdown of a blood-brain barrier, an increase in ICP and cerebral edema [2], [47], [49]. In contrast, hypotension in TBI patients can cause brain stroke [50], inadequate blood flow, kidney failure [51], [52] and heart disease [53]. In TBI patients, hypotension is also associated with morbidity and mortality. Even a single occurrence of hypotension may increase the risk of mortality [54]. It can be classified as orthostatic, postprandial, acute and chronic. Orthostatic is known as one of the most common form of hypotension.

Blood pressure management is critical for TBI patients, and its fluctuation can lead to fatal health conditions. Modern multimodal brain monitoring systems may be helpful for BP management in TBI patients [47], [55], [56]. A multimodal monitoring system is a tool used to measure multiple parameters. It has several invasive and non-invasive modules to monitor different physiological activities such as cerebral hemodynamics, ICP, CPP, cerebral blood flow, brain tissue oxygenation and cerebral auto-regulation. It can also provide clinically significant information prior to the occurrence of any irreversible damage [47], [57]. For example, Bouzat [58] and Dias [59] suggested its usage to optimize cerebral blood flow, brain oxygenation and cerebral perfusion pressure. The current study proposes novel indices which might be adopted in modern brain monitoring systems to identify IH episodes in TBI patients for blood pressure management.

We have provided confirmatory findings regarding variations in information flow patterns following IH episodes through analysis of TBI patients. Our study presents some of the first findings that analyse causal interactions between cardiovascular and cerebrovascular mechanisms in a complex closed-loop network from a multi-signal dataset of TBI patients. The bi-directional interactions dominated by MAP, and apprehended by GC analysis, may imitate a process of causal information flow between MAP, HR and ICP. The findings of the present study are in accordance with those of Gao [42]. They reported a significant increase of information flow between ICP, HR and MAP in the stable TBI patients, whereas there was a decreased information flow in the severe TBI patients, which leads to a higher mortality rate and unfavorable outcomes.

Our findings also suggest that GC examination provides additional clinically significant information through directional information flow analysis in TBI patients. It is evident from the dominating nature of MAP that it influences HR and there is also a direct association between cardiac output (product of stroke volume and HR) and MAP. In response to fluctuations in MAP, baroreceptors produce afferent signals in the negative feedback mechanism to the medulla oblongata that keeps MAP in the normal range. Remarkably, MAP has a strong causal inference to HR whenever cerebral auto-regulation is in place [42].

Similarly, the effect of HR variations on ICP dynamics may not look intuitive at first glance, and can be attributed to some direct and indirect physiological processes [42], [60]–[62]. For example, HR variations can cause changes in cardiac output which lead to fluctuations in carbon dioxide (CO_2) level. In response to CO_2 variations, cerebral circulation adjusts ICP [42], [60], [62]. Moreover, HR variations also change diastole time which causes changes in the cerebrospinal fluid volume or compartmental blood, leading to ICP fluctuations.

The findings of the present study are in accordance with existing literature [36], [42], [63]. For example, Gao [42] examined bi-directional causal interactions between MAP, HR and ICP for the second 24 hours following TBI, and its association with mortality. According to this study, MAP has a strong influence on both HR and ICP, however no dominant unidirectional causal interactions were observed between ICP and HR. Strong causal information flow was observed in patients who were stable after 24 hours while reduced or no information flow was found among those who died. Another study [63] used an approximate entropy analysis to examine

the relationship between the complexity of MAP, ICP and HR in TBI patients. Significant associations between the complexity of MAP, ICP and HR were found. These associations demonstrated the complexity as an independent mortality predictor. Its findings also suggest that the complexity monitoring of these physiological signals for the early six hours can be helpful for better management of patients in intensive care units.

A study by Zeiler [36] used logistic regression analysis and suggests that a decrease in multiscale entropy (MSE) of cerebral physiological (ICP) and cardiovascular (MAP and HR) signals is directly linked to worse outcomes and a higher mortality rate in TBI patients. The study used the Extended Glasgow Outcome Scale (GOSE) score for rating patients. Logistic regression analysis also confirms that a lower HR MSE-complexity index (MSE-ci) and ICP MSE-ci have direct associations with unfavorable outcomes and death.

According to the Monro-Kellie doctrine, the intracranial compartment is composed of fixed volume, and it can be further decomposed into three sub-compartments: blood, brain and cerebrospinal fluid (CSF). Consequently, any decompensation such as elevation in intracranial pressure may be provoked by a disturbance in (i) cerebral blood circulation (namely vascular component of ICP), (ii) CSF circulation (namely CSF circulatory component), and (iii) associated brain edema. Analogously, ICP waveform embeds different spectral components associated with distinct physiological mechanisms including respiration, slow vasogenic waves and long-standing trends (due to edema or acute impairment of CSF circulation) [64], [65]. With the aim to characterize IH episodes, the objective of the present study was to develop indices across an entire spectral range of ICP waveform. However, a future study is intended to comprehend the associated physiological processes that play vital roles in ICP dynamics.

Traumatic brain injury can cause loss of physiological regulators of hemodynamic control in the brain (such as cerebral perfusion auto-regulation, baroreceptor reflex mechanism and Cushing reflex) which results in disruption in the control of ICP. According to the Monro-Kellie hypothesis, an increase in ICP can be controlled by decreasing CPP. This decrease in CPP dictates that there is a decrease in blood pressure which subsequently results in initiating auto-regulation of ICP [66]. When ICP rises above 16 mmHg, the brain blood vessels constrict to reduce the blood flow to the cranium, and ultimately reduce the ICP. Therefore, when homeostatic functions of the brain are lost due to traumatic brain injury, the ICP increases and physiological regulatory functions are inoperable [66], [67]. This degree of impairment of auto-regulation might be directly associated with the onset of an IH event, resulting in intra-individual variability. However, a future study is needed to explore the role of each physiological compartment, i.e. MAP, HR and ICP towards intra-individual variability.

Though the findings of the present study, using the parametric dependent sample t-test, are encouraging, the scenario of multiple patients having many IH episodes may be better handled by a mixed-effects model [68] to test the statistical significance of the proposed indices.

V. CLINICAL SIGNIFICANCE

Causal information flow analysis between different cerebrovascular and cardiovascular processes is of clinical significance. Its findings might be useful for the predictive modelling of intracranial hypertension management in TBI patients. The quantitative analysis of a physiological system against any disruption might be vital, not only for long-term prognosis but also for short-term forecast. The information gained from causal analysis may be helpful for prospective modelling of physiological systems, which can play an important role during early critical intensive care unit stay of TBI patients.

VI. CONCLUSION

The present study indicates that there is a significant causal relationship between intracranial pressure, heart rate and mean arterial pressure in traumatic brain injured patients. Causal information flow between these cerebrovascular and cardiovascular signals is directly associated with an IH event. It can be considered as a potential index for its onset in TBI patients. Disruption in information flow can increase the probability of IH occurrence and vice versa. Additionally, IH events in TBI patients also exhibit more inconsistency in terms of GC values as an intra-individual variability measurement. Currently, there is no consensus on aggressive treatment of intracranial hypertension in TBI patients, and physicians have to decide at the individual patient level for intracranial hypertension management. The present study suggests adopting GC values as potential indices for multimodal monitoring systems to quantify intracranial hypertensive episodes for its better management in TBI patients. A future study may be intended to comprehend the associated physiological processes such as cerebral auto-regulation and CSF, which play important role in ICP dynamics.

DATA AVAILABILITY

Data analyzed in the current study were obtained from the Physionet [34].

REFERENCES

[1] A. I. R. Maas, D. K. Menon, P. D. Adelson, N. Andelic, M. J. Bell, A. Belli, P. Bragge, A. Brazinova, A. Büki, R. M. Chesnut, and G. Citerio, "Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research," *Lancet Neurol.*, vol. 16, no. 12, pp. 987–1048, 2017.

[2] T. Shiozaki, "Hypertension and head injury," *Current Hypertension Rep.*, vol. 7, no. 6, pp. 450–453, Nov. 2005.

[3] L. Buttler, M. T. Jordão, M. G. Fragas, A. Ruggeri, A. Ceroni, and L. C. Michelini, "Maintenance of blood-brain barrier integrity in hypertension: A novel benefit of exercise training for autonomic control," *Frontiers Physiol.*, vol. 8, p. 1048, Dec. 2017.

[4] A. Setiadi, W. S. Korim, K. Elsaafien, and S. T. Yao, "The role of the blood–brain barrier in hypertension," *Exp. Physiol.*, vol. 103, no. 3, pp. 337–342, 2018.

[5] M. A. Johnson, M. A. Borgman, J. W. Cannon, N. Kuppermann, and L. P. Neff, "Severely elevated blood pressure and early mortality in children with traumatic brain injuries: The neglected end of the spectrum," *Western J. Emergency Med.*, vol. 19, no. 3, pp. 452–459, 2018.

[6] C. M. Lawes, S. V. Hoorn, and A. Rodgers, "Global burden of blood-pressure-related disease, 2001," *Lancet*, vol. 371, no. 9623, pp. 1513–1518, May 2008.
[7] N. Carney, A. M. Totten, C. O'Reilly, J. S. Ullman, G. W. J. Hawryluk, M. J. Bell, S. L. Bratton, R. Chesnut, O. A. Harris, N. Kissoon, and A. M. Rubiano, "Guidelines for the management of severe traumatic brain injury," *Neurosurgery*, vol. 80, no. 1, pp. 6–15, 2017.
[8] T. M. S. Wettervik, A. Lewén, and P. Enblad, "Fine tuning of traumatic brain injury management in neurointensive care—Indicative observations and future perspectives," *Frontiers Neurol.*, vol. 12, p. 124, Feb. 2021.
[9] G. Fuller, R. M. Hasler, N. Mealing, T. Lawrence, M. Woodford, P. Juni, and F. Lecky, "The association between admission systolic blood pressure and mortality in significant traumatic brain injury: A multi-centre cohort study," *Injury*, vol. 45, no. 3, pp. 612–617, Mar. 2014.
[10] I. Butcher, A. I. R. Maas, J. Lu, A. Marmarou, G. D. Murray, N. A. Mushkudiani, G. S. McHugh, and E. W. Steyerberg, "Prognostic value of admission blood pressure in traumatic brain injury: Results from the IMPACT study," *J. Neurotrauma*, vol. 24, no. 2, pp. 294–302, Feb. 2007.
[11] S. N. Zafar, F. H. Millham, Y. Chang, K. Fikry, H. B. Alam, D. R. King, G. C. Velmahos, and M. A. de Moya, "Presenting blood pressure in traumatic brain injury: A bimodal distribution of death," *J. Trauma Acute Care Surg.*, vol. 71, no. 5, pp. 1179–1184, 2011.
[12] C. J. Murray and A. D. Lopez, "Mortality by cause for eight regions of the world: Global burden of disease study," *Lancet*, vol. 349, no. 9061, pp. 1269–1276, May 1997.
[13] L. Rangel-Castilla, J. Gasco, H. J. W. Nauta, D. O. Okonkwo, and C. S. Robertson, "Cerebral pressure autoregulation in traumatic brain injury," *Neurosurg. Focus*, vol. 25, no. 4, p. E7, Oct. 2008.
[14] A. Silverman and N. H. Petersen, "Physiology, cerebral autoregulation," Yale School Med., Yale Univ., Treasure Island, FL, USA, Tech. Rep., 2021.
[15] K. Heusser, J. Tank, F. C. Luft, and J. Jordan, "Baroreflex failure," *Hypertension*, vol. 45, no. 5, pp. 834–839, 2005.
[16] J. D. Filippone and J. D. Bisognano, "Baroreflex stimulation in the treatment of hypertension," *Current Opinion Nephrol. Hypertension*, vol. 16, no. 5, pp. 403–408, 2007.
[17] C. E. Schwartz and J. M. Stewart, "The arterial baroreflex resets with orthostasis," *Frontiers Physiol.*, vol. 3, p. 461, 2012.
[18] A. Kroon and P. de Leeuw, "Baroreflex activation in drug-resistant hypertension," *Eur. Cardiol.*, vol. 4, no. 2, pp. 56–58, 2008.
[19] R. Freeman and M. W. Chapleau, "Testing the autonomic nervous system," in *Handbook of Clinical Neurology*, vol. 115. Amsterdam, The Netherlands: Elsevier, 2013, pp. 115–136.
[20] A. Kazimierska, M. M. Placek, A. Uryga, P. Wachel, M. Burzyńska, and M. Kasprowicz, "Assessment of baroreflex sensitivity using time-frequency analysis during postural change and hypercapnia," *Comput. Math. Methods Med.*, vol. 2019, pp. 1–17, Feb. 2019.
[21] T. Shahzad, S. Saleem, S. Usman, J. Mirza, Q.-U. Islam, K. Ouahada, and T. Marwala, "System dynamics of active and passive postural changes: Insights from principal dynamic modes analysis of baroreflex loop," *Comput. Biol. Med.*, vol. 100, pp. 27–35, Sep. 2018.
[22] S. Reule and P. E. Drawz, "Heart rate and blood pressure: Any possible implications for management of hypertension?" *Current Hypertension Rep.*, vol. 14, no. 6, pp. 478–484, Dec. 2012.
[23] D. Sapoznikov, M. D. Elhalel, and D. Rubinger, "Heart rate response to blood pressure variations: Sympathetic activation versus baroreflex response in patients with end-stage renal disease," *PLoS ONE*, vol. 8, no. 10, Oct. 2013, Art. no. e78338.
[24] M. Di Rienzo, G. Parati, A. Radaelli, and P. Castiglioni, "Baroreflex contribution to blood pressure and heart rate oscillations: Time scales, time-variant characteristics and nonlinearities," *Phil. Trans. Roy. Soc. A, Math., Phys. Eng. Sci.*, vol. 367, no. 1892, pp. 1301–1318, Apr. 2009.
[25] S. Saleem, A. Saeed, S. Usman, J. Ferzund, J. Arshad, J. Mirza, and T. Manzoor, "Granger causal analysis of electrohysterographic and tocographic recordings for classification of term vs. preterm births," *Biocybern. Biomed. Eng.*, vol. 40, no. 1, pp. 454–467, Jan. 2020.
[26] S. Saleem, P. D. Teal, C. A. Howe, M. M. Tymko, P. N. Ainslie, and Y.-C. Tzeng, "Is the cushing mechanism a dynamic blood pressure-stabilizing system? Insights from Granger causality analysis of spontaneous blood pressure and cerebral blood flow," *Amer. J. Physiol.-Reg., Integr. Comparative Physiol.*, vol. 315, no. 3, pp. R484–R495, Sep. 2018.
[27] S. Saleem, Z. K. Sarafis, A. H. X. Lee, J. W. Squair, O. F. Barak, E. Sober-Williams, R. Suraj, G. B. Coombs, T. Mijacika, C. R. West, A. V. Krassioukov, P. N. Ainslie, Z. Dujic, Y.-C. Tzeng, and A. A. Phillips, "Spinal cord disruption is associated with a loss of cushing-like blood pressure interactions," *J. Neurotrauma*, vol. 36, no. 9, pp. 1487–1490, May 2019.
[28] L. Price, C. Wilson, and G. Grant, "Blood–brain barrier pathophysiology following traumatic brain injury," in *Translational Research in Traumatic Brain Injury*, D. Laskowitz and G. Grant, Eds. Boca Raton, FL, USA: CRC Press, 2016, pp. 1–12.
[29] H. B. Lim and M. Smith, "Systemic complications after head injury: A clinical review," *Anaesthesia*, vol. 62, no. 5, pp. 474–482, Apr. 2007.
[30] M. J. Kenney and C. K. Ganta, "Autonomic nervous system and immune system interactions," *Comprehensive Physiol.*, vol. 4, no. 3, pp. 1177–1200, 2011.
[31] C. P. Doherty, E. O'Keefe, E. Wallace, T. Loftus, J. Keaney, J. Kealy, M. M. Humphries, M. G. Molloy, J. F. Meaney, M. Farrell, and M. Campbell, "Blood–brain barrier dysfunction as a hallmark pathology in chronic traumatic encephalopathy," *J. Neuropathol. Exp. Neurol.*, vol. 75, no. 7, pp. 656–662, Jul. 2016.
[32] R. Daneman and A. Prat, "The blood–brain barrier," *Cold Spring Harbor Perspect. Biol.*, vol. 7, no. 1, 2015, Art. no. a020412.
[33] Y. Wu, H. Wu, X. Guo, B. Pluimer, and Z. Zhao, "Blood–brain barrier dysfunction in mild traumatic brain injury: Evidence from preclinical murine models," *Frontiers Physiol.*, vol. 11, p. 1030, Aug. 2020.
[34] A. L. Goldberger, L. A. N. Amaral, L. Glass, J. M. Hausdorff, P. C. Ivanov, R. G. Mark, J. E. Mietus, G. B. Moody, C.-K. Peng, and H. E. Stanley, "PhysioBank, PhysioToolkit, and PhysioNet: Components of a new research resource for complex physiologic signals," *Circulation*, vol. 101, no. 23, pp. e215–e220, Jun. 2000. [Online]. Available: http://circ.ahajournals.org/content/101/23/e215
[35] N. Kim, A. Krasner, C. Kosinski, M. Wininger, M. Qadri, Z. Kappus, S. Danish, and W. Craelius, "Trending autoregulatory indices during treatment for traumatic brain injury," *J. Clin. Monit. Comput.*, vol. 30, no. 6, pp. 821–831, Dec. 2016.
[36] F. A. Zeiler, A. Ercole, M. M. Placek, P. J. Hutchinson, N. Stocchetti, M. Czosnyka, and P. Smieleweski, "Association between physiologic signal complexity and outcomes in moderate and severe traumatic brain injury: A CENTER-TBI exploratory analysis of multiscale entropy," *J. Neurotrauma*, vol. 38, no. 2, pp. 272–282, Aug. 2020.
[37] A. Müller, J. F. Kraemer, T. Penzel, H. Bonnemeier, J. Kurths, and N. Wessel, "Causality in physiological signals," *Physiol. Meas.*, vol. 37, no. 5, pp. R46–R72, May 2016.
[38] N. Wiener, *The Theory of Prediction. Modern Mathematics for the Engineer*. New York, NY, USA: McGraw-Hill, 1956, pp. 165–190.
[39] C. W. J. Granger, "Investigating causal relations by econometric models and cross-spectral methods," *Econ., J. Econ. Soc.*, vol. 37, no. 3, pp. 424–438, 1969.
[40] G. F. Reed, F. Lynn, and B. D. Meade, "Use of coefficient of variation in assessing variability of quantitative assays," *Clin. Diagnostic Lab. Immunol.*, vol. 9, no. 6, pp. 1235–1239, Nov. 2002.
[41] H. Azami, A. Fernández, and J. Escudero, "Refined multiscale fuzzy entropy based on standard deviation for biomedical signal analysis," *Med. Biol. Eng., Comput.*, vol. 55, no. 11, pp. 2037–2052, 2017.
[42] L. Gao, P. Smielewski, M. Czosnyka, and A. Ercole, "Early asymmetric cardio-cerebral causality and outcome after severe traumatic brain injury," *J. Neurotrauma*, vol. 34, no. 19, pp. 2743–2752, Oct. 2017.
[43] T. G. Buchman, "Nonlinear dynamics, complex systems, and the pathobiology of critical illness," *Current Opinion Crit. Care*, vol. 10, no. 5, pp. 378–382, Oct. 2004.
[44] B. Goldstein, D. H. Fiser, M. M. Kelly, D. Mickelsen, U. Ruttimann, and M. M. Pollack, "Decomplexification in critical illness and injury: Relationship between heart rate variability, severity of illness, and outcome," *Crit. Care Med.*, vol. 26, no. 2, pp. 352–357, Feb. 1998.
[45] S. M. Bishop, S. I. Yarham, V. U. Navapurkar, D. K. Menon, and A. Ercole, "Multifractal analysis of hemodynamic behavior: Intraoperative instability and its pharmacological manipulation," *Anesthesiol. J. Amer. Soc. Anesthesiol.*, vol. 117, no. 4, pp. 810–821, 2012.
[46] A. Porta, P. Castiglioni, M. Di Rienzo, T. Bassani, V. Bari, L. Faes, G. Nollo, A. Cividjan, and L. Quintin, "Cardiovascular control and time domain Granger causality: Insights from selective autonomic blockade," *Phil. Trans. Roy. Soc. A, Math., Phys. Eng. Sci.*, vol. 371, no. 1997, Aug. 2013, Art. no. 20120161.

[47] V. Krishnamoorthy, N. Chaikittisilpa, T. Kiatchai, and M. Vavilala, "Hypertension after severe traumatic brain injury: Friend or foe?" *J. Neurosurg. Anesthesiol.*, vol. 29, no. 4, pp. 382–387, 2017.

[48] M. J. Rosner and D. P. Becker, "Origin and evolution of plateau waves: Experimental observations and a theoretical model," *J. Neurosurg.*, vol. 60, no. 2, pp. 312–324, Feb. 1984.

[49] Y. Liang, Z. Chen, R. Ward, and M. Elgendi, "Hypertension assessment via ECG and PPG signals: An evaluation using MIMIC database," *Diagnostics*, vol. 8, no. 3, p. 65, Sep. 2018.

[50] M. L. Eigenbrodt, K. M. Rose, D. J. Couper, D. K. Arnett, R. Smith, and D. Jones, "Orthostatic hypotension as a risk factor for stroke: The atherosclerosis risk in communities (ARIC) study, 1987–1996," *Stroke*, vol. 31, no. 10, pp. 2307–2313, 2000.

[51] N. Franceschini, K. M. Rose, B. C. Astor, D. Couper, and S. Vupputuri, "Orthostatic hypotension and incident chronic kidney disease: The atherosclerosis risk in communities study," *Hypertension*, vol. 56, no. 6, pp. 1054–1059, Dec. 2010.

[52] L.-W. Lehman, M. Saeed, G. Moody, and R. Mark, "Hypotension as a risk factor for acute kidney injury in ICU patients," in *Proc. Comput. Cardiol.*, 2010, pp. 1095–1098.

[53] K. M. Rose, M. L. Eigenbrodt, R. L. Biga, D. J. Couper, K. C. Light, A. R. Sharrett, and G. Heiss, "Orthostatic hypotension predicts mortality in middle-aged adults: The atherosclerosis risk in communities (ARIC) study," *Circulation*, vol. 114, no. 7, pp. 630–636, Aug. 2006.

[54] D. W. Spaite, C. Hu, B. J. Bobrow, V. Chikani, B. Barnhart, J. B. Gaither, K. R. Denninghoff, P. D. Adelson, S. M. Keim, C. Viscusi, T. Mullins, and D. Sherrill, "The effect of combined out-of-hospital hypotension and hypoxia on mortality in major traumatic brain injury," *Ann. Emergency Med.*, vol. 69, no. 1, pp. 62–72, Jan. 2017.

[55] N. Tasneem, E. A. Samaniego, C. Pieper, E. C. Leira, H. P. Adams, D. Hasan, and S. Ortega-Gutierrez, "Brain multimodality monitoring: A new tool in neurocritical care of comatose patients," *Crit. Care Res. Pract.*, vol. 2017, pp. 1–8, May 2017.

[56] M. M. Tisdall and M. Smith, "Multimodal monitoring in traumatic brain injury: Current status and future directions," *Brit. J. Anaesthesia*, vol. 99, no. 1, pp. 61–67, Jul. 2007.

[57] D. Roh and S. Park, "Brain multimodality monitoring: Updated perspectives," *Current Neurol. Neurosci. Rep.*, vol. 16, no. 6, p. 56, Jun. 2016.

[58] P. Bouzat, N. Sala, J.-F. Payen, and M. Oddo, "Beyond intracranial pressure: Optimization of cerebral blood flow, oxygen, and substrate delivery after traumatic brain injury," *Ann. Intensive Care*, vol. 3, no. 1, pp. 1–9, 2013.

[59] C. Dias, M. J. Silva, E. Pereira, S. Silva, A. Cerejo, P. Smielewski, A. P. Rocha, A. R. Gaio, J.-A. Paiva, and M. Czosnyka, "Post-traumatic multimodal brain monitoring: Response to hypertonic saline," *J. Neurotrauma*, vol. 31, no. 22, pp. 1872–1880, Nov. 2014.

[60] J. Claassen, S. A. Rahman, Y. Huang, H.-P. Frey, J. M. Schmidt, D. Albers, C. M. Falo, S. Park, S. Agarwal, E. S. Connolly, and S. Kleinberg, "Causal structure of brain physiology after brain injury from subarachnoid hemorrhage," *PLoS ONE*, vol. 11, no. 4, Apr. 2016, Art. no. e0149878.

[61] A. Bashan, R. P. Bartsch, J. W. Kantelhardt, S. Havlin, and P. C. Ivanov, "Network physiology reveals relations between network topology and physiological function," *Nature Commun.*, vol. 3, no. 1, pp. 1–9, Jan. 2012.

[62] D. J. Sharp, G. Scott, and R. Leech, "Network dysfunction after traumatic brain injury," *Nature Rev. Neurol.*, vol. 10, no. 3, pp. 156–166, 2014.

[63] L. Gao, P. Smielewski, M. Czosnyka, and A. Ercole, "Cerebrovascular signal complexity six hours after intensive care unit admission correlates with outcome after severe traumatic brain injury," *J. Neurotrauma*, vol. 33, no. 22, pp. 2011–2018, Nov. 2016.

[64] D.-J. Kim, Z. Czosnyka, M. Kasprowicz, P. Smieleweski, O. Baledent, A.-M. Guerguerian, J. D. Pickard, and M. Czosnyka, "Continuous monitoring of the Monro–Kellie doctrine: Is it possible?" *J. Neurotrauma*, vol. 29, no. 7, pp. 1354–1363, May 2012.

[65] M. Harary, R. G. Dolmans, and W. Gormley, "Intracranial pressure monitoring—Review and avenues for development," *Sensors*, vol. 18, no. 2, p. 465, Feb. 2018.

[66] C. Ordookhanian, M. Nagappan, D. Elias, and P. E. Kaloostian, "Management of intracranial pressure in traumatic brain injury," in *Traumatic Brain Injury: Pathobiology, Advanced Diagnostics and Acute Management*, vol. 177. London, U.K.: InTech, 2018.

[67] K. Nakagawa and W. S. Smith, "Evaluation and management of increased intracranial pressure," *CONTINUUM, Lifelong Learn. Neurol.*, vol. 17, pp. 1077–1093, Oct. 2011.

[68] J. Pinheiro and D. Bates, *Mixed-Effects Models in S and S-PLUS*. Springer, 2006.

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