Simultaneous Transients of Intracranial Pressure and Heart Rate in Traumatic Brain Injury: Methods of Analysis

Giovanna Maria Dimitri, Shruti Agrawal, Adam Young, Joseph Donnelly, Xiuyun Liu, Peter Smielewski, Peter Hutchinson, Marek Czosnyka, Pietro Lio, and Christina Haubrich

Abstract *Objectives*: The detection of increasing intracranial pressure (ICP) is important in preventing secondary brain injuries. Before mean ICP increases critically, transient ICP elevations may be observed. We have observed ICP transients of less than 10 min duration ,which occurred simultaneously with transient increases in heart rate (HR). These simultaneous events in HR and ICP suggest a direct interaction or communication between the heart and the brain. Methods: This chapter describes four mathematical methods and their applicability in detecting the above heart–brain cross-talk events during long-term monitoring of ICP. Results: Recurrence plots, cross-correlation function and wavelet analysis confirmed the relationship between ICP and HR time series. Using the peaks detection algorithm with a sliding window approach we found an average of 37 cross-talk events (± SD 39). The number of events detected varied among patients, from 1 to more than 150 events. Conclusion: Our analysis suggested that the peaks detection algorithm based on a sliding window approach is feasible for detecting simultaneous peaks, e.g. cross-talk events in the ICP and HR signals.

Keywords Intracranial pressure · Heart rate · Cross-talk · Recurrence plots · Wavelet analysis · Peaks detection

Introduction

Intracranial pressure (ICP) after severe brain injuries or similar life-threatening conditions can be continuously monitored [1]. The ICP signal contains useful information for predicting critical conditions such as intracranial hypertension. So far, monitoring approaches are focusing mainly on the relationship between arterial blood pressure and intracranial pressure. There are however, transient elevations of heart rate (HR) and ICP, which occur simultaneously. These transients appear variable in rate and intensity. Our hypothesis, therefore, is that these "cross-talk" events in the HR–ICP relationship can be quantified via methods of complex event processing. There are only a few papers modelling the dynamics of intracranial pressure. Hu et al. for instance, presented an estimation algorithm based on a hidden state estimation approach and nonlinear Kalman filters to estimate unobserved variables in the monitoring data of ICP and cerebral blood flow velocity (CBFV) [2]. Various methods have been applied to investigate the interrelationship between ICP and cardiovascular parameters. Hu et al. also presented ApEN, an algorithm based on the adaptive calculation of approximate entropy, integrated with a causal coherence analysis that is able to exploit the potential interaction between ICP and R wave intervals [3]. The same authors have shown that causal spectral measures and generalised synchronisation measures can be used to extract indices from beat-to-beat mean intracranial pressure measurements and intervals between consecutive normal sinus heart beats (ICP

Pietro Lio and Christina Haubrich contributed equally to this work.

G.M. Dimitri • P. Lio
Computer Laboratory, University of Cambridge, Cambridge, UK

S. Agrawal
Department of Pediatric Intensive Care, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK

A. Young • P. Hutchinson
Division of Academic Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK

J. Donnelly • X. Liu • P. Smielewski • M. Czosnyka
Brain Physics Laboratory, Division of Neurosurgery, Department of Clinical Neuroscience, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK

C. Haubrich (✉)
Brain Physics Laboratory, Division of Neurosurgery, Department of Clinical Neuroscience, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK

Faculty of Neurology, RWTH Aachen University, Aachen, Germany
e-mail: ch723@cam.ac.uk

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and RR intervals; [4]). To systematically detect simultaneous transients in HR and ICP, e.g., cross-talk events from our initially described observations, we applied different mathematical methodologies to identify the relationships between the two time series. We then implemented a sliding window approach to detect simultaneous HR and ICP peaks (see section "Peaks Detection Algorithm: A Sliding Window Approach"), obtaining promising results.

Monitoring Data

The data in this study were collected prospectively from 27 pediatric TBI patients admitted to Addenbrooke's Hospital, Cambridge, Pediatric Intensive Care Unit (PICU) between August 2012 and December 2014. Consecutive TBI patients with a clinical need for ICP monitoring were included for analysis. The insertion of an intracranial monitoring device is part of routine clinical practice and as such did not require ethical approval. The data are routinely collected for clinical purposes and guide the management of patients. The analysis of data within this study for the purposes of service evaluation was approved by the Cambridge University Hospital NHS Trust, Audit and Service Evaluation Department (Ref: 2143) and did not require ethical approval or patient consent. ABP mean arterial pressure was measured in mmHg, heart rate (HR) in Hz and intracranial pressure (ICP) in mmHg. The data sampling rate was 200 Hz.

Methods

We describe in this section the methods used for performing the analysis of the two time series and to study the behaviour of the ICP with regard to the HR. In the following section we describe the results obtained.

Recurrence Plots

We used recurrence plots (RP) to further analyse nonlinear dynamics simultaneously occurring in ICP and HR time series. The data are visualised through a graph in a square matrix (column and rows represent a pair of times). The elements represent the time points at which a specific state of the dynamical system recurred [5]. In mathematical terms, RP represents the time stamps in which the phase space trajectory of the system under consideration passes through the same area in the phase space [6]. In recurrence plots there are two parameters to be fixed, the so-called d and m: the time delay and the embedding dimension respectively [7]. This is in fact derived from recurrence plots theories and the way in which the time series is represented in the phase space. In particular, the mathematical description comes from Takens' embedding theorem. For details on the theorem please see Takens [8].

Cross-Correlation Function and Wavelet Analysis

In signal theory, cross-correlation represents the similarity between two signals, as a function of the shift or temporal translation applied to one of the two signals [9]. In particular, if g and f are two continuous functions, the cross-correlation is defined as:

$$(f \otimes g)(\tau) = \int_{-\infty}^{\infty} f^*(t)\, g(t+\tau)\, dt.$$

where f^* is the complex conjugate of f and τ is the time displacement.

Another methodology we used to understand the behaviour of the system is wavelet analysis. The method is based on the decomposition of a time series into the time–frequency space. This allows us to determine and study the variability of a given time series and its behaviour. In particular, the continuous wavelet transform (CWT) is able to decompose the time series in the time–frequency domain by convolving the time series with a scaled and translated form of the so-called mother wavelet function, a continuous function both in frequency and time domain [10, 11]. The wavelet coherence method determines and visualises areas with a high common power (i.e. high common correlation) between time series [12]. Wavelet coherence analysis is based on the CWT. The CTW given scaling factor $\alpha \in \mathbb{R}^+$ and a value for translation $\beta \in \mathbb{R}$ is defined as:

$$\chi_\omega(\alpha,\beta) = \frac{1}{|\alpha|^{\frac{1}{2}}} \int_{-\infty}^{\infty} x(t)\, \Psi(t)^* \left(\frac{t-\beta}{\alpha}\right) dt$$

where $\Psi(t)$ is the mother wavelet. $\Psi(t)^*$ is the complex conjugate of the mother wavelet function.

Peaks Detection Algorithm: A Sliding Window Approach

After the relationship between the ICP and HR time series was confirmed, the next step was to implement a peak detection algorithm to systematically collect the ICP-HR cross-talk events from initial observations (as shown in Fig. 1). We

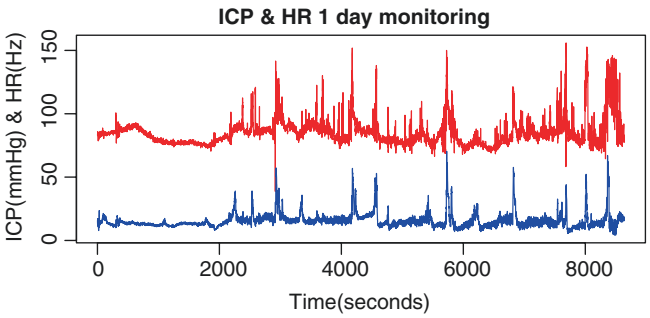

Fig. 1 Plot of the intracranial pressure (ICP; *blue*) and heart rate (HR; *red*) behaviour in a day time span of a patient in our cohort. As we can see, there are multiple cross-talk events happening in the time range considered (some of them are highlighted in *green*). Each time stamp in the x axis is 10 s

first followed the algorithm suggested in Palshikar [13]. Our aim was to find visual correlations between peaks happening in the ICP and in the HR series and to consider the temporal correlation between events. To take into account the fact that both time series originate from biological systems, we implemented a peaks detection algorithm based on a naive sliding window approach. This algorithm works as follows:

1. Consider two time series $X=x_1,x_2,x_3,\ldots,xT$ and $Y=y_1,y_2,y_3,\ldots,yT$ (which in our case are the HR and ICP time series)
2. Consider a window W of length L (in our case we considered a window with a dimension of 10 min)
3. Consider all the simultaneous sub-windows of length (L) in the two time series x and y
4. If the maximum value in the i-th time window considered is at least a 20% increase with regard to the minimum value in this time window, and if after the maximum value, there is a decrease of at least 20%, then a peak is detected.
5. If in both time series such a peak is detected, then a cross-talk event is registered in that particular time window.

Results

As a starting point of our analysis, we first plotted the time series for each patient, to visually explore ICP–HR cross-talk events. Figure 1 is an sample plot of ICP and HR time series monitored from a patient in our cohort. Figure 1 show several simultaneous transients in ICP and HR. The ICP time series is coloured in blue, whereas the HR is red and several peaks appear to take place in the same time window (i.e. cross-talk events). Starting from this visual observation, we further analysed such cross-talk events, using several statistical and time series analysis approaches, such as recurrence plots, cross-correlation function, wavelet analysis and peak detection algorithms.

We used recurrence plots to explore the behaviour of the two time series, as explained in section "Methods". In Fig. 2a, b, the black dots represent recurrent points and the lines parallel to the diagonal line show the determinism of the system. This happens both for the ICP and HR and is coherent with the nature of the two signals. Moreover, the two recurrent plots look quite similar, suggesting our hypothesis of an interaction between the two time series considered. The presence of parallel lines and similarity between the HR and ICP were verified in the plots of 27 patients from the cohort.

We then performed the cross-correlation function between the two time series ICP and HR. Figure 3c exemplifies the correlation between the two time series and provides further support for the hypothesis of an interdependency between the two signals.

In Table 1, we report the Pearson correlation coefficient between the ICP and HR for the 27 patients available.

We then performed wavelet analysis on the ICP and HR time series of 27 patients. Before performing this analysis, we checked for the normality of the two time series considering the Shapiro–Wilk test for normality. As the test showed normality of the data proposed, we performed the wavelet

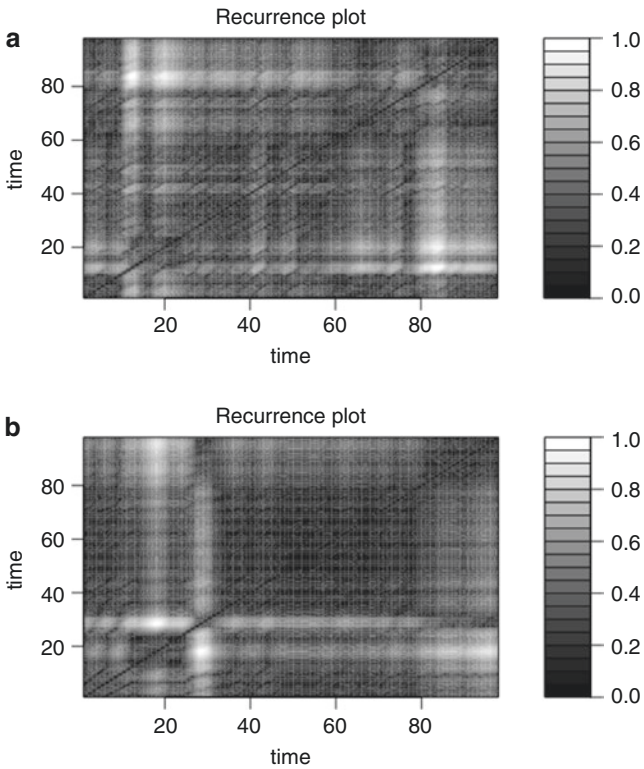

Fig. 2 Recurrence plots for a patient in our cohort for (**a**) ICP and (**b**) HR. The parameters used for the recurrence plots were (d = 2 and m = 3, where m is the embedding dimension and d is the delay. Those two parameters are needed for setting the time window in which the recurrence of the system is analysed using the recurrence plot method.). See Marwan et al. [5] for details

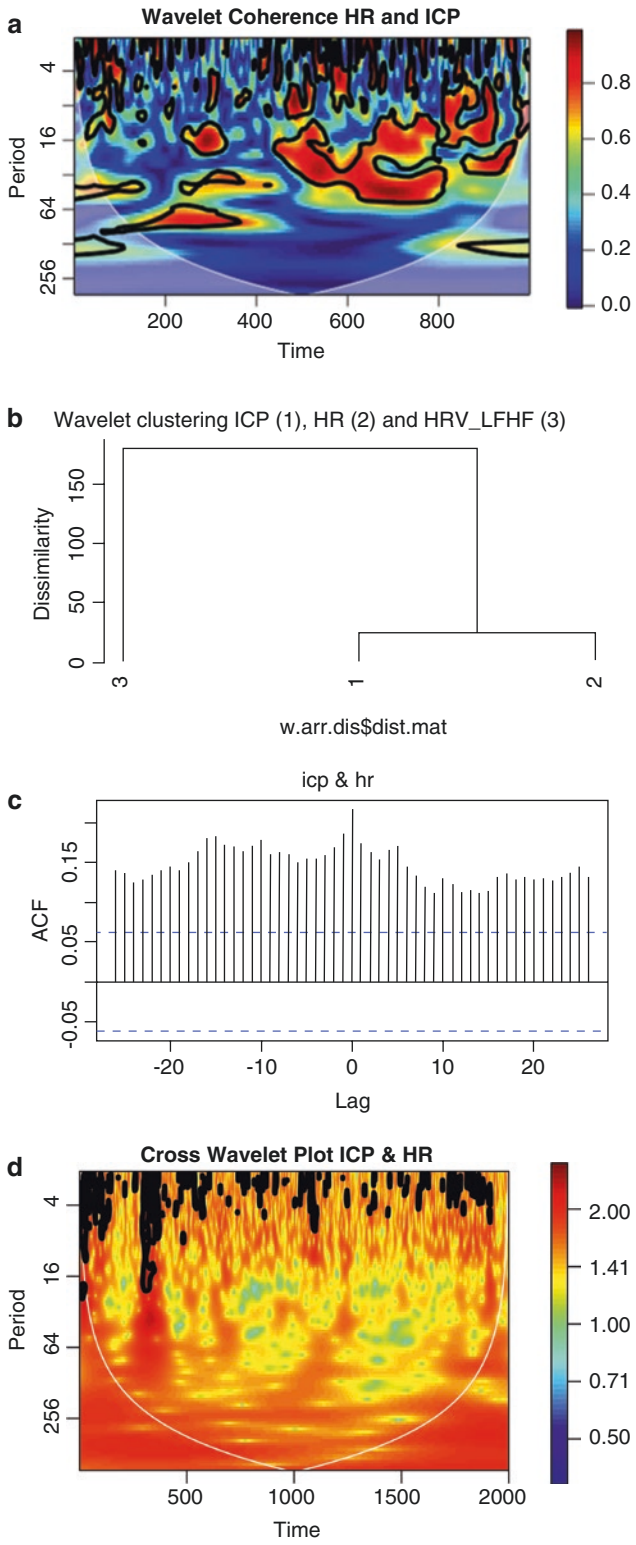

Fig. 3 (**a**) Wavelet coherence; (**b**) wavelet clustering; (**c**) cross-correlation; (**d**) cross-wavelet

coherence between HR and ICP time series, as shown in Fig. 3d. The resulting plot shows particularly interesting characteristics. In fact, it identifies regions (in red) where the two signals show high correlation, and it also tells us in which time instants such a correlation happens. This is particularly useful for our analysis, because we are looking for a correlation in particular time instances (i.e. when peaks occur). Moreover, we performed two additional analyses with wavelets, in particular, wavelet correlations and wavelet clustering. The wavelets showed a high correlation between the ICP and HR, as we can see from Fig. 3a, where the red parts indicate the presence of highly correlated episodes. In the case of clustering, we have so far analysed the wavelet power clustering considering three time series, HR, ICP and HRVLF/HF. As we can see from Fig. 3b, the ICP and HR time series are clustered together (1 and 2 in the tree) and further away from the frequency domain-derived parameter, LF/HF ratio, supporting even further our hypothesis about the similarity between HR and ICP behaviours.

Finally, we applied our sliding window approach to detect cross-talk events between ICP and HR described in section "Peaks Detection Algorithm: A Sliding Window Approach". This enabled us to identify multiple cross-talk events happening in the HR and ICP time series. We found an average of 37 cross-talk events (±SD 39).

The number of events detected varied among patients, from 1 to more than 150 events (Table 2).

Discussion and Conclusions

This analysis was performed with no a priori regard for a possible relationship between HR and ICP. The 27 records of monitored data are consecutive samples of pediatric patients admitted to Addenbrooke's Hospital, Cambridge. We performed a series of correlation analyses and tests to understand the behaviour and the relationship between peaks happening in the ICP and HR. The two parameters were obtained independently one from the other and with no previous assumption regarding the causal relationship or behavioural relationship between the two time series. Recurrence plots, cross-correlation function and wavelet analysis confirmed the relationship between ICP and HR time series. These were performed as part of a preliminary analysis to understand if the two time series correlated and showed similar behaviours.

In a first instance, we applied recurrence plots analysis to study the determinism and behaviour of each individual time series (ICP and HR considered separately). We then introduced wavelet analysis to study the interaction between HR and ICP. Using wavelet coherence and cross wavelets, we were able to understand that correlated behaviours were occurring. We also obtained the Pearson correlation coefficients, which allowed us to evaluate even further the presence of a correlation between the ICP and HR series of each patient. As a next step, we implemented a sliding window peaks detection

Table 1 Pearson correlation coefficient of the 27 patients between intracranial pressure (ICP) and heart rate (HR)

P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**
0.46	−0.1	0.01	−0.50	0.17	−0.02	0.11	0.33	−0.22
P10	**P11**	**P12**	**P13**	**P14**	**P15**	**P16**	**P17**	**P18**
−0.01	0.10	0.12	0.31	0.40	0.23	0.04	0.11	0.24
P19	**P20**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**
0.24	−0.13	−0.39	0.09	0.47	0.30	−0.6	0.09	−0.32

P patient

Table 2 Number of HR–ICP cross-talk events detected for each patient

P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**
17	32	65	20	1	23	22	43	55
P10	**P11**	**P12**	**P13**	**P14**	**P15**	**P16**	**P17**	**P18**
67	20	142	27	29	7	35	2	0
P19	**P20**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**
1	19	188	55	2	15	0	14	17

algorithm. With this algorithm, we were able to detect the cross-talk events happening in the two time series for each patient. The sliding window peaks detection algorithm detected a significant number of cross-talk-events using the peaks detection algorithm. Using a sliding window approach, we found an average number of simultaneous peaks in HR and ICP. We found an average of 37 cross-talk-events (±SD 39).

The results showed that a peaks extraction method may be a feasible approach for the automated detection of simultaneous peaks in HR and ICP. On the one hand, however, we do not know about a causal relationship between the transient elevations of HR and ICP. Hence, further work will include the analysis of the time series using the Granger causality method, trying to understand the causality of correlations between the ICP and HR time series. When considering the inter-individual variations in the number of cross-talks events, on the other hand, influencing factors such as the pressure–volume reserve or the autonomic nervous activity should be analysed as well. Therefore, we are currently extending our analysis, investigating the relationship between ICP–HR cross-talk events and measures derived from time- and frequency domains.

Conflicts of interest statement We declare that we have no conflicts of interest.

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