**Analysing cardio-cerebral crosstalks in an adult cohort from CENTER-TBI**

Giovanna Maria Dimitri (1), Erta Beqiri (2,3,4), Marek Czosnyka (2), Ari Ercole (2),

Peter Smielewski * (2), Pietro Lio' * (1); CENTER-TBI High Resolution Sub- Study Participants and Investigators

*1) Computer Laboratory University of Cambridge (UK)*

*2) Brain Physics Laboratory, Division of Neurosurgery, Department of Clinical Neuroscience, University of Cambridge (UK)*

*3) Department of Anaesthesia, University of Cambridge, (UK)*

*4) Department of Physiology and Transplantation, Milan University, Italy*

*senior authors contributed equally

Corresponding author: Giovanna Maria Dimitri, gmd43@cam.ac.uk

**Abstract**

**Objective**: In a previous study we observed the presence of simultaneous increases of Intracranial pressure ICP and heart rate (HR), which we denominated cardiocerebral crosstalks (CC), and related the number of such events to patients' outcome in a paediatric cohort. We present now an extension to an adult cohort from CENTER-TBI. **Methods**: We implemented a sliding window algorithm to detect CCs. We consider subwindows of observations of 10 minutes. If simultaneous increase of HR and ICP happens, of at least 20% with respect to the minimum value in the windows, a CC event is detected. Then correlation between the number of CCs and mortality was then obtained. **Results:** The cohort consisted of 226 adults (aged 16-85). The number of CC events detected varied (mean of 50, s.d. 58). A point biserial correlation coefficient [8] of -0.13 between mortality and CC was found. Despite correlation being lower than the paediatric case (-0.30) the negative direction is replicated. **Conclusions:** In this work we first extract CCs from ICP and HR observations of TBI adult patients, relating then number of CCs to patients outcome. Consistency with previous results in a paediatric cohort is shown. The higher the number of crosstalks the better the patient outcome.

Key words: Intracranial Pressure, Heart Rate, Cross-Talk, Recurrence Plots, Peaks Detection, CENTER-TBI

## 1. Introduction

Treatment and management of Traumatic Brain Injury (TBI) remains a leading research priority in clinical practice, with TBI being a worldwide cause of death and disabilities. While focusing on the brain monitored information such as Intracranial Pressure (ICP), importance should also be given to the interaction between heart and brain. Previous research in the field has shown the presence of a bidirectional causality existing between ICP, Mean Arterial Pressure (MAP) and Heart Rate (HR) in 24 hours period post TBI, linking this to the mortality rate [6].

The interest in the interaction between heart's and brain's homeostatic processes, is in fact part of a wide field of research that has been developed in the last few years [7]. The physiological coupling between the two systems, has been shown to be an important signal and biomarker for pathological and traumatic events [7].

In our previous study, with paediatric patients, we observed the presence of simultaneous onsets of ICP and heart rate (HR) transient increases and related the number of such events to patients' outcome [4]. In this work we present an extension of the previous work to an adult cohort from the CENTER-TBI study to explore the relationship between cardio-cerebral crosstalks (CC) behaviour and patients outcome.

## 2. Dataset

The data used for the present study is a subset cohort from the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) project, a consortium born in 2011 with the goal of improving classification and treatment of TBI patients [3]. Data was collected following the national or local regulatory ethical approvals. The CENTER-TBI study (EC grant 602150) was conducted according to the European regulations if applicable and the locally existing country laws, where the recruiting sites were based. Among those, laws regarding privacy, data protection, human materials, guidance related to clinical studies (for example the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects". Informed Consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the electronic case report form (e-CRF).

As part of the recruitment process, demographics and clinical data were collected prospectively, together with monitoring information coming from ICU. Intracranial pressure (ICP) was collected via an intra-parenchymal strain gauge probe (Codman ICP MicroSensor; Codman & Shurtleff Inc., Raynham, MA), parenchymal fiber optic pressure sensor (Camino ICP Monitor, Integra Life Sciences, Plainsboro, NJ, United States; https://www.integralife.com/) or external ventricular drain. The signals were recorded through a digital data transfer or alternatively digitized using an A/D converter (DT9801; Data Translation, Marlboro, MA), where appropriate, sampled at frequency of 100 Hertz (Hz) or higher, using the ICM+ software (Cambridge Enterprise Ltd, Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk) or Moberg CNS Monitor (Moberg Research Inc, Ambler, PA, USA). For the purpose of the present study, 271 patients from the CENTER-TBI High Resolution sub-cohort were screened. Only non-EVD patients with good quality of data and outcome available at the time of the analysis (total n= 226) were included. ICP and HR waveforms were processed with ICM+ software [5]. Demographic data as per version 1.0 were retrieved. The outcome variable we considered in the present analysis was the binary variable indicating the mortality of the patients.

## 3. Methods

High resolution waveforms were cleaned partially manually, to remove larger sections of invalid data, and partially automatically to exclude non-physiological transients like arterial line flushing periods, and down-sampled to 0.1 Hz by coarse graining using 10s moving average filter. For each patient the whole monitored period was considered.

We then used our own sliding window approach to detect the presence of cardio cerebral crosstalks, in the 0.1 Hz time series, similarly to the paediatric case [4]. Briefly, the algorithm considers sub-windows of observations of 10 minutes and if a simultaneous increase of HR and ICP is present, of a magnitude of at least 20% with respect to the minimum value in the windows, then a cardio-cerebral crosstalk event is detected (Figure 1).

Since the total length of recordings varied per patient, we normalized the number of CCs per patient by dividing it by the total number of data points in the time series.

We denominated the normalized CC measure $ct\_np$. Such measure is the ratio between the absolute number of observation and the total length of the time series. For subsequent statistical analysis the patient cohort was split into fatal (patients who died) and non-fatal (patients who survived) groups and the normalised count of cross-talks compared between the groups. Point biserial correlation coefficient was then computed between the number of CC events and mortality.

## 4. Results

The age range was 16-85 (mean 47) with 46 females and 180 males. The raw number of crosstalks detected was on average 50 per patient, with a high standard deviation of 58. The distribution of the number of normalized crosstalks per patient is shown in Figure 2. We then computed the point biserial correlation coefficient between the new variable and mortality, obtaining a point biserial correlation coefficient of -0.13. Boxplot chart of mortality with respect to the distribution of number of normalized crosstalks is shown in Figure 3.

The median value for $ct\_np$ in the case of mortality is 0.064, while in the case of non-mortality corresponds to 0.11 as shown by the figure. Moreover in Figure 3, we can also see the resulting p-value from the Welch two sample t-test between the two vectors of $ct\_np$ (in case of mortality or not mortality. The choice of the Welch two sample t-test was made given its higher reliability with unequal sample sizes). The test returns a significant p-value of 0.03, therefore exhibiting statistically significant difference between the distribution of $ct\_np$ in the case of mortality and not mortality. Such finding is interesting, as it confirms the findings of the paediatric cohort [4]. At the same time it shows a slightly different behaviour. In fact, despite being slightly less correlated than the case of the paediatric cohort (-0.30 value for the point biserial correlation coefficient) the negative sign of the correlation is replicated.

## 5. Discussion and conclusion

In this work we presented a computational workflow where we first computed the presence of events of simultaneous increase of ICP and HR, and then related it to TBI patients mortality. The quantification of the number of CCs was pursued using the sliding window algorithm proposed in [4]. Here simultaneous subwindows of 10 minutes of observations for ICP and HR are considered and a CC is detected if an increase of at least 20% with respect to the minimum value of the window takes place. The value of 10 minutes and 20% increase was kept in this work, in order to be comparable with the previous paediatric study we conducted.

We are aware that the identification of only such events of simultaneous increase may be a limitation of the present study. However we leave to future work the investigation of different time windows lengths where brain-heart crosstalks may be detected. The analysis of the CCs vectors for the case of mortality and non mortality shows also interesting results. First of all, from the Welch Two Sample T-test a significant p-value of 0.03 was detected, showing significant difference between the two cases of mortality and non mortality when considering

CCs distribution. No significant difference was found in the number of crosstalks per gender. The CCs were then related to mortality of the patients. Doing this, we detected consistency with previous results in the paediatric cohort studied. The negative direction of the correlation between mortality and number of crosstalks is retained between the two cohorts. However the adult cohort from the CENTER-TBI study presents a lower correlation (-0.13) with respect to the case of the paediatric cohort studied (-0.30). In both cases, nevertheless, the higher the number of CCs, the better the patients outcome. This is an interesting finding as it sheds more light on healthy-cardiovascular interaction between the two [4]. The study could be enriched along many different paths, and these represent limitations and future directions for the work presented. The parameters of the sliding window algorithm could be varied according to different clinical hypothesis to be tested, as for example the size of the window considered in the sliding window algorithm, as well as the percentage increase with respect to the minimum value of the ICP and HR in the time window frame. Moreover, more variables, such as mean ICP, cerebral autoregulation, GCS and age could be included into a multivariate modelling of the system.

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CENTER-TBI High Resolution (HR ICU) Sub-Study Participants and Investigators:

Audny Anke [1], Ronny Beer [2], Bo-Michael Bellander[3], Andras Buki[5], Manuel Cabeleira[6], Marco Carbonara[7], Arturo Chieregato[4], Giuseppe Citerio[8,9], Endre Czeiter[10], Bart Depreitere[11], Shirin Frisvold[13], Raimund Helbok[2], Stefan Jankowski[14], Danile Kondziella[15], Lars-Owe Koskinen[16], Ana Kowark[17], David K. Menon[12], Geert Meyfroidt[18], Kirsten Moeller[19], David Nelson[3], Anna Piippo-Karjalainen[20], Andreea Radoi[21], Arminas Ragauskas[22], Rahul Raj[20], Jonathan Rhodes[23], Saulius Rocka[22], Rolf Rossaint[17], Juan Sahuquillo[21], Oliver Sakowitz[24,25], Nino Stocchetti[26], Nina Sundström[27], Riikka Takala[28], Tomas Tamosuitis[29], Olli Tenovuo[30], Peter Vajkoczy[31], Alessia Vargiolu[8], Rimantas Vilcinis[32], Stefan Wolf[33], Alexander Younsi[25], Frederick A. Zeiler[12,34]

[1] Department of Physical Medicine and Rehabilitation, University hospital Northern Norway

[2] Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria

[3] Department of Neurosurgery & Anesthesia & intensive care medicine, Karolinska University Hospital, Stockholm, Sweden

[4] NeuroIntensive Care, Niguarda Hospital, Milan, Italy

[5] Department of Neurosurgery, Medical School, University of Pécs, Hungary and Neurotrauma Research Group, János Szentágothai Research Centre, University of Pécs, Hungary

[6] Brain Physics Lab, Division of Neurosurgery, Dept of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

[7] Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

[8] NeuroIntensive Care Unit, Department of Anesthesia & Intensive Care, ASST di Monza, Monza, Italy

[9] School of Medicine and Surgery, Università Milano Bicocca, Milano, Italy

[10] Department of Neurosurgery, University of Pecs and MTA-PTE Clinical Neuroscience MR Research Group and Janos Szentagothai Research Centre, University of Pecs, Hungarian Brain Research Program (Grant No. KTIA 13 NAP-A-II/8), Pecs, Hungary

[11] Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium

[12] Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

[13] Department of Anesthesiology and Intensive care, University Hospital Northern Norway, Tromso, Norway

[14] Neurointensive Care, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

[15] Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark

[16] Department of Clinical Neuroscience, Neurosurgery, Umeå University, Umeå, Sweden

[17] Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany

[18] Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium

[19] Department Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark

[20] Helsinki University Central Hospital, Helsinki, Finland

[21] Department of Neurosurgery, Vall d'Hebron University Hospital, Barcelona, Spain

[22] Department of Neurosurgery, Kaunas University of technology and Vilnius University, Vilnius, Lithuania

[23] Department of Anaesthesia, Critical Care & Pain Medicine NHS Lothian & University of Edinburg, Edinburgh, UK

[24] Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany

[25] Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany

[26] Department of Pathophysiology and Transplantation, Milan University, and Neuroscience ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy

[27] Department of Radiation Sciences, Biomedical Engineering, Umea University, Umea, Sweden

[28] Perioperative Services, Intensive Care Medicine, and Pain Management , Turku University Central Hospital and University of Turku, Turku, Finland

[29] Neuro-intensive Care Unit, Kaunas University of Health Sciences, Kaunas, Lithuania

[30] Rehabilitation and Brain Trauma, Turku University Central Hospital and University of Turku, Turku, Finland

[31] Neurologie, Neurochirurgie und Psychiatrie, Charité – Universitätsmedizin Berlin, Berlin, Germany

[32] Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania

[33] Department of Neurosurgery, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

[34] Section of Neurosurgery, Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

**Figures**

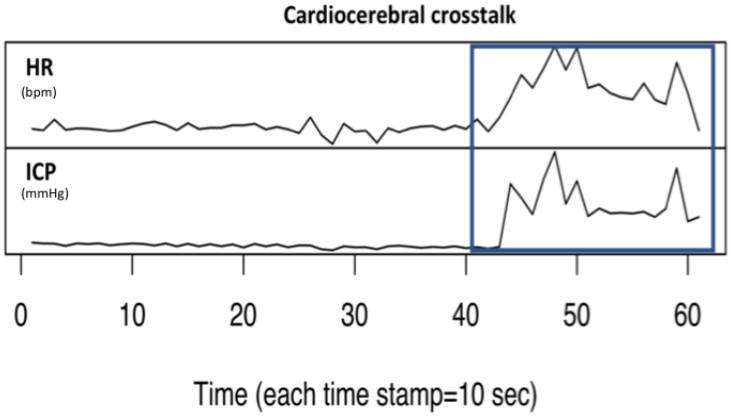


**Figure 1**: the figure shows the presence of 1 CC crosstalks (highlighted with the blue square) for a 10 minutes observations of HR (bpm) and ICP (mmHg) in one patient of our cohort. Each time stamp in the x axis corresponds to 10 seconds of observations. *HR*, heart rate; *ICP*, Intracranial pressure.

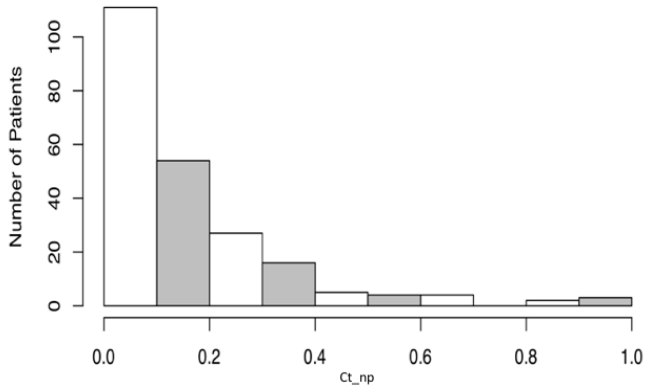


**Figure 2**: Distribution of the normalized crosstalks per patient in the adult cohort.

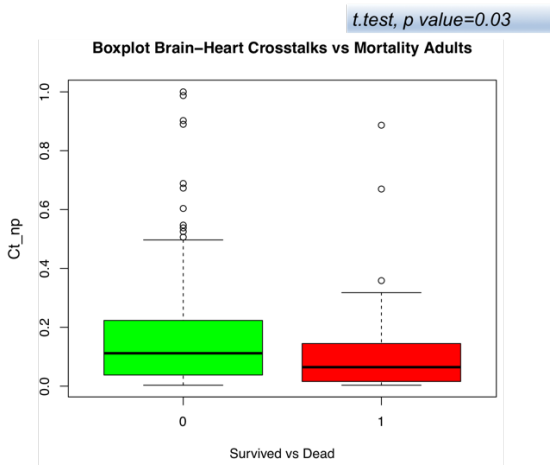


**Figure 3**: Boxplot showing the distribution of brain-heart crosstalks and mortality in the cohort analysed. As we can see from the picture the boxplot shows a higher number of cross-talks for the survived patients. A significant p-value of 0.03 is returned from the Welch Two Sample t-test of the two vectors of brain-heart crosstalks for the two groups of dead and alive patients.

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