AUTONOMIC NERVOUS SYSTEM ACTIVITY DURING REFRACATORY RISE IN INTRACRANIAL PRESSURE

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Refractory intracranial hypertension (RIH) is a dramatic increase in intracranial pressure (ICP) which cannot be controlled by treatment. Recent reports suggest that the autonomic nervous system (ANS) activity may be altered during changes in ICP. Our study aimed to assess ANS activity during RIH and the causal relationship between rising in ICP and autonomic activity.

We retrospectively reviewed 24 multicentre (Cambridge, Tromso, Berlin) patients who developed RIH as a pre-terminal event after acute brain injury (ABI). They were monitored with ICP, arterial blood pressure (ABP), and electrocardiography (ECG) using ICM+software. Parameters reflecting autonomic activity were computed in time and frequency domain through the measurement of heart rate variability (HRV) and Baroreflex sensitivity (BRS).

Our results demonstrated that a rise in ICP was associated to a significant rise in HRV and BRS with a higher significance level in the high-frequency HRV (p<0.001). This increase was followed by a significant decrease in HRV and BRS above the Upper-Breakpoint of ICP where ICP pulse-amplitude starts to decrease whereas the mean ICP continues to rise. Temporality measured with Granger test suggests a causal relationship from ICP to ANS.

The above results suggest that a rise in ICP interact with ANS activity mainly interfacing with the parasympathetic-system. The ANS seems to react to the rise in ICP with a response possibly focused on maintaining the cerebrovascular homeostasis. This happens until the critical threshold of ICP is reached above which the ANS variables collapse, probably due to low perfusion of the brain and the central autonomic network.
INTRODUCTION

According to Monro-Kellie doctrine, ICP is the result of the craniospinal-system ability to maintain a constant volume of craniospinal components.  

A rise in the ICP above the normal range (intracranial hypertension or ICH) can be attributed to an increase in the one or more of three-volume components of craniospinal space: parenchyma (cytotoxic or vasogenic edema, brain tumor, contusion), blood (hemorrhage, vasodilatation, venous congestion) or cerebrospinal fluid (CSF) (acute hydrocephalus). During the last few decades different phenomena of ICP elevation have been studied and different pathophysiological pathways have been identified underlying the concept that not all the ICP elevations are the same.

In the clinical context after ABI, ICH requires medical or surgical interventions in order to avoid low cerebral perfusion and risk of herniation and death.  

Refractory intracranial hypertension (RIH) is a severe increase in ICP which happens after an ABI and is usually resistant to medical or surgical treatment. RIH commonly leads to brain death or major brain damage. ICP runs from normal or moderately increased values to a dramatic ICH. Detrimental effects of elevation in ICP per se can be attributed to the development of trans-tentorial pressure gradient with damage on the brainstem also, an increase in cerebral pressure causes the compression of bridging veins and a reduction in cerebral blood flow (CBF). However the complete pathophysiological picture of this cascade remains unclear at this time.

The autonomic nervous system could be one of the potential factors involved in the refractory elevation of ICP. Variability in the beat-by-beat period of heart contraction is an intrinsic characteristic of a healthy neuro-cardiological system. ANS activity has been demonstrated to correlate with outcome in acute brain-injured patients with ANS impairment associated with higher mortality and long term outcome. The causal relationship of autonomic changes on
ABI sequelae remains hypothetical: ABI-related ANS dysfunction affects crucial organs of our body, specifically the heart.\textsuperscript{16,17}

According to guidelines,\textsuperscript{18} we can assess the autonomic system through the analysis of heart rate variability and baroreflex sensitivity which has been proposed, as a marker of healthy ANS. A significant number of studies have been conducted since the first studies done by Lowensohn (1977) and Leipzig (1986)\textsuperscript{19,20} exploring the relationship between ANS and ICP. More recent reports showed that ANS activity is altered during changes in ICP.\textsuperscript{21,22,12,23} The mechanisms involved, however, have not been clarified. Different methods have been used during the last decades producing results which have not been always consistent. It follows that more translational research is necessary since understanding the relationships between ANS and ICP and potential therapeutic targets will certainly improve patient outcomes.\textsuperscript{24,25,12,26,27}

The primary aim of our study was to assess changes in autonomic activity during the development of RIH and to explore the causal relationship between ICP and autonomic activity in patients with ABI. We focused our analysis on physiological data occurring during RIH as a pre-terminal event. Clinical variables such as medical or surgical interventions, ABI aetiology, different physiopathological brain injury features had not been taken into account.

\textbf{MATERIALS AND METHODS}

\textbf{Data collection}

The study was conducted as a retrospective analysis of a prospectively maintained database cohort (2009-2018) in which physiological monitoring data had been archived in three different hospitals: Department of Neurosurgery Charite Hospital, Berlin, Germany; Department of Intensive Care, University Hospital, Tromso, Norway and Neurocritical Care, Addenbrooke’s University Hospital, Cambridge. Monitoring was conducted using ICM+© software (Cambridge Enterprise, ltd, Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk ).
Acute brain-injured patients with a clinical need for ICP monitoring and computerized signal were included. The monitoring was part of standard patient care and archived in an anonymized way. All demographic/clinical data were extracted from the hospital records and were fully anonymized, no data on patient identifiers were available, and therefore formal patient or proxy consent and institutional ethics approval were not obtainable. Institutional reviewing was not required due to the retrospective design of the study which consisted of the analysis of data acquired during routine care.

Patients were monitored with at least invasive intraparenchymal ICP, invasive ABP, and ECG. 61 patients with Refractory intracranial hypertension (RIH) were initially selected and 37 were excluded due to either the absence of the ECG signal, frequent artefacts, or absence of baseline ICP recording before RIH evolved, which was crucial for dynamic analysis of ANS behavior. 24 ABI patients were therefore included in the final analysis. The patients who developed RIH had an initial baseline of ICP (mean ICP<20) followed by a rise to over 40 mmHg and then either fulfilled criteria of brain death or died following the withdrawal of treatment or cardiac arrest.

**Data Processing**

The signals were acquired digitally with a sampling frequency of at least 100 Hz. The time-averaged values of ICP and ABP were calculated on a 10-second calculation window. PRx was calculated as the moving Pearson correlation between ABP and ICP of a 5 minutes window, updated every minute. The amplitude of the cardiac pulse in ICP and ABP were determined as the fundamental harmonic of the Fourier transform of the pulse of ICP. RAP was calculated as the moving correlation coefficient between slow changes in ICP pulse amplitude (AMP) and mean ICP (10 seconds average data) over a period of 5 minutes, updating every minute.
The artefacts were manually cleaned in the raw data: in the ABP and ICP signal, the non-pulsatile chunks were removed. From ECG long, visible arrhythmic events and flat lines were manually removed, single ectopic beats were automatically detected by the software.

For each patient the recording was divided into three different segments: the first was called “baseline” or period one (P1) in which ICP mean was lower than 20 mmHg, the second period (P2) was the period during which the ICP started to rise, more or less continuously until elevated value of ICP. The third period (P3) was defined starting from the ICP/AMP “Upper Breakpoint” onwards. The “Upper Breakpoint” is a value of ICP and AMP of ICP above which pulse amplitude started to decrease with an ongoing increase in the mean ICP (figure2) if the “Upper Breakpoint” was not found the second period ended with the end of the recording when dramatic values of ICP were reached and which was followed by patient death.

**Autonomic variable calculation**

Secondary parameters reflecting autonomic activity were computed in time and frequency domain through the continuous measurements of HRV. According to the guidelines, we analysed HRV both in the time and in the frequency domain.

The analysis of oscillatory components of the ECG signal enables the assessment of the autonomic system since it is the primary regulator of cardiac chronotropy. The interval between R waves in ECG is the most commonly used to represent cardiac chronotropy and can be analysed both in the time domain and/or in the frequency domain.

In time domain we analysed global indexes of HRV such as standard deviation (SD), the standard deviation of the difference between sequential beats (SDSD) and square root of the mean squared difference between sequential beats (RMSSD).

In the frequency domain, we calculated the total power of the HRV spectrum, moreover, we calculated frequency-specific indexes. The High-Frequency component (HF) (0.15-0.4 Hz) is thought to be modulated by the parasympathetic system, whereas the Low Frequency (LF)
(0.04-0.15Hz) component is modulated by both the sympathetic and the parasympathetic system. The ratio between the two (LF/HF ratio) seems to mirror the sympathetic activity.\(^{33}\)^{18}

The HRV in the time domain was analyzed using a 300-second time series of R-R intervals that were updated every 10-seconds. In the frequency domain, the Lomb-Scargle periodogram was used to calculate the spectral power of the R-R interval time series.\(^{18}\)

Baroreflex sensitivity, which can be described as the magnitude of response in the heart-beat interval to a change in blood pressure, was measured using the cross-correlation method which had been shown to have the lowest intra and inter-individual variability in the EUROBAVAR database.\(^{34}\) The x-BRS calculation algorithm was implemented into the ICM+ software using a 10-second window moving along the time axis. In order to remove the influence of an unknown time delay of the baroreceptor response, a cross-correlation function was used to maximize the correlation coefficient which meant that the actual total window length used in each calculation was 17 seconds. Valid x-BRS was returned only if the correlation coefficient is significant at p < 0.01.

**Statistical Analysis**

R statistical language was used to perform the statistical analysis [R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/ version 3.3.3 ]. Alpha was set at 0.05 for significance. The non-normal distribution of the data was established by the Shapiro-Wilk test.\(^{35}\)

Wilcoxon test was used for comparisons after having extracted variables as mean value +/- SD during the three different periods.

The correlation between physiologic parameters was assessed using the Spearman method.

For establishing the direction of potential causal interactions in time series we used the model developed by Granger \(^{36}\) capable of causal inference. Understanding not only functional connectivity but also directional connectivity is becoming more and more important and
Granger causality is a statistical method for identifying the significance of directional information flow between a given set of time series. According to Granger, a time series $X$ is called to Granger-cause another time series $Y$ if the past value of $X$ contains information that helps to predict future values of $Y$. Granger test was applied to stationary time-series between ICP and autonomic variables during period 1 and period 2. The calculation of the Directionality Index (DI) was then applied.

RESULTS

We analysed 24 ABI patients who all died during RIH (4 fulfilling brain death criteria, 11 after the withdrawal of intensive care treatment for catastrophic brain injury, while the cause of death is not reported about 9 patients, however, their death occurred during RIH). The mean age was 37 years (SD +/- 15 years). 21 patients had a TBI, 3 patients had a SAH. 5 patients underwent a decompressive craniectomy before the recorded time series, 17 did not undergo decompressive craniectomy, we do not have information about surgical intervention about 2 patients. 5 patients had a cerebrospinal fluid (CSF) drainage with external ventricular drainage.

Mean ICP at baseline (P1) was 15 mmHg (SD +/- 8 mmHg) and increased by 25 mmHg (SD +/- 14 mmHg) during the transition period (P2). The third period (P3), after the “Upper Breakpoint” of ICP/AMP, was visible in 11 patients of 24. The “Upper Breakpoint” was reached at a different level of ICP. This means that the upper breakpoint identified in this population ranged from 21 mmHg to 100 mmHg. The overall mean value of ICP during the third period was 49 mmHg but with a high standard deviation of 22 mmHg. With regard to the cerebral perfusion pressure (CPP), the lowest value was 10 mmHg and the higher value of 74 mmHg with the mean value of 49 mmHg during the third period (Table1).

The mean values of variables in the three different periods are illustrated in Table1.
Comparison of the means values between baseline (P1) vs transition period (P2) of increasing ICP showed that the rise in ICP is associated with a significant rise in the global index of HRV both in time and frequency domain (p<0.001) and BRS (p<0.001). In terms of frequency-specific index, a significant difference was found in the HF and LF of HRV whereas no significant difference was found in the LF/HF ratio. (Figure 1; Table 1)

In 13 of 24 patients, an “Upper breakpoint” of ICP-AMP was identified above which ICP pulse AMP starts to decrease whereas ICP mean continues to rise (Figure 2).

The increase of autonomic variables during the rise in ICP was followed by a significant decrease of HRV and BRS after the “Upper Breakpoint” (P3) (p<0.05 of the total power of HRV, HF, LF, SDSD) (Figure1). The RAP index, which is the correlation between the amplitude of ICP waveform (AMP) and mean ICP, decreased towards zero or negative level after the Upper Breakpoint of ICP (Figure 2). This seems to occur when the cerebral autoregulatory capacity is exhausted and is consistent with previous descriptions.\textsuperscript{38,29,39} Moreover, in two patients, we observed an unexpected phenomenon: the upper breakpoint of ICP with a decrease in amplitude of ICP and main autonomic variables was then followed by a “recovery” in amplitude which started to increase again together with the ICPmean and sympathetic activity (Figure 4 supplementary material and Table 2 supplementary material).

ICP and global indexes of HRV were significantly correlated during the final steep rise in ICP when it was present (20 patients) with a strong correlation between ICP and SDSD (R > 0.7) in 10 of 21 patients, moderate correlation (0.4 < R < 0.7) in 5 of 21 patients and weak correlation (R < 0.4) in 5 patients.

The Granger test was applied showing a directional connectivity from ICP and autonomic variable in the majority of patients. In 15 patients directionality index was directed from ICP to ANS, in 5 patients was from ANS to ICP, in 4 the test was not significant. This directionality does not change significantly between period 1 (baseline) and period 2 (rise in ICP).
DISCUSSION

Our results suggest that there is a relationship with the rise in ICP and the ANS, more precisely this relationship seems to favor predictive causality from ICP to autonomic variables. To our knowledge, this is the first study that explores the causality in this area.

Our results showed that the rise in ICP is associated with an increase in HRV (both in time and frequency domain) and in the baroreflex sensitivity with the most significant rise involving the HF range of HRV, which represents the parasympathetic branch of ANS.

This relationship has been previously confirmed by Sykora et al.\textsuperscript{12} who have shown a positive correlation between ICP and the HF of HRV.

Our results are also consistent with the study of Tymko et al.\textsuperscript{23} which also demonstrated an increase in the global index of HRV and BRS during high ICP episodes of plateau waves.

On the other hand, an increase in the LF/HF ratio after the infusion of saline solution into the cerebrospinal system was found in the experimental studies of Ramchandra et al.\textsuperscript{22} and Schmidt et al.\textsuperscript{21} It was speculated by these authors that ICP might be a determinant of sympathetic output as a novel intracranial baroreflex. Other findings suggest a sympathetic control of CSF formation in experimental hydrocephalus.\textsuperscript{40}

Based on this previous evidence, it is highly likely that there are sensitive intracranial receptors which can respond to reduced cerebral blood flow and/or rise in ICP activating ANS.\textsuperscript{41} In rat cerebral arteries, mitochondria-rich nerve varicosities were interpreted as sensory in nature. These nerve terminal varicosities have been postulated to represent nerve specializations for pressure or tension reception based on the structural analogy they share with sensory or baroreceptor nerve terminals.\textsuperscript{42,43,44} If these findings were to be reported also in humans, in terms of nature and functionality, we would have the anatomical explanation of the starting point of a “brain driven response” likely involving ANS. In addition, our results reinforce this
concept underlying that temporality between ICP and ANS might suggest a causal relationship from ICP to ANS. However we cannot exclude the presence of a third unmeasured or untested cause of change in both ICP and ANS, therefore we did not measure true causality with Granger test.

HF of HRV was raised during the development of RIH; we speculate that the parasympathetic system might be triggered by the increase of ICP, or decrease in CPP, via stimulation of sensory nerves of the cerebrovascular system. It is well known that parasympathetic fibers innervate cerebral blood vessels exerting a vasodilatory action via nerves coming from sphenopalatine and optic ganglia. The rise in parasympathetic activity might, therefore, attempt to produce vasodilatation as an attempt to preserve the CBF in the context of CBF deterioration. This vasodilatation produces an increase in arterial brain blood volume and consequently a further increase in ICP. (Figure 3)

Moreover, the baroreflex was observed to rise together with the development of RIH and HRV HF, which suggests an intact baroreflex loop. The rise in both BRS and HRV HF is consistent since vagal activity has been shown to play a major role in BRS. It is also well known that the relative stability of CBF despite fluctuations in blood pressure is maintained by two regulatory mechanisms: the baroreflex and cerebral autoregulation (CA). Potential interactions between CA and ANS need further investigations.

Baroreflex controls blood pressure in the short term by the extent of the stretch of receptors in the walls of carotid arteries and of aorta it discharges differently to the central nervous system. Changes in baroreflex discharge trigger modulation of heart rate (HR), cardiac contractility and vascular tone and venous return through the modulation of the parasympathetic and sympathetic nervous system. Our results suggest the attempt of the autonomic system, specifically the parasympathetic system and the baroreflex, to maintain a constant CBF in response to a CBF impairment. In
terms of the potential “protective effect” of the parasympathetic nervous system, activation via vagal nerve stimulation has been proposed as a strategy to reduce the adverse effects of TBI-induced sympathetic hyperactivity.\textsuperscript{16} Lopez et al. speculated that stimulating the parasympathetic response may help alleviate the adverse effects on the blood-brain barrier that occur with hyper sympathetic autonomic dysfunction by decreasing its disruption.\textsuperscript{48} Some other studies suggest that vagal nerve stimulation attenuates post-TBI intestinal permeability and intestinal dysfunction after ABI.\textsuperscript{49}

The assumption that HF of HRV mirrors the parasympathetic branch whereas LF/HF ratio represents the sympathetic branch must be made with caution given the complex nonlinear interactions between the sympathetic and parasympathetic systems. It is likely that brain injury alters the fine balance between the sympathetic and parasympathetic arms of the autonomic nervous system, resulting in an imbalance of the homeostatic mechanisms that maintain normal organ system function and their interactions with each other.\textsuperscript{16} Another important finding of our study was that the increase in autonomic variable and BRS during ICP rise was followed by a significant decrease after the Upper Breakpoint of ICP. An Upper Breakpoint above which ICP pulse amplitude starts to decrease whereas ICP mean continues to raise has been observed both experimentally\textsuperscript{50} and clinically.\textsuperscript{29} It has been speculated that this phenomenon is related to the terminal closing of the cerebral arterial bed when the critical closing pressure approaches ABP.\textsuperscript{6} Another hypothesis is that it is strongly related to the state of the cerebrovascular system and point of autoregulation exhaustion at low perfusion pressure.\textsuperscript{51,52} If we assume these concepts are true, the sudden derangement of autonomic functionality after the Upper Breakpoint might be attributed to the cerebrovascular ischemic damage of the central autonomic network. This can occur at a different level of ICP/CPP depending on the haemodynamic response to acute ICH in different areas. The large
variability of ICP breakpoint value in our subjects implies large compliance differences before herniation occurs in the traumatized brain.

Even though great extent of literature has been focused on cerebral perfusion pressure only as the product rather than the driver of blood pressure dynamics, substantial experiments have been conducted demonstrating the paramount concept about the brain task to protect its own flow first and foremost. This is called “selfish brain theory”. According to Prof. Cushing and other more recent authors the “selfish brain theory” supports the idea that ICP can influence ABP by influencing the autonomic system.67,22

Donnelly et al6 described the cerebral haemodynamic in rabbits during artificial CSF infusion showing a response which, at a lower level of ICP, tries to maintain CBF reducing wall tension while at a higher level of ICP increases ABP. In the study of Schmidt et al, conducted in both animals and humans, ICP is described by the authors as a reversible determinant of efferent sympathetic outflow even at relatively low ICP levels.21 Rosner et al58 demonstrate in laboratory observations in cats a gradual and sustained increased in ABP directed to restore CPP likely driven by sympathetic activity. (Figure 3)

It can be supposed that we could not see any significant increase in sympathetic activity in the majority of the patients assessed in our study given the small number of patients and a possible condition of sympathetic system derangement.58

Therefore our observations, supported by the Granger results, might, suggest the presence of sophisticated mechanisms which underpin the concept of a “brain driven” rescue mechanism which involves both parasympathetic and sympathetic system playing a crucial role attempting to increase the CBF.

It still remains to be clarified if what we call “the Cushing response” is an acute and terminal pathological reflex to brain ischemia or part of this fine mechanism for ABP regulation, capable of sensing and integrating information possibly involving not only the sympathetic branches.
Transduction mechanisms are clearly not fully resolved but may include astrocytic–neuronal, as well as vascular–neuronal and vascular–astrocytic–neuronal signalling pathways, involving mediators such as ATP lactate, NO, shear stress and stretch-activated cation channels. Recent findings suggest the astrocytes could be potentially classified as baroreceptors responding to change in ICP or CPP.

Our study suggests that further investigation needs to be performed also to better assess the relationship and the directionality between ICP, autonomic systems and therefore ABP and CBF. Also in order to assess the behavior of autoregulation in this peculiar setting and interpret the autoregulation indexes which have been used during the last decades.

LIMITATIONS

Our data are retrospective, with a small patient number, recorded in three different hospitals, having obvious differences in management protocols. Even if all the patients were treated according to the Brain Trauma Foundation Guideline 4th edition, the physiology described here does not represent refractory intracranial hypertension in its purest form, as each patient was subjected to various treatment which could have influenced ICP, CPP, and ECG data recorded therefore precluding any reliable analysis on CA. Physiologic data could be subject to clinical noise such as sedation, drugs, mechanical ventilation, temperature, changes in body position. Moreover, the small number of patients did not enable us to provide reliable statistical analysis in terms of autonomic behaviours in different clinical subsets such as treatments or physiopathological brain injury features or aetiology.

However, despite these potential confounders, we were able to reconfirm findings coming from previous literature.

Concerning the two patients with the recovery of ICP amplitude and rise in LF/HF ratio. It could be theoretically hypothesized, that noradrenaline may have been administered in order to
raise the ABP and the CPP after the rise in ICP which can influence sympathetic nervous system activity and then LF/HF ratio. To explore this hypothesis, we analysed the same method in a patient in which ICP was stable, but noradrenaline was doubled in a couple of minutes for clinical reasons. It is shown that there is no difference in terms of LF/HF ratio change (Figure 5 supplementary material). These are, however, single observations. Dedicated studies are needed to confirm these descriptive results.

CONCLUSION

Rises in ICP are associated with changes in autonomic activity: increase in HRV and BRS. This association takes place mainly through the interaction between ICP and the parasympathetic system, which possibly attempts to restore deteriorating CBF. This happens until the Upper breakpoint of the AMP-pressure relationship is reached after which the autonomic system variables collapse possibly due to low brain perfusion of the central autonomic network. Furthermore, temporality between ICP and ANS might suggest a causal relationship from ICP to ANS.

The presence of sophisticated mechanisms that underpin the concept of a “brain driven” rescue process involving the ANS needs further investigation in a large multicentric prospective study.

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AUTHOR’S DISCLOSURE STATEMENT

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Table 1 Summary of mean values +/- standard deviation parameters and p-value of Wilcoxon test between mean values of period 1 (baseline) versus period 2 (increasing intra-cranial pressure) and period 2 versus period 3 (above upper breakpoint of Amplitude- mean intra-cranial pressure relationship).

CPP (cerebral perfusion pressure); ICP (intracranial pressure); ABP (mean arterial blood pressure); PRX (autoregulation index); AMP (amplitude of ICP waveform); HRbm (heart rate beat for minute); RAP (correlation between the AMP and ICP mean); HRV HF (heart rate variability high frequency range); HRV LF (heart rate variability low frequency range); HRV RATIO (ratio between Low Frequency and High Frequency of heart rate variability); HRV TOT (total power of heart rate variability); HRV SD (standard deviation of heart rate variability); HRV SDSD (standard deviation of the difference between sequential beats).

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>PERIOD 1</th>
<th>PERIOD 2</th>
<th>PERIOD 3</th>
<th>P VALUE P1VSP2</th>
<th>P VALUE P2VSP3</th>
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<td>70 +/-14</td>
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<td>&lt;0.01</td>
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<td>25 +/-14</td>
<td>49 +/-22</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ABP MMHG</td>
<td>93 +/-13</td>
<td>95 +/-12</td>
<td>95 +/-18</td>
<td>0.06</td>
<td>0.8</td>
</tr>
<tr>
<td>PRX</td>
<td>0.2 +/-0.4</td>
<td>0.4 +/-0.4</td>
<td>0.8 +/-0.2</td>
<td>0.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BAROINDEX MS/MMHG</td>
<td>9 +/-8</td>
<td>12 +/-15</td>
<td>7 +/-11</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RAP</td>
<td>0.4 +/-0.3</td>
<td>0.4 +/-0.3</td>
<td>0.3 +/-0.4</td>
<td>0.18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AMP</td>
<td>2.2 +/-1.3</td>
<td>3 +/-2</td>
<td>4 +/-4.1</td>
<td>&lt;0.01</td>
<td>0.1</td>
</tr>
<tr>
<td>HR BPM</td>
<td>71 +/-23</td>
<td>66 +/-19</td>
<td>93 +/-30</td>
<td>0.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HRV HF</td>
<td>152 +/-295</td>
<td>473 +/-1092</td>
<td>99 +/-202</td>
<td>&lt; 0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HRV POWER MS²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRV LF</td>
<td>55 +/- 95</td>
<td>163 +/- 415</td>
<td>149 +/- 300</td>
<td>&lt; 0.01</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>POWER MS³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRV RATIO</td>
<td>1.06 +/- 1.2</td>
<td>1.05 +/- 1.4</td>
<td>1.6 +/- 1.5</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>POWER MS³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRV TOT</td>
<td>388 +/- 611</td>
<td>1094 +/- 2290</td>
<td>529 +/- 932</td>
<td>&lt; 0.01</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>POWER MS³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRV SD</td>
<td>14 +/- 11</td>
<td>24 +/- 18</td>
<td>15 +/- 14</td>
<td>&lt; 0.01</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>HRV SDSD</td>
<td>15 +/- 14</td>
<td>30 +/- 26</td>
<td>12 +/- 12</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

**Figure 1** Neuromonitoring showing a time trend of intra-cranial pressure (ICP) rising to refractory values followed by the rise of the main autonomic variables: SDSD (standard deviation of the difference between sequential beats), HRV-TOT (total PSD, power spectral density, of heart rate variability) BRSX (baroindex). The figure also shows an «Upper Breakpoint» (yellow line) above which amplitude of ICP (AMP) starts to decrease together with the autonomic variables, while mean ICP continues to rise. The baseline period in which the ICP is around normal values is defined as P₁, transitional period in which ICP starts to increase to high value is P₂, the period after the upper breakpoint of ICP amplitude (AMP) is P₃.
Figure 2 Neuromonitoring showing a time trend of ICP, AMP, RAP (which is the correlation coefficient between amplitude and mean ICP) and scatter plot of AMP and ICP. The figure illustrates the upper breakpoint of AMP (yellow line) with a reduction of RAP which goes near zero around the upper breakpoint and below zero after the upper breakpoint when AMP markedly decrease.
Figure 3 Potential mechanisms involving the autonomic nervous system which might attempt to restore homeostasis in the context of CBF (cerebral blood flow) and CPP (cerebral perfusion pressure) derangement.

A decrease in CPP and/or CBF might activate the two branches of ANS (autonomic nervous system). The parasympathetic system causes brain vessel vasodilatation focused on maintaining brain CBF. At the same time the sympathetic system increases ABP (arterial blood pressure) and therefore CPP.

These assumptions could be considered in the context of not deranged ANS.
SUPPLEMENTARY MATERIAL

Table 2 Supplementary material

This table shows the difference in PT8 and PT21 in terms of the mean value of the power of heart rate variability low frequency/high frequency ratio (HRV RATIO) between the baseline period (P1) and the period (P4) after the “double breakpoint”. The sympathetic drive increased from period 1 to period 4 however the results obviously did not reach statistical significance for the small number of patients. In the other patients in which we had not observed any increase in sympathetic drive, we should consider that the sympathetic response could be absent because of the “exhaustion phase” of sympathetic activity which often happens in acute brain injury after the hyperdynamic phase.

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>HRV RATIO P1</th>
<th>HRV RATIO P4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT8</td>
<td>1.5</td>
<td>3.7</td>
</tr>
<tr>
<td>PT21</td>
<td>1.4</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Figure 4 Supplementary Material: “Double breakpoint” observed in two patients PT8 and PT21: after the period followed by the upper breakpoint of intra-cranial pressure (ICP) (P3) we can see a recovery of ICP amplitude (AMP) (P4) associated with a rise in HRVratio which mirrors the sympathetic activity. This finding could be similar to the one described by Rosner JM et all who experimented in cats that brain stem ischemia/low perfusion triggers a sympathetic discharge resulting in an increase in ABP and CPP in the context of sympathetic system still not deranged.
Figure 5 Supplementary Material: The figure shows a neuromonitoring of a control patient who did not develop RIH. The cursor is positioned when the dose of noradrenaline (nadr) was doubled. The boxplot shows that the rise in noradrenaline seems not followed by a rise in HRV ratio if we compare the mean values of the two highlighted periods before and after the rise in noradrenaline.

ICP (intracranial pressure) ABP-real (mean arterial blood pressure) PRX (autoregulation index) AMP (amplitude of ICP waveform) HRV HF (heart rate variability high frequency range) HRV LF (heart rate variability low frequency range) HRV RATIO (ratio between Low Frequency and High Frequency of heart rate variability)
REFERENCES


2. Kellie, G. (1824). Appearances observed in the dissection of two of three individuals presumed to have perished in the storm of the 3rd and whose bodies were discovered in the vicinity of Leith on the morning of 4th November 1821: some reflections on the pathology of the brain. 1:84-122 p.


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