Natália de Sousa Antunes

The utility of heart rate variability as a prognostic factor in children with traumatic brain injury
Natália de Sousa Antunes
A utilidade da variabilidade da frequência cardíaca como fator de prognóstico em crianças com traumatismo craniano
The utility of heart rate variability as a prognostic factor in children with traumatic brain injury

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Doutor Marta João Rodrigues da Silva

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Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

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Faculdade de Medicina da Universidade do Porto, 22/03/2018

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Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

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DESIGNAÇÃO DA ÁREA DO PROJECTO
Pediatría

TÍTULO MONOGRAFIA (riscar o que não interessa)
A utilidade da variabilidade da frequência cardíaca como fator de prognóstico em crianças com traumatismo craniano.
The utility of heart rate variability as a prognostic factor in children with traumatic brain injury.

ORIENTADOR
Dra. Marta João Rodrigues da Silva

COORIENTADOR (se aplicável)
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ASSINALE APENAS UMA DAS OPÇÕES:

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<th>É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.</th>
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Faculdade de Medicina da Universidade do Porto, 22/03/2018

Assinatura conforme cartão de identificação: Natália de Sousa Antunes
Purpose
Heart rate variability in children suffering from head trauma is not yet well studied. This study aimed to assess the cardiovascular repercussions of the autonomic nervous system, through the evaluation of heart rate variability (HRV), as a prognostic factor in children with traumatic brain injury (TBI).

Methods
Databases (Pubmed, World of Science and Scopus) - studies were conducted from 1996 to 2017, considering heart rate variability of pediatric patients (1 month to 18 years), based on Task Force guidelines (1996). We analyzed eight (8) studies that included our inclusion criteria.

Results
The normalized total power of 0.04 to 0.15 Hz was used to quantify the heart rate low frequency (LF) and from 0.15 to 0.40 Hz to quantify heart rate high frequency (HF). An LF / HF ratio was used as a measure of sympathetic heart rate modulation.

Patients with brain injury that became brain dead had a markedly lower LF/HF ratio (p <0.001), with a significant decrease after the first few hours of hospitalization. Patients with a more favorable prognosis had significantly higher LF/HF ratios.

Conclusions
Autonomic Nervous System (ANS) dysfunction in children suffering from brain injury leads to oscillations in heart rate variability.
After reviewing the literature, we concluded that HRV can be useful for the determination of the severity of neurological damage and a prognostic factor in the evaluation of its recovery.
LF/HF ratio may be useful to predict which patients will become brain dead and which ones will have a better prognosis.

KEYWORDS
Heart rate variability; Children; Head trauma; Pediatric patients; Dysautonomia;
INTRODUCTION

Heart Rate Variability (HRV) is defined as the variation over time of the interval between consecutive heartbeats. It reflects the heart’s ability to adapt and respond to changing circumstances by detecting and responding to unpredictable stimuli. It serves as an indicator of autonomous activity in the regulation of circulation. It is also considered as the method of analysis of autonomic nervous system activity. Changes in HRV have been associated with several pathological conditions.

HRV measurements can be grouped in time domain, frequency domain and non-linear measurements.

HRV derives from the difference in duration of intervals between two consecutive beats, called R-R intervals, and is measured in milliseconds. These intervals are obtained on the ECG: the QRS complexes correspond to heart beats and R-R1 and R-R2 are intervals between beats.

Several frequency bands have been defined in humans, namely, high frequency band (HF): between 0.15 and 0.4 Hz - modulated by the parasympathetic nervous system and generated by respiratory, low frequency band (LF): between 0.04 and 0.15 Hz - derives from the activity of the sympathetic system and is thought to reflect the delay in the baroreceptor reflex system. This delay is attributed to the fact that the sympathetic system uses a second messenger system known as cyclic AMP (cyclic adenosine monophosphate) and very low frequency band (VLF): between 0.01 and 0.04 Hz. It is of uncertain origin but has been attributed to a marker of sympathetic activity [1].

As the heart rate (HR) is a nonstationary signal, its variability (especially a reduction) may indicate the existence or eminence of current disease: the reduction of the HRV is associated to increased mortality. HRV is widely used to efficiently monitor the human body, more precisely in the evaluation of ANS, through its sympathetic and parasympathetic components. Therefore, it has become a relevant non-invasive clinical tool [2].

Cranioencephalic trauma (TBI), which is associated with autonomic dysfunction and corresponds to 40% of deaths in American children under 1 year of age [3], is the main cause of traumatic death [4].

Despite the vast experience and research in this field, the determinants of its occurrence in children is still not well defined.

TBI may result in dysautonomia, which is a condition characterized by marked, paroxysmal changes in blood pressure, heart rate, respiratory rate, temperature and/or sweating, and is associated to dysfunction of the autonomic nervous system [5].

Dysautonomy affects a small sub-group of survivors who have suffered severe TBI. They are more likely to suffer from severe physical or cognitive impairment, a prolonged period of hospitalization, as well as a long-term dependence on health care [6].

Therefore, the purpose of this review was to examine the relevance of HRV as a prognostic factor in children who suffered head trauma, in the belief that a decrease in HRV may lead to a lower probability of survival and a higher rate of mortality and morbidity.

METHODS

A systematic research of the literature was made in January 2018, based on three databases (Pubmed, World of Science and Scopus) with the keywords: (heart rate variability) and (children) and (head trauma) and (pediatric patients) and (dysautonomia). Two hundred and twenty one articles from Pubmed, 102 from the Web of Science and 2 from the Scopus database were found.
The abstracts were analyzed according to the following criteria: articles from 1996 to 2017, human studies in pediatric age (1 month to 18 years), without congenital diseases or comorbidities, of empirical investigations (excluding meta-analyses, review articles and reports of single cases), using time and frequency domain methods as VFC evaluation according to the Task Force guidelines [1] and available in full text in Portuguese or English.

Eight (8) articles were included according to the inclusion criteria and information included in the abstracts.

Integral texts of articles with matching predefined criteria were screened.

Data extraction records were performed for each of the ten selected articles.

The aim, study format, author and year, characteristics of participants, parameters used to measure HRV (time domain and frequency), experimental conditions and key ideas were extracted.

RESULTS

According to the Task Force of the European Society of Cardiology and the North American Society for Rhythm and Electrophysiology [1] and several studies [6-15] we used the time and frequency domains to determine the utility of HRV as a prognostic factor in children with TBI. The results are summarized in Tables 1 and 2.

The data extracted from the selected articles were summarized in table 3.

We verified that there was a variation (p = 0.027/ p = 0.59), between the low frequency (LF) and high frequency (HF) values, respectively, in the analyzed studies when compared with those suggested by the Task Force (Table 2).

The HF band starts at the value at which the LF band ends: 0.15Hz (Table 3).

Six studies excluded the very low frequency band (VLF), starting the LF band between 0.01 and 0.04Hz and those that included the VLF band, used the value 0.01Hz to start it (Table 3).

Baguley I et al (2006) investigated dysautonomia and HRV following severe traumatic brain injury through the analysis of HRV. Data was collected on age-matched subjects with and without dysautonomia and non-injured controls. The TBI group revealed significant differences in HRV parameters both compared to controls and between dysautonomic and non-dysautonomic subjects.

VLF power was relatively preserved between groups. Only LF was significantly lower in the TBI group (p = 0.009). The mean LF/HF ratio was in the normal range for controls and elevated in the TBI group (1.8 and 3.7, respectively, p < 0.05). The control group mean SDNN in TBI group was significantly lower than controls (p = 0.018). HRV data demonstrated that subjects with dysautonomia had significantly lower LF power (p < 0.05). There was no statistical difference between mean LF/HF ratio for the dysautonomic vs non-dysautonomic groups (p = 0.164).

In the current study, the dysautonomia group had significantly reduced LF power and greater LF/HF ratio variability (ranging from 0.3 – 12.3) compared to the non-dysautonomic group [6].

According to Bismas A et al (2000) patients who progressed to brain death had a very low LF / HF ratio (p <0.001), with a significant decrease in the first 4 hours of hospitalization. Patients with better prognosis had higher LF / HF ratios [7].

Goldstein B et al (1998) found significant correlations between survival and mean heart rate (p = 0.004) and LF (p = 0.009). In other words, the severity of the neurological injury, prognosis and survival were inversely related to the degree of cardiovascular variability. Brain death occurred at very low values of HRV (near zero). In addition, the cardiovascular and autonomic systems were proportionally decoupled at various levels during acute brain injury. Thus, monitoring the degree of decoupling in these systems allows a better understanding of neuroautonomic and cardiovascular interactions during acute brain injury [8].
Goldstein B et al (1998) found a negative correlation between the minimum value of LF (p < 0.001), HF (p < 0.001) and LF/HF (p = 0.007), recorded during hospitalization. At discharge from Intensive Care Unit (ICU), the prognostic showed a negative correlation between the minimum value of LF (p < 0.001), HF (p < 0.001) and LF/HF (p = 0.008), in other words, low values of HRV demonstrated a greater severity of the illness and a worse prognostic [9].

According to Goldstein B et al. (1996), maximal values of LF (p <0.001), and minimum values of HF (p < 0.001) demonstrated a higher probability of survival, suggesting that HRV may prove to be a sensitive and specific method useful in determining the severity of the neurological injury in children who suffered brain injury [10].

Almeida R et al (2013), concluded that the group of patients with brain death presented reduced HRV in all frequency bands (p <10^{-16}) [11].

Su et al. (2005) proved that a percentage increase in the LF band and in the LF / HF with the decrease in HF indicated a greater power on the part of the sympathetic nervous system and attenuated parasympathetic. These changes were related to the severity of damage to the brainstem.

It was also observed that in brain death, LF and HF presented very low values, concluding that HRV may be a useful tool in the evaluation of ANS functions in patients with various levels of brain injury [12].

Kim S et al (2017) found that a significant increase in LF (p = 0.0119) in patients with acute brain injury indicated a high sympathetic excitatory activity since LF had a sympathetic predominance. However, HF had a parasympathetic modulation. The significantly decreased values observed in the group of patients with acute brain injury (ABI) suggested a decreased parasympathetic activity. The significant increase in the LF / HF ratio of the group of patients with acquired brain injury infers a greater power on the part of their sympathetic nervous system (p = 0.0018). In the time domain, SDNN, which reflects every cyclic aspect that was related to the variability during the recording period, was decreased in ABI group (p = 0.0134); rmSSD, which represents the parasympathetic regulation of the heart, was significantly different between the two groups (p = 0.0240). In summary, according to this study, the group with acute brain injury had a sympathetic predominance when compared to the control group [13].

Discussion

The main result of this study is that HRV can be useful when determining the severity of neurological damage and a prognostic factor in the evaluation of its recovery. It was found that the more severe the neurological injury, the worse the prognosis and the lower the HRV. This suggests that as HRV is commonly used to efficiently monitor the human body in the evaluation of ANS, through its sympathetic and parasympathetic components, it is a relevant non-invasive clinical tool [2].

Short-term variations in heart rate are observed at all ages and are an important sign of normal homeostatic mechanisms of the cardiovascular system. The degree of heart rate variability provides information about how the nervous system interferes with heart rate and heart responsiveness. In addition, disorders of the central and peripheral nervous system have effects on HRV. Furthermore, all normal cyclic changes in heart rate are attenuated in the presence of severe brain damage [14].

Our interest in the present study was to explore HRV changes and to investigate their relationship in the prognosis of children with TBI. Even though not much has been published about this matter, in the analyzed studies, HRV was markedly depressed in children who progressed to brain death after TBI and in patients with dysautonomia. In addition, LF / HF ratio was significantly reduced in brain-dead children. The low LF / HF ratio was evident in all brain-dead and non-surviving patients, while in the control group there was a progressive increase in all measured variables. However, it
is hypothesized that these conclusions are biased in relation to the importance of each variable, due to the small sample size of each study. For this reason, we think that a similar study with a larger and more homogenous group could have a significant value in HRV as a predictive element, rather than simply associated, with mortality.

The most relevant limitation of this review was the lack of standardization of the Task Force guidelines for the pediatric population. The standard values described may not apply to children with the result that different authors used different frequency bands. Furthermore, the implementation of a standard method to collect and analyze HRV would contribute to more reliable findings. This and the fact that most studies included mostly adults and only a small number of children made it difficult to establish a comparison about the importance of HRV and its role in the prognosis of children with TBI. Hence, the importance of setting appropriate guidelines for the pediatric age as well as a cut-off to define the prognosis of children with TBI on admission. On the other hand, the fact that each study uses small samples only, limited the results of the studies. Nonetheless, is seems well established that LF/HF ratio may be helpful not only in identifying those patients who will progress to brain death but also in predicting which patients will have favorable outcomes.

Conclusions

In summary, according to the eligible studies the analysis of HRV in children with severe brain lesions caused by TBI and the prognosis of their recovery is inversely associated with HRV, with cerebral death levels of almost zero variability.

The frequency domain is used more frequently and the LF reflected the activity of the sympathetic component.

The evidence indicated that during severe brain injury, the cardiovascular and autonomic systems are proportionally decoupled at various levels in relation to the degree of neurological injury, and their monitoring may lead to a better understanding of neuroautonomic interactions.

Patients who after brain injury evolved to brain death had a markedly lower LF / HF ratio (p <0.001) with a significant decrease after the first hours of hospitalization. Patients with a more favorable prognosis had significantly higher LF / HF ratios. Thus, the LF / HF ratio may be useful in identifying patients who will progress to brain death, as well as in the prognosis of those who will recover favorably.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Description</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>ms</td>
<td>Standard deviation of all RR intervals</td>
<td>Estimates overall HRV.</td>
</tr>
<tr>
<td>SDANN</td>
<td>ms</td>
<td>Standard deviation of the average of RR intervals in all 5 min segments of entire recording</td>
<td>Estimates long-term components of HRV.</td>
</tr>
<tr>
<td>rmSSD</td>
<td>ms</td>
<td>The square root of the mean of the squares of differences between adjacent RR intervals</td>
<td>Estimates short-term components of HRV</td>
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\(ms\) – miliseconds

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Description</th>
<th>Frequency range</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>HF</td>
<td>ms²</td>
<td>Power in high frequency range</td>
<td>0.15 to 0.40 Hz</td>
<td>Heart rate changes related to the respiratory cycle (respiratory sinus arrhythmia). They are typically modulated by the parasympathetic.</td>
</tr>
<tr>
<td>LF</td>
<td>ms²</td>
<td>Power in low frequency range</td>
<td>0.04 to 0.15 Hz</td>
<td>Modulated by both sympathetic and parasympathetic, with sympathetic predominance in some specific situations, and reflecting the oscillations of the baroreceptor system.</td>
</tr>
<tr>
<td>VLF</td>
<td>ms²</td>
<td>Power in very low frequency range</td>
<td>≤0.04 Hz</td>
<td>Dependent on thermoregulatory mechanisms and the renin-angiotensin system, whose regulation is also effected by sympathetic and parasympathetic.</td>
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<td>LF/HF</td>
<td>ms²</td>
<td>Ratio LF/HF</td>
<td></td>
<td>It provides useful information on balance between the sympathetic and parasympathetic systems.</td>
</tr>
<tr>
<td>TP</td>
<td>ms²</td>
<td>Total power: variance of all NN intervals</td>
<td>Approximately ≤ 0.04 Hz</td>
<td>It provides useful information on balance between the sympathetic and parasympathetic systems.</td>
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\(Ms^2\) – miliseconds\(^2\), Hz - Hertz
Table 3 – HRV in children with TBI

<table>
<thead>
<tr>
<th>Aim design</th>
<th>Authors (year)</th>
<th>Participants</th>
<th>HRV measurement</th>
<th>Experimental conditions</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>To investigate disconnection theories postulated as a cause of dysautonomia following TBI through analysis of HRV</td>
<td>Baguley I et al (2006) [6]</td>
<td>16 patients (13 males/3 females) following severe TBI. Half had dysautonomia. Aged between: 15-65 years.</td>
<td>ADInstruments Powerlab®. Sampling rate: 1000 kHz. Duration of recording: 10-15 minutes. TD: SDNN. FD: VLF (0.01 to 0.04 Hz), LF (0.04 to 0.15) and HF (0.15 to 0.40 Hz) and LF/HF ratio.</td>
<td>The control group was age-matched. Exclusion criteria: History of cardiac disease diabetes or other neurological impairment or were taking cardiovascular medication. TCE was sub-divided: 8 patients with dysautonomia and 8 without. Assessed while resting supine and in the absence of any secondary acute medical condition.</td>
<td>VLF power was relatively preserved between groups. LF but not HF power was significantly lower in the TBI group. The mean LF/HF ratio was in the normal range for controls and elevated in the TBI group (LF / HF de 1.8 e 3.7, respectively, p &lt;0.05). The Control group mean SDNN was below normative values. However, the TBI group’s value was significantly lower than controls. HRV data demonstrated that subjects with dysautonomia had significantly lower LF power. There was no statistical difference between mean LF / HF ratio for the dysautonomic vs. non-dysautonomic groups (p = 0.164).</td>
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</tbody>
</table>
To evaluate HRV by power spectral analysis and outcomes in children with acute traumatic head injury.

| Biswas A et al (2000) [7] | 15 children (10 male/5 female) with TBI occurring within 8 hrs. of hospital admission. Data collected from April 1997 to June 1998 in Pediatric Intensive Care Unit (ICU) in a level II trauma center. Age between: 7 months to 12 years. | Semiautomated system (Fukuda-Denshi and DMS 300: Total Disclosure Analyzer, Diagnostic Monitoring Software, Santa Ana, CA). This system received the electrocardiogram (ECG) signal from bedside monitors in real-time and sampled the ECG signal at 128 Hz. Duration of recording: 1 hour. RR intervals: 5 min. - series of 256 points. FD: LF (0.04 to 0.15 Hz) and HF (0.15 to 0.40 Hz) and LF/HF ratio. | Relationship between intracranial pressure, cerebral perfusion pressure and HRV in children with TBI was studied. Inclusion criteria: TBI occurring within 8 hrs. of hospital admission, Glasgow Coma Scale (GCS) ≤8 and placement of an intracranial pressure monitor. Exclusion criteria: Recent cardiopulmonary arrest, β-adrenergic receptor antagonist and/or atropine use within the previous 24 hrs., history of preexisting neurologic injury or disease, moderate dose of infusions of catecholamine, sepsis or suspicion of significant infection, and history of heart disease or other pathology associated with abnormal HRV. | There was a significant decrease in the LF/HF ratio when the intracranial pressure was > 30mmHg (p < 0.001) or the cerebral perfusion was < 40 mmHg (p < 0.001). Children with a GCS score of 3-4 had a lower LF/HF ratio compared with those who had a GCS score of 5-8 (p < 0.005). Patients who progressed to brain death had a markedly lower LF/HF ratio (p < 0.001). Patients with more favorable outcomes had significantly higher LF/HF ratios. |

Uncoupling of the autonomic and cardiovascular systems in acute brain injury.

| Goldstein B et al (1998) [8] | 24 children with brain injury (10 males/14 females). Data were obtained within the first 24h of admission to the pediatric ICU between September 1994 and March 1997. Aged from 0.2 to 17.5 years (mean = 5.9 ± 5.1 years) 5 children had TBI. | HRView software (Boston Medical Technologies, Boston, MA). Sampling rate: 1 kHz. Duration of recording: 600 secs. 128 secs time series that was artifact free was chosen for analysis by one author. FD: LF (0.01 to 0.15 Hz). | Included pathologies: anoxic/ischemic injury, multiple trauma, head trauma, central nervous system infection and intracranial. There were 17 survivors and 7 non-survivors, 3 of which were diagnosed as brain dead. | Neurological injury and survival was associated with LF (0.01-0.15Hz). Brain death patients showed decreased LF (p = 0.03) compared with non-brain-dead patients. The more severe the neurological injury, the worse the prognosis and the lower the HRV. |
To determine if decomplexification of heart rate dynamics occurs in critically ill and injured pediatric patients.

<table>
<thead>
<tr>
<th>Goldstein B et al (1998) [9]</th>
<th>135 consecutive pediatric ICU admissions. 21 children were excluded. 13 children had TBI.</th>
<th>ECG using monitors 78213C, Hewlett-Packard, Palo Alto, CA. Sampling rate: 1 kHz. Duration of recording: 256 secs. A 128 secs segment was selected for determination of heart rate power spectra and analyzed. FD: LF (0.01 to 0.15 Hz), HF (0.15 to 2.0 Hz) and LF/HF ratio.</th>
<th>HRV was compared with a previously validated measure of severity of illness – Pediatric Risk of Mortality (PRISM) and with validated measures of outcome from pediatric intensive care – Pediatric Overall Performance Category (POPC) e Pediatric Cerebral Performance Category (PCPC). Exclusion criteria: Patients who were not physically in the ICU at the time of study, Were off electrocardiographic monitoring, had a high cervical cord tumor, had cardiac dysrhythmias at the time of ECG recording or were receiving anticholinergic medications or other drugs that may have significantly impaired analysis of HRV. All patients were studied in the supine position.</th>
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<td>The lower the HRV, the greater the severity of illness (LF p=0.001 e HF p=0.004). The lower the HRV, the worse the outcome (LF p=0.002 e HF p=0.011). LF or sympathetic modulation of HRV, showed a consistently higher degree of correlation with PRISM, POPC and PCPC scores than did HF suggesting that sympathetic modulation of heart rate may be a more sensitive measure of severity of illness and outcome than parasympathetic activity.</td>
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<tr>
<td>Study</td>
<td>Authors --------------</td>
<td>Participants</td>
<td>Methods</td>
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<tr>
<td>To study sequential changes in HRV in patients with acute brain injury and correlate it with the severity of neurologic dysfunction and patient outcome.</td>
<td>Goldstein B et al (1996) [10]</td>
<td>42 children, 5 were excluded. 37 children (13 males/24 females) with brain injury (injury occurring within 24h of hospital admission). 25 children had TBI. Data were obtained within the first 24h of admission to the Strong Children’s Critical Care Center between August 1990 and March 1992.</td>
<td>ECG using monitors 78213C e 78212D, Hewlett-Packard, Waltham, MA. Sampling rate: 1 kHz. Duration of recording: 256secs. FD: VLF (0.01 to 0.04 Hz), MLF (0.04 to 0.07 Hz), LF (0.01 to 0.15) and HF (0.15 to 0.50 Hz).</td>
</tr>
<tr>
<td>Exploring QT variability dependence from heart rate in coma and brain death on pediatric patients.</td>
<td>Almeida R et al (2013) [11]</td>
<td>16 children with acute brain injury. These data were integrated of a larger database (45 cases) collected between 2006 and 2011. Only children within 11 and 14 years were included. 8 children had TBI (7 survived and 1 was brain death confirmed).</td>
<td>ECG Holter recordings. FD: VLF (&lt;0.04 Hz), LF (0.04 to 0.15) and HF (0.15 to 0.40 Hz).</td>
</tr>
<tr>
<td>To investigate the autonomic function in patients with brain damage of various extents.</td>
<td>Su C et al (2005) [12]</td>
<td>121 patients 31 subjects were excluded. 90 patients (67 males/23 females) aged from 4 to 84 years (mean 45 years). Patients were divided in 5 groups according with GCS. There were children in I, II, IV and V group.</td>
<td>Precordial ECG Sampling rate: 256 kHz. Duration of recording: 5 minutes. FD: LF (0.04 to 0.15 Hz) and HF (0.15 to 0.40 Hz) and LF/HF ratio.</td>
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</tbody>
</table>
To find evidence of autonomic imbalance and present the severity of paroxysmal sympathetic hyperactivity in children with acquired brain injury.

| Kim S et al (2017) [13] | 13 children (8 males/5 females) with acute brain injury who were admitted from October 2013 to January 2016. 4 children had TBI | SA-6000 device (Medicore Co., Seoul, Korea). Duration of recording: 5 minutes. TD: SDNN and rmSSD. FD: LF (0.04 to 0.15), HF (0.15 to 0.40 Hz) and LF/HF ratio. | 13 age-and sex-matched patients with cerebral palsy were selected as the control group. Test were conducted in a noise-free environment after 30 minutes of rest, in a relaxed supine position. In order to avoid the influence of circadian changes in the HRV results, data was collected between 1:00 PM and 3:00 PM in every patient. The room temperature during data collection was 24-26ºC. Exclusion criteria: History of cardiac disease, diabetes or other peripheral neurological impairment, patients taking cardiovascular medications and sépsis or suspicion of significant infection. | There was a statistically significant increase in the mean heart rate of the acute brain injury group compared to the control group (p = 0.0119). According to the time domain analysis, the rmSSD was significantly different between the two groups (p = 0.0240). All indices of the frequency domain analysis demonstrated a statistically significant difference between the two groups. The LF and HF decreased in the acute brain injury group compared to the control group. Only the LF/HF ratio increased in the acute brain injury group compared to the control (p=0.0018 and p=0.0018 respectively). |

| LF – low frequency; VLF – very low frequency; MLF – mid-low frequency; HF – high frequency; Secs - seconds; FD – frequency domain; TD – time domain; |
References


Attachments

- Review articles and invited papers
  Review papers may be narrative or systematic and are subject to the peer review process. They should offer exhaustive information on a given subject. The Editor will invite experts in the various fields of the neurosciences to publish Invited papers, although unsolicited reviews may also be considered. The Abstract must not be structured and the text may be arranged freely. The contribution should not be signed by more than 7 authors, while the text should not exceed 4000 words. Up to 15 figures or tables and 70 references are allowed. Exceptions at the discretion of the Editor in Chief.

Abstract
Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Purpose (stating the main purposes and research question)
- Methods
- Results
- Conclusions

Keywords
Please provide 4 to 6 keywords which can be used for indexing purposes.

Text Formatting
Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Headings
Please use no more than three levels of displayed headings.

Abbreviations
Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes
Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.
Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols. Always use footnotes instead of endnotes.

Acknowledgments
Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

Citation
Reference citations in the text should be identified by numbers in square brackets. Some examples:
1. Negotiation research spans many disciplines [3].
2. This result was later contradicted by Becker and Seligman [5].
3. This effect has been widely studied [1-3, 7].

Reference list
The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list. Reference list entries should be alphabetized by the last names of the first author of each work and numbered consecutively.

Tables
- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.
- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.