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Daniel da Silva Areias

Evaluation of Heart Rate Variability After Cerebral Injury in ICU Patients

Avaliação da Variabilidade da Frequência Cardiaca Após Lesão Cerebral Aguda em Doentes da UCI

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TÍTULO DISSERTAÇÃO

Evaluation of Heart Rate Variability After Cerebral Injury in ICU Patients

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Dedicatória

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Evaluation of Heart Rate Variability After Cerebral Injury in ICU Patients

Avaliação da Variabilidade da Frequência Cardíaca Após Lesão Cerebral Aguda em Doentes da UCI

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Abstract

Introduction: Autonomic dysfunction affecting internal homeostasis, namely cardiovascular control is a frequent phenomenon after acute brain injury. The inclusion of orthostatic training with the tilt table in the rehabilitation protocols of these patients, may improve cerebral autoregulation and induce faster recovery of sensorimotor, balance and autonomic systems.

Purpose: Preliminary pilot study to describe the systemic and cerebral physiological adaptation of critically ill patients with acute brain injury submitted to orthostatism using the tilt table.

Methods: Rehabilitation with orthostatism was applied to patients recovering from acute brain injury admitted in a Neurocritical care unit. The orthostatic trial was achieved according to the tilt table protocol: the body position was gradually elevated from 0º to 60º. For each slope degree 0º, 15º, 30º, 45º and 60º, the patient stayed in the same position for 15 minutes. The trial was concluded by gradually lower the slope every 5 min for 15º until the 0º position was reached. During the procedure we continuously recorded arterial blood pressure, electrocardiogram, heart rate and cerebral oximetry with near-infrared spectroscopy. We made offline analysis of cerebrovascular reactivity index using cerebral oximetry, heart rate variability in frequency domain and baroreflex. Data recording and processing was performed using ICM+ software ® developed at Cambridge University.

Results: We studied 7 patients (mean age 58) with acute brain injury (3 Traumatic Brain Injury, 3 Intracerebral Haemorrhage and 1 Acute Hydrocephalus). The median Glasgow Coma Scale was 11(1), the mean Simplified Acute Physiology Score II was 31±23, the mean length of stay in Neurocritical care unit and hospital was 67±26 and 107±26, respectively. In supine position, baroreflex sensitivity and heart rate variability total power was decreased. Low-frequency and high-frequency components of heart rate variability were decreased and low-frequency/high-frequency ratio was increased. Cerebral autoregulation, expressed by cerebrovascular reactivity index, remained mostly under 0.3 during orthostatism. During tilt test only heart rate demonstrated an increase with statistical significance from 15º to 45º and 60º (83 vs 94, p=0.037) and (83 vs 95, p=0.037). No other statistical difference was identified during orthostatism.

Conclusion: The results of this pilot study in acute brain injury patients submitted to orthostatism challenge demonstrate that it is feasible to apply the tilt table in an acute care setting. The increase of low-frequency/high-frequency ratio and decrease of baroreflex sensitivity suggest sympathetic predominance supporting autonomic nervous system impairment. The clinical relevance of online monitoring of cerebral autoregulation with cerebrovascular reactivity index during the tilt test warrants further evaluation.

Keywords: Acute Cerebral Lesion; Heart Rate Variability; Autonomic Nervous System; Tilt Table

1. Introduction

1.1 Interconnection between acute brain injury (ABI) and dysautonomia

Autonomic dysfunction affecting internal homeostasis, namely cardiovascular control, may occur after acute brain injury (ABI) of different etiologies (Leipzig et al., 1986; Lacquaniti et al., 1993). The first study that explored the relationship between heart rate pattern and severe brain damage was conducted by Valbona et al in 1965 (Leipzig et al., 1986). Leipzig et al (1986) reported that decreased heart rate variability (HRV), from beginning to end or at any time, is an accurate indicator of poor outcome. However, it also stated that, in patients with acute brain injury, the variability is less accurate than Glasgow Coma Scale (GCS) to predict outcome.

The relationship between brain and heart and the autonomic nervous system (ANS) modulation of sinus rate has been studied through the analysis of the tachogram, which is a mathematical series derived from RR intervals (Lacquaniti et al., 1993). Lacquaniti, L. et al (1993) revealed that the absence of HRV in patients with severe brain injury led to brain death or vegetative status. Similarly, Freitas, J. et al (1996) reported that HRV is lower in comatose and brain death patients, being the parameters significantly lower in the last group.

Woolf et al (1987) postulated that following head trauma there is an activation of the sympathetic nervous system with an increase of circulating catecholamines. Consequently, among other alterations cardiac arrhythmias and myocardial necrosis may occur. The possible reason behind this fact is the autonomic imbalance or over-reactivity of sympathetic outflow following ABI and such consequences may be prevented by alpha- and beta-adrenergic blockade. Kolin, A. et al (1984) found similar results in the autopsies of 58 patients with intracranial lesions. They reported increased levels of plasma catecholamines and myocardial damage significantly higher in patients with intracranial hypertension (62%) in comparison with controls (26%). There are other circumstances affecting the brain, where HRV is also diminished, such as familial amyloid neuropathy, which involves severe autonomic imbalance in advanced stages. Not surprisingly, these patients present near zero HRV (Carvalho et al., 1991). This premise sustains the hypothesis of a close relationship between ABI and dysautonomia.

In a normal heart, the sinus node dictates the basal heart rate which is modulated by the parasympathetic and sympathetic nervous system which centres are mainly located in the hypothalamus and brainstem. In normal circumstances the heart rate is maintained between a certain range (60 to 100 beats per minute) increasing or decreasing depending on the autonomic nervous system reaction to the day-to-day challenges (Boron et al., 2012). This Heart Rate Variability (HRV), reflects beat-to-beat changes in RR intervals (Camm et al., 1996) imposed by the ANS function. Heart rate changes as a response to mental or physical stress and several diseases, such as ABI (Boron et al., 2012) with high intracranial pressure (Kolin et al., 1984).

The HRV can be analysed through time domain methods or frequency domain methods. Considering the frequency domain, HF component reflects mainly the efferent vagal activity, whereas LF component is more controversial, reflecting mostly the sympathetic activity but has also vagal influences (Camm et al., 1996). Therefore, LF/HF ratio is considered to mirror of sympathetic-vagal balance (Camm et al., 1996). A detailed description of these methods can be found in the guidelines “Standards of measurement, physiological interpretation, and clinical use”. As the HRV is a time series generated by the difference between the R-R intervals modulated by sympathetic and vagal tonus

(Sztajzel, 2004) is expected a less variability (compared to the normal values of standard measures of heart rate variability (Camm et al., 1996)) in the presence of ANS dysfunction.

1.2 Autonomic Nervous System, Cerebral Autoregulation and Orthostatism

The ANS, through HRV and the baroreflex, is the main component of the adaptive response to body position change (Appenzeller, 1990; Nasr et al., 2018). Upon assuming orthostatic position there is a 500-1000 ml of blood movement from the upper body to the lower segments (Robertson, 2008). This rapid redistribution of blood leads to a relative hypovolemia, sensed by the baroreceptors (carotid sinus and aortic cross) causing a sympathetic reflex, increasing heart rate, contractibility and peripheral vasoconstriction (Levine et al., 2014). Consequently, the increased cardiac output leads to obliteration of the ventricular chamber, activating the mechanic C fibers, triggering a parasympathetic reflex, through the vagus nerve, resulting in vasodilatation and decreased heart rate (Levine et al., 2014).

The baroreflex may be assessed in the time domain, by the baroreflex sensitivity (BRS) which is given by the slope of RR interval versus systolic ABP regression line (Nasr et al., 2018). High sympathetic system activity or ANS imbalance is correlated to baroreflex impairment (Nasr et al., 2005) and altered baroreflex activity has been associated with poor outcome in ABI (V. Papaioannou et al., 2005).

During orthostatic challenge, the hemodynamic adaption may affect cerebral blood flow and therefore cerebral function, which is counterbalanced by cerebral autoregulation that assures constant blood flow within a limited interval of variation of ABP, by changing cerebrovascular reactivity (Tzeng et al., 2014). This vital physiological mechanism may be continuously monitored at bedside with bilateral cerebral oximetry (CO) with the Near-Infrared Spectroscopy (NIRS) technology and its correlation with ABP (Brady et al., 2010). The moving correlation coefficient between CO and ABP, so called cerebral oximetry index reactivity score (COx), may vary between -1 and +1 and the values below 0.3 are related to preserved brain autoregulation (Moerman et al., 2017).

1.3 Advantages of the tilt table test as a rehabilitation tool

Recent Intensive Care rehabilitation methods include the orthostatic position with a tilt table, to stimulate vestibular, somatosensory and visual function, challenging the ANS adaptive response (Turner-Stokes et al., 2005). In fact, during the upright position the axial tonic activity links all parts of the body with improvement of autonomic control, oxygenation, ventilation, alertness and prevention of contractures and pressure ulcers. This rehabilitation tool minimizes the adverse effects of immobility and lying position, improves recovery and decreases morbidity promoting better outcome (Gurfinkel et al., 2006; Brodal, 2010; Roy et al., 2013; Vlutters et al., 2015).

Aim: to describe the autonomic and cerebral physiological adaptation of critically ill patients with acute brain injury submitted to orthostatism challenge, using the tilt table.

2. Materials and Methods

2.1 Individuals

We submitted patients recovering from severe acute brain injury, admitted to the neurocritical care unit at São João University Hospital to the tilt test protocol of

rehabilitation. Exclusion criteria were body weight greater than 130kg and/or height greater than 210cm, unstable or unconsolidated fractures, rib fractures or thoracic cutaneous lesions, contraindication for lower limb load and patients with deep venous thrombosis, hemodynamic or neurological instability in the last 48 hours, with external ventricular drainage or lumbar drainage or prior medical history of orthostatic intolerance. Baseline neurological status was calculated using the Glasgow Coma Scale (GCS) score on first session. The Simplified Acute Physiology Score II (SAPS II) was used to determine the overall disease severity and mortality prediction on admission.

2.2 Data Acquisition and Processing

Patients were continuously monitored with ECG, heart rate (HR), invasive arterial blood pressure (ABP) through the radial artery, pulse oximetry (SpO2) and bilateral transcutaneous cerebral oximetry with near-infrared spectroscopy (NIRS). The systemic variables were acquired using Philips Intellivue MP70 multiparameter monitor (Philips medical systems, Eindhoven, the Netherlands). NIRS was monitored with INVOS 5100C (Covidien, Mansfield, USA). All signals were recorded, sampled at a frequency of 250 Hz, using a laptop computer with ICM+® software, version 8.5 (Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam. ac.uk/icmplus). The same software was later used for offline analysis of cerebral oximetry (CO) and calculation of cerebrovascular reactivity index using cerebral oximetry (COx). CO was defined as the average between the left and right NIRS values. COx was calculated as a moving Pearson correlation coefficient between ABP and NIRS data with consecutive, paired, 10-second averaged values from a 5 minutes length window. Example of data monitoring from one patient is shown in figure 1.

2.3 Heart Rate Variability

For HRV study, we used offline frequency domain analysis and calculated spectral power of RR time series in the low frequency range (0.04-0.15Hz), the high frequency range (0.15-0.4Hz), the total power (0.04-0.4Hz) and the LF/HF ratio. Tolerance to ectopics was 20%.

2.4 Baroreflex Sensitivity

Baroreflex sensitivity (BRS) was assessed through a cross-correlation method that uses systolic ABP and RR time series. The slope of the linear regression was calculated using a moving 30-second window. Tolerance to ectopics was 20%. BRS is presented in ms/mmHg.

2.5 Rehabilitation Protocol for Orthostatism

The protocol applied was based on the publications of Silvério et al. 2014 and Sibinelli et al. 2012 and was approved by local Ethics Committee of the Faculty of Medicine, University of Porto. The body position was gradually elevated from 0º to 60º. For each slope, at 0º, 15º, 30º, 45º and 60º degrees, the patient stayed in the same position during 15 minutes (Fig. 1). The trial was concluded by gradually lower the slope every 5 min in the reverse way until the 0º position was reached. In case of hemodynamic instability during the rise phase, defined as HR and ABP changes beyond ± 20% from baseline or consciousness changes the test was aborted.

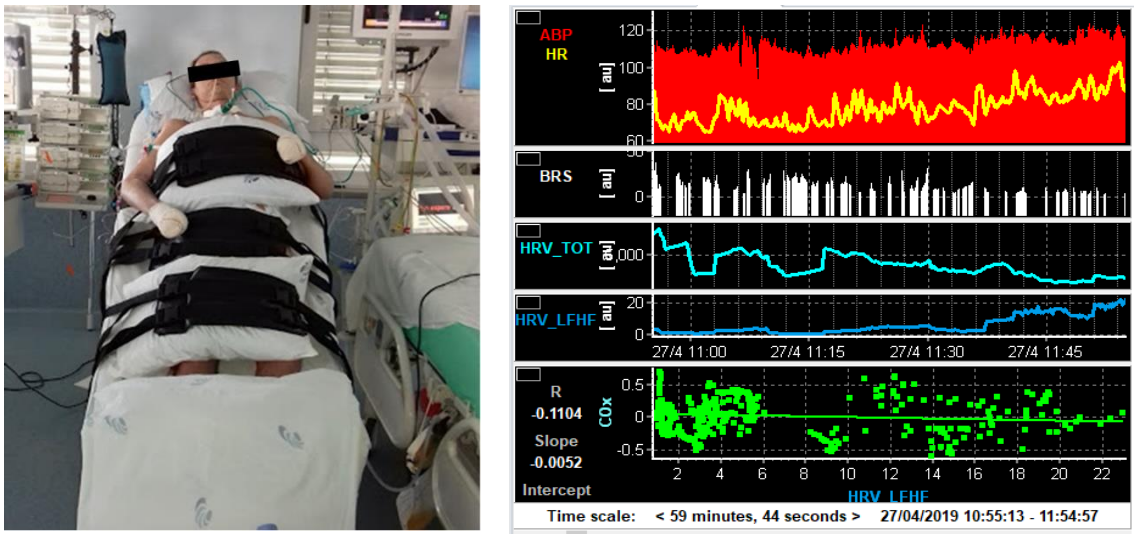


Figure 1. Patient in the tilt table during "up period" and screen of ICM+ software with offline analysis of data monitoring of arterial blood pressure (ABP), heart rate (HR), baroreflex sensitivity (BRS), heart rate variability with total power (HRV_TOT) and balance (HRV_LF/HF) and the linear correlation between balance and cerebral oximetry index (COx), as a surrogate of autoregulation.

2.6 Data Analysis

The data are presented as mean values and standard deviations (mean ± SD) or medians (med) and interquartile range (IQR). Non-parametric Wilcoxon test was performed to compare mean values of ABP, HR, left NIRS, right NIRS, CO, COx, HRV total power, LF and HF components, LF/HF ratio and BRS across tilt table sessions. Non-parametric Friedman test with post-hoc comparisons was used to compared mean values of every variable at different slopes during orthostatism. All statistics were performed using the SPSS version 21.0 for Windows. In all tests, values of $p<0.05$ were considered statistically significant.

3. Results

3.1 Demographic Data

Seven critically ill patients recovering from ABI (3 TBI, 3 ICH, 1 Hydrocephalus) were analysed. The mean age of the patients was 58±24 years old and 6 (86%) were male. Median GCS at first session was 11(1) and mean SAPS II on admission was 31±23 with predicted mortality of 24%. Mean length of stay in the NCCU and hospital was respectively 67±26 and 107±26. Demographic data is summarized in table 1.

Table 1. Demographic characteristics of the patients

Case	Sex	Age	Diagnosis	SAPSII	P_SAPS II	NCCU stay	Hospital stay	GCS
1	F	62	ICH	37	19,6	67	113	11
2	M	22	TBI	33	14,0	40	67	10
3	M	73	TBI	66	78,5	29	53	12
4	M	83	HyCP	6	0,5	60	115	11
5	M	68	ICH	53	53,0	78	116	11
6	M	27	TBI	6	0,5	78	78	6
7	M	69	ICH	18	2,9	107	107	11
Mean		58		31	24	67	107	
SD		24		23	30	26	26	
Median								11
IQR								1

SAPS II, Simplified Acute Physiology Score II; P_SAPS II, mortality prediction; NCCU, Neurocritical Care Unit; GCS, Glasgow Coma Scale; ICH, Intracerebral haemorrhage; TBI, Traumatic Brain Injury; HyCP, hydrocephalus; SD, Standard Deviation; IQR, Interquartile Range

3.2 Monitoring Data

Mean and standard deviation for the physiologic variables ABP, HR and NIRS (left and right) at the slopes 0º, 15º, 30º, 45º, 60º and at the end of protocol, for the first and second sessions, are presented in table 2 and in figure 2 (in appendix).

Table 2. Monitoring Data recorded during upright phase of the orthostatic tilt test for the first and second sessions at 0º, 15º, 30º, 45º, 60º and the end of the protocol.

	Diagnosis	**0º begin**	**15º up**	**30º up**	**45º up**	**60º up**	**0º end**
Session 1 (n=7)	**ABP**	105±20	104±19	104±19	97±17	97±10	101±18
	HR	81±10	83±10	90±10	94±4	95±6	87±16
	NIRS_L	57±30	52±28	63±15	62±14	54±11	68±12
	NIRS_R	61±33	59±32	60±25	51±28	47±17	69±21
Session 2 (n=4)	**ABP**	109±10	107±11	106±10	106±14	112±9	107±8
	HR	85±8	86±11	89±10	90±4	92±1	88±6
	NIRS_L	62±10	61±7	61±9	61±10	63±10	64±11
	NIRS_R	61±13	59±10	59±11	61±9	60±1	61±11

Mean and Standard Deviation of ABP (Arterial Blood Pressure), HR (Heart Rate), NIRS_L (left cerebral oximetry with near-infrared spectroscopy) and IRS_R (Right cerebral oximetry with near-infrared spectroscopy).

Statistically significant differences between slopes during orthostatism were only identified for HR in the first session with a consecutive increase between 15º, 45º and 60º (*p=0.037*).

The mean and standard deviation for the calculated variables CO, COx, HRV LF, HRV HF, HRV LF/HF, HRV TOT, BRS at the slopes 0º, 15º, 30º, 45º, 60º and at the end of protocol, for the first and second sessions, are presented in table 3 and in figure 3 (in annex).

Table 3. Calculated variables during upright phase of the orthostatic tilt test for the first and second sessions at 0º, 15º, 30º, 45º, 60º and the end of the protocol.

		0º begin	15º up	30º up	45º up	60º up	0º end
Session 1 (n=7)	**CO**	55±30	56±26	59±16	56±17	50±8	69±14
	COx	0,1±0,2	0±0,2	0,1±0,2	0,2±0,2	0,2±0,2	0,2±0,3
	HRV_LF	517±453	381±365	318±335	230±214	259±262	493±364
	HRV_HF	575±690	428±530	328±500	293±446	305±403	629±716
	HRV_LF/HF	4±6	4±5	4±4	5±6	4±4	4±4
	HRV_TOT	3115±2576	2774±2464	2030±1679	2173±2261	1656±1410	3628±3482
	BRS	0,42±0,10	0,44±0,09	0,46±0,10	0,42±0,11	0,43±0,09	0,43±0,11
Session 2 (n=4)	**CO**	62±11	60±8	60±10	61±10	62±4	62±10
	COx	0±0,2	0,3±0,2	0,4±0,2	0,2±0,2	0,1±0,2	0,3±0,3
	HRV_LF	283±288	276±260	222±217	293±280	120±138	230±238
	HRV_HF	359±572	289±423	228±393	246±406	6±6	224±412
	HRV_LF/HF	4±6	5±8	5±6	9±7	16±7	5±6
	HRV_TOT	2292±2431	1922±1850	1632±1663	1737±1245	932±1082	1773±1904
	BRS	0,44±0,17	0,51±0,12	0,43±0,16	0,42±0,11	0,39±0,09	0,52±0,17

Mean and Standard Deviation of CO (Cerebral Oximetry), Cox (Cerebral Oximetry index), HRV LF (Low Frequency component of Heart Rate Variability), HRV HF (High Frequency component of Heart Rate Variability), HRV LF/HF (Low Frequency and High Frequency components of Heart Rate Variability ratio), HRV TOT (Total power of Heart Rate Variability) and BRS (Baroreflex Sensitivity).

Among the calculated variables, no statistical differences were identified ($p>0.05$).

4. Discussion

This pilot study assessed the systemic and cerebral physiological adaptation of critically ill patients with acute brain injury submitted to orthostatism using the tilt table. To our best knowledge, this is the first study to evaluate the effect of orthostatism on systemic and cerebral variables in patients with acute cerebral injury during intensive care staying. We found evidence of decreased LF and HF powers and increased LF/HF ratio, suggesting sympathetic predominance in critically ill patients with cerebral damage. Considering the interpretation of HF as a mirror of parasympathetic tonus, LH of sympathetic tonus and LF/HF as the balance between them, our results were consistent with previous studies. Goldstein et al (1993) reported that lower LF and HF were associated with severe brain injury and brain death. Szabo et al (2018) studied patients with acute intracerebral haemorrhage and found decreased total power of LF and HF. Another acute ischemic cerebral infarction series found decreased values of HF and LF and increased LF/HF ratio (Tokgözoglu et al., 1999; Kuriyama et al., 2010; Hilz et al., 2011). However, some previous observations on critically ill patients with TBI, ICH and SAH showed increased HF powers and decreased LF/HF ratio in these patients, suggesting increased vagal activity (Kox et al., 2012; Sykora et al., 2016).

Supporting the sympathetic predominance, we found low BRS values. Reduced BRS has also been observed in other pathologies like myocardial infarction (La Rovere et al., 1998), heart failure (Pinna et al., 2005) and acute brain injury (Vasilios Papaioannou et al., 2008; Sykora et al., 2008), suggesting autonomic nervous system impairment.

In this study, during orthostatism, it was observed an increase of HR, with statistical significance, from 15º to 45º and 60º. This onset of tachycardia is another factor suggesting sympathetic predominance in these patients with acute cerebral lesions (Hilz

et al., 2011). The same pattern was not observed in ABP. In terms of cerebral oximetry, it was seen low, although normal, initial values that mainly increase during orthostatism, suggesting favourable cerebral adaption to head-up position. Indeed, cerebral autoregulation, expressed by COx, remained mostly under 0.3 during orthostatism, reflecting integral autoregulation. Even though, it was observed periodic autoregulation impairment, eventually related to a certain delayed dynamics of autoregulation (Lazaridis et al., 2013). As discussed previously, HRV and BRS were decreased before orthostatism, maintaining a relatively unchanged linear progression.

In our protocol we establish some security measures to prevent hemodynamic instability during orthostatism. So, in case of HR variability and ABP>20% from baseline or consciousness changes the test would be aborted. However, there is no security protocol concerning cerebral autoregulation, apart from clinical evaluation of neurological status. As previously discussed, we demonstrated with offline analysis, that cerebral autoregulation was mostly preserved with COx values under 0.3 throughout most of the length of protocol. Since cerebral autoregulation is a vital process it would be more appropriate in the next patients to introduce the online processing of COx to allow continuously monitoring of autoregulation.

Another goal of our study is to assess the tilt table as a rehabilitation tool in order to understand its role in autonomic cardiovascular control. Our results showed no statistical differences between both sessions, probably because of the reduced number of participants and sessions in this study. Nevertheless, in patients with second session we documented higher sympathetic-vagal balance, which may suggest autonomic control improvement. However, because no statistical difference was found, no further conclusions can be made.

4.1 Study limitations

The small sample size of this study must be considered the major limitation. Still, it is a prospective pilot study about the systemic and cerebral physiological adaptation during orthostatism, which results may allow future research in larger cohorts with systematic tilt table application. A strength of this study was that our patients were not sedated or ventilated, which has been proved to affect HRV *per se* (Kasaoka et al., 2010). However, other medication including beta blockers and anti-hypertensives were used in the treatment of our patients. Therefore, there is the possibility of our measurements be skewed by this medical therapy.

Another important limitation is the lack of monitoring of cerebral autoregulation during the procedure and its comparison with a more standard validated method such as the bilateral continuous monitoring of cerebral blood velocity with transcranial Doppler.

5. Conclusions

The results of this pilot study in acute brain injury patients submitted to orthostatism challenge demonstrate that it is feasible to apply the tilt table in an acute care setting. The increase of HRV LF/HF and decrease of BRS suggest sympathetic predominance supporting autonomic nervous system impairment. The autoregulation monitoring with cerebral oximetry during the tilt test seems to be appropriate, although warrants further investigation.

References

Appenzeller, Otto. 1990. *The Autonomic Nervous System : An Introduction to Basic and Clinical Concepts*, fourth ed. Elsevier.

Boron, W F, and E L Boulpaep. 2012. *Medical Physiology, 2e Updated Edition. ISBN: 9781455711819.* Elsevier Health Sciences. p.147-178 . http://books.google.com.br/books?id=54mxMgO5H_YC.

Brady, Kenneth, Brijen Joshi, Christian Zweifel, Peter Smielewski, Marek Czosnyka, R Blaine Easley, and Charles W Hogue. 2010. “Real Time Continuous Monitoring of Cerebral Blood Flow Autoregulation Using Near-Infrared Spectroscopy in Patients Undergoing Cardiopulmonary Bypass.” *Stroke*, *41*(9), 1951-1956. https://doi.org/10.1161/STROKEAHA.109.575159.

Brodal, Per. 2010. *The Central Nervous System : Structure and Function*. Oxford University Press.

Camm, A. J., Malik, M., Bigger, J. T., Breithardt, G., Cerutti, S., Cohen, R. J., . . . Singer, D. (1996). "Heart rate variability—Standards of measurement, physiological interpretation, and clinical use". *Circulation*, *93*, 1043–1065. https://doi.org/10.1161/01.CIR.93.5.1043

Carvalho, Mario J., Arie J. Man in ’t Veld, Ovidio Costa, Joao Freitas, Jorge Puig, and Falcao De Freitas. 1991. “Spectral Analysis of the Heart Rate as an Assessment of Autonomic Function in Familial Amyloid Polyneuropathy.” *Journal of Hypertension* 9: S62–63. https://doi.org/10.1097/00004872-199112006-00015.

Freitas, J., J. Puig, A. P. Rocha, P. Lago, J. Teixeira, M. J. Carvalho, O. Costa, and A. Falcão De Freitas. 1996. “Heart Rate Variability in Brain Death.” *Clinical Autonomic Research* 6 (3): 141–46. https://doi.org/10.1007/BF02281900.

Goldstein, B., D. DeKing, D. J. DeLong, M. H. Kempski, C. Cox, M. M. Kelly, D. D. Nichols, and P. D. Woolf. 1993. “Autonomic Cardiovascular State after Severe Brain Injury and Brain Death in Children.” *Critical Care Medicine* 21 (2): 228–33. https://doi.org/10.1097/00003246-199302000-00014.

Gurfinkel, Victor, Timothy W. Cacciatore, Paul Cordo, Fay Horak, John Nutt, and Rachel Skoss. 2006. “Postural Muscle Tone in the Body Axis of Healthy Humans.” *Journal of Neurophysiology* 96 (5): 2678–87. https://doi.org/10.1152/jn.00406.2006.

Hilz, Max Josef, Sebastian Moeller, Aynur Akhundova, Harald Marthol, Elisabeth Pauli, Philipp De Fina, and Stefan Schwab. 2011. “High NIHSS Values Predict Impairment of Cardiovascular Autonomic Control.” *Stroke* 42 (6): 1528–33. https://doi.org/10.1161/STROKEAHA.110.607721.

Kasaoka, Shunji, Takashi Nakahara, Yoshikatsu Kawamura, Ryosuke Tsuruta, and Tsuyoshi Maekawa. 2010. “Real-Time Monitoring of Heart Rate Variability in Critically Ill Patients.” *Journal of Critical Care* 25 (2): 313–16. https://doi.org/10.1016/j.jcrc.2009.06.047.

Kolin, A, and J W Norris. 1984. “Myocardial Damage from Acute Cerebral Lesions.” *Stroke* 15 (6): 990–93. https://doi.org/10.1161/01.STR.15.6.990.

Kox, Matthijs, Maarten Q. Vrouwenvelder, Jan C. Pompe, Johannes G. Van Der Hoeven, Peter Pickkers, and Cornelia W. Hoedemaekers. 2012. “The Effects of Brain Injury on Heart Rate Variability and the Innate Immune Response in Critically Ill Patients.” *Journal of Neurotrauma* 29 (5): 747–55. https://doi.org/10.1089/neu.2011.2035.

Kuriyama, Nagato, Toshiki Mizuno, Fumitoshi Niwa, Yoshiyuki Watanabe, and Masanori Nakagawa. 2010. “Autonomic Nervous Dysfunction during Acute Cerebral Infarction.” *Neurological Research* 32 (8): 821–27. https://doi.org/10.1179/016164109X12464612122696.

Lacquaniti, Luigi G., Marco Irone, Stefano Barbacini, Fulgido Merlo, Paolo Demo, Carlo Pellegrin, and Maurizio Dan. 1993. “Heart Rate Variability and Severe Brain Damage: Preliminary Data.” *International Journal of Clinical Monitoring and Computing* 10 (3): 181–85. https://doi.org/10.1007/BF01246453.

Lazaridis, Christos, Piotr Smielewski, Luzius A. Steiner, Ken M. Brady, Peter Hutchinson, John D. Pickard, and Marek Czosnyka. 2013. “Optimal Cerebral Perfusion Pressure: Are We Ready for It?” *Neurological Research* 35 (2): 138–48. https://doi.org/10.1179/1743132812Y.0000000150.

Leipzig, T. J., and R. I. Lowensohn. 1986. “Heart Rate Variability in Neurosurgical Patients.” *Neurosurgery* 19 (3): 356–62. https://doi.org/10.1227/00006123-198609000-00004.

Levine, Paul A. 2014. “Papel Da Estimulação Artificial Na Administração Da Síncope Neurocardiogênica.” *St. Jude Medical CRMD*, 1-9.

Moerman, Anneliese, Stefan De Hert, and Amit M Mathur. 2017. “Open Peer Review Recent Advances in Cerebral Oximetry. Assessment of Cerebral Autoregulation with near-Infrared Spectroscopy: Myth or Reality? [Version 1; Referees: 2 Approved],” 1615. https://doi.org/10.12688/f1000research.11351.1.

Nasr, Nathalie, Rita Gaio, Marek Czosnyka, Karol Budohoski, Xiuyun Liu, Joseph Donnelly, Marek Sykora, et al. 2018. “Baroreflex Impairment after Subarachnoid Hemorrhage Is Associated with Unfavorable Outcome.” *Stroke* 49 (7): 1632–38. https://doi.org/10.1161/STROKEAHA.118.020729.

Nasr, Nathalie, Anne Pavy Le Traon, and Vincent Larrue. 2005. “Baroreflex Sensitivity Is Impaired in Bilateral Carotid Atherosclerosis.” *Stroke* 36 (9): 1891–95. https://doi.org/10.1161/01.STR.0000177890.30065.cb.

Papaioannou, V., M. Giannakou, N. Maglaveras, E. Sofianos, and M. Giala. 2005. “Heart Rate and Blood Pressure Variability and Baroreflex Sensitivity in Patients with Acute Brain Injury.” *Journal of Critical Care* 20 (4): 394. https://doi.org/10.1016/j.jcrc.2005.09.048.

Papaioannou, Vasilios, Maria Giannakou, Nikos Maglaveras, Efthymios Sofianos, and Maria Giala. 2008. “Investigation of Heart Rate and Blood Pressure Variability, Baroreflex Sensitivity, and Approximate Entropy in Acute Brain Injury Patients.” *Journal of Critical Care* 23 (3): 380–86. https://doi.org/10.1016/j.jcrc.2007.04.006.

Pinna, Gian Domenico, Roberto Maestri, Soccorso Capomolla, Oreste Febo, Elena Robbi, Franco Cobelli, and Maria Teresa La Rovere. 2005. “Applicability and Clinical Relevance of the Transfer Function Method in the Assessment of Baroreflex Sensitivity in Heart Failure Patients.” *Journal of the American College of Cardiology* 46 (7): 1314–21. https://doi.org/10.1016/j.jacc.2005.06.062.

Robertson, David. 2008. “The Pathophysiology and Diagnosis of Orthostatic Hypotension.” *Clinical Autonomic Research*. https://doi.org/10.1007/s10286-007-1004-0.

Rovere, Maria Teresa La, J. Thomas Bigger, Frank I. Marcus, Andrea Mortara, and Peter J. Schwartz. 1998. “Baroreflex Sensitivity and Heart-Rate Variability in Prediction of Total Cardiac Mortality after Myocardial Infarction.” *Lancet* 351

(9101): 478–84. https://doi.org/10.1016/S0140-6736(97)11144-8.

Roy, Anindo, Larry W Forrester, Richard F Macko, and Hermano I Krebs. 2013. “Changes in Passive Ankle Stiffness and Its Effects on Gait Function in People with Chronic Stroke” 50 (4): 555–72. https://doi.org/10.1682/JRRD.2011.10.0206.

Sykora, Marek, Marek Czosnyka, Xiuyun Liu, Joseph Donnelly, Nathalie Nasr, Jennifer Diedler, Francois Okoroafor, Peter Hutchinson, David Menon, and Peter Smielewski. 2016. “Autonomic Impairment in Severe Traumatic Brain Injury: A Multimodal Neuromonitoring Study.” *Critical Care Medicine* 44 (6): 1173–81. https://doi.org/10.1097/CCM.0000000000001624.

Sykora, Marek, Jennifer Diedler, André Rupp, Peter Turcani, Andrea Rocco, and Thorsten Steiner. 2008. “Impaired Baroreflex Sensitivity Predicts Outcome of Acute Intracerebral Hemorrhage.” *Critical Care Medicine* 36 (11): 3074–79. https://doi.org/10.1097/CCM.0b013e31818b306d.

Szabo, Jozef, Peter Smielewski, Marek Czosnyka, Stanislava Jakubicek, Stefan Krebs, Pavel Siarnik, and Marek Sykora. 2018. “Heart Rate Variability Is Associated with Outcome in Spontaneous Intracerebral Hemorrhage.” *Journal of Critical Care* 48 (December): 85–89. https://doi.org/10.1016/j.jcrc.2018.08.033.

Sztajzel, Juan. 2004. “Heart Rate Variability: A Noninvasive Electrocardiographic Method to Measure the Autonomic Nervous System.” http://boccignone.di.unimi.it/CompAff2016_files/Heart-rate-variability_a-noninvasive-electrocardiographic-_2004.pdf.

Tokgözoglu, Sadberk Lale, Mustafa Kemal Batur, Mehmet Akif Topçuoglu, Okay Saribas, Sirri Kes, and Ali Oto. 1999. “Effects of Stroke Localization on Cardiac Autonomic Balance and Sudden Death.” *Stroke* 30 (7): 1307–11. https://doi.org/10.1161/01.STR.30.7.1307.

Turner-Stokes, Lynne, Ajoy Nair, Imad Sedki, Peter B Disler, and Derick T Wade. 2005. “Multi-Disciplinary Rehabilitation for Acquired Brain Injury in Adults of Working Age.” In *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd. https://doi.org/10.1002/14651858.cd004170.pub2.

Tzeng, Yu-Chieh, and Philip N Ainslie. 2014. “Blood Pressure Regulation IX: Cerebral Autoregulation under Blood Pressure Challenges.” *European journal of applied physiology*, *114*(3), 545-559 https://doi.org/10.1007/s00421-013-2667-y.

Vlutters, M., T. A. Boonstra, A. C. Schouten, and H. van der Kooij. 2015. “Direct Measurement of the Intrinsic Ankle Stiffness during Standing.” *Journal of Biomechanics* 48 (7): 1258–63. https://doi.org/10.1016/j.jbiomech.2015.03.004.

Woolf, Paul D., Robert W. Hamill, Louyse A. Lee, Christopher Cox, and Joseph V. McDonald. 1987. “The Predictive Value of Catecholamines in Assessing Outcome in Traumatic Brain Injury.” *Journal of Neurosurgery* 66 (6): 875–82. https://doi.org/10.3171/jns.1987.66.6.0875.

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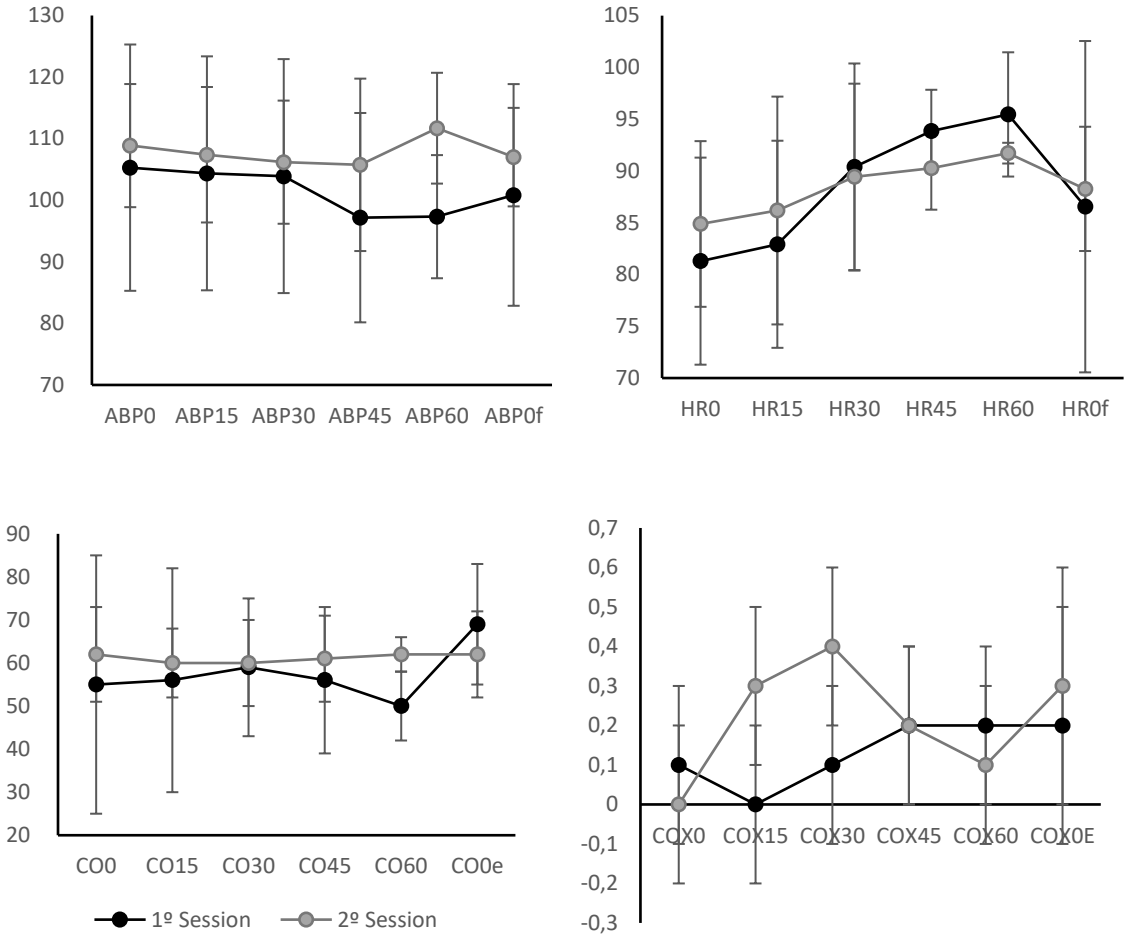


Figure 2. Line chart showing mean and standard deviation for Arterial Blood Pressure (ABP), Heart Rate (HR), Cerebral Oximetry (CO) and Cerebral Oximetry index (COx) at the slopes 0º, 15º, 30º, 45º, 60º and at the end of protocol, for the first and second sessions.

HRV and BRS

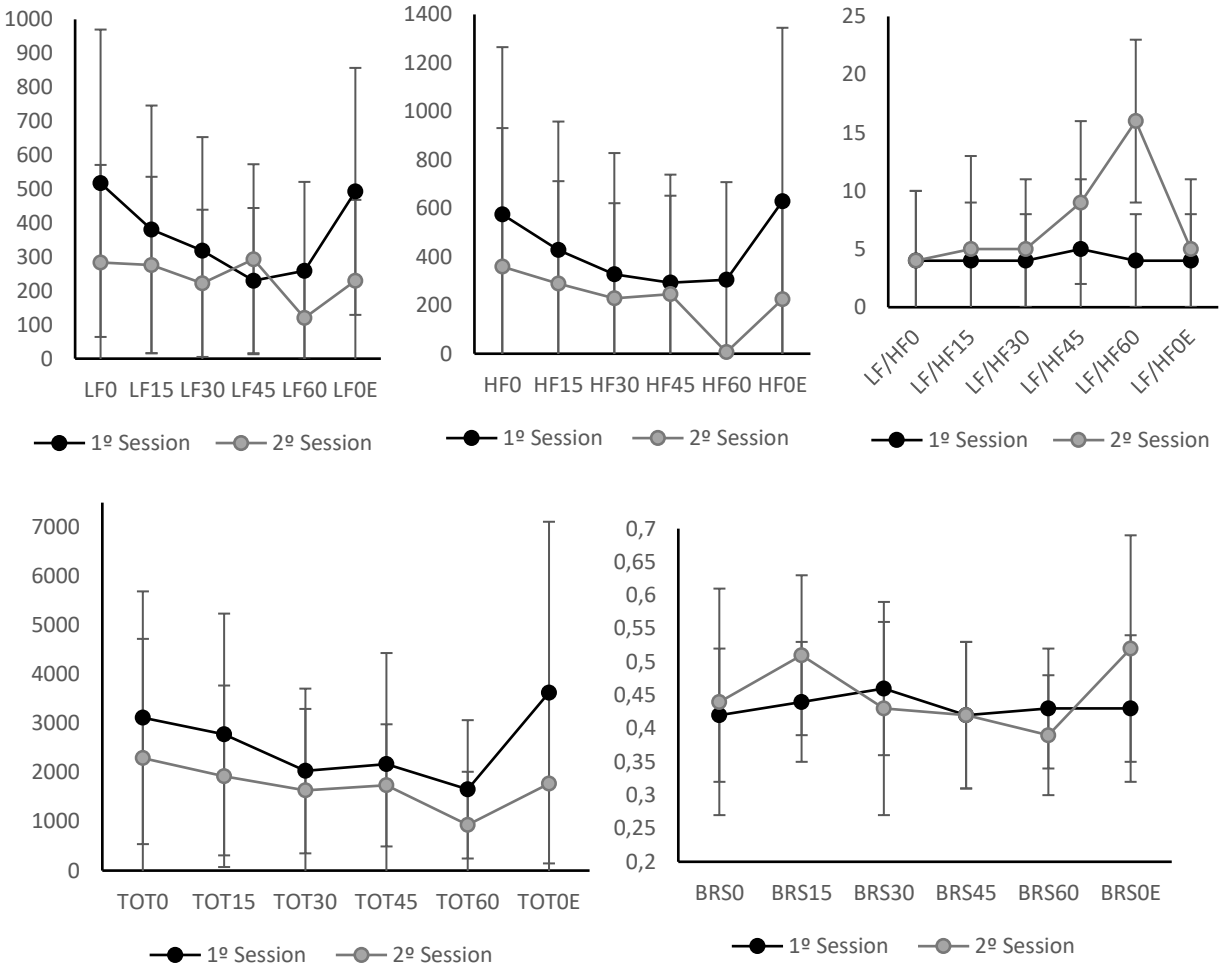


Figure 3. Line chart showing mean and standard deviation for Low and High Frequency component of Heart Rate Variability (HRV_LF, HRV_HF), balance (L/HF), total power (TOT) and Baroreflex Sensitivity (BRS) at the slopes 0º, 15º, 30º, 45º, 60º and at the end of protocol, for the first and second sessions.

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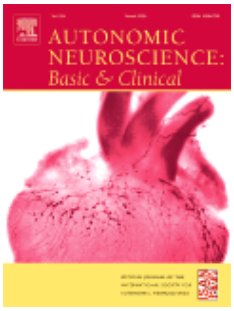
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This is an international journal with broad coverage of all aspects of the **autonomic nervous system** in man and animals. The main areas of interest include the innervation of **blood vessels** and **viscera**, **autonomic ganglia**, efferent and afferent **autonomic pathways**, and **autonomic nuclei** and pathways in the **central nervous system**.

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