Assessment of Neuro-Cardiovascular Uncoupling in Acute Brain Injury Patients

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Abstract

Acute brain injury results in decreased heart rate variability (HRV) and baroreflex function. The aim of the study was a longitudinal investigation of heart rate dynamics and relation with the severity of neurological dysfunction and outcome.

Metrics used were performed in 20 consecutive brain injured patients and included power spectral analysis, approximate entropy (ApEn) and transfer function (TF), as a measure of baroreflex sensitivity. There was no significant difference between survivors with different Glasgow Outcome Score (GOS =2-5), while the six non-survivors (brain dead) with GOS=1 had decreased variability, ApEn and TF values in relation with survivors. Mean and minimum values of different frequency components of the power spectrum were significantly associated with survival.

1. Introduction

Investigators have proposed that critical illness, multisystem trauma and organ dysfunction are characterized by the phenomenon of decomplexification. Healthy state exhibits some degree of random variability in physiologic variables, such as heart rate. Loss of such variability means loss of complexity that accompanies critical illness and trauma [1].

Acute brain injuries result as well in decreased heart beat oscillations and baroreflex sensitivity, indicating uncoupling of the autonomic and cardiovascular systems. This uncoupling is proportional to the degree of neurological injury [2].

Several analytic techniques are used to measure neuro-autonomic regulation of heart rate and blood pressure oscillations. One such method is the analysis of heart rate variability (HRV) that is the variability of the R-R series in the electrocardiogram (ECG). HRV is accepted as a measure of autonomic regulation of cardiac activity, and can reflect for example the coupling between the. autonomic nervous system (ANS) and the sinoatrial node [3]. There is wide evidence that a strong association exists between low measures of HRV and severity of neurological injury. Haji-Michael related changes in autonomic cardiovascular control in critically ill neurosurgical patients to the quality of subsequent outcome and survival and demonstrated a positive correlation between low HR and blood pressure (BP) power and GOS. Baroreflex sensitivity was also altered in patients with adverse outcome [4].

Another method of analysis of such complex interactions is the use of approximate entropy (ApEn) that distinguishes data sets by their amount of regularity. Based on numerous studies, ApEn may correlate with ‘hidden’ changes in various signals such as the ECG, often undetected by other methods of time series analysis, including HRV. Many researchers have found that ApEn of intracranial pressure (ICP) decreases during acute elevations, while increased periodicity (low ApEn) in ECG is correlated with adverse outcome in acute brain injury patients.

This study aims to evaluate spontaneous heart rate and blood pressure variability, longitudinally over time, in patients with acute brain injury, being treated in a multidisciplinary Intensive Care Unit (ICU), detect their possible dynamic change during hospitalization in relation with outcome and finally, estimate alterations in ApEn and spontaneous baroreflex sensitivity, correlating at the same time these variables with the severity of neurological dysfunction and outcome.

2. Methods

A total of 20 consecutive brain injured patients admitted for ≥ 5 days to the ICU, from June to November 2005, with a Glasgow Coma Scale (GCS) upon. admission ≤ 8 were enrolled in the study, after approval by the Institutional Ethics Committee at AHEPA Teaching Hospital (Thessaloniki, Greece). Mean GCS was 6 ± 2. All patients underwent emergency CT scanning of the central nervous system (CNS) upon arrival at the hospital. Diagnoses included multiple trauma (n=4), head trauma (n=7), intracranial hemorrhage (n=6) and subarachnoid hemorrhage (n=3). The Glasgow

Outcome Score (GOS) was determined upon discharge from the ICU. Individuals with previous history of atrial flutter or fibrillation, with ventricular ectopic beats and use of anti-arrhythmic medication were excluded from the study, as there was an inherent alteration in HRV parameters. None of the patients was taken medications that affect autonomic or cardiovascular function prior to admission to the hospital. All patients were studied in the supine position. There were 4 females and 16 males. The age range was from 54 to 65 years and the mean age was 61.3 ± 17.9 (Standard Deviation). The mean length of stay (LOS) was 9.8 ± 3.2 days. ECG and blood pressure were recorded on a daily basis (early in the morning when the workload was minimal) for all patients, from their admission and until their discharge from the ICU.

There were 14 survivors (70%), [multiple trauma: 2 with Injury severity score (ISS) < 45, head trauma: 7 with diffusion lesions type II (4 patients) and III (3 patients), according to the Traumatic Coma Data Bank (TCDB) grading system, intracranial hemorrhage: 3 with diffusion lesions type II and subarachnoid hemorrhage: 2 with admission grade IV, according to the Hunt-Hess classification] and 6 non-survivors (30%), [multiple trauma: 2 with Injury severity score (ISS) > 45, intracranial hemorrhage: 3 with diffusion lesions type IV and subarachnoid hemorrhage: 1 with admission grade V of the H-H classification system], who were diagnosed as brain dead (BD), according to published criteria [5]. From the survivors group, all patients underwent emergency operation upon arrival at the hospital and subsequently, they were transferred immediately to the ICU. None from the BD group, except for the two patients with multiple traumas, was operated initially or during his stay in the hospital. Monitoring of intracranial pressure (ICP) was not performed in any of our patients.

Analog ECG signals were obtained from monitors (Envoy Mennen Medical Ltd, Israel) with a low-pass filter at 100 Hz, while intra-arterial pressure (BP) was measured by a catheter inserted into the radial artery. Data were collected and analyzed using an L8400K Asus 850MHz Pentium III PC. Sampling rate for data collection was done at 250Hz. The ECG signal was recorded for 600 secs from a standard lead II ECG. From each 600-s data set, a 128-s time series that was artifact free was chosen for analysis. The spectral power of each spectrum ($msec^2$/Hz) was calculated at high [0.15-0.4Hz] and low frequency [0.04-0.15 Hz], according to open-source software via the Web Site Physionet, which is a public service of the Research Resource for complex physiologic signals. Fast periodicities (HF) are largely due to the influence of the respiratory phase on vagal tone. Low-frequency periodicities (LF) are produced by baroreflex feedback loops, affected by both sympathetic and parasympathetic modulation of the heart [3].

Similarly, spectral analysis of arterial pressure waveform consists of a high frequency component, that is related to the effects of respiration on cardiovascular control and a low frequency component (Mayer waves), that is under sympathetic regulation.

Baroreflex sensitivity was estimated by the transfer function magnitude (TF) between systolic blood pressure and heart rate, on a daily basis, every morning in all patients. The TF estimates the relative power and timing of two signals over a range of frequencies. The transfer magnitude represents the relative amplitude or gain of the output signal for a given input signal at a given frequency. The estimation of the TF was obtained by computing the alpha (α) index. Briefly, both HF and LF power spectra of systolic blood pressure and heart rate were computed and the root squared ratios between them (αHF & αLF), along with a global index α=(αHF + αLF)/2 were taken as an estimate of the baroreflex sensitivity.

ApEn is a family of statistics that addresses the question, "given a sequence of two (or three or four) inter-beat intervals, what is the probability that the next consecutive interval falls within a predetermined range?" Thus, approximate entropy is a measure of short-range correlation. ApEn in general quantifies the creation of information in a time series. A low value indicates that the signal is deterministic; a high value indicates randomness.

We used for data analysis a commercially available computer package (MATLAB 5.3, the Mathworks, USA). The total power was considered equal to the variance of the signal. The ratio of low to high frequency (LF/HF) was also used to assess sympathovagal balance.

Data are expressed as mean ± standard deviation (SD). Because of the wide range of values, heart rate power data were logarithmically transformed to satisfy the requirements of normal data distribution. Differences between patients of different outcome (as assessed by the Glasgow Outcome Score-GOS) were evaluated by one-way analysis of variance (ANOVA). Linear (GCS, GOS) and logistic regression (survival, brain death) was performed in order to detect any possible influence of different measured variables on outcome. Tests were performed with SPSS Software Version 8 and values of $p<0.05$ were considered to be significant.

3. Results

Patients with GOS=1 (brain dead) did not differ from those with GOS=2-5 (survivors) in terms of age (years), (58 ± 17 versus 62 ± 14) or weight (kg), (81±15 versus 76 ± 11) Admission GCS was significantly lower in non survivors compared to survivors, (4.25 ± 1.26 vs 6.38 ± 2.78, $p< 0.05$).

Table 1. Mean values (m) of measured variables [log variance, LF and HF of heart rate and blood pressure (BP) signals, their ratio, transfer function and ApEn] in patients with different Glasgow Outcome Score (GOS).

Variables	GOS=1 (m±SD) (n=6)	GOS=2 (m±SD) (n=4)	GOS=3 (m±SD) (n=2)	GOS=4 (m±SD) (n=3)	GOS=5 (m±SD) (n=5)
Log variance (Heart rate)	0.48 ± 0.54	1.24 ± 0.15	1.21 ± 0.10	1.15 ± 0.66	1.51 ± 0.38
Log LF (Heart rate)	0.31 ± 0.88	0.87 ± 0.51	1.08 ± 0.30	1.25 ± 0.82	1.08 ± 0.27
Log HF (Heart rate)	0.27 ± 0.42	0.30 ± 0.46	0.59 ± 0.4	0.64 ± 0.95	0.51 ± 0.68
Log LF/HF	0.22 ± 0.29	0.85 ± 0.34	0.59 ± 0.21	0.48 ± 0.30	0.70 ± 0.40
Log variance (BP)	1.72 ± 0.39	2.04 ± 0.30	1.94 ± 0.32	1.89 ± 0.17	1.67 ± 0.23
Log LF (BP)	1.25 ± 0.50	1.16 ± 0.20	1.48 ± 0.18	1.47 ± 0.21	1.38 ± 0.25
Log HF (BP)	0.63 ± 0.20	0.19 ± 0.17	0.48 ± 0.10	0.66 ± 0.17	0.55 ± 0.55
Transfer function (TF)	0.43 ± 0.29	0.84 ± 0.15	1.27 ± 0.26	1.25 ± 1.35	0.96 ± 0.47
ApEn mean	0.65 ± 0.24	0.77 ± 0.12	0.71 ± 0.32	0.96 ± 0.24	0.88 ± 0.35

There were significant correlations between admission GCS and mean HR power (r^2=0.57, p=0.02), mean LF (r^2=0.53, p=0.03) and minimum HF power (r^2=0.70, p=0.004). GOS correlated with the same variables (r^2 = 0.64, 0.54 and 0.60, p=0.009, 0.03 and 0.018 respectively).

The mean (p=0.01) and maximum values (p=0.01) of total heart rate power, the mean (p=0.04) and minimum values (p=0.01) of LF heart rate power, the minimum values of HF (p =0.02) heart rate power and the mean values of LF/HF ratio (p=0.02) were significantly associated with survival. It seems that patients relatively less injured and with better neurological outcome exhibited higher HRV with higher sympathetic regulation over their heart rate rhythms.

Differences between patients with different outcome were calculated using ANOVA on log-transformed data (Table 1). There was no significant difference in any measured metrics between the 14 non brain-dead patients with different GOS. The small size of the 4 sub-groups of survivors may be responsible for the negative results of the analysis.

Concerning the 6 non-survivors, they had signifycantly decreased HR power mean values ($msec^2$ /Hz), (p <0.01), low frequency (LF) and high frequency (HF) heart rate power minimum values (both with p<0.01), ratio (LF/HF) mean values (p<0.01) and TF mean values (p<0.05), when compared with survivors. Consequently brain death, that is the permanent cessation of any brain stem function, is associated with loss of variability of heart rate signals, low sympathetic control over cardiovascular dynamics and low baroreceptor reflexes.

ApEn mean values were lower in non survivors in relation with survivors (p<0.05). The individuals who died had more periodic and predictable heart rate signals, as they exhibited lower degree of randomness in their R-R time series.

In figures 1 and 2 we can see the distributions over time of mean variance, LF, HF, and LF/HF, for the survivors and non-survivors respectively. Concerning the first group, we can see a progressive increase in all measured metrics, from the admission to the ICU and until final discharge. The majority of survivors (11 subjects, 79%) were discharged between the 10^{th} and 13^{th} day, while 3 patients (2 with head trauma and 1 with subarachnoid hemorrhage, 21%) were discharged between the 5^{th} and 6^{th} day of stay. There are two upward shifts in the values of the measured parameters, before the 10^{th} and 13^{th} day. The first peak could be attributed to the fact that anesthesia, which adversely affects HRV metrics, was discontinued after the first 3 to 4 days of stay in the ICU. However, the second peak and the subsequent increase in values of HRV components, could be attributed to the restoration of coupling between autonomic and cardiovascular systems, with a parallel increase in ApEn (not shown in the figure) something that indicates an increased amount of information within heart rate time series.

The distribution in time of the above parameters in the second group displays an increase in variance and subsequently, a downward shift until approximately the 5^{th}

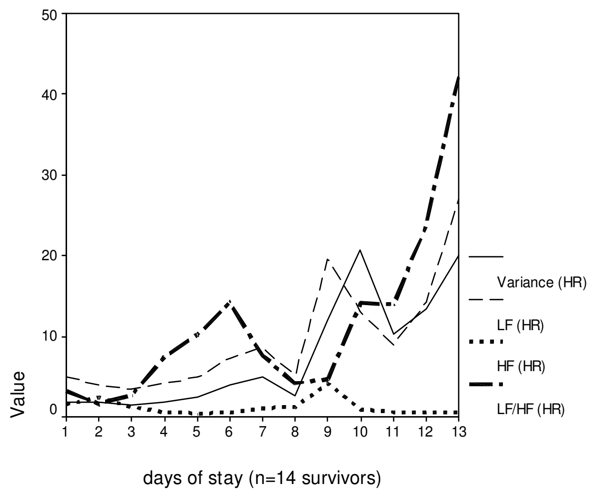

Figure 1. Distribution in time of mean values of variance, LF, HF and LF/HF ratio for the survivors group (GOS=2-5).

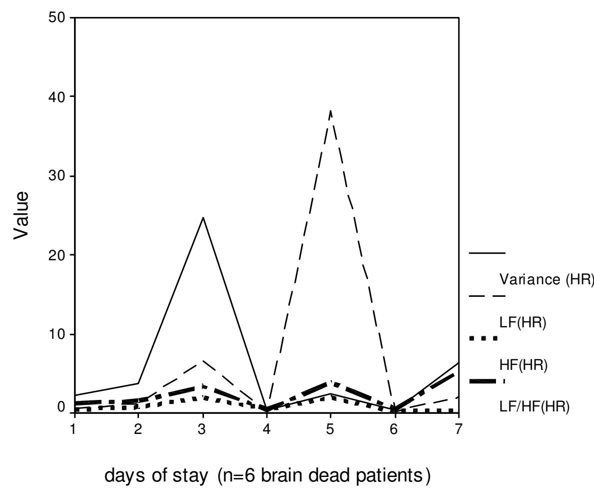

Figure 2. Distribution in time of mean values of variance, LF, HF and LF/HF ratio for non-survivors group (GOS = 1).

day of stay, when all patients were pronounced officially as brain dead, except for a major increase in the LF component, just prior of their death. Due to their poor prognosis based on high admission severity scores, anesthesia was discontinued during the second day of their stay in ICU. Although the withdrawn of anesthetic effects could be responsible for these transient upward shifts, there is no subsequent increase in values of HRV parameters, contrary to what happens to the survivors group.

4. Discussion and conclusions

In the present study we considered the uncoupling between cardiovascular and autonomic systems by evaluating the heart rate and blood pressure variability, the approximate entropy of the ECG and the sensitivity of the baroreflex control of the heart, longitudinally over time, in a heterogeneous group of patients who suffered acute brain injury from multiple causes.

In the present series, HRV was shown to be most markedly depressed in the patients with low GCS of admission, due both to trauma and hemorrhage.

Moreover, the normal spectral components of heart rate variability were significantly reduced in patients with low GOS, especially the minimum values of LF and HF while in brain dead individuals, they had almost disappeared.

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