Journal of Critical Care (2008) **23**, 380–386

ELSEVIER

Journal of Critical Care

Clinical Research

Investigation of heart rate and blood pressure variability, baroreflex sensitivity, and approximate entropy in acute brain injury patients

Vasilios Papaioannou MD, PhD[a,b,*], Maria Giannakou[a], Nikos Maglaveras[b], Efthymios Sofianos[a], Maria Giala[a]

[a]*Department of Anesthesiology and Intensive Care Medicine, Intensive Care Unit, AHEPA Teaching Hospital, Thessaloniki, Greece, 54006*
[b]*Laboratory of Medical Informatics, School of Medicine, Aristotle University of Thessaloniki, Greece, 54124*

Keywords:
Heart rate variability;
Blood pressure variability;
Baroreflex sensitivity;
Approximate entropy;
Acute brain injury

Abstract

Purpose: The purpose of the study was to investigate longitudinally over time heart rate (HR) and blood pressure variability and baroreflex sensitivity in acute brain injury patients and relate them with the severity of neurologic dysfunction and outcome.

Methods: Data from 20 brain injured patients due to multiple causes and treated in the intensive care unit were used, with HR and blood pressure recorded from monitors and analyzed on a daily basis. We performed power spectral analysis estimating low frequencies (LF: 0.04-0.15 Hz), high frequencies (HF: 0.15-0.4 Hz), and their ratio and calculated the approximate entropy, which assesses periodicity within a signal and transfer function (TF), that estimates baroreflex sensitivity. Heart rate variance was considered as a measure of HR variability.

Results: Nonsurvivors (brain dead) had lower approximate entropy (0.65 ± 0.24 vs 0.84 ± 0.26, $P < .05$) and lower variance mean values (0.48 ± 0.54 vs 1.29 ± 0.42 ms^2/Hz, $P < .01$), lower LF and HF minimum values (0.31 ± 0.88 vs 1.11 ± 0.46, $P < .01$; and 0.27 ± 0.42 vs 0.86 ± 0.30, $P < .01$, respectively), lower LF/HF (0.22 ± 0.29 vs 0.62 ± 0.28, $P < .01$), and lower TF mean values (0.43 ± 0.29 vs 1.11 ± 0.74, $P < .05$) during their whole stay in the intensive care unit in relation with survivors. The mean variance ($P < .05$), mean TF ($P < .05$), and mean LF/HF ($P < .05$) were significantly successful in separating survivors from nonsurvivors.

Conclusions: We conclude that in acute brain injury patients, low variability, low baroreflex sensitivity, and sustained decrease in LF/HF of HR signals are linked with a high mortality rate.

1. Introduction

Healthy state exhibits some degree of random variability in physiologic variables, such as heart rate (HR). Loss of

* Corresponding author. Tel.: +302310 437281.
E-mail address: papabil69@panafonet.gr (V. Papaioannou).

0883-9441/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.jcrc.2007.04.006

such variability means loss of complexity that accompanies critical illness and trauma such as acute brain injury, indicating uncoupling of the autonomic and cardiovascular systems [1-4].

Several analytic techniques are used to measure neuroautonomic regulation of HR and blood pressure oscillations. One such method is the analysis of heart rate variability (HRV), which is the variability of the R-R series in the electrocardiogram (ECG) [5-7]. There is wide evidence that a strong association exists between low measures of HRV and severity of neurologic injury [8,9]. Haji-Michael et al [8] 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 HRV and blood pressure variability (BPV) and Glasgow Outcome Score (GOS). Another method of analysis of such complex interactions is the use of approximate entropy (ApEn), which distinguishes data sets by their amount of regularity [10-13]. Increased regularity means greater autonomy, whereas decreased regularity indicates enhanced external coupling. Hornero et al [14], using the above formula, found that decreased complexity of intracranial pressure (low ApEn) coincides with periods of intracranial hypertension in brain injury.

This study was designed to determine the effects of longitudinal alterations of different variables estimating HRV, BPV, and baroreflex sensitivity on neurologic dysfunction and outcome in acute brain injury patients treated in the intensive care unit (ICU). Our hypothesis is that the pattern of change in different parameters could discriminate survivors vs nonsurvivors due to severe brain damage and predict final outcome.

2. Material and methods

2.1. Patients' characteristics

A total of 20 consecutive brain injured patients admitted for ≥5 days to the ICU from April 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 computed tomographic scanning of the central nervous system upon arrival at the hospital. The GOS was determined upon discharge from the ICU. Individuals with history of atrial flutter or fibrillation, ventricular ectopic beats, and use of antiarrhythmic or other medications affecting autonomic or cardiovascular function were excluded from the study, as there was an inherent alteration in HRV parameters not associated with the severity of trauma and critical illness [5,6]. All patients were studied in the supine position. There were 4 women and 16 men. The age range was from 54 to 65 years, and the mean age was 61.3 ± 17.9 (SD) years. The mean length of stay was 9.8 ± 3.2 days. There were 14 survivors (70%) and 6 nonsurvivors (30%) with different diagnosis of admission (Table 1) [15,16]. All nonsurvivors were diagnosed as brain dead according to published criteria [17], whereas those with multiple traumas and brain injuries who did not meet them were excluded from the study. In these cases, death could not be attributed exclusively to the neurologic injury per se, limiting the reliability of our results concerning neuroautonomic uncoupling in severe brain damage. All patients from the survivors' group underwent emergency operation upon arrival at the hospital and were subsequently transferred immediately to the ICU. None from the nonsurvivors' group, except for the 2 patients with multiple traumas, was operated initially or during his or her stay in the hospital.

2.2. HRV analysis

Heart rate variability is performed through the Fast Fourier transformation of the R-R time series (E: Methods). It displays in a plot the relative contribution (amplitude) of each frequency and includes fast periodicities in the range of 0.15 to 0.4 Hz (high frequency; HF), low-frequency (LF) periodicities in the region of 0.04 to 0.15 Hz, and very low frequency periodicities in the frequency range less than 0.04 Hz [5-7,18-20].

3. BPV analysis

Similarly, spectral analysis of arterial pressure waveform (systolic) consists of an HF component that is related to the effects of respiration on cardiovascular control and an LF component (Mayer waves) that is under sympathetic regulation [21].

Table 1 Admission diagnosis of the study group

Patients (n = 20)	Multiple trauma (ISS classification)	Head trauma (TCDB classification) [14]	Intracranial hemorrhage	Subarachnoid hemorrhage (H-H classification) [15]
Survivors (n = 14)	2 (ISS <45)	4 (grade II) 3 (grade III)	3 (TCDB grade II)	2 (H-H grade IV)
Nonsurvivors (brain dead) (n = 6)	2 (ISS >45)		3 (TCDB grade IV)	1 (H-H grade V)

ISS indicates Injury Severity Score; TCDB, Traumatic Coma Data Bank; H-H, Hunt-Hess.

3.1. Baroreflex sensitivity

Baroreflex sensitivity was estimated by the transfer function magnitude (TF) between systolic BP and HR, on a daily basis and every morning in all patients, by computing the α index (E: Methods) [22-25].

3.2. Approximate entropy

Approximate entropy 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 (E: Methods) [11,26].

3.3. ECG and BP signals

Considering the fact that HRV parameters are influenced by many factors such as respiratory rate and posture, it is important to maintain standard conditions (same time and period of measurements) [5,6]. Heart rate signals were studied in all patients admitted to the ICU and until their final discharge every morning and at the same time. Analog ECG signals were obtained from monitors (Envoy Mennen Medical Ltd, Rehovot, Israel), whereas intraarterial pressure was measured by a catheter inserted into the radial artery. Data analysis was performed with MATLAB 5.3 (Mathworks, Milwaukee, WI, USA) (E: Methods for details) [22,27,28].

3.4. Statistical analysis

Because of the wide range of values, HR and BP power data were logarithmically transformed to satisfy the requirements of normal data distribution, which was confirmed with a Kolmogorov-Smirnov test. Differences between patients of different outcome (survivors vs nonsurvivors and patients with different GOS) were evaluated by 1-way analysis of variance and by Kruskal-Wallis test for the parameters that did not meet the criteria of normal distribution. Linear and logistic regression was performed to evaluate different patterns of change over time of the measured parameters and detect their possible influence on outcome, whereas receiving operating characteristic (ROC) curves identified cut-point values of statistically significant variables that predicted final outcome (survivors vs nonsurvivors). Tests were performed with SPSS Software Version 11.0 (SPSS Inc, Chicago, Ill), and values of $P < .05$ were considered to be significant (E: Methods).

4. Results

4.1. Patients' characteristics

Patients with GOS = 1 (brain dead) did not differ from those with GOS = 2 to 5 (survivors) in terms of age (years) (58 ± 17 vs 62 ± 14), weight (kilograms) (81 ± 15 vs 76 ± 11), and height (centimeters) (170 ± 0.09 vs 167 ± 0.08). Admission GCS was significantly lower in nonsurvivors compared with survivors (4.25 ± 1.26 vs 6.38 ± 2.78, $P < .05$).

4.2. HRV analysis

Differences of the mean values of the parameters being studied from admission and until final discharge from the ICU between patients with different GOS were calculated using analysis of variance on log-transformed data (Table E-2). There were significant correlations between admission GCS and mean variance of HR ($r^2 = 0.57$, $P = .02$), mean LF ($r^2 = 0.53$, $P = .03$), and minimum HF power ($r^2 = 0.70$, $P = .004$). The GOS correlated with the same variables ($r^2 = 0.64$, 0.54, and 0.60; $P = .009$, .03, and .018, respectively). Admission values did not differ significantly between survivors and nonsurvivors, although there was a trend toward lower values in brain dead patients. There was no significant difference in any measured parameter between the 14 survivors. The small size of their 4 subgroups could be responsible for the negative results of the analysis. Concerning the 6 nonsurvivors, they had significantly decreased mean values of variance (millisecond squared per hertz, $P < .01$) and ratio (LF/HF) ($P < .01$) when compared with survivors (Table E-2). It seems that patients relatively less injured and with better neurologic outcome exhibited higher variability of their HR signals along with higher sympathetic regulation over their HR rhythms. Statistical evaluation of trends over time revealed a significant increase in mean variance, mean LF, and LF/HF ratio mean values in the survivors' group (Fig. 1A-D) and an increase in mean variance and ratio in the whole group of study (not shown in the figures, $P < .05$).

4.3. BPV analysis

Survivors vs nonsurvivors did not differ in variability of systolic BP signals. Their distribution in time could not meet the criteria of normal data distribution, and nonparametric tests (Kruskal-Wallis test, regression analysis with nonlinear curve estimation) did not detect any significant change in their values during hospitalization in either group of patients (Fig. E-2B).

4.4. Transfer function

The α index method of estimating baroreflex sensitivity revealed significant (Kruskal-Wallis test) increase in TF mean values in survivors (Fig. E-2A, $P < .05$) in relation with nonsurvivors (Table E-2), whereas its trend over time decreased in brain dead patients (Fig. E-2A,

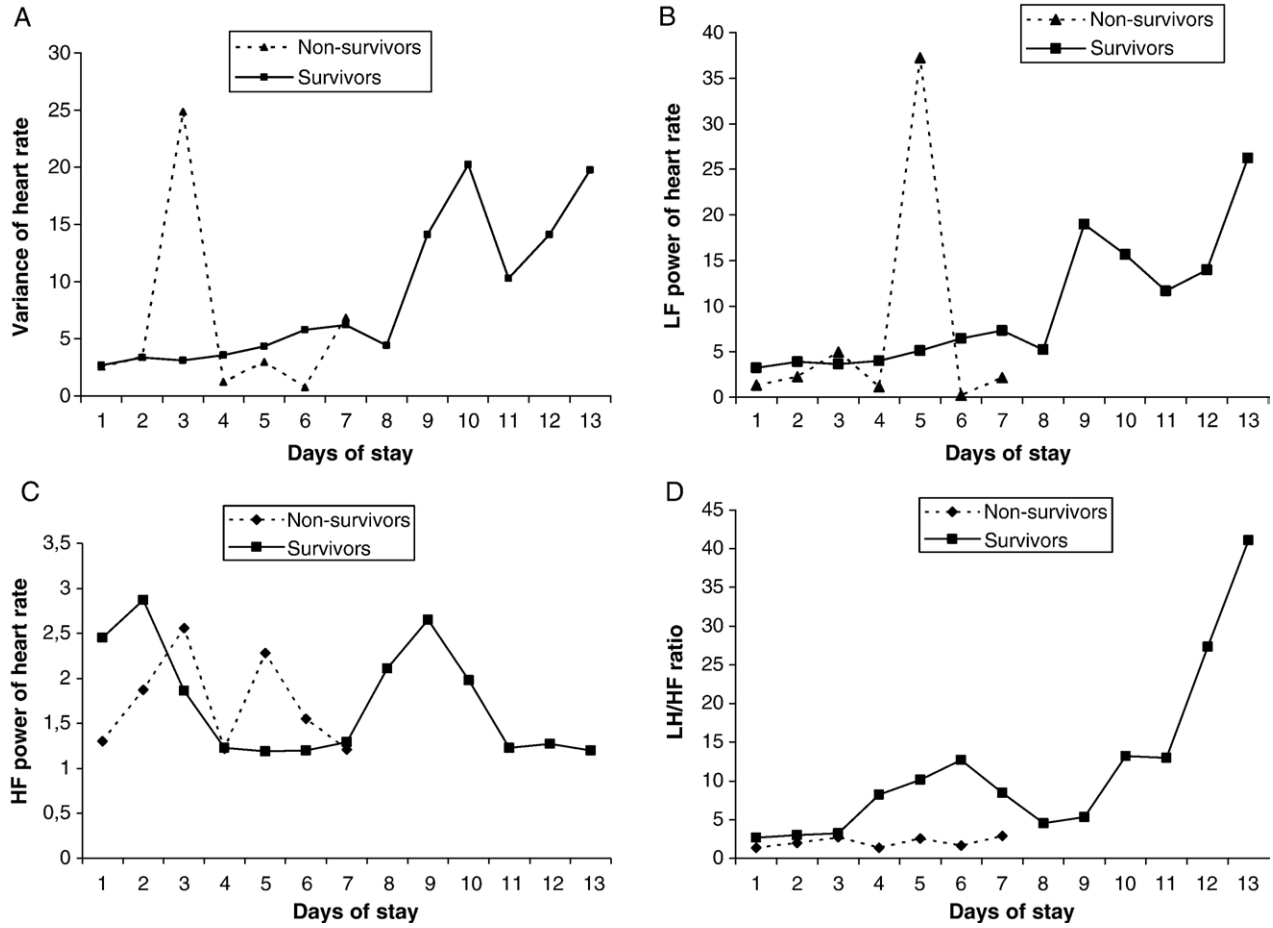

Fig. 1 A, Longitudinal alterations over time of the variance of HR signals in survivors vs nonsurvivors. Concerning the first cohort, there is a progressive upward shift in variance values from the patient's admission to the ICU and until final discharge. Statistical evaluation of trends (linear regression) identified a significant increase ($P < .05$) during ICU stay. For the nonsurvivors' group, the distribution in time of the variance values displays an increase and, subsequently, a downward shift until approximately the sixth day of stay, when all patients were pronounced officially as brain dead. Statistical evaluation of trends did not reveal significant alterations over time. B, Longitudinal alterations over time of the LF power of HR signals in survivors vs nonsurvivors. In the first group, there is a progressive increase in its values and a statistically significant increase in its trends ($P < .05$) during ICU stay. In the nonsurvivors' group, after a slight upward shift in the third day of stay, just prior the discontinuation of anesthesia, there is a significant drop and a subsequent major increase in the fifth day of stay, approximately 24 hours before patients were pronounced as brain dead. Statistical evaluation of trends did not reveal significant alterations over time. C, Longitudinal alterations over time of the HF power of HR signals in survivors vs nonsurvivors. In the first cohort, after a slight decrease in its values during the first 4 days, there is a progressive upward shift, especially in the 9th and 10th day, when most of the patients were discharged from the ICU. Trend values were not increased in a significant way. Concerning the second group, the distribution of HF displayed nonsignificant alterations over time. D, Longitudinal alterations over time of the LF/HF ratio of HR signals in survivors vs nonsurvivors. Concerning the first cohort, there is a progressive upward shift in its values from the patient's admission to the ICU and until final discharge. Statistical evaluation of trends identified a significant increase ($P < .05$) during ICU stay. For the nonsurvivors' group, the distribution of LF/HF displayed nonsignificant alterations over time.

$P < .05$) and increased significantly in survivors (Fig. E-2A, $P < .05$).

4.5. Approximate entropy

Approximate entropy mean values were lower in nonsurvivors in relation with survivors ($P < .05$) (Table E-2).The individuals who died had more periodic and predictable HR signals, as they exhibited lower degree of randomness in their R-R time series.

4.6. Multiple logistic regression and ROC curves

Logistic regression analysis with forward stepwise regression identified 3 parameters (mean values during ICU stay) as mostly associated with outcome: variance (regression coefficient: 1.16, standard error: −0.15, R^2: 0.54), ratio LF/HF (regression coefficient: 0.93, standard error: −0.07, R^2: 0.57), and TF (regression coefficient: 0.80, standard error: −0.25, R^2: 0.65) mean values. As shown in Table E-3, the ROC curve revealed that the above parameters

can predict outcome ($P < .05$) and discriminate accurately survivors vs nonsurvivors, with particular cut-point values that were chosen to maximize the sum of sensitivity (probability of positive test vs condition present) and specificity (probability of negative test vs condition absent).

5. Discussion

Acute brain injuries may impair cardiovascular variability because of either direct loss of integrity of central neural structures or by inducing baroreflex dysfunction. Brain death is also characterized by attenuated cardiovascular variability [29-31].

In the present study, we wanted to explore the alterations in neurocardiovascular dynamics and to investigate the possibility of discriminating survivors vs nonsurvivors using different patterns of change of HRV and BPV parameters. To our knowledge, this is the first investigation whose purpose was to track subjects longitudinally and study HR dynamics on an intrapatient and interpatient basis.

In the present series, variance of HR signals was shown to be markedly depressed in nonsurvivors and in patients with low GCS upon admission. Moreover, the normal spectral components of HRV, especially the mean LF/HF ratio and the TF, were significantly reduced in brain dead patients.

According to the baroreflex feedback loop theory, the LF oscillations are largely an index of baroreflex gain, whereas a change in BP is sensed by baroreceptors; and accordingly, the central nervous system adjusts the HR by both the fast vagal and the slower sympathetic action [32-34]. Goldstein et al have shown that acute brain injury adversely affects the above baroreflex loops, resulting in decreased HRV [4]. It seems that in severely ill neurosurgical patients, the uncoupling between cardiovascular and autonomic nervous system is the final result of a "functional opening" and deactivation of the baroreflex loop. This mechanism is responsible for a reduction in LF and HF components and their ratio [32], whereas the increased variance, LF/HF ratio, and TF in survivors result from enhanced efferent signals to the sinoatrial node through intact baroreceptor sensitivity. The same results have been described by Winchell and Hoyt in brain injury patients, whereas the decrease in variance and LF/HF ratio was accompanied by a 13-fold increase in their mortality [35]. The above information was also driven from the ApEn and TF data, as their values were significantly higher in survivors, indicating increased neurocardiovascular coupling along with less periodic time series.

Fig. 1A-D shows the distribution in time of different measured variables in survivors vs nonsurvivors. In the first group of patients, we can see a progressive increase ($P < .05$) in all measured HRV data (except for the HF component of HRV), especially the LF/HF ratio, during their whole stay in the ICU. The variance of systolic BP demonstrated a parallel increase with HRV, but not in a statistically significant way. Most of the survivors (11 subjects, 79%) were discharged between the 10th and 13th day, whereas 3 patients (2 with head trauma and 1 with subarachnoid hemorrhage, 21%) were discharged between the 5th and 6th day of stay (Fig. E-4). There are 2 upward shifts in the values of the measured parameters in the survivors group before the 10th and 13th day. The first peak could be attributed to the fact that anesthesia, which adversely affects HR and BPV [36], was discontinued after the first 3 to 4 days of stay in the ICU (Fig. E-3A). However, the second peak and the subsequent increase in values of HRV and BPV components (Fig. E-2B) could be attributed to the restoration of coupling between autonomic and cardiovascular systems, with a parallel increase in TF, something that indicates an increased amount of information being integrated through the baroreflex loops (Fig. E-2A).

Concerning nonsurvivors, because of their poor prognosis based on high admission severity scores, anesthesia was discontinued during the second day of their stay in ICU (Fig. E-3B). We can see an abrupt increase in HR variance and LF (Fig. 1A, B) just before brain death diagnosis, which was made on sixth day (third and fifth day of stay respectively, Fig. E-4), whereas variance (Fig. E-2B) demonstrates parallel alterations with the LF component and a subsequent increase in the seventh day. Motion or arrhythmia artifact was ruled out as a cause of these changes. The HF and the LF/HF ratio (Fig. 1C, D) do not demonstrate any significant change, whereas TF decreases ($P < .05$) progressively from the third day of hospitalization, indicating uncoupling of baroreflex (Fig. E-2A). Although the withdrawal of anesthesia 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. It has been hypothesized that an intrinsic vascular contractile mechanism might be present, at least after brain death, facilitating the occurrence of very low frequency BP oscillations due to reduced neural control, as that found in isolated arterial vessels [20,29,37,38]. However, others investigating conscious resting dogs with baroreflex denervation found increased BPV originating from the central nervous system and suggested that this may result from the loss of coordination between cardiac output and peripheral resistance [39,40]. An established hypothesis to explain the pronounced peaks before brain death diagnosis is generated by a resonance phenomenon due to time constants and delays of the baroreflex loop [37,38,41], whereas others attribute this trend to "vegetative storms" due to an increased release of catecholamines before brain death [42,43]. As their plasma levels were not determined in this study, we cannot rule out the probability that vegetative reflexes of spinal origin or thalamic storms could be associated with such an increase in LF components and BP variance. Furthermore, it has been shown that in patients

with septic shock and severe heart failure, there is an inverse relation between LF/HF and plasma norepinephrine levels, implying that high sympathetic drive may lead to saturation of LF oscillatory systems and compromise central autonomic controls [44]. However, experimental evidence supports that the above mechanisms are present mainly during brain death, whereas the continuous administration of catecholamines in healthy volunteers has not been found to reduce the sensitivity of the baroreflex [37,45]. Only 2 from the 6 brain dead patients had received a continuous infusion of epinephrine for a period of 1 day before the establishment of brain death diagnosis, whereas none was considered as a potential organ donor.

Sedation and analgesia were provided to our patients with propofol (2-3 mg/[kg min]) and fentanyl (0.1 μg/[kg min]), respectively. None of the patients took barbiturates during their management in the ICU. It has been observed that sedatives and opioids can produce a decrease in HRV parameters [36,46]. Because of different sources of variation, as well as variation between individuals, possible influence of sedatives on HRV parameters cannot be accurate. Because of the small period of infusion, the high lipid solubility, the very short initial distribution half-life ($t_{1/2\alpha}$), and the high clearance rate of both propofol and fentanyl [47,48], residual effects of those medications on HRV and BPV data, long after their discontinuation, do not seem to be significant.

It has also been recognized that controlled mechanical ventilation produces an increase in HF and may also lead to a reduction in LF band as well [49]. The last mechanism does not seem to be the cause of LF and HF changes in brain dead patients, while in the survivors' group, differences in respiratory patterns cannot be excluded as a cause of HF alterations.

In conclusion, the downward shift of TF and the failure of LF/HF ratio to increase during ICU stay were prominent in all nonsurvivors, whereas in survivors, there was a progressive increase in all measured variables. It seems that the combination of LF/HF ratio as an index of sympathovagal balance and baroreflex sensitivity could provide a prognostic tool in brain injury patients. However, there is a chance of an overoptimistic model selection derived by stepwise regression, with respect to the importance of each variable, because of the small sample size and the multiple tests at each step. For that reason, we think that a similar study with a more homogeneous and larger group of patients, especially with matching patients with different GCS scores, could be of significant value in determining whether the impairment of HRV and baroreflex sensitivity is predictive of, rather than simply associated with, mortality. The association of different HRV variables with different neuromonitoring data (intracranial pressure, flow velocities, or microdialysis data) on a longitudinal basis and under standardized monitoring could accomplish better prognostic tools for acute brain injury patients.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jcrc.2007.04.006.

References

[1] Goldstein B, Fiser DH, Kelly MM, et al. Decomplexification in critical illness and injury: relationship between heart rate variability, severity of illness, and outcome. Crit Care Med 1998;26:352-7.

[2] Kennedy H. Heart rate variability—a potential, noninvasive prognostic index in the critically ill patient. Crit Care Med 1998; 26:213-4.

[3] Seely AJ, Christou NV. Multiple organ dysfunction syndrome: exploring the paradigm of complex nonlinear systems. Crit Care Med 2000;28:2193-200.

[4] Goldstein B, Toweill D, Lai S, et al. Uncoupling of the autonomic and cardiovascular systems in acute brain injury. Am J Physiol Regul Integr Comp Physiol 1998;275:1287-92.

[5] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-65.

[6] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Standards of measurement, physiological interpretation and clinical use. Eur Heart J 1996;93:354-81.

[7] Akselroad S, Gordon D, Madwed JB, et al. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220-2.

[8] Haji-Michael PG, Vincent JL, Degaute JP, et al. Power spectral analysis of cardiovascular variability in critically ill neurosurgical patients. Crit Care Med 2000;28(7):2578-83.

[9] Baillard C, Vivien B, Mansier P, et al. Brain death assessment using instant spectral analysis of heart rate variability. Crit Care Med 2002;30(2):306-10.

[10] Pincus SM. Approximate entropy (ApEn) as a complexity measure. Chaos 1995;5:110-7.

[11] Pincus SM, Goldberger AL. Physiological time-series analysis: what does regularity quantify? Am J Physiol Heart Circ Physiol 1994;266:1643-56.

[12] Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol 2000;278(6):2039-49.

[13] Godin PJ, Buchman TG. Uncoupling of biological oscillators: a complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med 1996;24(No 7): 1107-16.

[14] Hornero R, Aboy M, Abasolo D, et al. Interpretation of approximate entropy: analysis of intracranial pressure approximate entropy during acute intracranial hypertension. IEEE 2005;52(10):1671-80.

[15] Marshall LF, Gautille T, Klauber MR, et al. A new classification of head injury based on computerized tomography. J Neurosurg 1991;75 (suppl):514-20.

[16] Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg 1968;28:14-20.

[17] Guidelines for the determination of death. Report of the medical consultants on the diagnosis of death to the President's Commission for the study of ethical problems in medicine and biomedical and behavioural research. JAMA 1981;246:2184-6.

[18] Pomeranz B, Macaulay RJB, Caudill MA, et al. Assessment of autonomic function in human by heart rate spectral analysis. Am J Physiol 1985;248:151-3.

[19] Malik M, Camm AJ. Components of heart rate variability: what they really mean and what we really measure. Am J Cardiol 1993; 72:821-2.
[20] Pagani M, Lombardi F, Guzzeti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympathovagal interaction in man and conscious dog. Circ Res 1986;59:178-93.
[21] Weis FD, Laude A, Girard P, et al. Effects of cold pressor test on short-term fluctuations of finger arterial blood pressure and heart rate in normal subjects. Clin Auton Res 1993;3:303-10.
[22] Saul JP, Berger RD, Albrecht P, et al. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol 1991;261:1231-45.
[23] Pagani M, Somers V, Furlan R, et al. Changes in autonomic modulations induced by physical training in mild hypertension. Hypertension 1988;12:600-10.
[24] Parati G, DiRienzo M, Bertinieri G, et al. Evaluation of the baroreceptor-heart rate reflex by 24-hour intra-arterial blood pressure monitoring in humans. Hypertension 1988;12:214-22.
[25] Lucini D, Pagani M, Mela GS, et al. Sympathetic restraint of baroreflex control of heart period in normotensive and hypertensive subjects. Clin Science 1994;86:547-56.
[26] Ho KK, Moody GB, Peng CK. Predicting survival in heart failure case and control subjects by use of fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics. Circulation 1997;96:842-8.
[27] Moody GB, Mark RG. A database to support development and evaluation of intelligent intensive care monitoring. IEEE Comput Cardiol 1996;23:657-60.
[28] Kaplan D, Furman MI, Pincus SM, et al. Aging and the complexity of cardiovascular dynamics. Biophys J 1991;59:945-9.
[29] Novak V, Novak P, De Marchie M, et al. The effect of severe brainstem injury on heart rate and blood pressure oscillation. Clin Auton Res 1995;5:24-30.
[30] Kita Y, Ishise J, Yoshita Y, et al. Power spectral analysis of heart rate and arterial blood pressure oscillation in brain-dead patients. J Auton Nerv Syst 1993;40:101-7.
[31] Goldstein B, DeKing DE, Delong D, et al. Autonomic cardiovascular state following severe brain injury and brain death. Crit Care Med 1993;21:228-33.
[32] DeBoer RW, Karemaker JM, Strackee J. Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. Am J Physiol 1987;253:680-9.
[33] Malpas SC. Neural influences on cardiovascular variability: possibilities and pitfalls. Am J Physiol Heart Circ Physiol 2002;282: H6-H20.
[34] Lanfranchi PA, Somers VK. Arterial baroreflex function and cardiovascular variability: interactions and implications. Am J Physiol Regul Integr Comp Physiol 2002;283:815-26.
[35] Winchell RJ, Hoyt DB. Analysis of heart rate variability: a noninvasive predictor of death and poor outcome in patients with severe head injury. J Trauma 1997;43:927-33.
[36] Kanaya N, Naoyuki H, Kurosawa S, et al. Differential effects of propofol and sevoflurane on heart rate variability. Anesthesiology 2003;98:34-40.
[37] Conci F, Di Rienzo M, Castiglioni P. Blood pressure and heart rate variability and baroreflex sensitivity before and after brain death. J Neurol Neurosurg Psychiatry 2001;71:621-31.
[38] Johansson B, Bohr DF. Rhythmic activity in smooth muscle from small subcutaneous arteries. Am J Physiol 1966;210:801-6.
[39] Just A, Wagner CD, Ehmke H, et al. On the origin of low frequency blood pressure variability in the conscious dog. J Physiol 1995;489.1: 215-23.
[40] Cowley AW, Liard J, Guyton AC. Role of the baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. Circ Res 1973;32:574-6.
[41] Di Rienzo M, Castiglioni P, Parati G, et al. Effects of sino-aortic denervation on spectral characteristics of blood pressure and pulse interval variability: a wide-band approach. Med Biol Eng Comput 1996;34:133-41.
[42] Mancia G, Parati G, Castiglioni P, et al. Effects of sino-aortic denervation on frequency-domain estimates of baroreflex sensitivity in conscious cats. Am J Physiol 1999;276:1987-93.
[43] Crenna P, Conci F, Boselli L. Changes in spinal reflex excitability in brain-dead humans. Electroencephalogr Clin Neurophysiol 1989;73: 206-14.
[44] Annane D, Trabold F, Sharshar T, et al. Inappropriate sympathetic activation at onset of septic shock. Am J Respir Crit Care Med 1999; 160:458-65.
[45] Tulen JHM, Tveld AJ, Van Roon AM, et al. Spectral analysis of hemodynamics during infusions of epinephrine and norepinephrine in men. J Appl Physiol 1994;76:1914-21.
[46] Estafanous FG, Brum JM, Ribeiro MP, et al. Analysis of heart rate variability to assess hemodynamic alterations following induction of anesthesia. J Cardiothorac Vasc Anesth 1992;6:651-7.
[47] Stein C. Peripheral mechanisms of opioid analgesia. Anesth Analg 1993;76:182-91.
[48] Bryson HM, Fulton BR, Faulds D. Propofol: an update of its use in anaesthesia and conscious sedation. Drugs 1995;50:513-59.
[49] Brown TE, Beightol LA, Koh J. Important influence of respiration on human R-R interval power spectra is largely ignored. J Appl Physiol 1993;75:2310-7.