Heart Rate Variability and Nonlinear Analysis of Heart Rate Signals of Patients During their Stay in a Multidisciplinary Intensive Care Unit

V Papaioannou[1,2], N Maglaveras[1], I Chouvarda[1], G Vretzakis[3], E Antoniadou[2]

[1]Laboratory of Medical Informatics, Aristotle University, Thessaloniki, Greece
[2]Intensive Care Unit, G.Genimatas Hospital, Thessaloniki, Greece
[3]Department of Cardiothoracic Anesthesia, University of Alexandroupolis, Greece

Abstract

Neuroautonomic modulation of heart rate was assessed in patients admitted to a multidisciplinary ICU. Metrics used were performed in 47 patients and included power spectral analysis, approximate entropy (ApEn) estimation and detrended fluctuation analysis (DFA). The resulting values were compared with a previously validated measure of severity of illness, the Sequential Organ Failure Assessment Score (SOFA). We found decreased variability and approximate entropy and increased DFA scaling exponent α in patients with the highest SOFA, incidence of death and length of stay. Correlations concerning α exponent were stronger for surgical patients with past medical history while decreased ApEn was associated with increased morbidity of surgical patients without medical history.

1. Introduction

Heart rate variability (HRV) has been extensively studied and is of particular importance in critical care medicine. Whereas a normal heart rate displays considerable beat to beat variability, a decrease in HRV is associated with several pathological states. A reduction in HRV was found in septic patients, and the observed loss was correlated with disease severity. It has been suggested that reduction in HRV may represent increased isolation of the heart from its interactions with other organs [1]. This hypothesis, presented by Godin and Buchman, suggests that organ systems act as biological oscillators and are coupled to one another. According to Pincus work [3] the uncoupling of stochastic (random) oscillators causes a loss in variability in each oscillator. The uncoupling of organs from each other is thought to be a consequence of systematic inflammatory response syndrome (SIRS).

Investigation of heart rate signals may also be useful in assessing the nonlinear characteristics of neuroautonomic modulation of heart rate. One such method is detrended fluctuation analysis (DFA) that assesses the degree of long-range correlation in a nonstasionary time series. In addition, approximate entropy (ApEn) is a nonnegative statistical measure that distinguishes data sets by their amount of regularity, with larger numbers indicating more randomness [3]. An increased DFA scaling exponent α and a decrease in ApEn have been correlated by many authors with postoperative ventricular dysfunction and increased severity of illness [2,3,5]. In the work we studied different kind of patients (medical, surgical with and without past medical history) who were admitted to our ICU and all these parameters where measured and correlated with the everyday SOFA score of severity of illness.

2. Methods

2.1 Study population

We studied 47 patients who were admitted to the ICU from December 2002 until April 2003.Two cohorts of surgical patients (n=19 for each group, 11/8 m/f) with mean age 69.52±3.7 and 58.21±3.15 years respectively were identified on the basis of the presence or absence of past medical history such as: hypertention (as determined by prior diagnosis and the use of antihypertensive medication), diabetes, COPD, heart failure (NYHA II or more) and coronary artery disease. Two trauma cases were included in the second group (CNS injury with Glasgow Coma Scale of admission 3). From the 36 patients 25 (70%) underwent major urology operations for renal and bladder cancer. The rest 11 (30%), underwent urgent (4) general surgery operations and scheduled operations (7) for gastric and gallbladder disease. One more cohort of medical patients (n=9, 4/5 m/f) admitted to the ICU (age 59.44±8.5) with diagnosis of admission acute respiratory failure with past history of COPD, was included in the study. Within this group there were two cases of sudden cardiac arrest. Patients with previous history of atrial flutter or fibrillation, with ventricular ectopic beats and long use of antiarrythmic medication were excluded from the study. All patients were studied in the supine position within 24 hours of admission to the ICU. Daily, SOFA score and electrocardiogram (ECG) were recorded until the patients were discharged from the ICU. Finally, 11 patients (26%) died.

2.2 ECG, heart rate variability and power spectrum analysis

The ECG signal was recorded for 20 minutes from a standard lead II ECG. Analog ECG signals were obtained with monitors (Marquette 8000, GE, Milwaukee, USA) with a low-pass filter at 100Hz. Data were collected and analyzed using an L8400K Asus 850MHz Pentium III PC. Sampling rate for data collection was done at 250Hz. Power spectral analysis (Non-parametric) software was used according to Kaplan after data had been read into Matlab format in a Matlab version 5.3 environment [4]. The total power from 0.04 to 0.15 Hz (low frequency power) was used to quantify sympathetic modulation of heart rate and the total power from 0.15 to 0.4 Hz was used as a measure of parasympathetic modulation. The ratio of low to high frequency heart rate power was also used to assess sympatheticovagal balance. The total energy of the signal has been considered equal to the variance of the signal.

2.3 Approximate entropy and detrended fluctuation analysis

ApEn was introduced by Pincus to quantify the creation of information in a time series [3]. A low value indicates that the signal is deterministic; a high value indicates randomness. Past work on HRV has suggested setting the 'filter factor' r to be 0.2 times the standard deviation of the data. The embedding lag in Kaplan is set to one beat. ApEn calculation software was used according to Kaplan in matlab format [4].

In DFA, the numerical value of the scaling exponent α is indicative of the type and degree of correlation present in the heart rate data. A α=0.5 indicates random white noise and no long-range correlations, 0.5<α<1 indicates persistent power-law correlations and α=1 indicates long-range power-law correlations of the type 1/f (pink noise). For α>1, correlations exist but no longer of the power-law form; i.e. α=1.5 indicates the presence of Brownian noise and therefore, a much smoother time series. It has been noted that the scaling exponent behavior for very short time scales (n<10 beats) tends to differ from that for longer time scales. For very short time scales the physiologic fluctuations in heart rate primary reflect smooth oscillations due to respiratory efforts; whereas for longer scales reflect the 1/f behavior [2]. Values of α were determined according to Pincus in matlab format for only the longer time scale (α2).

2.3 Statistical analysis

Because of the 10.000-fold range of values, heart rate power data were logarithmically transformed to satisfy the requirements of normal data distribution. Differences between the groups were evaluated by analysis of variance (ANOVA-test). In addition, regression analysis with curve estimation was performed between power spectral values, ApEn, α2 and SOFA scores with admissions, minimum, maximum metrics obtained during the ICU stay, length of stay (los), discharge values of SOFA and ΔSOFA (admission-discharge). Tests were performed with SPSS Software Version 8 and values of $p<0.05$ were considered to be significant. Values are expressed as mean±SD.

3. Results

Table 1 shows the average values of the physiologic variables and parameter measurements for the three cohorts of patients (medical, surgical, both medical and surgical).

Table 1. Number, age, length of stay (los) HRV parameters, ApEn, DFA α2 exponent, SOFA and ΔSOFA values for both, medical and surgical patients.

	Both	Medical	Surgical
Number	19	9	19
Age	62.52±3.7	59.44±8.5	58.21±3.15
Los	4±4.24	8.5±4.99	3.24±3.42
Variance	8.44±18.78	3.73±8.44	8.09±8.95
LF/HF	2.93±1.01	2.82±1.12	4.03±1.78
ApEn	0.54±0.26	0.53±0.36	0.77±0.28
DFA α2	1.05±0.22	0.97±0.23	1.04±0.24
SOFA	6.82±3.52	8±1.97	5.29±1.21
ΔSOFA	-0.12±2.29	0.25±4.53	-0.71±2.39

Age (years), los (days), variance (bpm^2/Hz), LF/HF (ratio), ApEn (approximate entropy), DFA α2, SOFA (sequential organ failure assessment score), ΔSOFA (SOFA admission-SOFA discharge).

Log variance values were significantly different between medical and surgical groups ($p<0.05$) and between both and surgical as well but not between both and medical cohorts of patients. We observed the same statistically significant differences concerning ApEn and exponent α2 values between the same groups ($p<0.05$).

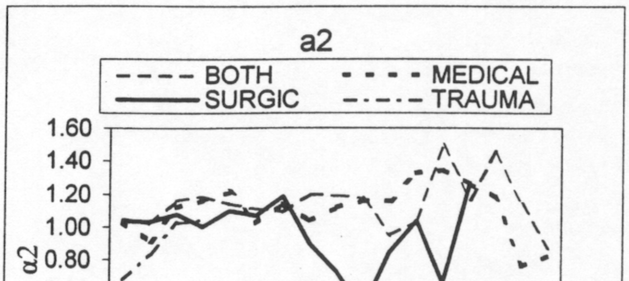

Figure 1.Variations of mean values of α2 during the whole stay (days) in ICU.

Medical patients were more severely ill than surgical with and without past medical history ($p<0.05$). However, ΔSOFA did not differ between the three groups. We can see from figures 1, 2 and 3 that the variance after an increase during the first days, especially in medical patients decreases progressively and reaches its lowest values after 9 to 10 days of hospitalization in ICU.

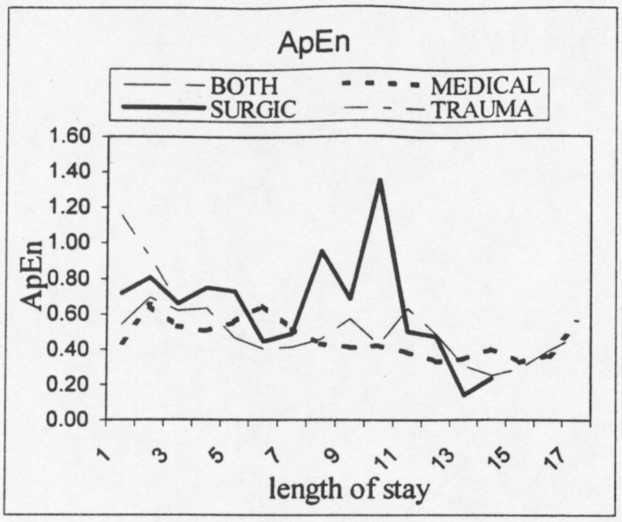

Figure 2. Variations of mean values of ApEn during the whole stay (days) in ICU.

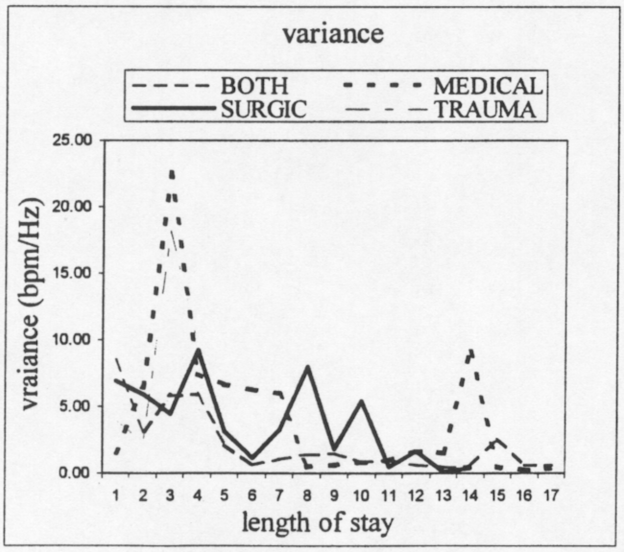

Figure 3. Variations of mean values of variances (bpm^2/Hz) during the whole stay (days) in ICU.

In surgical and medical groups of patients the variance appears to increase slightly after 10 to 15 days of stay. At the same time ApEn seems to decrease for the whole period of the study, except for the surgical patients, where we observe an increase between the 7th and 12th day and then a final fall of its value. A2 also increases slowly, especially in medical and both (surgical+medical history) groups while we observe a decrease in surgical patients, parallel to the ApEn upward change. The correlations between power spectral, DFA and ApEn values at admission to the ICU, and the minimum values versus SOFA maximum, SOFA discharge, ΔSOFA and length of stay (los) are shown in table 2.

Table 2. Correlations of ApEn, α2 and power spectral values between the three groups of patients.

Correlation	r^2	p value
$A2_{both}$ vs $\Delta SOFA_{both}$	0.59	0.0019
$A2_{both}$ vs $SOFA_{max\text{-}both}$	0.48	0.035
$A2_{both}$ vs $SOFA_{dis\text{-}both}$	0.42	0.02
$A2_{both}$ vs LOS_{both}	0.31	0.019
$A2_{med}$ vs LOS_{med}	0.72	0.039
$A2_{both}$ vs $Death_{both}$	0.44	0.016
$ApEn_{mintotal}$ vs $SOFA_{maxtot}$	0.47	0.001
$ApEn_{minsurg}$ vs $SOFA_{maxsurg}$	0.92	0.0001
$ApEn_{minsurg}$ vs $\Delta SOFA_{surg}$	0.73	0.0004
$ApEn_{minboth}$ vs $\Delta SOFA_{both}$	0.42	0.015
$ApEn_{minsurg}$ vs $SOFA_{dis\text{-}surg}$	0.89	0.0001
$ApEn_{minboth}$ vs $SOFA_{dis\text{-}both}$	0.51	0.005
$ApEn_{surg}$ vs $SOFA_{surg}$	0.41	0.0001
$ApEn_{surg}$ vs LOS_{surg}	0.72	0.0001
$ApEn_{surg}$ vs $Death_{surg}$	0.72	0.0001
$LogLF/HF_{admboth}$ vs $SOFA_{admboth}$	0.41	0.024
$LogLF/HF_{minboth}$ vs $SOFA_{maxboth}$	0.83	0.009
$LogLF/HF_{minmed}$ vs $\Delta SOFA_{med}$	0.57	0.029
$Log\ LF/HF_{minmed}$ vs $SOFA_{dismed}$	0.79	0.019
$LogLF/HF_{minboth}$ vs $SOFA_{disboth}$	0.68	0.003
$LogTP_{adtot}$ vs $SOFA_{admtot}$	0.37	0.054
$LogTP_{adboth}$ vs $SOFA_{adboth}$	0.59	0.047
$LogTP_{minsurg}$ vs $SOFA_{maxsurg}$	0.80	0.0006
$LogTP_{minsurg}$ vs $\Delta SOFA_{surg}$	0.81	0.0005
$LogTP_{admsurg}$ vs LOS_{surg}	0.76	0.0001

$Values_{adm,min,max,surg,tot,med,both,dis}$ represent admission, minimum, maximum, surgical patients, all together, medical, surgical with past medical history and discharge values.

The strongest correlations were between α2 and length of stay (los) of medical patients, α2 and ΔSOFA of surgical+medical (both) group. The minimum ApEn was correlated strongly with SOFA maximum, SOFA discharge, ΔSOFA and length of stay in surgical patients. The same strong correlation was found between log LF/HF minimum and SOFA maximum, ΔSOFA and SOFA discharge for both and medical patients respectively. Finally, minimum and admission values of logTP (total power or variance) were also correlated with SOFA maximum, ΔSOFA and los for surgical patients respectively in a similar manner. In figure 4 we can see the quadratic relationship of α2 and minimum ApEn with ΔSOFA and SOFA maximum for the medical+surgical and the surgical group respectively and the linear best curve fitting of α2 with length of stay for the both group.

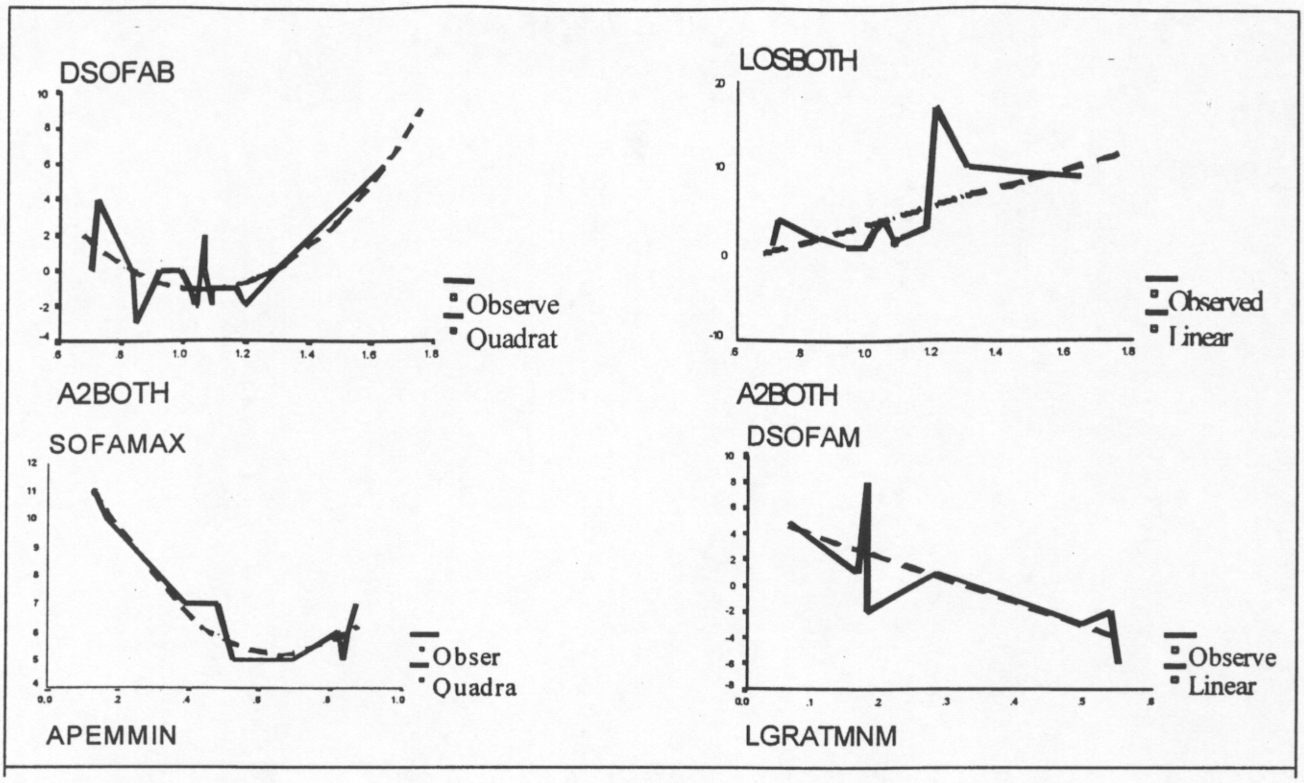

Figure 4. Results from curve estimation (curve fitting with the biggest r^2) between α2, ApEn (APENMIN : minimum for surgical patients) and logLF/HF (LGRATMNM: minimum for medical patients) with los (both), DSOFAB and M (ΔSOFA for both and medical patients) and SOFAMAX (maximum for surgical patients).

4. Discussion

Many mechanisms such as damaged neural transmission, the release of myocardial depressant factors and inhibition of numerous neurohumoral responses, including the response to endogenous or exogenous catecholamines, play their role to the 'decomplexification' seen in critical illness. Our results suggest that the parallel increase of α2 with SOFA and length of stay in medical+surgical (both) group indicates persistent phenomena, where positive feedback mechanisms enhance the inflammatory response (probably immunoparalysis in long term disease) [2,4]. The decrease in ApEn, especially in surgical patients, is correlated with the use of inotropic drugs and ventricular dysfunction [5] and is maybe altered in state of chronic pathology and use of medication, in both and medical group of patients. Its pre-terminal increase in surgical patients could be correlated with increased sympathetic tone and dynamic equilibrium (low α2) before the onset of septic shock [6].

5. Conclusions

We conclude that DFA and ApEn may prove to be useful in ICU in whish issues of nonstationarity in the data are a constant concern. Ultimately, continuous real time monitoring may provide a method of data interpretation during long ICU hospitalization.

References

[1] Godin PJ, Buchman TG. Uncoupling of biological oscillators: A complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med. 1996; 24: 1107 -16.

[2] Towell D, Sonnenthal K, Kimberly B, Lai S, Goldstein B. Linear and nonlinear analysis of hemodynamic signals during sepsis and septic shock. Crit Care Med 2000; 28: 2051-7.

[3] Pincus SM. Approximate entropy (ApEn) as a complexity measure. Chaos. 1995; 5: 110-117.

[4] Kaplan D, Furman MI, Pincus SM, Ryan SM, Lipsitz LA, Goldberger AL. Aging and the complexity of cardiovascular dynamics. Biophys.J. 1991; 59 : 945-949.

[5] Fleisher LA, Pincus SM, Rosenbaum SH. Approximate Entropy of heart rate as a correlate of postoperative ventricular dysfunction. Anesthesiology 1993; 78: 683-91.

[6] Annane D, Trabold F, Sharshar T, Jarrin I, Blanc AS, Raphael JC, Gajdos P. Inappropriate sympathetic activation at onset of septic shock: a spectral analysis approach. Am J Respir Crit Care Med 1999; 160(2): 458-65.

Address for correspondence: Vasilios Papaioannou, MD, MSc, Department of ICU, G. Genimatas Hospital, Ethnikis Amynis 41, Thessaloniki, GREECE. e-mail: papabil69@panafonet.gr