HRV Complexity as a Diagnostic Tool for Late Onset Sepsis in Sick Premature Infants

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Abstract—**In this paper, the objective was to investigate the heart rate variability in two selected groups of premature infants (sepsis vs non-sepsis). We studied the RR interval series not only by linear methods — time domain and frequency domain, but also by non-linear methods – chaos theory and information theory, in order to find the optimal parameters to distinguish sepsis premature infants from non-sepsis ones. The results show that indexes of information theory are useful parameters for the diagnosis of late neonatal infection in premature infants with recurrent apnea-bradycardia.**

I. INTRODUCTION

Late-onset sepsis, defined as a systemic infection in neonates older than 3 days, occurs in approximately 7% to 10% of all neonates and in more than 25% of very low birth weight infants who are hospitalized in Neonatal Intensive Care Units (NICU) [1]. The clinical manifestations of neonatal sepsis, whatever the source of infection, are always not so evident. Accordingly, lacking in early and adapted interventions always leads to life risk. [1]Therefore, this disease is a major problem resulting in high morbidity and mortality for premature infants [2].

As we know, sick preterm newborns do not show any fever, only with blood culture, the possible signs of sepsis may be detected. However, on one hand, the hematological and biochemical markers which have been used in this symptom, not only require invasive procedures which should not be frequently repeated, but also have low predictive values in the early phase of sepsis. On the other hand, it has been observed experimentally that phenomena of apnea-bradycardia happened more frequently in sepsis preterm newborns than in non-sepsis ones [3].

The heart rate variability (HRV) analysis in neonatology is a useful tool to understand the cardiovascular control system behavior in late-onset sepsis of premature infants. Starting from the obvious increase in apnea-bradycardia crisis related with the state of sickness, a way to evaluate the relationship between the infection and its manifestation was investigated. In particular, since apnea-bradycardia was an indication of altered mechanisms of cardiovascular regulation, the HRV investigation on these subjects is an immediately consequent decision. Therefore, we investigated the RR interval series extracted from ECG signals.

In this paper, we study both linear methods and non-linear methods in order to find the optimal parameters to discriminate between infected and non-infected premature infants. In section II, we will refer to linear methods. In section III, non-linear methods are presented in details. We offer experimental protocol in section IV. Results are demonstrated in section V. Finally, we discuss and conclude with summary in section VI.

II. LINEAR METHODS

Linear indexes are proposed in both time domain and frequency domain [4].

A. Time Domain

Time domain analysis consisted in the extraction of the standard deviation (SD) as an estimation of global variability,

$$SD = \frac{1}{N-1}\sqrt{\sum_{i=1}^{N}(RR_i - \overline{RR})^2} \quad (1)$$

and square root of the mean of squared successive differences (rMSSD) as an estimation of short term beat to beat variability.

$$rMSSD = \frac{1}{N-1}\sqrt{\sum_{i=1}^{N}(RR_i - RR_{i-1})^2} \quad (2)$$

B. Frequency Domain

Concerning frequency domain, a 10-order autoregressive model was used in power spectral analysis for RR. The order was estimated from all the experiments as the one which most often provided the minimum of

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Akaike criteria. The following spectral bands were defined: very low frequency (VLF, 0.002 to 0.02 Hz), low frequency (LF, 0.02 to 0.2 Hz), and high frequency (HF, 0.2 to $[0.5/\overline{RR}]$ Hz) where $\overline{RR}$ is the mean RR in the corresponding window containing 1024 beats [5][6]. The areas below each peak as well as the total power spectral density (0.002 to $0.5/\overline{RR}$ Hz) were calculated and expressed in ms^2 for RR[7][8]. Power of HF (p_HF), LF (p_LF) and VLF (p_VLF) are also computed after natural logarithm transformations (ln ms^2)

III. NON-LINEAR METHODS

We also use two kinds of non-linear methods: chaos theory and information theory.

A. Chaos theory

To test for the scale invariance, the detrended fluctuation analysis (DFA) was evaluated in the methods described by Peng et al [9]. The fluctuations were characterized by the scaling exponent α, a self-similarity parameter representing the long-range fractal correlation properties of the signal. The exponent α is 0.5 for white noise with uncorrelated randomness, 1 for $1/f$ noise and long-range fractal correlations, and 1.5 for Brown motion [9][10]. In most cases, the log-log plot was not strictly linear but rather consisted of two distinct linear regions of different slopes separating at a break point near 40 beats. Therefore, in accordance to previous study, we evaluated the fractal scaling exponent α_{fast} from 4 to 40 beats, and α_{slow} from 40 to 1000 beats [11].

B. Information theory

Information theory is derived from the ideas about entropy of random variables and processes provided by Claude E Shannon. Entropy is defined in terms of a discrete random event *x*, with possible states *1...n* as:

$$H(x) = \sum_{i=1}^{n} p(i)\log_2\left(\frac{1}{p(i)}\right) = -\sum_{i=1}^{n} p(i)\log_2(p(i)) \qquad (3)$$

The concept of entropy in information theory describes how much 'uncertainty' there is in a signal or random event. An alternative way to look at this notion is to talk about how much information is carried by the signal.

So, according to the same reasoning that led to the definition of entropy, it is possible to find the same quantity for pairs of random events, which is called the joint entropy, written as $H[x, y]$.

Then, when the state of one of the two variables, let us say, *y* is known, the possible states for the *x* variable are expressed by the cross-conditional entropy, i.e. the entropy of *x* conditioned on *y*, written as $H[x/y]$.

Entropy, as it relates to dynamical systems, is the rate of information production. However, methods for estimating the entropy of a system represented by a time series are not well suited to analysis of the short and noisy data sets encountered in cardiovascular and other biological studies.

Recently, it has been observed that non-linear indexes based on information theory may be useful to discern sepsis from non-sepsis babies [12]. Thus, analysis of non-linear variables has been performed in order to assess randomness of the series. Four metrics were considered: Approximate Entropy, Sample Entropy, Permutation Entropy and Regularity.

1) Approximate Entropy: Pincus [13] introduced approximate entropy (AppEn), a set of measures about system complexity closely related to entropy, which has been extensively applied to biological series analysis. It allows discriminating signals depending on their regularity without considering the model of the system. Consequently, regardless of their nature, whatever it is stochastic or purely deterministic, linear or non-linear, AppEn allows calculating indirectly signal correlation and persistence.

Given a sequence S_N, consisting of *N* instantaneous Heart Rate measurements *HR(i), i=1,...,N*. We must choose values for two input parameters—*m* and *r*, to compute the *AppEn(S_N,m,r)* of the sequence, where *m* refers to the pattern length, and *r* defines the criterion of similarity. We denote a pattern of *m* HR measurements, beginning at *i* within S_N, by the vector $x_m(i)$. Two patterns, $x_m(i)$ and $x_m(j)$, are similar if the difference between any pair of corresponding measurements in the patterns is less than *r*, i.e., if

$$\left|HR(i+k) - HR(j+k)\right| < r \quad \text{for} \quad 0 \le k < m \qquad (4)$$

Now given the set x_m of all patterns of length m $[x_m(1), x_m(2), \cdots, x_m(N-m+1)]$ within S_N, it is possible to define

$$C_{im}(r) = \frac{n_{im}(r)}{N-m+1} \qquad (5)$$

Where $n_{im}(r)$ is the number of patterns in x_m that are similar to $x_m(i)$(given the similarity criterion *r*). The quantity $C_{im}(r)$ is the fraction of patterns of length *m* that resemble the pattern of the same length that begins at interval *i*.

Finally, we define the AppEn of S_N, for patterns of length *m* and similarity criterion *r*, as following:

$$AppEn(S_N, m, r) = \ln\left[\frac{C_m(r)}{C_{m+1}(r)}\right] \qquad (6)$$

where $C_m(r)$ is the mean value of $C_{im}(r)$.

2) Sample Entropy: Sample entropy (SamEn) is derived from approaches developed by Grassberger and his co-workers [14-17]. *SamEn(m,r,N)* is precisely the negative natural logarithm of the conditional probability that two sequences similar for *m* points remain similar at the next point, where self-matches are not included in

calculating the probability. Thus a lower value of SamEn also indicates more self-similarity in the time series.

We began from the work of Grassberger and Procaccia[16], who defined

$$C^m(r) = (N-m+1)^{-1} \sum_{i=1}^{N-m+1} C_i^m(r) \tag{7}$$

The average of the $C_i^m(r)$ defined above. This differs from $\Phi^m(r)$ only in that $\Phi^m(r)$ is the average of the natural logarithms of the $C_i^m(r)$. They suggest approximating the Kolmogorov entropy of a process represented by a time series by

$$\lim_{r\to 0} \lim_{n\to\infty} \lim_{N\to\infty} -\ln[C^{m+1}(r)/C^m(r)] \tag{8}$$

Self-matches are counted and

$$C^{m+1}(r)/C^m(r) = (N-m+1)\sum_{i=1}^{N-m} A_i \Big/ (N-m)\sum_{i=1}^{N-m+1} B_i \tag{9}$$

Where A_i is the number of vectors $x_{m+1}(j)$ within r of $x_{m+1}(i)$, and B_i is the number of vectors $x_m(j)$ within r of $x_m(i)$.

In this form, however, the limits render it unsuitable for the analysis of finite time series with noise. We therefore made two alterations to adapt it to this purpose. Firstly, we followed their later practice in calculating correlation integrals [14-17] and did not consider self-matches when computing $C^m(r)$. Secondly, we considered only the first *N-m* vectors of length *m*, ensuring that, for $1 \le i \le N-m$, $x_m(i)$ and $x_{m+1}(i)$ were defined.

We defined $B_i^m(r)$ as $(N-m-1)^{-1}$ times the number of vectors $x_m(j)$ within r of $x_m(i)$, where j ranges from *1* to *N - m*, and $j \neq i$ to exclude self-matches. We then defined

$$B^m(r) = (N-m)^{-1}\sum_{i=1}^{N-m} B_i^m(r) \tag{10}$$

Similarly, we defined $A_i^m(r)$ as $(N-m-1)^{-1}$ times the number of vectors $x_{m+1}(j)$ within r of $x_{m+1}(i)$, where j ranges from *1* to *N - m* ($j \neq i$), and set

$$A^m(r) = (N-m)^{-1}\sum_{i=1}^{N-m} A_i^m(r) \tag{11}$$

$B^m(r)$ is then the probability that two sequences will match for *m* points, whereas $A^m(r)$ is the probability that two sequences will match for *m+1* points. We then defined the parameter

$$SamEn(m,r) = \lim_{N\to\infty}\left\{-\ln\left[A^m(r)/B^m(r)\right]\right\} \tag{12}$$

which is estimated by the statistics

$$SamEn(m,r,N) = -\ln\left[A^m(r)/B^m(r)\right] \tag{13}$$

Where there is no confusion about the parameter r and the length m of the template vector, we set

$$B = \left\{\left[(N-m-1)(N-m)\right]/2\right\} B^m(r) \tag{14}$$

and

$$A = \left\{\left[(N-m-1)(N-m)\right]/2\right\} A^m(r) \tag{15}$$

So that B is the total number of template matches of length m and A is the total number of forward matches of length $m+1$. We note that $A/B = \left[A^m(r)/B^m(r)\right]$, so SamEn can be expressed as

$$SamEn(m,r,N) = -\ln(A/B) \tag{16}$$

3) Permutation Entropy: Permutation entropy (PermEn) was introduced by Bandt and Pompe[18] as a convenient means of mapping a continuous time series onto a symbolic sequence. To illustrate the idea, let us first embed a scalar time series $\{x(i), i = 1, 2, \cdots\}$ to a *m*-dimensional space [19]:

$$X_i = [x(i), x(i+L), \cdots, x(i+(m-1)L)] \tag{17}$$

where m is called the embedding dimension and L the delay time. For a given, but otherwise arbitrary i, the m number of real values X_i can be sorted in an increasing order:

$$[x(i+(j_1-1)L) \le x(i+(j_2-1)L) \le \cdots \le x(i+(j_m-1)L)]$$

When an equality occurs, e.g.

$$x(i+(j_{i1}-1)L) = x(i+(j_{i2}-1)L) \tag{18}$$

we order the quantities x according to the values of their corresponding j's, namely if $j_{i1}<j_{i2}$, we write

$$x(i+(j_{i1}-1)L) \le x(i+(j_{i2}-1)L) \tag{19}$$

This way, the vector X_i is mapped onto $(j_1, j_2, \ldots, j_m)$, which is one of the *m!* permutations of m distinct symbols $(1, 2, \ldots, m)$. It is clear that each point in the *m*-dimensional embedding space, indexed by i, can be mapped to one of the *m!* permutations. When each such permutation is considered as a symbol, then the reconstructed trajectory in the *m*-dimensional space is represented by a symbol sequence. The number of distinct symbols can be at most *m!*. Let the probability distribution for the distinct symbols be $P_1, P_2, \ldots, P_K$, where $K \le m!$. Then the PermEn for the time series $\{x(i), i = 1, 2, \cdots\}$ is defined [18] as the Shannon entropy for the K distinct symbols

$$H_p(m) = -\sum_{j=1}^{K} P_j \ln P_j \tag{20}$$

When P_j=1/m!, then $H_p(m)$ attains the maximum value ln(m!). For convenience, we always normalize $H_p(m)$ by ln(m!), and denote

$$0 \le \bar{H}_p = H_p(m)/\ln(m!) \le 1 \tag{21}$$

Thus H_p gives a measure of the departure of the time series under study from a complete random one: the smaller the value of H_p, the more regular the time series is.

4) Regularity: Regularity (Reg) can be defined as the degree of recurrence of a pattern in a signal. The evaluation of the regularity for a process x is based on the calculation of corrected conditional entropy (CCE_x),

representing the amount of information carried by the most recent samples of the series when some past samples are known [20]. To derive an index of complexity which is independent of the different probability distribution of the process, the CCE_x is normalized by the Shannon entropy of the process, so the normalized corrected conditional entropy ($NCCE_x$) is obtained.

The index of Reg of the process x is defined as:

$$\mathrm{Re}\, g = 1 - \min(NCCE_x(L)) \qquad (22)$$

where L is the maximum of length for patterns.

From equation (22), it is obvious that Reg ranges from 0 to 1. In detail, Reg tends to 0, if the series is a fully unpredictable process. On the contrary, it tends to 1, if the series is a really periodic signal. Besides, Reg assumes intermediate values for those processes that can be partially predicted by the knowledge of the past samples.

IV. EXPERIMENTAL PROTOCOL

Data were obtained from two groups of premature infants (9 sepsis vs 11 non-sepsis) hospitalized from the NICU in the Center of Hospital affiliated to University of Rennes 1 (CHU-Rennes) between 2001 and 2006. This research was approved by the local ethics committee in France (03/05-445). Furthermore, the parents of these babies were informed and gave common consents.

Inclusion criteria were: more than one bradycardia per hour and/or need for bag-and-mask resuscitation and/or the intention of the attending physician to investigate for a suspected infection. Exclusion criteria were: ongoing inflammatory response with or without confirmed infection, medication known to influence autonomic nervous system (ANS) including morphine, catecholamine, sedative drugs, intra-tracheal respiratory support, intra-cerebral lesion or malformation.

"Sepsis" is defined as the combination of an inflammatory response, i.e. C-reactive protein (CRP) higher than 5mg/l 24 hours after the recording, and positive blood cultures. "No-sepsis" is defined as the association of an absence of inflammatory response, i.e. a CRP less than 5mg/l 24 hours after the recording, and negative blood cultures.

All recordings were performed in the NICU and data were recorded in standard conditions. The monitoring (Powerlab system®, ADInstruments) included one-hour recording of two electrocardiogram (ECG), electrooculogram (EOG), electroencephalogram (EEG) leads, one pulse oxymetry saturation (SaO2), nasal flow and abdominal respiration trace.

Continuous ECG signals were sampled at 400HZ, which was also carried on for the other biological signals. There were no significant differences in gender, gestational age, chronological age (>72 hours), post-menstrual age (<33 weeks), weight and haematocrit between sepsis and non-sepsis groups.

V. RESULTS

Data analysis was conducted on home-made signal processing tools designed with the software Matlab® 7.1 Release 14 (The Mathworks, Inc.). Consecutive sequences of successive cardiac cycle length (RR series) were extracted from ECG recordings and employed into time domain, frequency domain, chaos theory and information theory. The parameters were calculated in the windows covering 1024 beats.

Kruskal-Wallis test is used to evaluate p-value for each parameter. The Kruskal-Wallis test is a nonparametric version of one-way Analysis of Variance (ANOVA). The low p-value means the Kruskal-Wallis test results agree with the one-way ANOVA results.

The Kruskal-Wallis test evaluates the **null hypothesis H0** (all samples come from populations that have the same median) against the **alternative hypothesis H1** (the medians are not all the same).

The Kruskal-Wallis test makes the following assumptions about the test data:

- All samples come from populations having the same continuous distribution, apart from possibly different locations due to group effects.
- All observations are mutually independent.

The Kruskal-Wallis test is based on an analysis of variance using the ranks of the data values, not the data values themselves. It is preferable to perform a test to determine which pairs are significantly different, and which are not.

Table 1
Values of Parameters Extracted from HRV

	Sepsis	Non-Sepsis
SD	16.83 ± 13.67	10.40 ± 4.15
rMSSD	1.83 ± 0.78	1.45 ± 0.34
p_HF(ln)	5.99 ± 1.18	5.75 ± 0.65
p_LF(ln)	7.76 ± 1.18	7.88 ± 0.64
p_VLF(ln)	6.66 ± 0.86	6.67 ± 0.60
α_{slow}	0.89 ± 0.16	1.03 ± 0.08
α_{fast}	1.49 ± 0.13	1.47 ± 0.08
AppEn*	0.63 ± 0.15	0.84 ± 0.15
SamEn*	0.39 ± 0.16	0.68 ± 0.25
PermEn*	0.73 ± 0.05	0.78 ± 0.03
Reg*	0.79 ± 0.05	0.71 ± 0.05

* Kruskal-Wallis test, $p<0.05$, sepsis vs non-sepsis

Referring to information theory, the index of AppEn, a measure quantifying the complexity and regularity of time series, was calculated from the continuous 1024 beats segments with fixed input variables m = 2 and r = 0.2. About SamEn, m = 3 and r = 0.2. With regard to PermEn, we choose the most suitable values: the embedding dimension m = 6, the window size w = 1024. As for Reg, the maximum of length for patterns L is 10. Furthermore, we box plot these four indexes as following and see them in detail.

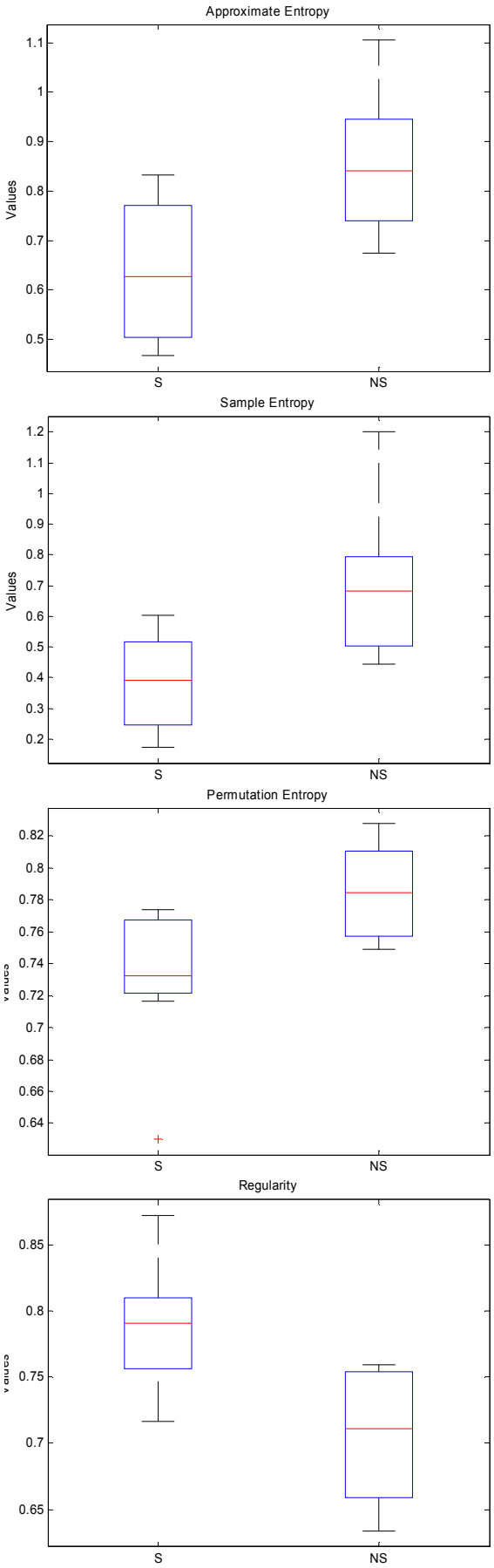

Figure 1. Indexes of information theory

In figure 1, Red lines in boxes stand for mean values of indexes separately for sepsis group (S) and non-sepsis group (NS).

HRV analysis shows that the mean values of AppEn, SamEn and PermEn are lower in sepsis infants than in non-sepsis ones, while, the mean values of Reg index give lower values for non-sepsis than for sepsis. These performances above express a decrease in information content in the newborns suffering from infection. Here, HRV analysis confirmed the previous studies based on entropy analysis, giving higher regularity values in sepsis cases.

Compared with these three entropy indexes, SamEn (p=0.0201) is superior to AppEn (p=0.035) and PermEn (p=0.025) to distinguish sick babies from healthy ones.

VI. DISCUSSIONS AND CONCLUSIONS

In this paper, the aim of the work was to find quantitative mathematical criteria for the diagnosis of late-onset sepsis happened in premature infants by a non-invasive way. The clinical manifestations of neonatal sepsis, whatever the source of infection, are frequently nonspecific.

The aim was achieved by means of RR signal analysis. HRV characteristics such as quantitative linear estimates (SD, rMSSD, p_HF, p_LF, p_VLF) and chaos indexes (α_{slow} and α_{fast}), we were unable to find a correlation between these parameters and sepsis. However, four metrics from information theory were considered: Approximate Entropy, Sample Entropy, Permutation Entropy and Regularity. Results confirmed the relationship between the occurrence of disease and a reduction of information carried by cardiovascular signals. AppEn, SamEn and PermEn showed that a decrease of entropy is associated with sepsis condition, and coherently, the Reg index measured a higher value for the same group of patients.

In conclusion, an increase in regularity coincides with a decrease in entropy contents in HRV signals from sepsis neonates. The distinctive variation in heart rate behavior related with sepsis could be useful in the field of neonatology.

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REFERENCES

[1] Beck-Sague C, Azimi P, Fonseca S, Baltimore R, Powell D, Bland L, Arduino M, McAllister S, Huberman R, Sinkowitz R. “Bloodstream infections in neonatal intensive care unit patients: results of a multicenter study”. *Pediatr Infect Dis*, 1994, 13:

1110-1116.
[2] Philip A. “Diagnostic tests for bacterial infection in the new-born”. *Infection in the Newborn*, 1990, 6: 49-59.
[3] Cao H, Lake D, Griffin M, Moorman J. “Increased nonstationarity of neonatal heart rate before the clinical diagnosis of sepsis”, *Ann Biomed Eng*, 2004, 32: 233-244.
[4] ESC. “Heart rate variability: standards of measurement, physiological interpretation and clinical use”, task force of the European society of cardiology and the North American society of pacing and electrophysiology. *Circulation*, 1996, 93(5): 1043-65. 0009-7322 Guideline Journal Article Practice Guideline.
[5] Chatow U, Davidson S, Reichman BL, Akselrod S. “Development and maturation of the autonomic nervous system in premature and full-term infants using spectral analysis of heart rate fluctuations”, *Pediatr Res*, 1995, 37: 294-302.
[6] Rosenstock EG, Cassuto Y, Zmora E. “Heart rate variability in the neonate and infant: analytical methods, physiological and clinical observations”, *Acta Paediatre*, 1999, 88: 477-482.
[7] Baselli G, Cerutti S, Civardi S, *et al*. “Spectral and cross-spectral analysis of heart rate and arterial blood pressure variability signals”, *Comput Biomed Res*, 1986, 19: 520-534.
[8] Beuchee A, Pladys P, Senhadji L, Betremieux P, Carre F. “Beat-to-beat blood pressure variability and patent ductus arteriosus in ventilated, premature infants”, *Pflugers Arch*, 2003, 446:154-160.
[9] Peng CK, Havlin S, Stanley HE, Goldberger AL. “Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series”, *Chaos*, 1995, 5: 82-87
[10] Yum MK, Park EY, Kim CR, Hwang JH. “Alterations in irregular and fractal heart rate behavior in growth restricted fetuses”, *Eur J Obstet Gynecol Reprod Biol*, 2001, 94: 51-58
[11] Nakamura T, Horio H, Miyashita S, et al. “Identification of development and autonomic nerve activity from heart rate variability in preterm infants Alterations in irregular and fractal heart rate behavior in growth restricted fetuses”, *Biosystems*, 2005, 79: 117-124
[12] Douglas E. Lake, Joshua S. Richman, M. Pamela Griffin, and J. Randall Moorman. ¨Sample entropy analysis of neonatal heart rate variability¨, *Am J Physiol Regul Integr Comp Physiol*, 2002, 283: 789-797.
[13] Pincus S. “Approximate entropy as a measure of system complexity”, *Proc Natl Acad Sci USA*, 1991(88): 2297-2301
[14] Ben-Mizrachi A, Procaccia I, and Grassberger P. “The characterization of experimental (noisy) strange attractors”. *Phys Rev A*, 1984, 29A: 975.
[15] Grassberger P. “Finite sample corrections to entropy and dimension estimates”. *Phys Lett A*, 1988, 128: 369.
[16] Grassberger P, Procaccia I. “Estimation of the Kolmogorov entropy from a chaotic signal”. *Phys Rev A*, 1983, 28: 2591–2593.
[17] Grassberger P, Schreiber T, and Schaffrath C. “Nonlinear time sequence analysis”. *Int J Bifur Chaos*, 1991, 1: 547.
[18] Bandt. C, Keller G, Pompe B. *Nonlinearity*, 2002, 15: 1595-1602.
[19] Takens F. “in Dynamical Systems and Turbulence”, *Lecture Notes in Mathematics*, edited by D.A. Rand and L.S. Young (Springer-Verlag, Berlin) 1981, Vol. 898, p.366.
[20] Porta A, Baselli G, Liberati D, Montano N, Cogliati C, Gnecchi-Ruscone T, Malliani A, Cerutti S. “Measuring regularity by means of a corrected conditional entropy in sympathetic outflow”, *Biol Cybern*, 1998, 78: 71-78.