Heart Rate and Respiration Relationships as a Diagnostic Tool for Late Onset Sepsis in Sick Preterm Infants

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Abstract

The objective of the study was to test the heart rate variability (HRV) and the association between RR interval and the spontaneous respiration in a selected population of sick premature infants. Approximated Entropy (ApEn) and Regularity index were computed for RR series while four numerical indexes able to quantify association between signals were compared: (quadratic spectral coherence, linear correlation index, non linear association functions, and synchronization index). From a methodological point of view, both linear and non linear indexes were able to enhance the relationships between the signals. From a clinical point of view, lower relationships values were strongly associated with Sepsis Group while the Non Sepsis Group was characterized by a stronger relationship between RR series and the respiration. These results suggest that the exploration of RR and respiration relationships may help revealing systemic infection in premature newborns.

1. Introduction

The heart rate variability analysis in neonatology is a useful tool to understand the cardiovascular control system behavior in premature newborn late-onset sepsis. Late-onset sepsis is defined as a systemic infection in neonates older than 3 days. It occurs in approximately 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 frequently nonspecific and the lack of early and adapted intervention can lead the baby to risk of life. Late-onset sepsis in the NICU is a major problem associated with high morbidity and mortality [2].

Sick preterm newborns don't show fever: so, only with blood culture the possible sepsis event may be detected. But the haematological and biochemical markers require invasive procedures that cannot be frequently repeated. In addition, they have low predictive value in the early phase of sepsis, even because they are too long procedures among required intervention times. On the other hand, it has been observed experimentally that apnea-bradycardias phenomenons are more frequent in sepsis preterm newborns than in not sepsis ones [3]. Starting from the evidence of an increase in apnea-bradycardias crisis in conjunction with the state of sickness, a way to assess the relationship between the infection and its manifestation was investigated. In particular, since apneas and bradycardias were evidences of altered mechanisms of cardiovascular regulation, the HRV investigation on these subjects is an immediately consequent decision. We therefore investigated the heart rate (HR) variability and its relationships, linear and not, with the respiratory signal.

The first part of this study has the aim to distinguish sepsis/non-sepsis cases by means of RR series. Even if linear indexes have been proposed in both time-domain and frequency domain [4], it has been recently observed that non-linear indexes, such as those based on Approximate Entropy may be useful to discriminate sepsis vs non-sepsis babies [5]. Thus a non-linear index analysis has been performed in order to assess randomness of the series. Two metrics are considered: Approximate Entropy (ApEn) and Regularity (R).

The second part of the work constitutes a new way of approaching to the problem of monitoring sepsis in the newborns. Different mechanisms are involved in the generation of cardiovascular variability rhythms which have been extensively studied as markers of the sympatho-vagal interaction controlling cardiovascular functions. In particular, multichannel signal analysis can be employed to analyze cardio-respiratory coordination. Physiologists had already investigated cardiorespiratory coordination in the human organism as early as the 1960s [6]. Calculating the distance between an inspiratory onset and its preceding R-peak, they found intermittent coordination between heartbeat and respiration. In the 1970s, this interesting topic was no longer followed up, presumably because the phys-

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iological interpretation of the results was limited [7, 8]. The investigation of cardiorespiratory coordination has recently been revived mainly by physicists and mathematicians [9].

In this work, the multisignal study is based on a measurement of linear and non-linear relationships and delay times assessment between RR and respiratory signals. Linear indexes were correlation (r^2) and coherence function (k^2), while non-linear regression coefficient (h^2) and synchronization index (S) were used to analyze non-linear relationships.

2. Methods

2.1. Experimental protocols

Data were obtained from a cohort of 28 premature infants (post-menstrual age < 33 weeks and chronological age > 72 hours) hospitalized in the NICU at the University Hospital of Rennes between June 2003 and June 2004. Inclusion criteria were: unusual and recurrent bradycardias with more than one occurrence 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. "Sepsis" was defined as the combination of an inflammatory response, i.e. CRP higher than 5 mg/l 24 hours after the recording, and positive blood cultures. "No-Sepsis" was defined as the association of an absence of inflammatory response, i.e. a CRP less than 5 mg/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) consisted in a one hour recording at 400Hz sampling rate of two electrocardiogram (ECG), electro-oculogram and electroencephalogram leads, one pulse oxymetry saturation (SaO2), nasal flow and abdominal respiration trace. The need of the two traces was to distinguish between Obstructive Sleep Apnea (OSA) and Central Sleep Apnea (CSA). Thus, OSA can be detected by absence of nasal respiration, but not of the abdominal one. Respiration was recorded in 11 patients and multivariate indexes are computed on this subpopulation only.

Continuous ECG signals were sampled at 400 Hz. The same sampling frequency was used for the respiratory traces and the other biological signals. There were no significant differences in gender, gestational age, chronological age, postmenstrual age, weight, haematocrit, between sepsis and non-sepsis groups.

2.2. Monovariate indexes

2.2.1. Approximate entropy

Pincus [10] introduced approximate entropy (ApEn), a set of measures of system complexity closely related to entropy, which has been extensively applied to biological series analysis. It allows to discriminate signals depending on their regularity without considering the data generating model of the system, thus regardless of their nature, whatever it is stochastic or purely deterministic, linear or not. ApEn allows to calculate indirectly signal correlation and persistence. A reduced value of this parameter suggests high regularity and it is defined by:

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

where C_m(r) is the mean of $C_{im}(r)$, i.e. the fraction of patterns of length *m* that resemble the pattern of the same length that begins at sample i and where *r* defines the criterion of similarity.

2.2.2. Regularity

Regularity (R) can be defined as the degree of recurrence of a pattern in a signal. The evaluation of the regularity of a process *x* is based on the calculation of corrected conditional entropy (CCE_x), representing the amount of information carried by the most recent sample of the series when some past samples are known [11]. It may be defined as:

$$R = 1 - \min(CCE_x/E_x) \tag{2}$$

where E_x is the Entropy of the process. R tends to 0 if the series is a fully unpredictable process, it tends to 1 if the series is a periodic signal and it assumes intermediate values for those processes that can be partially predicted by the knowledge of the past samples.

2.3. Multivariate indexes

2.3.1. Linear correlation

Correlation (r^2) indicates the strength and direction of a linear relationship between two random variables: In general, it refers to the departure of two variables from independence and equals:

$$r^2_{1,2} = \frac{E\left\{\left(X_1(t) - E\left\{X_1(t)\right\}\right)\left(X_2(t) - E\left\{X_2(t)\right\}\right)\right\}}{\left[Var(X_1(t)) * Var(X_2(t))\right]^{1/2}} \tag{3}$$

where Var(.) is the variance, E(.) is the expected value. The process X_2 can be delayed with the time-lag (τ) and the maximum of $r^2_{1,2}(\tau)$ is considered (r^2).

2.3.2. Coherence

Coherence function provides both amplitude and phase information about the frequencies held in common between the two sequences and is defined by :

$$C_{1,2}(\omega) = \frac{\phi_{X_1X_2}(\omega)}{[\phi_{X_1X_1}(\omega)\phi_{X_2X_2}(\omega)]^{1/2}} \tag{4}$$

where $\Phi_{X1X1}(\omega)$ $\Phi_{X2X2}(\omega)$ are the power spectral densities of X_1 and X_2 respectively, and $\Phi_{X1X2}(\omega)$ the cross-spectral density between these two signals. In this work the maximum of $\|C_{1,2}(\omega)\|^2$ is computed (k^2).

2.3.3. Non-linear regression

Non-linear regression coefficient (h^2) allows to measure statistical dependence between observations obtained in a bound temporal support and be computed by:

$$h^2_{1,2} = \frac{var(X_2(t)) - \|X_2(t) - f(X_1(t)\|^2}{var(X_2(t))} \tag{5}$$

where f is a non-linear regression function, allowing to measure the similarity, more or less linear, between the two observed processes X_1 and X_2. The process X_2 can be also delayed with the time-lag (τ) and a non linear $h^2(\tau)$ function can be computed. As for ${r^2}_{1,2}(\tau)$ the maximum of $h^2_{1,2}(\tau)$ is considered (h^2).

2.3.4. Synchronization

Synchronization index (S) is the extension of R index to multivariate case. It quantifies the degree of synchronization between two patterns. Synchronization occurs when patterns involving two signals contemporaneously are repetitive. It is approximated by:

$$Sx,y = 1 - min(UFx,y(L)) \tag{6}$$

where $UF_{x,y}(L)$ is the uncoupling function in order to measure the amount of information carried by one signal that can't be derived from the knowledge of past samples of the other signal [12].

3. Results

Heart rate variability analysis shows (Tab1) that ApEn values are lower in sepsis cases (p<0.02). Regularity index gives a lower value for non-sepsis population, thus expressing a decrease in information content in the population suffering from infection. Heart rate variability analysis confirmed here previous studies based on entropy analysis, giving higher regularity values in sepsis cases [5].

Concerning multivariate algorithms, correlation index (r^2), non-linear regression index (h^2), and synchronization index (S) allowed distinguishing between sepsis and non-sepsis populations. Results were coherent among themselves. They show a lower degree of relationships between RR and respiration signals, in sepsis cases. Only coherence function (k^2) couldn't distinguish between the two populations. Values are reported on the table 2. Some examples of $h^2(\tau)$ are depicted for a non-sepsis case (figure 1) and a sepsis case (figure 2). It is worth noting that a clear maximum is evident in the non-sepis group, but it disappears in the sepsis case.

Table 1. Monovariate Analysis results, * p<0.02

	Sepsis	Non-Sepsis
ApEn	*0.43± 0.08*	*0:79± 0.25**
Reg	*0.69± 0.08*	*0.65 ± 0.06**

Table 2. Multivariate Analysis results, * p<0.05

Type	Sepsis	Non-Sepsis
Respiration	**Nasal**	**Nasal**
r^2	*0.24± 0.19*	*0.30± 0.14*
k^2	*0.43± 0.18*	*0.39± 0.14*
h^2	*0.25± 0.14**	*0.31± 0.17**
S	*0.11± 0.08*	*0.12± 0.05*

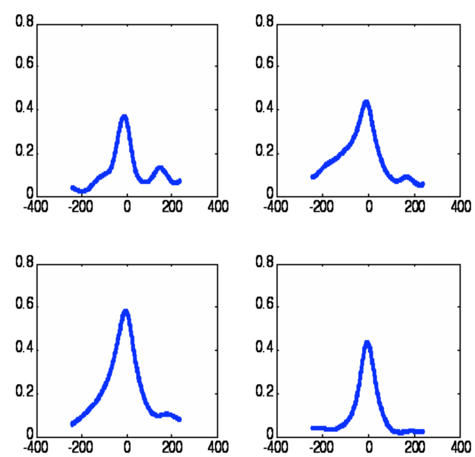

Figure 1. Behaviour of $h^2(\tau)$ for 4 non sepsis cases.

4. Discussion and conclusions

The aim of the work was to find quantitative mathematical criteria for the diagnosis of late-onset sepsis in premature newborns in a non-invasive way (using biomedical signals analysis). The clinical manifestations of neonatal sepsis, whatever the source of infection, are frequently nonspecific.

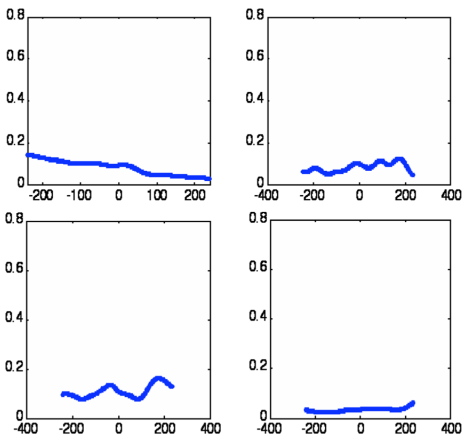

Figure 2. Behaviour of $h^2(\tau)$ for 4 sepsis cases.

In the first part of the analysis, the aim was achieved by means of RR signal analysis. Two metrics were considered: approximate entropy and regularity. Results confirmed the association between the occurrence of disease and a reduction of information carried by cardiovascular signals. ApEn showed that a decrease of entropy is associated with sepsis condition, and coherently, the regularity index measured a higher regularity for the same class of patient. That is, an increase in regularity coincides with a decrease in entropy contents in heart rate variability (HRV) signals in “sepsis” newborns.

In the second part, statistical tools were then tested in this work to look for relationships between respiratory and cardiovascular system, both of them involved in the systemic response to the sepsis. Linear and non-linear relationships between RR and respiratory signals were explored. Linear indexes were correlation (r^2) and coherence function (k^2). A lower correlation resulted for sepsis cases rather than for non-sepsis ones, together with a bigger negative delay between RR and respiratory signal. So, sepsis seems to disturb the match between the two systems, determining a delay and a decrease in linear correlation between them. The same result was obtained in non-linear analysis, thus demonstrating that the uncoupling effect of the sepsis appears also in non-linear relationships. A nonlinear Regression coefficient (h^2) and a synchronization index were tested in non-linear analysis. Both of them well distinguished the two classes under study, showing higher values to be associated to non-sepsis cases. Again, the difference in delay times was evident.

This work resulted in the finding of statistical indexes, overall h^2, able to distinguish between a sepsis and a non-sepsis group of premature newborns, that is, to give a noninvasive diagnosis of infection for these “special” patients. These indexes could be a useful tool for fast diagnoses, since they allow discrimination in a non-invasive way. They can be implemented in more developed monitoring system thus becoming part of the analyzing process.

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 newborn. 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] Lake D, Richman S, Griffin M, Moorman J. Sample entropy analysis of neonatal heart rate variability. Am J Physiol Regul Integr Comp Physiol 2002;283(R789-R797).

[6] Stutte K, Hildebrandt G. Untersuchungen ber die koordination von herzschlag und. Atmung beim Menschen Pflugers Arch ;289:R47–R48.

[7] Raschke F. The respiratory system features of modulation and coordination in rhythms in physiological systems. Edited by Haken H Koepchen HP Berlin Springer 1991; 155–164.

[8] Raschke F. Coordination in the circulatory and respiratory systems in temporal disorder in human oscillatory systems. Edited by Rensing L an der Heiden U Mackey MC Berlin Springer 1987;152–158.

[9] Cysarz D. A quantitative comparison of different methods to detect cardiorespiratory coordination during nighttime sleep. BioMedical Engineering OnLine 2004;3:44 doi:10.1186/1475–925X–3–44.

[10] Pincus S. Approximate entropy as a measure of system complexity. Proc Natl Acad Sci USA 1991;(88):2297–2301.

[11] 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.

[12] Mainardi L, Porta A, Calcagnini G, Censi F, Bartolini P, Michelucci A, Cerutti S. Discrimination of atrial rhythms by linear and non-linear methods. Ann Ist Super Sanit 2001; 37(3):335–340.

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