Interest of RR Deceleration for Diagnosis of Late Onset Sepsis

Romain Billois[1,2], Fabienne Porée[1,2], Alain Beuchée[1,2,3], Guy Carrault[1,2,4]

[1] Inserm U1099, Rennes, France
[2] Université de Rennes 1, LTSI, Rennes, France
[3] CHU Rennes, Pôle Médico-Chirurgical de Pédiatrie et de Génétique Clinique, Néonatologie, Rennes, France
[4] INSERM CIC-IT 804, Rennes, France

Abstract

Diagnosis of late onset sepsis in premature infants remains difficult because clinical signs are subtle and none of the laboratory tests, including CRP and blood culture, have high predictive accuracy. In this study, we investigate interest of the beat-to-beat Decelerations and Accelerations Runs of n included in [1,20] cycles duration (DR_n and AR_n) counted over periods of 30 minutes. The two hypotheses (H_0: sepsis vs. H_1: non-sepsis) were confronted in a case control study including 16 infected premature infants and 16 non-infected infants. Both groups were seen significantly different mainly on deceleration. Lower DR_1 and higher DR_3, DR_4 values were associated with the sepsis group. We also observed the benefit of the data fusion level. Area under the ROC curves grows up with OR fusion compared to the best local detector. This study confirmed the interest of heart rate variability to reveal infection.

1. Introduction

The Late Onset Sepsis (LOS) is frequent in premature babies (25% of the admitted infants) and is associated with a risk of mortality (13%) and morbidity since it prolongs hospitalization, increases the risk of chronic lung disease and adverse neurodevelopmental outcome.

The diagnosis of LOS remains difficult in premature infants because clinical signs are non-specific and none of the laboratory tests, including CRP, procalcitonine and blood culture, have low predictive accuracy at the early phase of the disease. This lack of reliability of laboratory tests often results in anticipatory antimicrobial treatments that increase the potential for resistance to emerge. Moreover, these laboratory tests require blood sampling and then cannot be used as real time monitoring of the sepsis risk.

Heart Rate Variability (HRV) analysis recently emerged as a promising diagnostic tool. Entropy and long-range fractal correlation are decreased in premature infants with proven sepsis presenting frequent bradycardias [1, 2]. In the meantime, real time diagnosis of late onset sepsis requires appropriate and adapted signal processing techniques if one would like to use HRV as a first diagnosis step.

In this paper, a novel estimator for characterizing, quickly and with few computational resources the evolution of the HRV, is proposed. This estimator is based on the computation of the deceleration and the acceleration of the HRV [3]. A brief state-of-the-art is proposed in the second section. The method is described in the third section. Then, the protocol -including data collection, statistical tools, inclusion and exclusion criteria-, is detailed. Results are reported in the fourth section while discussion and perspectives are drawn in the conclusion section.

2. State-of-the-art

It is now well known that HRV, respiration and interrelationships between respiration and HRV may help the diagnosis of infection in premature infants. The following paragraphs summarize the main results previously obtained and underline the purpose of the study we undergo for several years.

We recently investigated [1], on a collection of electrocardiogram recordings in 51 premature infants with a postmenstrual age < 33 weeks with frequent bradycardias, RR series distribution (mean, median, skewness, kurtosis, sample asymmetry), magnitude of variability in time and frequency domain, fractal exponents (α_1, α_2) and complexity measurements such as approximate entropy (ApEn). Results showed that low entropy measurements and long-range fractal exponent were associated with sepsis. No other heart rate parameter was associated with sepsis.

Infection has a pronounced impact on apnea in infants aged under 30 weeks and then respiration was explored as

a diagnosis tool [4]. It has been analyzed using statistical, signal processing and chaos techniques in order to correlate any relationships between the breathing patterns and infection. From the respiratory signal, the ratio between the inspiratory t_i and expiratory t_e times was relevant. Analyzing the respiratory variability with chaos techniques, it has been found that the Hurst exponent is lower in the infected population, which implies a more complex breathing pattern. Moreover, we observed that duration of central apneas have a different distribution in each group: the infected newborns exhibit generalized extreme value distribution, the non-infected tend to lognormal distribution.

As apneas and bradycardias are more severe and recurrent when a systemic infection is present, we studied if the respiratory signal and its relationship to HRV may help as a risk predictor of infection in premature infants with cardiac decelerations. During the last decades, numerous works aimed at measuring the degree of association between signals for several delays τ. Linear methods were first used (linear cross-correlation or coherence function). Mutual information and non-linear regression coefficient $h(\tau)$ [5, 6] were also introduced. We observed that non-linear regression coefficient $h(\tau)$ is the most powerful and reveals that the relationship disappears partially during infection periods. We also proposed a novel estimator of the linear relationship between non-stationary signals based on the cross-correlation of narrow band filtered signals $R^2(t, f)$ [7]. The tests performed on our cohort showed that the non-stationary estimator $R^2(t, f)$ may enhance the readability of the time-frequency representation of relationship and, thus, can improve the interpretation of interdependencies in signals. The results showed that the correlation in the very low frequency band tended to be higher in the sepsis group. A correlation in higher frequencies was associated with the non-sepsis group.

All these analyses are interesting but suffer from the same limitation: their computational burdens. The objective of this complementary contribution consists in proposing a procedure, working in real-time in an embedded system, using the deceleration and acceleration of consecutive RR sinus intervals.

3. Methods

The proposed method assessed the interest of deceleration and acceleration runs as diagnosis tools of sepsis. In a heart rate sequence, deceleration runs of n cycles were defined as n consecutive cardiac periods between sinus rhythm cycles which progressively lengthening as depicted in Figure 1.

More formally, let us denoted RR_i, the i^{th} RR interval on the recording. The duration n of the runs is defined as:

$$RR_{i-1} \geq RR_i < RR_{i+1} < \dots$$

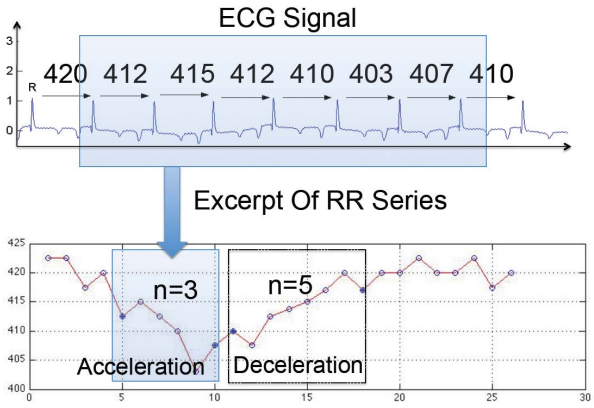

Figure 1. Principle of assessing deceleration and acceleration runs in an ECG recording.

$$\dots < RR_{i+n-1} < RR_{i+n} \geq RR_{i+n+1} \qquad (1)$$

For each n value, the total number of deceleration runs of n cycles over a period of 30 minutes, DR_n, was computed.

The DR_n values were computed from RR intervals derived from home-made QRS detector [8]. All the runs were assumed to be not interrupted by non-sinus rhythm beats and/or by artifacts (technical, movement, ...).

We proceeded in the same manner for the acceleration runs of n cycles (AR_n). They were defined as n consecutive cardiac periods between sinus rhythm cycles which progressively shortening (see figure 1). For each n value, the AR_n values were expressed as the total number of acceleration runs of n cycles over a period of 30 minutes.

4. Results

This section is divided in four parts. The first one presents the protocol and the database. The second one examines run by run the interest of the deceleration and acceleration by taking into account or by excluding the bradycardia's episodes respectively. This last study was undergone in order to discover if the deceleration and acceleration of the heart rhythm can be used as a predictive marker of infection without taking into account the major clinical sign represented by bradycardias. The third part discusses interest of a multivariate decision process.

Data were obtained from a cohort of 32 premature infants (post-menstrual age $<$ 33 weeks and chronological age $>$ 72 hours) hospitalized in the neonatal intensive care unit at the university Hospital of Rennes. The two hypotheses (H_0: sepsis vs. H_1: non-sepsis) were confronted in a case control study including 16 infected premature infants who were matched (birth weight, postnatal and gestational age) with 16 non-infected infants. The infants were placed in bassinets, positioned on their side, wrapped by a single blanket roll, and loosely covered by another. The monitor-

ing (Powerlab system, ADInstruments) consisted of two ECG, EOG and EEG leads, one pulse oxymetry saturation (SaO2), nasal flow and abdominal respiration recordings (sampling rate 400 Hz). The study was approved by the local ethics committee. Inclusion and exclusion criteria's were already described elsewhere [7]. Parents were informed and consent was obtained. Thirty minutes selected randomly over four hours were extracted from ECG recordings and were subjected to analysis of heart rate variability parameters. The duration n of the runs were investigated in the interval [1, 20] either for deceleration and acceleration. Representative examples of boxplots in the sepsis and non-sepsis groups are displayed in Figure 2 for $n = 1$ and in Figure 3 for $n = 4$.

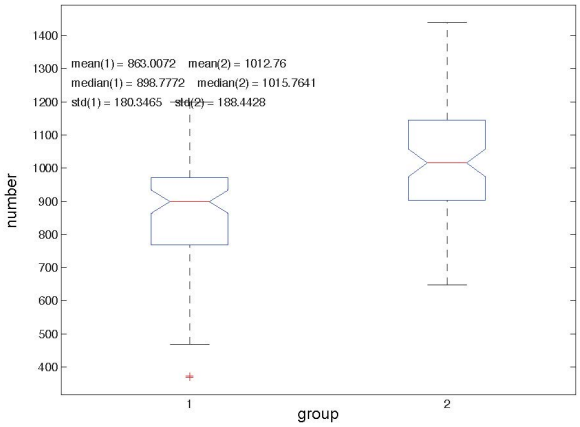

Figure 2. Boxplot of the DR_1 for the sepsis (group 1) and non-sepsis babies (group 2).

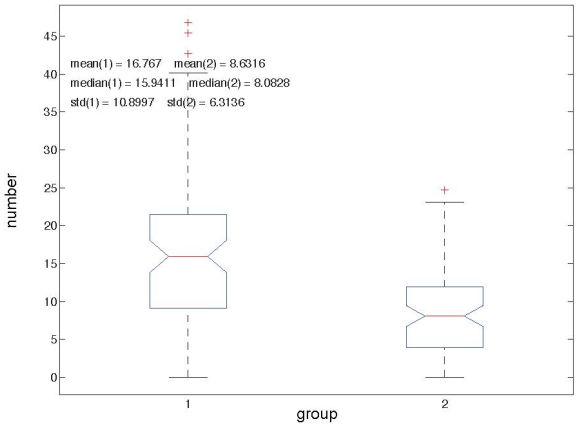

Figure 3. Boxplot of the DR_4 for the sepsis (group 1) and non-sepsis babies (group 2).

Typical values of DR_n for n = 1 to 5 outside the bradycardia's episodes are reported in Table 1. Results are presented as the median-25th-75th percentiles of numbers of DR_n. Both sepsis and non-sepsis groups were compared using Mann and Withney or Kruskall-Wallis tests. The level of significance was tuned at $p = 0.05$. When the result is significant, the line is set in bold character.

Table 1. Values of DR_n for n = 1 to 5.

	group 1			group 2		
Run	median	25%	75%	median	25%	75%
Run 1	**892**	**762**	**967**	**1013**	**892**	**1140**
Run 2	145	113	194	140	105	166
Run 3	**42**	**25**	**53**	**27**	**13**	**36**
Run 4	**14**	**7**	**18**	**8**	**3**	**12**
Run 5	7	3	12	5	7	2

The analysis of these typical values indicates two main typical signatures: a lower value in the run 1 and a higher value in the run 3 and run 4 in the sepsis group. After $n = 5$, no significant differences were observed between the two groups.

When including the bradycardia's episodes, the observed values were almost the same. These findings confirm that the heart rate deceleration is a suitable descriptor to distinguish sepsis and non-sepsis groups.

As regarded the acceleration, we do not observe the same behavior. Significative differences occur for $n = \{1, 5\}$. In the case of $n = 5$, the number of n cycles is too small ($AR_5 \approx 2$) to allow a statistical analysis of the difference.

A multivariate analysis was then performed using a data fusion detection level combining the three best univariate detectors (DR_1, DR_3, DR_4). In each case, the Receiver Operating Characteristics (ROC) were plotted and areas under the curves computed. Three fusion nodes were tested (the logical AND, logical OR and majority laws). Table 2 summarizes the computed area under the ROC while Figure 4 plots the univariate ROC and the best multivariate ones.

Table 2. Area under the ROC for univariate statistics DR_1, DR_3, DR_4 and for the logical AND, logical OR and majority fusion laws.

Univariate	Statistics	DR_1	DR_3	DR_4
	Area	0.7002	0.6959	0.7405
Multivariate	Statistics	AND	**OR**	Majority
	Area	0.6403	**0.7906**	0.7314

Analysis of Table 2 and Figure 4 show the interest of the logical OR fusion node that increases the area under the ROC.

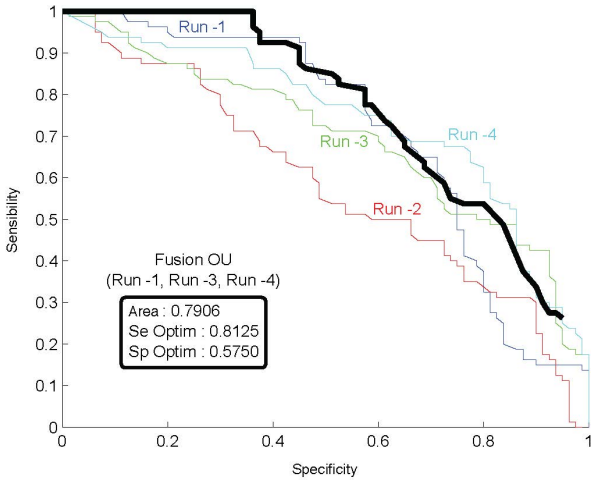

Figure 4. Examples of ROC for the three univariate detectors $n = \{1, 3, 4\}$ and for the multivariate logical OR fusion node.

5. Discussion and conclusion

This study has explored the interest of heart rate decelerations and acceleration to distinguish the sepsis and non-sepsis premature infants. Univariate analysis where deceleration runs span in length between 1 and 20 RR intervals were investigated. We observed that lower DR_1 and higher DR_3, DR_4 values were associated with the sepsis group and confirmed the interest of RR to reveal infection. It appears that sepsis babies were also characterized by a higher value of deceleration runs of length 2, 5 cycles but these last values, on our dataset, were not judged significant. Our observations are in agreement with the risk markers derived from others studies [9].

We also investigated heart rate acceleration runs. They have a distinct behavior and seem to have a lower prognosis value than the deceleration runs.

The results enhance that the heart rate deceleration properties have an interesting prognosis value in risk classification of sepsis. Nevertheless, combination of deceleration runs with others studied features already reported [1,4,5,7] is for further investigations. We now develop a two-step detection procedure as depicted in Figure 5 where step 2 -using approximate entropy, α_1, α_2, Hurst exponent on respiratory signal, relationships between respiration and HRV-, would be activated in case of suspicion of sepsis detected by deceleration markers as proposed in this work.

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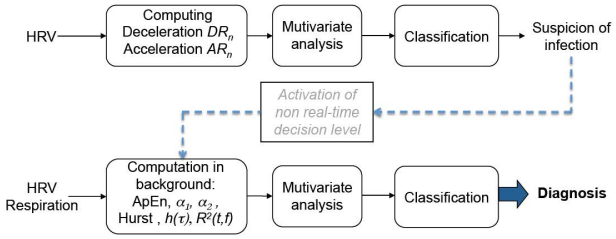

Figure 5. The general framework for sepsis detection.

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Address for correspondence:

Guy CARRAULT
LTSI-INSERM U1099
Université de Rennes, Campus de Beaulieu
35042 Rennes Cedex, France
guy.carrault@univ-rennes1.fr