Respiration Signal as a Promising Diagnostic Tool for Late Onset Sepsis in Premature Newborns

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Abstract

The purpose of this study was to find out differences between septicemic and healthy premature newborns from the respiratory signal. An statistical analysis of breathing trace's temporal features showed significant differences between the inspiration/expiration ratio, being its average value shorter in healthy patients. All patient's total respiratory cycle time exceeding the apnea threshold were classified, and two different distributions had been found: log-normal for non septicemic and GEV (Generalized Extreme Value) distribution for septicemic. Finally, assessing fractal signal properties, we found an increased Hurst exponent (H) in non infected population. Results suggest that respiratory parameters could be helpful in sepsis diagnosis together with heart rate variability (HRV), demonstrated a relevant marker by our research team.

1.   Introduction

Late-onset sepsis is defined as a systemic infection after the third day of life in neonates and, whatever the source of infection, there are nonspecific clinical manifestations. It occurs in approximately 10% of all newborns, increasing to more than 25% when the infants are born with a very low weight and have to be hospitalized in the NICU (Neonatal Intensive Care Units) [1]. Late-onset sepsis is thus a major problem associated with high morbidity and mortality.

Currently, only blood culture can determine whether there is infection, because preterm neonates do not show fever and other evident signs. This practice is not only invasive, but also poorly predictable in early phases of infection [2]. Nevertheless, it has been experimentally observed that septic premature infants have more frequent and severe episodes of bradycardia and apnea than the non septic ones [3]. The need to find alternative fast noninvasive markers to diagnose late-onset sepsis led to some works in our research team to assess the ECG and respiratory signals,

with results confirming the association between the occurrence of disease and a reduction of information carried by cardiovascular signals [4]. Specifically, parameters such as sample entropy (SampEn) and regularity in HRV have shown significance in several studies [5], [6].

The aim of the present work is to find additional biomedical indicators to help the late-onset diagnosis by analyzing the respiratory signal with time-domain and fractal techniques. They are described in the next section, as well as the study protocol and database; in section 3 we present significant parameters and statistical distributions of apnea, while the last section concludes and discusses the perspectives of the assessment.

2.   Materials and methods

2.1.   Database and study protocol

The tests were performed on a cohort study of 26 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 (France) over two periods: June 2003 to June 2004 and January to July 2007. 13 of them were septicemic (group Sepsis) and 13 non septicemic (group No-sepsis). Sepsis is defined as the combination of an inflammatory response and positive blood cultures.

The inclusion criteria were: Unusual and recurrent bradycardia (more than one per hour) and/or need for bag-and-mask resuscitation and/or cases where the physician suspected an infection. The exclusion criteria were: ongoing inflammatory response with or without infection, medication known to influence autonomic nervous system including morphine, catecholamine, sedative drugs and Doxapram, intra-tracheal respiratory support, intra-cerebral lesion or malformation. The study was approved by the local ethics committee (03/05-445).

The monitoring (Powerlab system®, ADInstruments, Oxfordshire, UK) consisted in a one hour recording at 400Hz

sampling rate of two electrocardiogram (ECG), electrooculogram and electroencephalogram leads, one pulse oximetry saturation (SaO2), nasal flow and abdominal trace from strain gauges sampled at 4Hz. The need of the two breathing traces was to distinguish between Obstructive Apnea and Central Apnea. In this work only abdominal trace (thus, central apnea) will be taken in account.

2.2. Breathing temporal features

We have chosen to deal with breathing temporal features rather than processing the respiratory trace. In fact, it is a wave-like signal from where temporal parameters can be obtained: t_i (inspiration time), as the measure between a maximum and its consecutive minimum; t_e (expiration time) from a minimum and its consecutive maximum, and t_{tot}, (total respiratory cycle time) as the measure between two minima.
To proceed with parameter extraction, we have firstly filtered and resampled the respiratory signal to 40Hz. Afterwards, we use a criterion to define the valid respiratory cycles to avoid the influence of extreme amplitudes such as deep breaths, cries and body movements: we divide the time-series by the inter-quartile range of all maxima, and then, we select cycles which maxima exceed a threshold established in 0.3.
Similarly to the HRV, the respiratory variability signal or inter-breath interval (IBI) represents t_{tot} as a function of the breathing cycle (Figure 1)
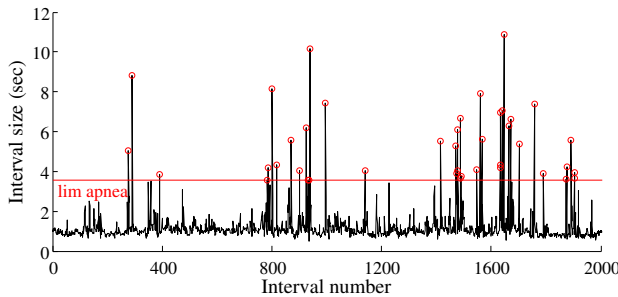

Figure 1. Respiration variability signal with apnea threshold drawn in red.   Each inter-breath interval over the threshold (red circles) corresponds to an apnea episode.

In order to detect apneas from the IBI signal, another threshold to this purpose has been defined. Since we are concerned with moderate to severe apnea, the chosen criterion is to find breathing cessations exceeding three times the average of t_{tot} in the analyzed time-series. Once all apnea episodes are identified, we proceed to classify them in two groups, those from infected and healthy infants.
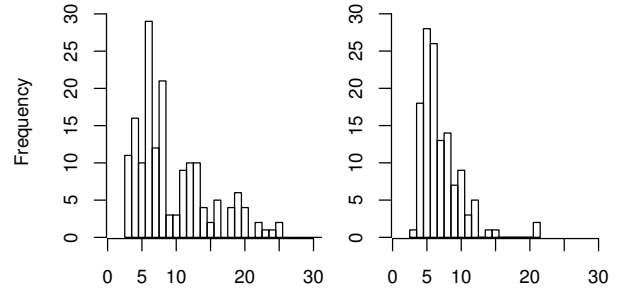

Figure 2.   Histograms classifying all episodes of apnea by their duration (in seconds). Left: Group Sepsis ; right: Group No-sepsis

2.3.   Statistical analysis

To assess the distribution law followed by the duration of apnea in Sepsis and No-sepsis, we have assumed some models based in the histogram observation (see figure 2). Apnea's positive and left skewed distribution appoints Log-normal (Lgn) and Generalized Extreme Value (GEV) as good candidates. Lgn probability density function (pdf) is:

$$f(x) = \frac{e^{-\frac{(lnx-\mu_l)^2}{2\sigma_l^2}}}{x\sigma_l\sqrt{2\pi}} \qquad x \geq 0; \sigma > 0$$

where μ_l and σ_l are the mean and standard deviation of the logarithm [9]. GEV is a three parameter distribution which has the following pdf:

$$f(x) = \alpha^1 e^{-(1-\kappa)y} e^{-e^{-y}}$$

where $y = (x - \beta)/\alpha$ if $\kappa = 0$ and $y = -\kappa^{-1}log[1 - \kappa(x - \beta)/\alpha]$ for any other value of κ [10]. The parameters α, β and κ are called scale, location and shape, respectively. The first parameter is analogous to the standard deviation, the second is analogous to the mean, while the third governs the shape of the tail of the distribution.
By means of the MLE (Maximum Likelihood Estimation) method we estimate the parameters in each distribution law and finally we test the validity of the hypotheses measuring the goodness of fit using the Anderson Darling (AD) and Kolmogorov-Smirnov (KS) tests.
Wilcoxon and Mann-Whitney nonparametric rank-based tests were used in order to assess the statistical significance when comparing values of t_i, t_e, t_{tot} and t_i/t_e parameters between infected/not infected infants. Significant differences were taken into account when p<0.05.
All analysis were performed with R statistics language version 2.9.2 under Linux environment (GNU Public License).

2.4.   Fractal analysis

We used the Hurst exponent estimation method to study the fractal properties of the inter-breath time series.
Fractal (scale-invariant or self-similarity) behavior is present in many biological processes [7] like HRV and IBI. The Hurst exponent quantifies the fractal dynamics with the analysis of the time-series on different scales. The rescaled range (R/S) characterizes the divergence of the time-series and is the base of the calculation of H. Being R the sum of the deviations of data from the mean and S the sample standard deviation, it is expressed as $R/S = kT^H$ where k is a constant depending on the time-series and H is the Hurst exponent. This exponential law reflects the long-term dependence (or persistence) in a process. H is dimensionless and its values go from 0 to 1. For example, brownian noise is a self-affine fractal with a Hurst exponent H=0.5; white noise may be considered as having H=0, and an exactly self-similar process would be characterized by H=1. More generally, H<0.5 indicates that future events tend to an inverse behavior (anti-persistence) and H>0.5 proves the tendency for an event to correlate positively with subsequent events (persistence) [8].
Calculations had been performed in Matlab® by an unbiased estimator of the Hurst exponent in each patient's IBI.

3.   Results

3.1.   Respiratory parameters

The statistical analysis of respiratory parameters showed differences in the inspiration to expiration ratio, t_i/t_e. The mean in infected infants (0.917), is greater than in non infected ones (0.814) with statistically significant differences (p=0.002) according to Mann-Whitney U test. The same p-value is obtained when comparing the standard deviation of infected (0.541) with healthy (0.313). The other descriptive statistics (see table 1) and respiratory parameters related to t_i and t_e were not significantly different between the two populations.

Table 1.   Mean ± standard deviation of descriptive statistics. t_{tot} is measured in seconds. t_i/t_e is dimensionless.

Parameter	Statistic	Sepsis	No-sepsis	p-value
t_{tot}	Mean	1.530±0.505	1.445±0.287	0.960
	Median	1.286±0.496	1.311±0.286	0.362
	Std dev	1.214±0.802	0.806±0.297	0.264
	Kurtosis	81.80±162.5	95.27±80.31	0.081
	Skewness	5.857±5.204	7.005±3.225	0.125
t_i/t_e	Mean	0.917±0.095	0.814±0.058	0.002
	Median	0.844±0.064	0.810±0.063	0.362
	Std dev	0.541±0.260	0.313±0.086	0.002
	Kurtosis	57.44±81.49	30.14±32.71	0.223
	Skewness	3.967±2.757	2.572±2.285	0.081

Differences between t_i/t_e in the breathing trace can be

interpreted in physiological terms. This variable, which value is always under the unity, illustrates that expiration is slightly longer than inspiration. This is generalized pattern in all patients, but more noticeable for the infected ones.

3.2.   Apnea distribution

We found distribution law parameters in both populations (see table 2). From the GEV a positive shape parameter (κ) is found, thus the specific extreme value distribution is type III or Frechet.

Table 2.   MLE estimated parameters for each distribution in groups Sepsis and No-sepsis

	GEV param estimates			Log-normal param estimates	
	α	β	κ	μ	σ
Sepsis	3.220	6.553	0.317	2.099	0.550
No-sepsis	1.645	5.497	0.260	1.868	0.361

Regarding the p-values from the AD and KS tests, results under the significance level would reject the null hypothesis (*i.e.* empirical samples and the theoretical values come from the same distribution), hence the highest probability is the closest model to the real data. This is why, as reported in table 3 log-normal distributions describe apneas with more accuracy in infected population (p=0.490 in AD and p=0.370 in KS test) and Frechet distribution does in healthy patients (p=0.625 and 0.879 respectively).

Table 3.   Results of goodness of fit by the Anderson Darling and Kolmogorov-Smirnov test

	AD p-value		KS p-value		
	GEV	Log-norm	GEV	Log-norm	Better fit
Sepsis	0.430	0.490	0.353	0.370	Log-normal
No-sepsis	0.625	0.300	0.879	0.299	GEV

It can be observed that fitting results in Sepsis are very close, (GEV with p=0.430 and 0.353 versus p=0.490 and 0.370 in log-normal) , on the contrary, No-sepsis is clearly characterized by a GEV distribution law with more separated p-values. To have a more visual idea of the goodness of fit, in figure 3 the empirical cumulative distribution function (ecdf) and the corresponding theoretical function (cdf) are represented.

3.3.   Fractal dynamics

The Hurst exponent revealed differences in the complexity between the groups Sepsis and No-sepsis. The Mann-Whitney U test found significant differences in the respiratory variability signal of the two groups with a p-value
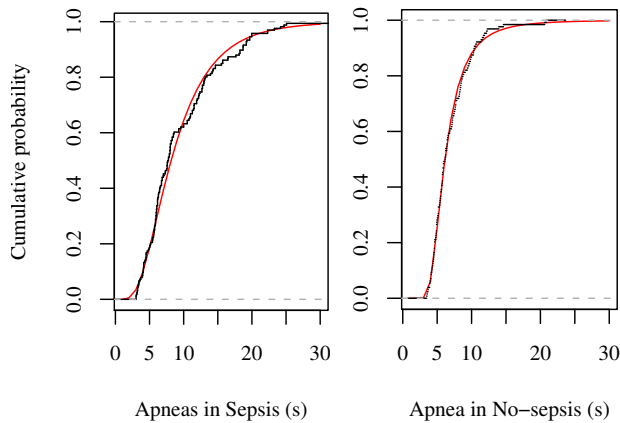
Figure 3. cdf plots of empirical data (in black) and the best fitted distribution (red). Left: Log-normal for Sepsis ; right: GEV for No-Sepsis.

of 0.0292. The average value of H in Sepsis (0.616) is slightly lower than H in healthy babies (0.686), so a more complex and unpredictable breathing pattern is observed for infected patients (See figure 4).
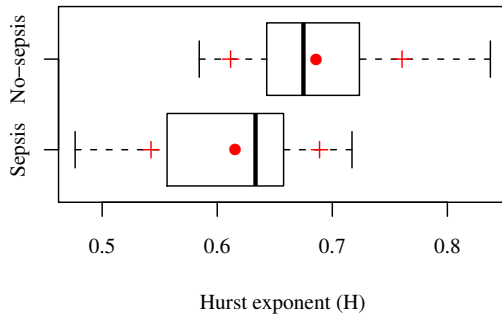

Figure 4. Boxplots of H in infected/healthy populations. Red symbols are: mean (circle) and standard deviation (+).

4.   Discussion and conclusions

Several parameters related to respiration in premature newborns have been analyzed in this paper. The complete respiratory cycle (t_{tot}) itself does not reveal differences between infected and not infected groups. However, the ratio t_i/t_e is lower in infected patients.

Distributions concerning the duration of apneas in the two groups constitute as well a subject of interest. Septicemic are prone to have more frequent and severe (longer) apneas; this is why their distribution is rather right skewed with a longer tail. After fitting distributions with different models, we proved that log-normal distribution characterizes better infected babies, and that GEV (Frechet)

distribution does better with healthy. Despite this is a case control study, we believe that it could be useful to estimate probability laws *a priory* in order to classify and predict individually the presence of infection in a prospector study. Moreover, IBI fractal behavior provides more information to this purpose. It has been proven that estimated fractality by the Hurst exponent is lower in infected infants, hence, a less predictable breathing pattern seems to characterize this population in relationship with the healthy one.

The results shown here are in accordance with previous studies performed by our team about HRV [4] and cardio-respiratory relationships [5], [6] in premature newborns, where differences between septicemic and healthy patients had been described. These observations bring additional inputs into our current research project, the construction of multivariate indexes for early detection of sepsis.

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