Time-Domain, Frequency Domain and Non-Linear Measurements in Neonates' Heart Rate Variability with Clinical Sepsis

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Abstract

Sepsis, a critical bacterial infection of the bloodstream, is a serious cause of illness in neonatal period in both premature and at term newborns. It is important to look for parameters that can help earlier detection of sepsis in the newborn. Previous studies have shown that Heart Rate Variability is reduced when associated with sepsis and diminish the adaptive capacity of the individual, degrading the information transported by their signals. To test for the statistical significance in discriminating between healthy and sepsis diagnosed neonates we analyzed the Inter-Beat-Interval derived from 90 minutes electrocardiographic recordings obtained from 45 newborn, 17 with clinical diagnosis of sepsis and 28 healthy newborn as control. Statistically significant time-domain measures ($p<0.05$) of the time series produced paradoxical results comparing sepsis with healthy subjects. Frequency-domain and Time-Frequency analysis show reduced low-frequency power and low/high frequency ratio ($p<0.05$) in subjects with sepsis; conversely high-frequency power was significantly higher ($p<0.05$) in the sepsis group. Non-linear Sample-Entropy measure showed significant difference between groups ($p<0.01$) and lower values in subjects clinically diagnosed with sepsis suggesting lower Inter-Beat-Interval signal complexity.

1. Introduction

Sepsis, a critical bacterial infection of the bloodstream, is a serious cause of illness in neonatal period in both premature and at term newborns.

Early signs of sepsis are neither specific for the disease, nor very sensitive [1].

Diagnostic testing by blood cultures is reserved until signs of illness appear, but they have a high false - negative rate when based on small amounts of blood that can be removed from a newborn [2]. The early diagnosis, before clinical signs of illness, is an important objective but difficult to achieve.

The aim of this study was to assess the significance of parameters derived from HRV analysis at the time of the early diagnosis of sepsis in neonates.

2. Methods and results

Subjects included in the study were neonates with clinical diagnosis of sepsis and healthy neonates as control group. We analyzed the Inter-Beat-Interval derived from 90 minutes electrocardiographic recordings obtained from 45 newborn, 17 with clinical diagnosis of sepsis and 28 healthy. The study was performed at the department of pediatrics in the Hospital General Universitario of Valencia.

2.1. Processing of the IBI signal

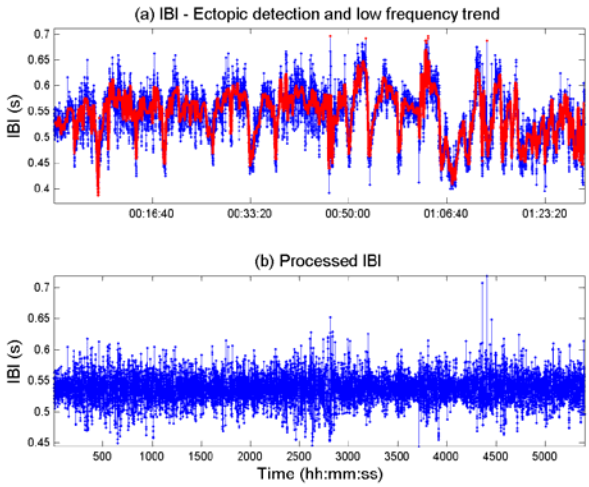

Figure 1 (a) Ectopic intervals and trend detection (red); b) IBI time series after ectopic correction and detrending (blue).

ECG recordings were processed both manually and automatically using computerized beat recognition

algorithms [3] [4] and the IBI time series generated were pre-processed for ectopic interval detection and correction and detrending to reduce the analysis errors [5] [6] [7], (Figure 1).

2.2. Statistical analysis

The HRV statistics were checked for normality by the Shapiro-Wilk normality test. If both groups passed the normality test, a two-sample, two-tailed t-test (α=0.05) was used to determine between group significance. The Levene's test for equally of variances was used to determine whether to assume equal or unequal variances. If either group failed normality test, group significance was determined by the non-parametric Mann-Whitney U test (α=0.05).

2.3. Results

Table 1 lists the HRV analysis results of all analyzed variables. All HRV measures showed a statistically significant difference ($p<0.05$) between healthy neonates and sepsis diagnosed neonates except for the following measures: Time-Domain SDNN, pNN50, RMSSD, SDANN, and TINN; Frequency-Domain aLF, aTotal; Non-Linear SD1, SD2, DFA (α2); and the Time-Frequency aLF, aHF, and aTotal.

The Figure 2 illustrates the Time-Frequency analysis of healthy case vs, a case with clinical diagnosis of sepsis in the indicated frequency bands.

Table 1 HRV analysis results. Statistics are shown as mean ± standard deviation.

Groups		**Healthy** *n=28*	**Sepsis** *n=17*		
Measure	Sig.	Mean ± SD	Mean ± SD		Definition
Time-Domain measurements					
Mean IBI(ms)	0.0300	512.1 ± 40.8	479.4 ± 56.6	*↓	Mean value of all RR intervals
SDNN (ms)	0.0510	38.6 ± 10.0	46.6 ± 16.9	n.s.	Standard deviation of all normal RR intervals
pNN50 (%)	0.2550	1.29 ± 1.82	1.47 ± 1.38	n.s.	Percent difference between adjacent normal RR intervals
RMSSD (ms)	0.4630	14.45 ± 5.7	15.83 ± 6.6	n.s.	Root mean square between adjacent normal RR intervals
SDANN (ms)	0.8500	28.75 ± 8.2	28.21 ± 11.0	n.s.	Standard deviation of the mean of RR intervals
meanHR(bpm)	0.0130	118.6 ± 9.3	128.4 ± 16.1	**↑	Mean value of heart rate
Geometric measurements					
HRVti	0.0060	10.30 ± 2.2	8.15 ± 2.7	**↓	Measure based on histogram of IBI. HRV triangular index
TINN (ms)	0.8030	153.6 ± 52.9	159.3 ± 100	n.s.	As above the triangular interpolation of RR interval histogram
Frequency-domain measurements					
aLF (ms^2)	0.9720	0.01 ± 0.005	0.01 ± 0.006	n.s.	Absolute low-frequency spectral power
aHF (ms^2)	0.0130	0.004±0.001	0.006±0.003	*↑	Absolute high-frequency spectral power
aTotal (ms^2)	0.1750	0.02 ± 0.006	0.02 ± 0.010	n.s.	Absolute total spectral power
nLF (n.u.)	0.0040	0.78 ± 0.04	0.72 ± 0.08	***↓	Normalized low-frequency to total power
nHF (n.u.)	0.0040	0.21 ± 0.04	0.27 ± 0.08	***↑	Normalized high-frequency to total power
LF/HF (n.u.)	0.0100	3.93 ± 1.07	3.00 ± 1.17	**↓	Ratio of normalized low and high frequency
Non-Linear measurements					
SD1 (ms)	0.4570	10.21 ± 4.0	11.20 ± 4.6	n.s.	Poincare Plot. Standard deviation along ellipse's perpendicular
SD2 (ms)	0.0500	53.58 ± 13.9	64.90 ± 23.9	n.s.	Poincare Plot. Standard deviation along ellipse's line of identity
SampEn	0.0040	1.35 ± 0.4	0.99 ± 0.3	***↓	Sample entropy. Signal complexity.
DFA (α1)	0.0240	1.29 ± 0.1	1.18 ± 0.2	**↓	Detrended fluctuation analysis. Short term scaling exponent
DFA (α2)	0.2700	1.17 ± 0.08	1.14 ± 0.12	n.s.	Detrended fluctuation analysis. Long term scaling exponent
Time-Frequency measurements					
aLF (ms^2)	0.6060	0.71 ± 0.4	1.42 ± 2.3	n.s.	Time-frequency. Absolute low-frequency spectral power
aHF (ms^2)	0.1970	0.21 ± 0.1	1.02 ± 2.3	n.s.	Time-frequency. Absolute high-frequency spectral power
aTotal(ms^2)	0.3610	0.97 ± 0.5	2.92 ± 5.6	n.s.	Time-frequency. Absolute total spectral power
nLF (n.u.)	0.0009	0.78 ± 0.04	0.70 ± 0.11	***↓	Time-frequency. Normalized low-frequency to total power
nHF (n.u.)	0.0009	0.21 ± 0.04	0.29 ± 0.11	***↑	Time-frequency. Normalized high-frequency to total power
LF/HF (%)	0.0030	3.92 ± 1.1	2.77 ± 1.2	***↓	Time-frequency. Ratio of normalized low and high frequency
Significance:			*<0.05	**<0.01	***<0.005

Figure 2 (a) shows the waterfall plot of a healthy newborn with normal HRV presenting a component of LF=0.779 normalized units (n.u.) and a component of HF=0.221 n.u.; (b) shows the waterfall plot of a subject with clinical diagnosis of sepsis showing decrease variability, multiple transient decelerations, decreased component of LF=0.687 n.u., and increase component of HF=0.313 n.u.; (c) plots LF and HF power vs. time

for the healthy case; (d) plots LF and HF power vs. time for the subject with clinical diagnosis of sepsis; and (e) represents the Low frequency/High frequency ratio (LF/HF) vs. time for the healthy case and an average ratio LF/HF=3.531; and (f) represents Low frequency/High frequency ratio vs. time for the subject with clinical diagnosis of sepsis with a decreased average ratio LF/HF=2.193.

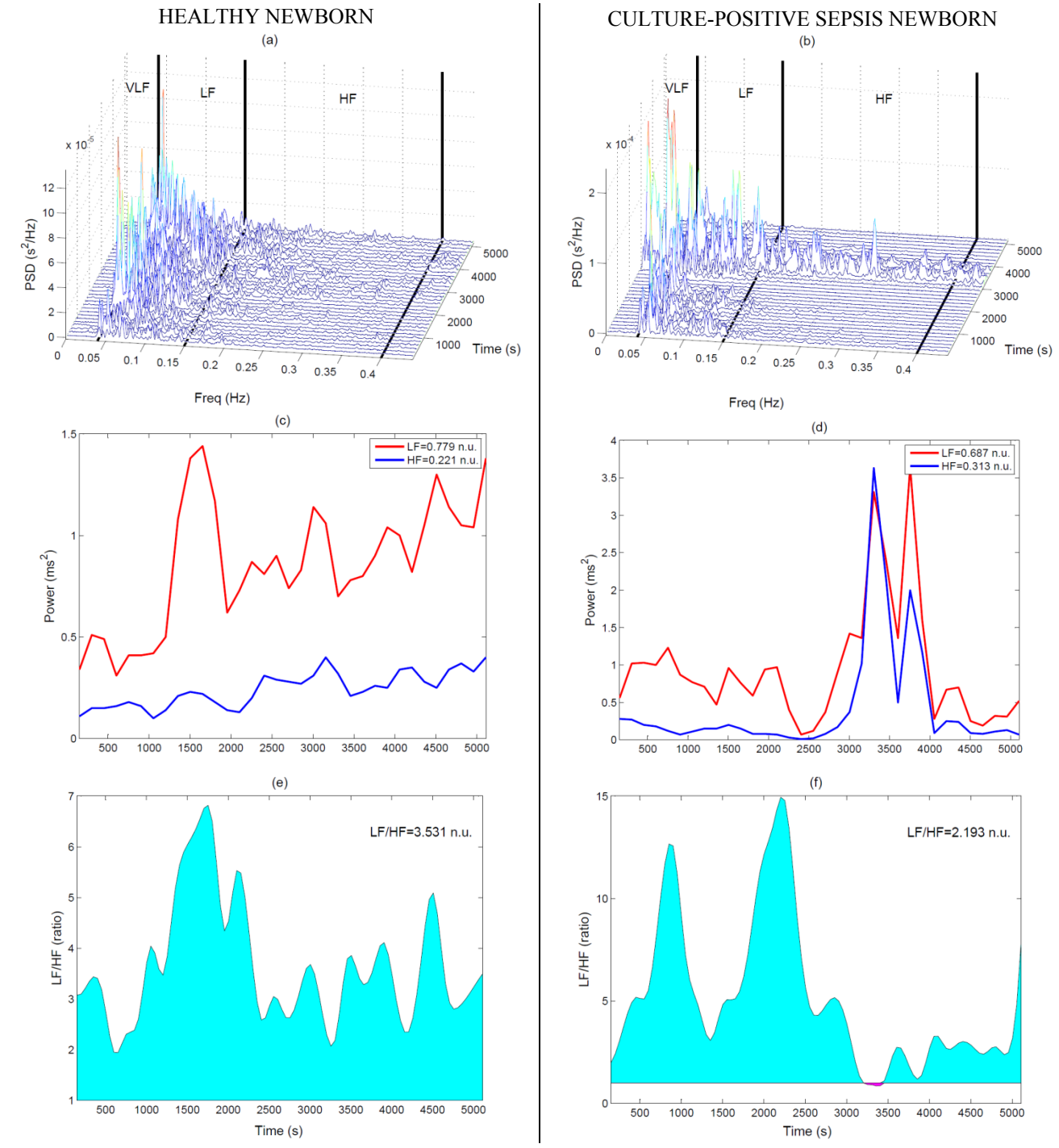

Figure 2 Time-frequency analysis (300s window, 150s overlap) of the IBI time series compering a healthy subject vs. a subject with clinical diagnosis of sepsis in the Very Low Frequency (VLF) (0.003-0.04 Hz), Low Frequency (LF) (0.04-0.15 Hz), and High Frequency (HF) (0.15-0.4 Hz) bands as indicated in the plots.

3. Discussion and conclusions

Previous studies have shown that HRV associated with congestive heart failure is reduced compared to healthy. The exact mechanisms of decreased HRV in disease processes still are not well understood, but there is evidence of abnormalities in both sympathetic and parasympathetic tone [8].

Under pathologic conditions, the structure of the time series variability may change in two ways: loss of variability and transient decelerations, and more random type of outputs. In both cases reveals a decrease in system complexity.

The time-frequency analysis (Figure 2) shows a decrease in the LF component of spectral power in sepsis, and a decrease in the LF/HF ratio that quantifies the sympatho-vagal balance.

The non-linear sample entropy also decreases with sepsis signifying a reduced variability and suggesting lower Inter-Beat-Interval signal complexity.

Although many of the HRV measures (Table 1) show significant difference between the two groups, many others have considerably overlapping distributions, thus any single observation is likely to fall within the values of overlap and make unclear any clinical result.

Our results highlight the importance of HRV to be used in the early diagnosis of sepsis in neonatal period given the increase mortality risk and the possibility of long term developmental damages.

We consider that outcomes of the HRV analysis might be improved deriving new measures of the IBI time series complexity using different mathematical approaches to be analyzed in prospective studies.

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