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Influence of sleep state and position on cardio-respiratory regulation in newborn babies

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Abstract

The paper presents results of a sleep study on 60 newborn infants and 22 one-month infants, in quiet and active sleep and in prone and supine position. During the study, HRV and respiration were acquired and then analyzed with a multi-parametric approach. Time, Frequency Domain and Non-Linear parameters were calculated, also encompassing indices from the adult and fetal field. The novelty of this study is the introduction of innovative measurements in a thorough investigation to characterize the effect of sleep state and position on the cardio-respiratory control in newborns. Results show that most parameters succeed in classifying different sleep states, while differences between positions were found in the one-month population only. This study comes as a continuation of previous analysis with the addition of respiratory signal. These results are encouraging for the aim of defining a set of parameters that could help characterizing the autonomic control of infants and early detect the onset of distress or particular pathologies.

I. Introduction

When an infant is born, his body faces many changes to adjust from intra-uterine to extra-uterine life. This adaptation goes on through the first weeks of life and strongly involves cardio-respiratory regulation, which was trained during pregnancy thanks to fetal breathing-like activity.

This regulation is coordinated by Autonomic Nervous System (ANS). With its two branches, sympathetic and parasympathetic, it strives toward an optimal equilibrium in human body's internal environment in response to changes in external conditions.

Among different environmental challenges for the infant, there are room temperature, type of blankets and position during sleep. Particularly, the latter variable assumes a significant importance in defining possible trigger causes leading to infant distress, till Sudden Infant Death Syndrome (SIDS) [1].

Many studies have been conducted to detect unequivocal early signs of SIDS, but to date no indisputable markers have been identified. Nonetheless, many researchers pointed out some

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differences in cardiovascular control in babies who later on incurred in SIDS episodes, which could be viewed as first markers toward the arousal of distress [2],[3].

This condition of distress is most likely due to a vulnerability of the infant, for example due to genetic abnormalities or premature birth, a critical developmental period, particularly 2–4 months, and external stressors as the one mentioned above [4]. In particular, epidemiological studies have indicated prone position to be a risk factor.

In order to examine this complex mechanism, methods based on signal processing could provide new insights.

This study is a multi-signal multi-parametric approach to the analysis of HR signals obtained from ECG recordings and respiration in a population of newborns. They were analyzed considering the influence on cardio-respiratory interaction of quiet and active sleep state and prone and supine position.

The novelty of this approach is in the attempt to define a set of parameters coming from Time Domain, Frequency Domain and Non-Linear techniques in order to fully characterize the physiological system.

Moreover, previous analysis employed a set of parameters that included measures typical of the fetal HR analysis [5], and of classical adult HR study [6] in order to characterize the same physiological system in severely premature infants with successful results [7]. For this reason these parameters have been included in the present analysis with the addition of respiration analysis.

Results obtained give insights on differences in regulation of the autonomic system across ages, showing a diverse behavior in newborns and one-month infant during different sleep states and positions.

II. Material and Methods

A. Population

This study is a sub-analysis of a prospective observational study of 122 newborn and 159 one-month infants recruited at the Pediatrics Department of Columbia University Medical Center.

Among these babies, measurements from 60 newborns and 22 one-month were selected. Gestational age at birth of the newborn group was 39.6±1 week and for the one-month 39.3±1 weeks. There were 33 females and 27 males in the newborn group and respectively 10 and 12 in the one-month.

All the infants were in good medical conditions; the study had the approval of the Ethical Committee of the hospital and mothers signed an informed consent before enrolling.

30 newborns were assigned to supine position and 30 to prone, while 15 one-month were assigned to supine and 7 to prone.

Infants evaluation lasted for about 30 minutes, with 10 minutes of baseline in the assigned position followed by tilts; our analysis focused on the baselines only.

ECG recordings were acquired at 500 Hz and respiration was acquired at 20 Hz with a respiration belt, with a customized acquisition system called DATAQ (Columbia property)

Sleep states were coded every 30 seconds by expert clinicians. States were assigned by direct observation with a scoring system developed and validated in our laboratory [8]. Shortly, active sleep was identified by at least one rapid eye movement (REM) per epoch. Moreover active sleep was characterized by movements of whole extremities and the torso and occasionally stretching, yawning, whimpering, sucking and grimacing. On the other hand, quiet sleep was assigned if the infant was asleep without any REM and if the infant was relaxed with movements limited to startles and non-nutritive sucking or jaw jerks. Indeterminate state was coded when small body movements were observed, without REM. Only segments of three minutes in the same sleep state were taken into consideration.

B. RR and respiration analysis

A customized algorithm for peak identification was applied on ECG to obtain the RR time series. A visual inspection of the series was performed in order to remove peaks due to arrhythmic beats or due to wrong identification during the automatic procedure.

Respiration was interpolated with a cubic spline and re-sampled at the same time instances of RR beats, in order to have two synchronous time series.

For each baby only those three minutes segments where both HR and respiration were of good quality were accepted.

The analysis performed in this paper includes techniques from Time Domain, Frequency Domain and Non-Linear analysis. Given that no clear guidelines for the application of these methods on neonates are given by the scientific community, our proposal has adapted parameters both from the fetal and the adult field.

For what regards Time Domain analysis on RR series, the following parameters were evaluated: Long Term Irregularity (LTI), Short Term Variability (STV), Interval Index (II) Differential Index (DI) [5], Standard Deviation of NN intervals (SDNN), HRV triangular index (HRVTI), Root Mean of Successive Differences (RMSSD) [6].

Regarding breathing rate analysis, mean and standard deviation were calculated. Moreover, the coefficient of variation (CV) was computed, defined as the standard deviation of the respiration rate divided by the mean respiration rate.

Frequency Domain analysis was performed with a non-parametric approach (Welch method) every 3 minutes of RR and respiration rate, both resampled at 5 Hz. The non-parametric approach was preferred for its high computational velocity, since the number of samples available was enough for the spectral resolution needed. Cross-spectral analysis was also performed, estimating cross-spectrum and coherence. Frequency bands selected were Low

Frequency (LF), 0.01–0.45 Hz, and High Frequency (HF), 0.45–1.5 Hz. Both spectral power and normalized spectral power were computed for each band.

For what regards Non-Linear methods, two measures of Entropy were employed. Approximate Entropy (ApEn) measures regularity, defined as the presence of repetitive patterns in a temporal series at different lags [9]. Since 1995, ApEn has been used in studies concerning cardio-vascular regulation, often proving to be capable in separating patho-physiological conditions [10]. Nonetheless, ApEn strongly depends on the length of temporal series analyzed and counts self matches, which does not agree with the purpose of measuring the generation of new information.

To address these issues, Sample Entropy (SampEn) was proposed: it reduces the bias given by the length of the signal and enhances the estimate consistency [11].

Both methods were evaluated on 3 minutes epochs, with differences of pattern length m=1,2,3 and tolerance r=0.2*std.

C. Statistical analysis

Before applying statistical tests, all the parameters were transformed applying a square root and Lilliefors test was employed to verify normal distribution in fact, some of the parameters were not normally distributed.

A 2-way Anova analysis was performed on RR and respiration parameters, considering as independent variables sleep states and positions, both for the newborn dataset and for the one-month. A p-value <0.05 was considered significant.

III. Results

The results of the analysis on newborn babies show that LTI, STD for respiration rate, CV for respiration rate, ApEn for RR and SampEn for RR were capable of distinguishing active from quiet sleep. Figure 1 shows Mean and STD for three of these parameters.

All the parameters obtained higher values in active sleep compared to quiet sleep, except for entropies which behaved oppositely.

In the comparison between positions during sleep, no parameter proved to be able of distinguishing the two conditions.

Moreover, not a single parameter showed a significant p-value regarding the interaction between sleep states and position. Table I reports p-values for 2-way Anova analysis of these parameters.

For what regards the analysis on the one-month group, differences between sleep states where reported for STD and CV for respiration rate, ApEn and SampEn for respiration rate. All these values were higher in active state rather than in quiet. Figure 2 reports Mean and STD for SampEn for respiration rate. In addition, ApEn and SampEn for RR series were capable of distinguishing when babies were in supine or prone position, showing higher values for supine position. Mean and STD for SampEn for RR series are shown in Figure 2. In this population, STV, SDNN, HRVTI showed significant p-values in terms of the interaction between the two independent factors of the analysis.

Table II lists all *p*-values for significant parameters in the one-month dataset 2-way Anova analysis.

IV. Discussion

Analysis on newborn data, encompassing parameters normally applied on adults and fetuses, proved to be efficient in characterizing sleep states. Measures of respiration rate variability strongly differentiated active and quiet sleep, together with LTI, a typical measure in the fetal field. Active sleep is identified as a period of more irregular breathing and accordingly more irregular RR series on the long term period (3 min). Interestingly, entropy measures showed an opposite behavior: entropy was lower in active and higher in quiet. It confirmed what already seen in day and night periods of adult subjects [12]. This finding confirms that entropy is complementary measure of variability behavior as it is sensitive to new information content, not only to the linear signal variability. In newborns, no difference was found in the parameters between supine and prone position.

For what regards the analysis on one-month infants, Time Domain variability in the respiration rate was still able of differentiating sleep states, together with values of entropy of the respiration rate. All these parameters showed higher values in active sleep.

Interestingly, at this developmental stage, differences between positions were also found: sleeping prone is defined as a risk factor for SIDS, and lower variability values were found precisely in this position. Moreover, it is notable that no difference was found right after birth, but one month after the parasympathetic system seems to decrease its activity, exactly at the start of what is defined the most critical period for SIDS (2–4 months of life).

A previous study by Mrowka et al. showed how the strength of the coupling between the respiratory and the cardiovascular system increases with the age of the infant, giving a possible insight of the different behavior of parameters at birth and one month after [13].

In both analyses, Frequency Domain parameters obtained with non-parametric methods did not obtain significant differences. We hypothesize that this must be due to the high variability in respiratory rate of each baby.

Among the possible weaknesses, we acknowledge that since this study is a sub-analysis of a major one, few babies possessed data in both positions or at different developmental stages, thus we could not perform a paired analysis.

Moreover, due to the difficulty of finding good data for HR and respiration at the same time, the analysis had to be limited to 3 minutes segments, excluding other investigations previously applied, such as PRSA or entropy measures applied to longer epochs. An ongoing study is addressing this limitation.

Future developments might include the analysis of other signals, such as oxygen saturation and blood pressure, and response to tilt challenge.

V. Conclusion

Results obtained in this study help to characterize autonomic control on cardio-respiratory activity at birth and one month after. Parameters from Time, Frequency and Non-linear domain were employed and show significant effects of sleep state on the regulation of HR and respiration in newborn and one-month infants.

In active sleep Time domain measures of RR variability are higher, while entropy measures are lower.

Only in the one-month group, differences between positions were found, with lower variability in prone position. This effect indicates that position provokes an alteration, possibly able to vary autonomic regulation in the prone position, in particular one month after birth. The direction of these effects suggests a diminished parasympathetic control in the prone position.

This multi-parametric and multi-signal analysis, characterizing HR variability and respiration, affords a new approach for SIDS risk assessment during infancy.

Further studies may benefit from integrating other complex analyses of physiological signals, such as blood pressure and temperature.

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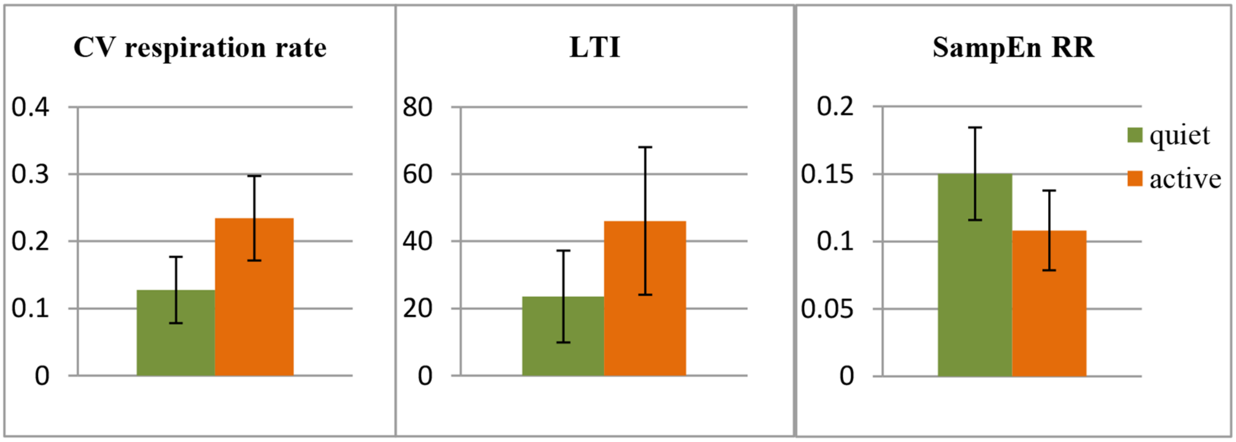

Figure 1.

Three significant parameters extracted from the Newborn dataset. In green are the values for quiet sleep while in orange for active. Values are reported as mean and std. The first paramter from left is the Coefficient of Variation for respiration rate, then the Long Term Irregulatiry is represented and lastly the Sample Entropy of RR.

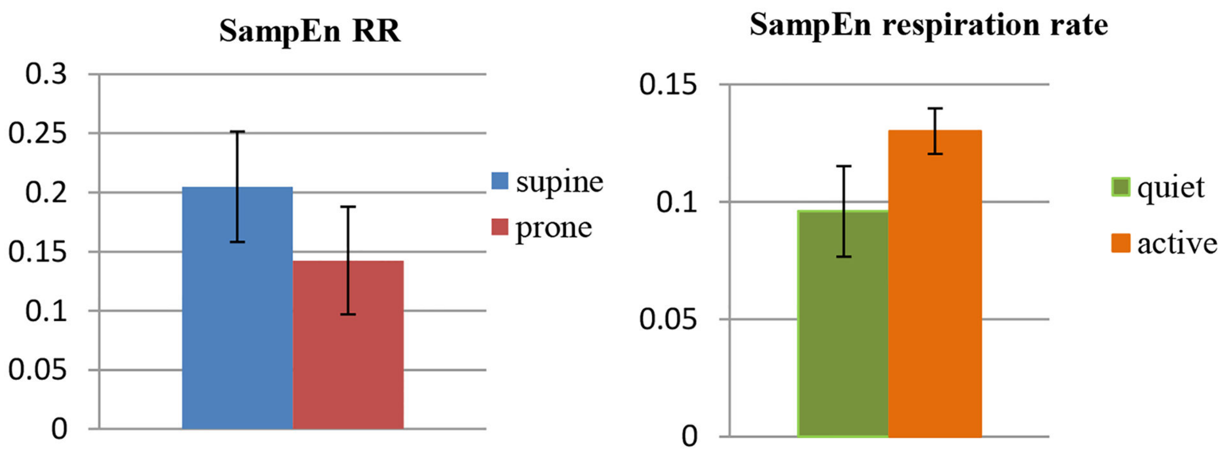

Figure 2.
Two significant parameters extracted from the One-month dataset. In green are the values for quiet sleep while in orange for active. In blue are the values for supine psition and in red the one for prone. Value s are reported as mean and std. The first paramter from left is the Sample Entropy of RR and then the Sample Entropy for the respiration rate is represented.

TABLE I.

P-values for Newborn dataset

P-values for Anova analysis. This statistical test was performed on parameters extracted from HR and respiration of 60 newborn infants, in active and quiet sleep and in prone and supine position during sleep.

	Newborn		
	p sleep state	***p position***	***p interaction***
ApEn RR	0.0019	0.53	0.29
LTI	0.0011	0.26	0.48
SampEn_RR	0.0034	0.24	0.20
Std_resp	0.0029	0.77	0.86
CV_resp	1 E-7	0.67	0.40

TABLE II.

P-values for One-month dataset

P-values for Anova analysis. The statistical test was performed on parameters extracted from HR and respiration of 22 one month old infants, in active and quiet sleep and in prone and supine position during sleep.

	One month		
	p sleep state	***p position***	***p interaction***
ApEn_RR	0.19	0.0036	0.78
SampEn_RR	0.21	0.004	0.55
ApEn_resp	0.0016	0.50	0.59
SampEn_resp	4 E-4	0.22	0.81
Std_resp	0.0011	0.32	0.57
CV_resp	2 E-4	0.17	0.86