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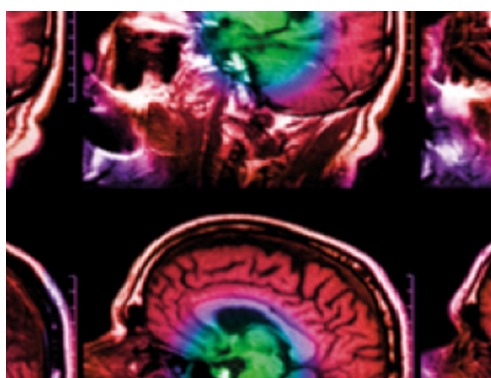
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# Novel heart rate parameters for the assessment of autonomic nervous system function in premature infants

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## Abstract

Autonomic nervous system (ANS) balance is a key factor in homeostatic control of cardiac activity, breathing and certain reflex reactions such as coughing, sneezing and swallowing and thus plays a crucial role for survival. ANS impairment has been related to many neonatal pathologies, including sudden infant death syndrome (SIDS). Moreover, some conditions have been identified as risk factors for SIDS, such as prone sleep position. There is an urgent need for timely and non-invasive assessment of ANS function in at-risk infants. Systematic measurement of heart rate variability (HRV) offers an optimal approach to access indirectly both sympathetic and parasympathetic influences on ANS functioning. In this paper, data from premature infants collected in a sleep physiology laboratory in the NICU are presented: traditional and novel approaches to HRV analyses are applied and compared in order to evaluate their relative merits in the assessment of ANS activity and the influence of sleep position. Indices from time domain and nonlinear approaches contributed as markers of physiological development in premature infants. Moreover, significant differences were observed as a function of sleep position.

**Keywords:** autonomic nervous system, heart rate variability, prematurity, non-linear analysis

(Some figures may appear in colour only in the online journal)

## 1. Introduction

The autonomic nervous system (ANS) is a part of the peripheral nervous system that acts to control physiology, functioning largely below the level of consciousness. It is divided in two branches, sympathetic and parasympathetic, which act synergistically. The ANS is responsible for the regulation of activity crucial for survival. It acts by maintaining homeostasis, a dynamical equilibrium that guarantees the optimal physiological function (Janig 2008). During the first months of life the development of the autonomic balance is rapidly changing: the sympathetic system develops early in pregnancy, while parasympathetic control emerges later in the perinatal period. The relative influence of parasympathetic activation increases throughout early development (Sahni *et al* 2000, Longin *et al* 2005) and is clearly evident when comparing neonatal and adult baseline heart rates (HR) (Walker *et al* 1978, Gournay *et al* 2002).

Many external conditions can affect ANS development, and also many factors related to maternal activity and metabolism can influence foetal and infant homeostatic control. For example, epidemiological studies showed that autonomic balance can be altered by prenatal factors such as alcohol and smoking exposure, and postnatal environmental influences, such as room temperature, bedding, and position during sleep (Fifer *et al* 2009, Yiallourou *et al* 2011).

These issues are particularly relevant for the investigation of the pathophysiology of sudden infant death syndrome (SIDS) (American Academy of Pediatrics 1996, Guntheroth and Spiers 2002). Alterations in heart beat regulation have been identified in infants who subsequently succumbed to SIDS and these findings suggested a relationship between SIDS and autonomic control impairment (Leistner *et al* 1980, Kluge *et al* 1988, Schechtman *et al* 1988). Many studies have explored differences in cardiovascular control in the context of risk conditions, in particular during sleep in the first months of life, in order to identify a possible fatal alteration during this vulnerable age (Schechtman *et al* 1988, 1990, Sahni *et al* 1999, Ariagno *et al* 2003, Menihan *et al* 2006, Ronald and Hannah 2010). At present however, the mechanisms leading to ANS control failure are still largely unexplained and quantification of potential risk for SIDS remains elusive.

What is clear is that the complexity underlying autonomic balance as reflected in heart rate variability (HRV), warrants further investigation and exploitation of novel analytic techniques. Indices extracted from both time and frequency domain analyses of HR have facilitated risk evaluation for pathological conditions in adult subjects (Malik *et al* 1996). In this study, we employed a multi-parametric approach for the analysis of HR signals in an at-risk population, prematurely born infants. Premature birth precludes full in-utero development of the ANS and may thereby increase the probability of SIDS occurrence (Malloy 2013, Yiallourou *et al* 2013). As sleep position has emerged as the primary SIDS postnatal risk factor we investigated the effects of prone versus supine position on a range of HRV parameters in this vulnerable population. Specifically, we incorporated a wide array of mathematical techniques to analyse HR signals in premature newborns collected prior to hospital discharge and then again 2 months later. This novel and comprehensive approach combined multiple indices utilizing time domain, frequency domain and non-linear methods. Furthermore, as premature infants share physiological characteristics of the foetus and the infant, we employed a set of parameters typically employed in foetal HR analysis (Signorini *et al* 2003), as well as in standard adult HR studies (Malik *et al* 1996).

The approach we utilized in this study also allowed investigation of several aspects of premature autonomic control that occur at different time scales, and involve different control mechanisms, known to be influenced by position and sleep state in the newborn. Moreover,

**Table 1.** Age and sex of subject population of premature infants (A) at the time of the first study right before hospital discharge and (B) at the time of the follow-up study approximately 2 months after hospital discharge.

Number of subjects	Gestational age	Post menstrual age
(A) 35 <sup>a</sup>	28.7 ± 2 weeks	37.7 ± 2.4 weeks
(B) 24 <sup>b</sup>	27.9 ± 1.6 weeks	49.2 ± 3.2 weeks

<sup>a</sup> 19 males and 16 females.

<sup>b</sup> 13 males and 11 females.

the availability of a follow-up study at two months of age allowed the evaluation of the development of ANS control during the postnatal period.

## 2. Materials and methods

### 2.1. Population

The dataset was acquired in the Infant Physiology Laboratory at Columbia University Medical Center, New York. This study included data collected at two time points: the first performed on 35 healthy premature infants immediately prior to discharge from hospital and repeated on 24 of these infants at follow-up study two months after discharge. Table 1 contains subjects' information concerning age and sex, both for the first study and the follow-up.

Inconsistent use of the terminology employed to define newborn testing ages has made cross study comparisons problematic. We chose to define gestational age (GA) at birth as the time elapsed between the first day of the last normal menstrual period and the day of delivery and postmenstrual age (PMA) as GA plus the time elapsed since birth.

The Institutional Review Board of the Columbia University Medical Center approved the study and mothers provided informed consent at enrolment.

The duration of the first study protocol was 6 h. During the first 3 h infants slept in supine position, and were then moved to prone for the rest of the study. Infants were fed right before the start of the study and again after 3 h.

The follow up study at 2 months was designed to last one hour, due to difficulties in maintaining periods of uninterrupted sleep with older infants. Thus, infants spent only 30 min in each position.

Experienced clinicians coded sleep states every 30 s and these behavioural codes were assigned by direct observation using a scoring system previously defined and validated in the laboratory (Stefanski *et al* 1984). In brief, active sleep (AS) was assigned if at least one rapid eye movement (REM) or body movement typical of AS was observed. Quiet sleep (QS) was assigned when the infant was sleeping without any observable REM activity. During QS, the infant was relaxed, with limited movements such as startles and non-nutritive sucking.

Since cardiorespiratory function is also affected by sleep state it was necessary to analyze the data within states. Nevertheless, only AS presented enough data for each baby, thus all results are summarized for AS only.

ECG was acquired at 500 Hz and the RR series in seconds were obtained using a customized peak detection algorithm, based on the cross-correlation of a QRS template with the ECG, followed by visual inspection of the series to remove peaks due to arrhythmic beats or due to erroneous automated identification of R-waves.

In the first study, only patients with at least three segments of good quality RR series of 3 min with continuous sleep state were accepted. In the follow up, due to the reduced length of the study, patients with at least one segment of 3 min good quality RR series with continuous sleep state were included.

This requirement reduced the number of infants available for the analysis: for the first study 20 infants met the criteria, while for the follow up 10 infants met these criteria.

## 2.2. HR analysis

In this paper, techniques from time domain, frequency domain and non-linear analysis were utilized.

As there are no standardized norms developed for this particular population, we chose to adapt the guidelines developed for adults. The Task Force of 1996 suggests the evaluation of parameters on 5 min windows for adults' HR (Malik *et al* 1996). However, since neonatal HR is higher, a similar number of beats occurs in 3 min time. Therefore, all parameters were evaluated on 3 min segments during which we allowed a maximum of 5 interruptions in the series due to noise and artefacts.

Table 2 summarizes all the parameters evaluated. The choice of the length of the window used to extract each parameter depends on the type of information investigated, for example short term or long term variability. Moreover, some specifics are determined by the algorithm itself of each parameter, which may require longer recordings, for example the phase-rectified signal averaging (PRSA) technique.

**2.2.1. Time domain analysis.** For the time domain analysis it was decided to include measures adapted from adult studies': SDNN, which is the standard deviation of normal to normal intervals (NN), defined as the RR distances excluding anomalous, e.g. ectopic beats. In addition standard deviation of the average NN interval, SDANN, the HRV triangular index, HRVTI and root mean of successive differences (RMSSD) (Malik *et al* 1996) were calculated. SDNN and HRVTI estimate overall HRV, SDANN estimates long-term components of HRV and RMSSD estimates short-term components of HRV.

In addition to these traditional parameters, measures from foetal HR analyses were computed: long term variability (LTV), short term variability (STV), interval index (II), differential index (DI) and long term irregularity (LTI) (de Haan *et al* 1971, Signorini *et al* 2003).

All these measures are calculated in seconds, with the exception of LTV which is defined in beats per minutes. Generally long-term variability parameters evaluate a combination of sympathetic and parasympathetic nervous systems. In contrast, measures related to the beat to beat variability are influenced largely by the parasympathetic nervous system, tied to rapid ANS reactivity.

**2.2.2. Frequency domain analysis.** For frequency domain analysis, each 3 min interval of RR series was interpolated with a cubic spline and re-sampled at 10 Hz. Then Power Spectral Density was estimated with a non-parametric approach based on the Welch method, preferred for its simplicity and computational rate.

Frequency bands chosen were low frequency (LF), 0.05–0.2 Hz, and high frequency (HF), 0.5–1.5 Hz (Rosenstock *et al* 1999, Sahni *et al* 1999). The literature does not provide precise values for these ranges, thus they were chosen based on the prior experience in our lab, on the observation of the spectra of these recordings and with consideration of the general breathing characteristics of premature infants (Sahni *et al* 2000).

**Table 2.** This table summarizes all the parameters evaluated in time domain, frequency domain and non-linear approaches, specifying the length of the sequence used to calculate them and their physiological interpretation.

Methods and parameters for the analysis of fetal heart rate			
Method	Parameters	Sequence length	Hypothesis
Time domain analysis: morphological HR modification and variability	SDNN (s)	3 min	Overall variability
	HRVTI (s)		Overall variability
	RMSSD (s)		Variability in the short period
	LTV (bpm)	1 min	Variability in the long period
	LTI (s)		Variability in the long period
	II (s)		Variability in the short period
	STV (s)		Variability in the short period
	DI (s)		Variability in the long period
Frequency domain	SDANN (s)	Entire recording	Variability in the long period
	Low frequency	3 min	HR power for long period oscillations
	High frequency		HR power for short period oscillations
Approximate entropy	ApEn( $m, r$ ) $m = 1, 2$ ; $r = 0.2$	3 min and 1500 samples	Recurrent patterns
Sample entropy	SampEn( $m, r$ ) $m = 1, 2$ ; $r = 0.2$		Recurrent patterns
Quadratic sample entropy	QSE( $m, r, M$ ) $m = 1, 2$ ; $r =$ variable based on optimal count of matches ( $M$ )		Recurrent patterns
PRSA	Acceleration/deceleration Phase Rectified Slope	Entire recording	Quasi-periodic oscillations

**2.2.3. Non-linear analysis.** Non-linear methods included three estimators of entropy and the PRSA technique.

Approximate entropy (ApEn), as proposed by Pincus, is a the quantification of regularity, defined as the presence of repetitive patterns in a time series within a certain tolerance  $r$  and at different lags (Pincus 1991, Pincus *et al* 1993). ApEn is seen as a significant analytic advancement over traditional approaches, which required very long and completely noise-free datasets to determine a precise value of entropy, since neither of these demands are typically met in *in vivo* biological datasets. Pincus *et al* advanced the field by positing that an ‘approximate’ estimate of entropy could be used to hierarchically rank sets of time series. ApEn has been useful in separating patho-physiological conditions, but a major limitation is a strong dependence on the length of the time series analyzed and the count of the self-matches of each pattern, which is incompatible with the aim of measuring new information generated in the signal.

To address these limitations, sample entropy (SampEn) was developed. This new estimator introduced by Richman and Moorman (2000), reduces the bias given by the length of the signal, does not count self-matches and enhances the estimate consistence (Lake *et al* 2002).

These two methods were applied to epochs of 3 min duration used for both the frequency domain and time domain analysis. We also analysed epochs defined by number of samples (1500). This was decided because in epochs of 3 min the average number of samples is typically in the range of 400–500 and this might be too small to obtain a reliable entropy estimate (Lake 2006, 2011). The tolerance  $r$  was set at 0.2 SD of the signal and the length of the pattern  $m$  varied from 1 to 3.

A challenging problem for entropy estimation is the choice of the tolerance  $r$ , to assess if two patterns could be defined similar. Lake (2006) proposed a new parameter called quadratic sample entropy (QSE). It converts the measured conditional probability of SampEn to a density, simply adding the log ( $2r$ ) to SampEn. The dependency on  $r$  is thus removed and  $r$  can be optimally varied for each data record, allowing direct comparison of the estimates.

Our study proposes an optimal choice of  $r$  based on the minimum numerator count, which means that the  $r$  was selected if it guaranteed a minimum number of matches, in order to obtain a robust entropy estimate (Lake 2011, Cirugeda-Roldána *et al* 2014). In fact, SampEn is defined as the logarithm of the conditional probability (cp), which is the ratio of the sum of the matches found for pattern of length  $m + 1$  ( $A$ ) divided by the sum of matches for pattern of length  $m$  ( $B$ ), as stated in equation (1)

$$\text{SampEn} = -\ln(\text{cp}) = -\ln(A/B) = -\ln(A) + \ln(B) \quad (1)$$

In order to improve the accuracy of conditional entropy rates, the ( $A/B$ ) ratio was calculated with a specified minimum number of matches for the numerator and the denominator. This algorithm guaranteed that each contribution to the total score had some minimum degree of statistical reliability.

The final step was to investigate PRSA as an alternative approach. It is a method used to synchronize the phases of quasi-periodic components of noisy and non-stationary signals, based on their temporal scale (Bauer *et al* 2006, Fanelli *et al* 2013). PRSA offers the ability to analyse separately HR accelerations and decelerations. This affords the opportunity to investigate rapid parasympathetic influences as well later acting sympathetic/parasympathetic ANS mechanisms. This measure requires relatively long recordings since it is based on averaging many segments to discard irrelevant data. This approach was implemented only in the initial 6 h studies, as the duration of follow up study was deemed inadequate for this analysis.

### 2.3. Statistical analysis

To test for significant differences in parameters as a function of sleep position in the first study a Student's  $t$ -test was used, because the population was normally distributed.

As the follow-up population was smaller in number and not normally distributed, a Wilcoxon Signed-Rank Test was applied, a non-parametric test for populations with matched samples. This test was also applied when examining within subjects repeated measures results for the 9 subjects with data at both time points.

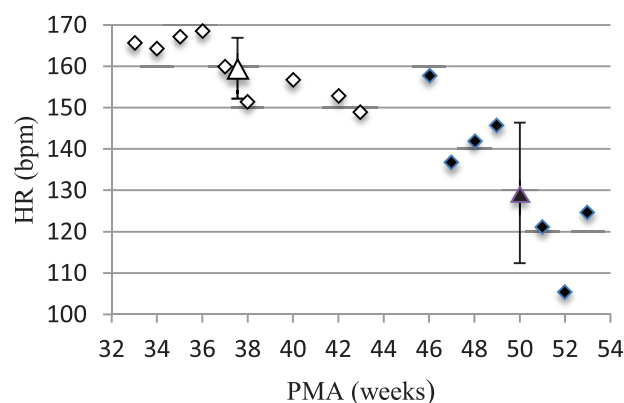
A  $P$ -value less than 0.05 was considered statistically significant.

## 3. Results

### 3.1. HR as a function of PMA

Before evaluating positional differences, the behaviour of parameters as a function of PMA was verified. As a matter of fact, we already have a general knowledge of what is happening in the first months of life at the level of autonomic control, so this preliminary investigation





**Figure 1.** Infants were divided in groups by week of their post-menstrual age (PMA) at the time of the study. Then mean HR for each group was plotted against the PMA. In this figure data are plotted for infants in the first study (in white) and for those who returned for the follow up (in black). Mean and SD for each of these two groups are depicted by the large white and black triangles.

was a way to test the performance of the proposed parameters before applying them in a less investigated topic.

Thus, infants were divided in groups according to their PMA at the time of each study. The mean HR of each group was calculated and plotted, as shown in figure 1.

This plot shows that mean HR decrease as infants get older, as would be predicted given the growing influence of the parasympathetic system action in the first months of life. Moreover, all the variability parameters in each domain show a clear increase from the first to the follow-up study, including both short term and long-term variability measures.

Table 3 summarizes results obtained for all parameters together with their statistical significance ( $p$ -values) and figure 2 shows the graphs of the significant parameters of the comparison.

### 3.2. Supine versus prone

Analysis by sleep position in the first study showed clear differences both in the long-term variability parameters (LTI and PRSA) and in the short-term variability parameters (SampEn and QSE), with higher values in the supine position. Data for each parameter are shown in table 4.

In the follow-up study, the most robust state differences were observed only for the parameters quantifying short-term variability, specifically, RMSSD, STV and entropies. As mentioned above PRSA could not be evaluated due to the short protocol duration at this time point. Results are shown in table 5.

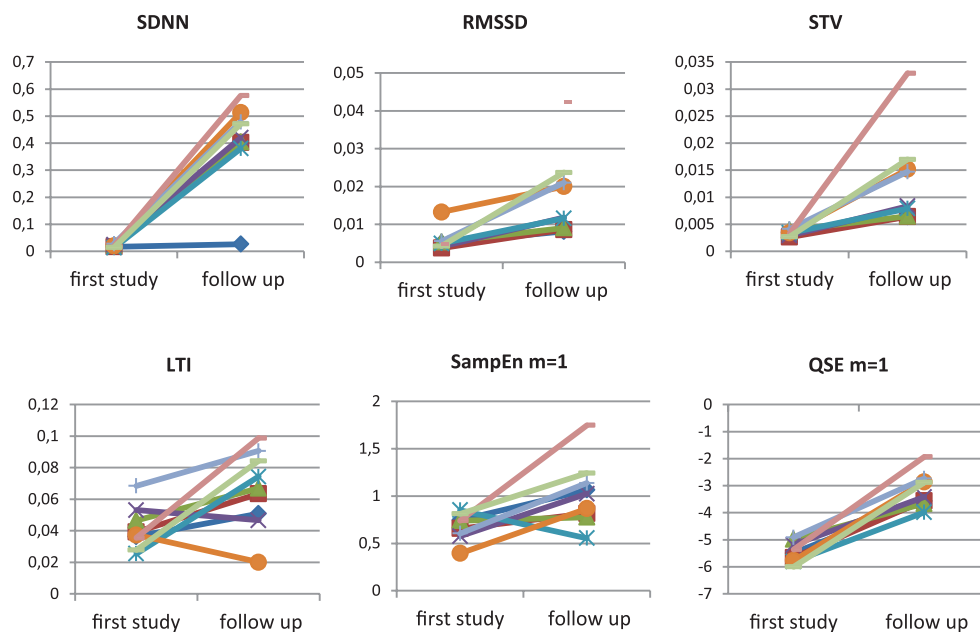
## 4. Discussion

Prematurity is a brief and transitory developmental stage in which the assessment of ANS maturation may require alternative approaches and novel combinations of analytic strategies. Furthermore, parameters both from foetal and adult studies may need to be adapted as the newborn ANS is still in transition from pre- to postnatal life and thus the periodicities and the regulation of HR are operating under distinctly different physiological demands.



**Table 3.** Parameters' results for the comparison of first study and follow up with subjects in AS and supine position (median  $\pm$  IQR). *P*-values were obtained with Wilcoxon signed-rank test on 9 subjects.

	First study	Follow up	<i>P</i> -val
SDNN	0.0182 $\pm$ 0.006	0.034 $\pm$ 0.009	<0.01
RMSSD	0.005 $\pm$ 0.001	0.012 $\pm$ 0.01	<0.01
STV	0.0034 $\pm$ 0.0006	0.0084 $\pm$ 0.009	<0.01
LTI	0.0374 $\pm$ 0.011	0.067 $\pm$ 0.033	<0.01
SampEn <i>m</i> = 1	0.74 $\pm$ 0.141	1.023 $\pm$ 0.321	<0.05
QSE <i>m</i> = 1	-5.48 $\pm$ 0.574	-3.42 $\pm$ 0.71	<0.01

**Figure 2.** Graphs showing the comparison between the first and the follow-up study. These images illustrate augmented HRV, shown by the increase for all the parameters in the follow-up study, as a proof of the development of the ANS during the first two months of life.**Table 4.** Parameters' results for first study with patients in AS (mean  $\pm$  SD). *P*-values were obtained with Student's *t*-test on 20 subjects.

	Prone	Supine	<i>P</i> -val
LTI	0.040 $\pm$ 0.018	0.049 $\pm$ 0.023	<0.001
SDNN	0.0212 $\pm$ 0.008	0.0237 $\pm$ 0.009	<0.05
PRSA $\Delta Y$	15.66 $\pm$ 10.18	18.71 $\pm$ 10.68	<0.01
SampEn	0.554 $\pm$ 0.183	0.443 $\pm$ 0.133	<0.001
QSE <i>m</i> = 1	-4.201 $\pm$ 0.415	-4.042 $\pm$ 0.304	<0.001

**Table 5.** Parameters' results for follow-up study with patients in AS (median  $\pm$  IQR). *P*-values were obtained with Wilcoxon signed-rank test on 10 subjects.

	Prone	Supine	<i>P</i> -val
Mean RR	0.414 $\pm$ 0.048	0.447 $\pm$ 0.072	<0.05
RMSSD	0.014 $\pm$ 0.009	0.015 $\pm$ 0.011	<0.05
STV	0.01 $\pm$ 0.006	0.011 $\pm$ 0.008	<0.05
QSE <i>m</i> =2	-3.27 $\pm$ 0.848	-3.15 $\pm$ 0.783	<0.05

The goal of this study was to evaluate a wide range of HR parameters with the greatest precision possible in this vulnerable subject population, in which there is limited access and physiological control is rapidly changing.

The results from a significant subset of the parameters were in line with the current understanding of neonatal physiology. RMSSD, STV, LTI, SDNN and QSE all showed robust increases as a function of age. These measures are not simple integrated measure of variability, but they decompose variability into its components associated with relevant physiological systems. Our finding of the increased influence of the parasympathetic system during the first months of life on HR control is consistent with other developmental studies: resting state HR is reduced and the ability to respond on a beat to beat time frame is enhanced.

The second interesting finding emerged from the comparison between sleep positions, as supine position showed increased variability and also at each age a different set of parameters characterized the effect of sleep position. Specifically, prior to hospital discharge HRV differences between the two positions were found in both the long term and short-term indices of HRV, showing a reduced variability in prone position. Two months later, only short term variability indices (STV, RMSS and QSE) showed robust differences as a function of sleep position.

These results point to different autonomic regulation depending on position; this is particularly interesting in light of the fact that prone position has been identified as a major risk factor for SIDS. Furthermore the peak of SIDS events lies between the 2nd and 4th month of life, the age of the subjects in the follow-up phase of our study (Yiallourou *et al* 2008).

A possible explanation for the positional effects obtained in the newborn infants prior to discharge might be related to the very premature condition of the infants; their early birth is a strong stressor for their physiological development since their systems were ill prepared for the relatively early transition to extra-uterine life. Cortisol and catecholamine levels change dramatically after the 30th week of pregnancy to begin a cascade of events that would lead to labor and birth. These two mediators play a crucial role in sympathetic regulation and thus infant expected maturational course may have been altered by the early delivery and physiological challenges in the NICU. In the follow-up study, at two months of postnatal age, the parameters most strongly associated with the effects of sleeping position, were measures of short-term variability, generally associated with parasympathetic regulation. This might be related to the fact that at birth sympathetic activity mediated by hormonal changes is the major influence on HRV, while at two months of age parasympathetic control is more vulnerable to environmental changes.

Environmental challenges during the first months play a crucial role in the development of the parasympathetic system. Thus, the fact that in prone position the short-term variability is lower than in supine, might highlight the fact that the parasympathetic system is still not sufficiently developed to appropriately adapt to this autonomic challenge.

The number of subjects available for the study is relatively small, particularly for the maturation evaluation since only 9 babies had signals both for the first study and the follow-up. Thus, our conclusions can be viewed as preliminary and an ongoing study on a bigger cohort is addressing this limitation.

Spectral analysis appears to be more limited and less revealing of age and positions differences in autonomic control. One possible explanation is that such analysis is more sensitive to the neonates' relatively high respiratory rate, which can result in cardiac aliasing. Cardiac aliasing is a phenomenon that occurs when HR is less than double the respiratory rate, and thus HR is fast enough to adjust to high respiratory movements (Harper *et al* 1982, Rother *et al* 1989).

## 5. Conclusion

This paper proposes a novel multi-parametric approach to investigate HRV to evaluate the development of ANS control in premature infants. A set of parameters both from adult and foetal HRV research contributed to our assessment of the effects of age and sleeping position.

This subset of parameters is particularly interesting because they appear to be sensitive to physiological mechanisms underlying cardiovascular control occurring under different environmental and maturational states. Since altered cardiovascular control is involved in many pathological conditions, these results seem to be promising for the development of more effective estimates of risk. Moreover, they could help in the assessment of an optimal timing for interventions aimed at optimizing the development of autonomic control during the recovery path of premature neonates.

In conclusion, a subset of parameters using a wide range of techniques, in this case LTI, RMSSD, PRSA  $\Delta Y$  and QSE, proved to be sensitive to the maturation of autonomic control and response to a physiological modification introduced by position and sleep state changes, offering promising tools for the evaluation of patho-physiological risk related to ANS impairment.

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