Multi-parametric Heart Rate Analysis in Premature Babies exposed to Sudden Infant Death Syndrome.

Maristella Lucchini , Maria G. Signorini, William P. Fifer, Rakhesh Sahni

Abstract— **Severe premature babies present a risk profile higher than the normal population. Reasons are related to the incomplete development of physiological systems that support baby's life. Heart Rate Variability (HRV) analysis can help the identification of distress conditions as it is sensitive to Autonomic Nervous System (ANS) behavior. This paper presents results obtained in 35 babies with severe prematurity, in quiet and active sleep and in prone and supine position. HRV was analyzed in time and frequency domain and with nonlinear parameters. The novelty of this approach lies in the combined use of parameters generally adopted in fetal monitoring and "adult" indices. Results show that most parameters succeed in classifying different experimental conditions. This is very promising as our final objective is to identify a set of parameters that could be the basis for a risk classifier to improve the care path of premature population.**

I. Introduction

Many external conditions can affect the functioning of the ANS; this is particularly true in a population of premature babies as the development of the physiological systems is not yet completed. In addition, many factors related to maternal activity and metabolism can affect to different extents the health condition of the newborn himself.

For example, alcohol and smoking exposure as well as room temperature, type of blankets and in particular the position during sleep, assume a relevant importance in evaluating possible causes leading to infant distress, till Sudden Infant Death Syndrome (SIDS) [1]. Moreover altered sleep state organization has been reported in SIDS victims [2].

In premature condition, the cardiovascular control plays a crucial role: changes in heart beat regulation have been identified in babies who later on incurred in SIDS episodes and thus could be viewed as first markers toward the arousal of distress [3].

A distressed condition is certainly generated by a set of factors all contributing to the unbalance of the physiological cardiovascular system control. In order to investigate this complex mechanism, methods based on signal processing could provide interesting and reliable tools. In particular, studies on heart rate (HR) demonstrated that indices extracted from time and frequency domain analyses could quantify the emergence of different pathological conditions in adult subjects [4].

In this paper we propose a multi-parametric approach to the analysis of HR obtained from ECG recordings in a population of severe premature infants in quiet and active sleep state and with alternating prone and supine position.

This novel approach combines different groups of indices from time domain, frequency domain and non-linear techniques. As a further innovation, the set of parameters is a combination of measures typical of the fetal HR [5], and the adult HR analysis [4]. The reason of this is that prematurity is a transition state from fetal to extra-uterine life and shares characteristics with both the conditions.

This approach allowed investigating several aspects of premature cardiovascular control that occur at different time scales, involve different autonomic control mechanisms and are influenced by the position and sleep state of the newborn.

II. Material and Methods

A. Population

The dataset was obtained at the Pediatrics Department of Columbia University Medical Center. 35 babies were recruited for the study, with avg. gestational age of 28.7 weeks and std. of 2 weeks, and post-menstrual age at the time of the study of 35.7 weeks and std. of 2.4 weeks. There were 19 males and 16 females in the study group.

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

Single newborn evaluation lasted for about 6 hours. For the first 3 hours, the babies were laid down in supine position. Afterwards, they were turned to prone position for the remaining 3 hours. All of them were fed before the beginning of the study and before the change to prone position. Sleep states were coded every 30 seconds by expert clinicians. Behavioural codes were assigned by direct observation each minute using a scoring system developed and validated in this laboratory [6].

Briefly, active sleep was coded whenever at least one rapid eye movement (REM) was observed during the epoch. In addition to small body movements were seen in this state.

Quiet sleep was designated when the infant was asleep without any REM. During quiet sleep the infant was relaxed; movements were limited to startles and non-nutritive sucking or jaw jerks.

Indeterminate state was coded when small body movements were observed, without REM. Codes were also assigned for wakefulness, crying and feeding. Only segments of three minutes in the same sleep state were taken into consideration.

Maristella Lucchini and Maria G. Signorini are with Dipartimento di Elettronica,Informazione e Bioingegneria (DEIB), Politecnico di Milano, Italy (908-494-0676; maristella.lucchini@mail.polimi.it).

William P. Fifer is with Department of Psychiatry, Columbia University College of Physicians & Surgeons, New York, NY 10032, USA, (e-mail: author@lamar. colostate.edu).

Rakesh Sahni is with the Department of Pediatrics, Columbia University College of Physicians & Surgeons, New York, NY 10032, USA, (e-mail: author@nrim.go.jp).

978-1-4244-7929-0/14/$26.00 ©2014 IEEE

ECG recordings were acquired at 500 Hz and a customized algorithm for peak identification was applied and the RR series were obtained, as shown in Figure 1.

A visual inspection of the series was performed in order to remove peaks due to arrhythmic beats or due to wrong identification of the automatic procedure.

B. HR analysis

Guidelines for the application of HR analysis methods on neonates are lacking: indications relative to adults are not applicable, since the average HR of neonate generally doubles adult's one and has its own characteristics. For this reason, time domain analysis included measures adapted both from adult (Standard Deviation of NN intervals SDNN, Standard Deviation of the Average NN interval SDANN, HRV triangular index HRVTI, Root Mean of Successive Differences RMSSD [4]) and fetal HR analysis (Long Term Variability LTV, Short Term Variability STV, Interval Index II, Differential Index DI and Long Term Irregularity LTI [5]).

Due to the relevance of LTI in the results obtained a brief explanation of the method will be given: fetal heart action understanding could be greatly ameliorated by second order interval distribution, which can be obtained by two-dimensional plotting of consecutive intervals against one another. If consecutive intervals are identical, all the points defined by (RR_{i-1}, RR_i) are found near a regression line through the origin with an angle with the abscissa of 45° degrees. This angle is called the argument and the distance from the origin to the point defined by (RR_{i-1}, RR_i) is called the modulus. The modulus is altered if consecutive intervals are almost equal but the interval length varies during the course of time. LTI is expressed as the interquartile range of this modulus.

All time domain parameters were evaluated on 3 minutes segments, allowing a maximum of 5 artefacts.

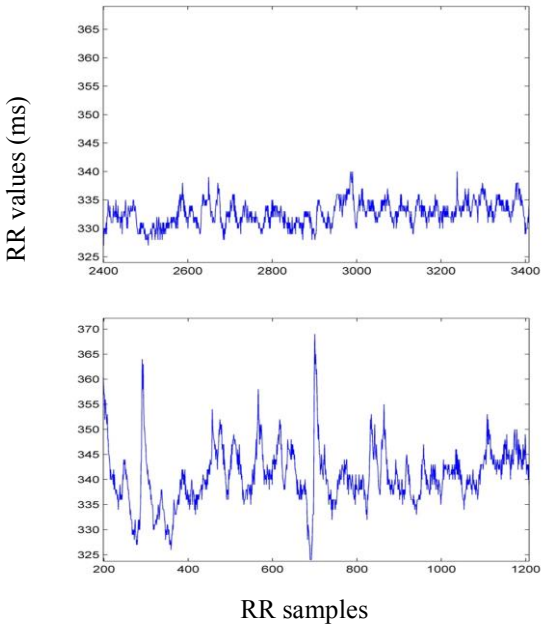

Figure 1: RR series. Above is presented a signal taken from a baby in prone position, while underneath a signal from a baby in supine position. A difference can be noted in terms of variability.

Frequency domain analysis was implemented with a non-parametric approach, chosen for its simplicity and computational velocity. Particularly, the Welch method was implemented every 3 minutes of RR series, resampled at 10 Hz. The frequency bands chosen are Low Frequency (LF), 0.05-0.2, Hz and High Frequency (HF), 0.5-1.5 Hz [7].

For what regards non-linear methods, two measures of Entropy and PRSA were employed. Approximate Entropy (ApEn) quantifies the regularity, intended as the presence of repetitive patterns in a temporal series at different lags [8]. One of ApEn limits is that it strongly depends on the length of temporal series analyzed, which needs to include a large number of samples (>1000).

To address some ApEn limits, Sample Entropy (SampEn) was proposed: it reduces the bias given by the length of the signal and enhances the estimate consistence [9]. Both methods were evaluated on 3 minutes epochs, the same lent of the frequency and time domain analysis, but also on 1500 samples epochs. This is due to the fact that in epochs of 3 minutes usually about 500 samples are present and this might be too small for good entropy estimate.

Only patients with at least 3 segments of the required length in the same sleep state and position were considered, otherwise patients were disregarded for the specific analysis.

Lastly, PRSA consists in an algorithm capable of synchronizing the phases of quasi-periodic components of noisy and non-stationary signals, based on their temporal scale [10]. It is a powerful tool to analyze accelerations and decelerations of HR. This peculiarity allows investigating separately the influence of sympathetic and parasympathetic systems.

To compute a PRSA curve a time series i=1,…,N is required. The first step is the identification of the so-called Anchor Points (AP), which are fiducial points, selected according to the equation (1), within a time window of length $2T$:

$$\frac{1}{T}\sum_{j=0}^{T-1} x_{i+j} > \frac{1}{T}\sum_{j=1}^{T} x_{i-j} \quad (1)$$

Equation (1) identifies APs that detect a signal increase. A similar inequality can identify decreases by substituting the > symbol with the < symbol. Generally, around half of the time series will be identified as an AP. The T parameter can be used to control the upper frequency of the periodicities that are detected by PRSA. In our analyses, T values from T= 3 to T=60, step 3, were tested.

Windows of $2L$ samples are built around each AP. The parameter L should be larger than the period of slowest oscillation that one wants to detect, in this case L=150.

2L windows were synchronized in their APs and averaged, in order to obtain a single PRSA curve per patient. The averaging process filters out all non-periodic components that are not synchronized, preserving events with a fixed phase relationship with the APs only.

Once obtained the PRSA curve, it is useful to summarize the information with parameters, which describe the dynamic characteristics of the curve [12]. We computed the distance between the maximum point both on the x and y axis (Δx and Δy). Moreover the slope of the central curve was calculated. These parameters are illustrated in Figure 2.

C. Statistics analysis

Firstly, a Gaussian Test was performed on the populations to verify that they were normally distributed. Secondly two different paired T-test to differentiate supine vs. prone position and active vs. quiet sleep were performed. In the case of a paired T-test, each value in one population has a natural partner in the other one. In particular, the comparison was implemented between the mean of the differences of the dependent samples, which were expected to be different.

III. Results

Depending on the segment length necessary for each method, in active and quiet sleep comparison 20 to 15 subjects were available for the T-test among neonates in supine position and 26 to 18 subjects among neonates in prone position. On the other hand, in prone and supine comparison, 33 to 29 subjects had enough continuous signal for the analysis when in active sleep and 19 to 10 for quiet Sleep. This situation has a physiological explanation, since premature babies tend to spend most of their sleep in active sleep.

Results of the most significant parameters are presented in Table 1, in terms of mean and standard deviation, and relative p-value obtained with the paired T-test.

All the methods were able to detect clear differences between the two sleep states. Particularly, Time Domain measures, ApEn and SampEn and PRSA gave the lowest p-values ($<10^{-5}$), as shown in Table 1. Moreover, ApEn e SampEn performed better with the 1500 samples approach. All PRSA parameters were effective both in the deceleration and acceleration approach and with a wide range of T. Frequency domain parameters showed a lower discriminatory capability, giving higher p-values (0.5-0.001).

SDNN, SDANN, STV, II and LTI parameters from Time Domain analysis were effective in separating the population in prone and supine position, only when the babies were in active sleep, as shown in Table 1, A and B. In quiet sleep babies were too few to obtain reliable results.

ApEn and SampEn calculated with 1500 samples approach provided good p-values, even in this case when babies were in Active sleep. Moreover these parameters were most performant when m was equal to 3, rather than 2 or 1.

In this case, only the Δy PRSA parameter was capable of finding differences between the two positions, with the deceleration approach and with T ranging from 36 to 60 samples. In Table 1 C the values for T=60 are presented.

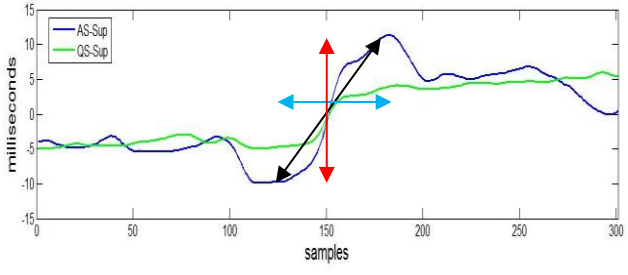

Figure 2: PRSA curve in blue for a baby in Active Sleep (AS) and in green for a baby in Quiet Sleep (QS) both is Supine (Sup) position. The black arrow indicates the slope parameter, the light blue one the Δx and the red the Δy.

It's interesting to notice that the values of the parameters in the different conditions, for the entire population may overlap. Nevertheless, in each baby there was a consistent difference between the parameters on prone and supine position and in active and quiet sleep.

IV. Discussion

Time domain analysis has adopted parameters normally applied on adults and others on fetuses. This innovative choice proved to be very efficient, since both categories gave good p-values in all the experimental conditions. Separation of prone and supine position is not straightforward. Nevertheless, four parameters (SDNN, STV, II, LTI) distinguished between prone and supine position. Most significant values for the classification were provided by fetal HR parameters, such as LTI which gave brilliant results.

In addition, parameters like LTI evaluating long-term variability (3 minutes) were more performant in terms of p-values, than those evaluating variability on few beats. It can be thus affirmed that this temporal scale (3 minutes, on average 500 beats) probably allows the observation of physiological variations typical of neonatal state.

Frequency domain parameters were obtained with non-parametric methods. In the comparison between supine and prone position, small differences were detected in the HF (p-value=0.02). This might be due to neonatal irregular breathing. As a matter of fact, almost none of the spectra showed the presence a clear peak in the HF band. For this reason, further work should be done in order to deepen the study of these mechanisms, combining the analysis of the respiratory frequency. Nonetheless, it is also crucial to observe that interpolation and resampling of the signal, may affect the estimation of spectral band contributions.

After the traditional techniques described, Entropy measures were implemented in order to study the system

Table 1

A) LTI	PRONE	SUPINE	P-val
Quiet	0.0188±0.008	0.0203±0.0036	0.572
Active	0.0400±0.018	<0.001	<0.001
P-val	<0.001	<0.001	

B) SDNN	PRONE	SUPINE	P-val
Quiet	0.0214±0.005	0.0132±0.006	0.512
Active	0.0212±0.008	0.0237±0.009	<0.05
P-val	<0.001	<0.001	

C) PRSA Dec ΔY	PRONE	SUPINE	P-val
Quiet	6.414±4.019	8.995±9.577	0.151
Active	15.66±10.18	18.71±10.68	<0.01
P-val	<0.001	<0.001	

D) SampEn 1500	PRONE	SUPINE	P-val
Quiet	0.881±0.352	0.878±0.370	0.938
Active	0.554±0.183	0.443±0.133	<0.001
P-val	<0.001	<0.001	

with a multi-parametric approach, capable of extracting information relative to possible non-linear contributions and complexity features.

Between the two approaches used to calculate ApEn and SampEn, 1500 samples provided better results, confirming what expected from the literature. In fact, these measures require signals at least 1000 samples long, to guarantee their stability.

Moreover, it can be affirmed that SampEn proved to be a robust parameter when changing the length of the pattern, which is the parameter *m* used in the algorithms for estimator implementation.

Lastly, PRSA is an interesting method since its nature is to focus on periodicities related to the increase or decrease of the signal, in this case due to the sympatho-vagal balance. Best results were obtained with the decreasing approach in the RR series, meaning an increase in HR, usually due to the action of the sympathetic system.

During the analysis it was noted that Entropy measures were showing dissimilar results from the LTI and PRSA parameters, for examples Entropy values were always higher in prone position rather than in supine, while for PRSA and LTI a higher variability was detected in Supine position, as highlighted in Figure 3. This behavior confirms what already found in adults subjects [12].

This point requires a deeper investigation, but a hypothesis is the different temporal scale investigated, which is in the beat-to-beat scale for entropy measures and in the range of 1-3 minutes for PRSA and LTI. Our results show that by combining powerfulness of different indices in classifying HRV signal we can describe more completely the complex regulation mechanisms involved.

Regarding the design choices of this study, it is important to recall that premature babies compose the population. Unfortunately, precise guidelines for HR signal analysis still wait for an international consensus on the processing procedures.

Therefore, important choices such as thresholds in the preprocessing or length of the segments considered were decided adapting values from study on adults or on fetuses, or referring to other reliable studies with similar populations.

Further development of this study has to consider all these aspects in the HRV analysis.. An enlargement of the population could reinforce the clinical reliability of the results. Future development will include the analysis of other signals, such as respiration and oxygen saturation, already available in the Columbia hospital database.

V. Conclusion

This paper proposes a novel multi-parametric approach to investigate HRV control in premature babies during different sleep states and in prone and supine position.

Parameters both from adult and fetal HRV analysis, both contribute to provide an extensive classification of the states of the baby. Parameters proved to be so performant due to the fact that they are capable of measuring different physiological mechanisms underlying cardiovascular control.

Since cardiovascular control is involved in many pathologies, these results seem to be promising for the development of a more effective and personalized diagnostic process.

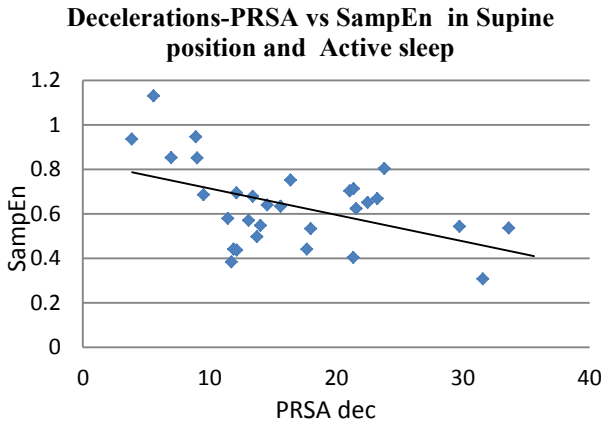

Figure 3: Graph of the relationship between Δy PRSA parameters with deceleration approach and T=60 and SampEn with 1500 samples approach and m=3. It is visible a negative correlation, with a Pearson coefficient of 0.48

References

[1] AAP Task Force on Infant Positioning and SIDS, "Positioning and SIDS," *Pediatrics*, vol. 89(6), pp. 1120-1126, 1992

[2] V. L. Schechtman, R. M. Harper, A.J. Wilson, D.P. Southall, "Sleep State organization in normal infants and victims of the Sudden Infant Death Syndrome," *Pediatrics*, vol. 89 (5), pp.865-879, May 1992

[3] R.S.C. Horne, N.B. Witcombe, S. R. Yiallourou, S. Scaillet, G. Thiriez, P. Franco, "Cardiovascular control during sleep in infants: Implications for Sudden Infant Death Syndrome," *Sleep Medicine,* vol. 11(7), pp. 615-621, August 2010

[4] M. Malik, J. Bigger, J. Camm,, "Heart rate variability: standards of measurement, physiological interpretations and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," *Circulation*, vol. 93(5), pp. 1043-1065,1996

[5] M. G.Signorini, G.Magenes, S. Cerutti, D. Arduini, "Linear and nonlinear parameters for the analysis of fetal heart rate signal from 124 cardiotocographic recordings*," Biomedical Engineering, IEEE Transactions*, vol. 50(3), pp. 365-374, 2003

[6] M. Stefanski, K. Schulze, D. Bateman, R. Kairam, T.A. Pedley, J. Masterson, et al. "A scoring system for states of sleep and wakefulness in term and preterm infants," *Pediatr Res*, vol. 18 (1), pp. 58–62. 1984

[7] S. Cerutti, S. Civardi, A. Bianchi, M.G. Signorini, E. Ferrazzi, G. Pardi, "Spectral analysis of antepartum heart rate variability," *Clin Phys Physiol Measure*, vol. 10 (supl. B), pp. 27-31,1989

[8] S. Pincus, "Approximate entropy as a complexity measure", *Chaos*, vol. 5(3), pp. R110-117. 1995

[9] E. L. Douglas, J. S. Richman, M. P. Grif, "Sample entropy analysis of neonatal heart rate variability", *Am J of Physiology*, vol. 283(3), pp. R789-97. 2002

[10] A. Bauer, J. W. Kantelhardt, A.Bunde, P. Barthel, R. Schneider, M. Malik, G. Schmidt "Phase-rectified signal averaging detects quasi-periodicities," *Physica A:Statistical Mechanics and its Applications,* vol. 364 (C), pp. 423-434, 2006.

[11] A. Fanelli, G. Magenes, M. Campanile, M. G. Signorini, "Quantitative assessment of fetal well-being through CTG recordings: a new parameter based on phase-rectified signal average," *IEEE Journal of Biomedical and Health Informatics* ,vol. 17(5), pp. 959 – 966, 2013

[12] F. Beckers, D. Ramaekers, A. E. Aubert, "Approximate Entropy of Heart Rate Variability: Validation of Methods and Application in Heart Failure," *Cardiovascular Engineering: An International Journal*, vol. 1(4),pp. 177-182, December 2001