Phase-Rectified Signal Averaging to Evaluate ANS Development in Premature Infants

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Abstract: Aim: Heart Rate Variability (HRV) is determined by the autonomic nervous system (ANS) and a low value of this parameter is related to neurological pathologies and infants mortality. This study aims to assess the utility and the advantages of HRV analysis by means of phase-rectified signal averaging (PRSA), a technique that obtains curves that are useful to determine the development of the ANS in preterm infants, with less obtrusive monitoring compared to electroencephalography.
Methods: For a preliminary study, 24-hour ECGs were taken in NICU at the University Hospital in Leuven, from 12 babies: 4 were term, 4 were born preterm but reached a term postmenstrual age, and 4 were preterm. Heart rate tracks of segments of 27 minutes were extracted and analyzed with the PRSA technique. The curves obtained were quantified by the slope and by an acceleration/deceleration related parameter (AC/DC). Two independent analyses on acceleration and deceleration were carried out to visualize the effects of the sympathetic and parasympathetic system separately. Moreover, the immediate response and the response after 5 seconds were taken into account.
Results and Conclusion: All the results were compared and validated with traditional HRV parameters. The results of slope and AD/DC in both types of analysis are promising in providing a simple parameter to assess neurological development deficiency in order to allow faster and preventive intervention. Further studies are needed in a larger population.

1 INTRODUCTION

In recent years, the study of heart rate variability (HRV) has gained growing importance. As a matter of fact, the cardiac rhythm is a crossroad of numerous systems of physiological control operation on different temporal scales: breathing, hormones, the autonomic nervous system (ANS), etc. The parasympathetic nervous system has the ability to decrease the heart rate, while the sympathetic one usually reacts to acute situations by increasing the rhythm. Researchers have shown that, in adults, a stable and predictable HR is usually associated with ongoing and upcoming pathologies (Rajendra et al., 2005). This fact opens up a new conception of homeostasis: in reality our body does not tend to a fixed situation but keeps its parameter in a range of fluctuation that allows it to properly respond to external stimuli (Bauer et al., 2006a).

An interesting aspect of HRV is that it can be acquired from non-invasive measurements like the electrocardiogram (ECG). Due to this fact, HRV is suitable to monitor premature babies, who are usually very sensitive and unstable, and to investigate their ANS development, which is a crucial issue in these kinds of patients. We hypothesize that babies affected by underdevelopment of the ANS, will be less capable of varying their HR in response to external and internal factors.

The specific aim of this study is to analyze recordings from term and preterm infants using the Phase-Rectified Signal Averaging (PRSA) method (Bauer et al., 2006b). This algorithm is capable of synchronizing the phase of all periodic components of a noisy, non-stationary signal with respect to their

frequencies and time scales. Moreover, it is a powerful tool to separately analyze the acceleration and deceleration of the HR, having thus the possibility to visualize the influence of the vagal and sympathetic system separately (Huhn et al., 2011). In this research, we will focus on the acceleration and deceleration of the HR, giving a qualitative description of the obtained PRSA signals and proposing parameters to evaluate the maturity of the ANS.

2 DATA AND METHODS

2.1 Data Acquisition and Preprocessing

In this research, 12 ECGs (sampling frequency f_s = 250 Hz) are analyzed: 4 signals are taken from premature babies (gestational age at birth < 37 weeks), 4 from prematurely born babies that reached a term postmenstrual age (PMA > 40 weeks) and 4 from term babies (gestational age at birth > 40 weeks), all hospitalized in the pediatric neurology department at the University Hospital in Leuven.

From 24-hour ECG recordings, a segment of 27 minutes was extracted for each patient. After that, the tracks were preprocessed in three steps: at first, the ECG segments were resampled to 1000 Hz using cubic spline interpolation to gain a better quality during the analysis, secondly they were filtered at 50 Hz to remove power line interference. In the third step, the heart beats were extracted using the Pan-Tompkins algorithm (Pan and Tompkins, 1985). Based on the time between consecutive beats, it was possible to calculate the heart rate.

2.2 Description of the PRSA Technique

The heart rate signals were processed using the PRSA technique, with the aim of compressing the signal into a shorter sequence without losing any relevant quasi-periodicities, and eliminating at the same time non-stationarities, artifacts, and noise. This technique consists of 3 simple steps outlined in Figure 1 (Bauer et al., 2006b).

At first, anchor points (AP) are chosen based on a certain property of the signal x_i. In this study, increases or decreases in the signal are taken into account, as well as averages of T values of the time series.

$$x_i > x_{i-1} \tag{1}$$

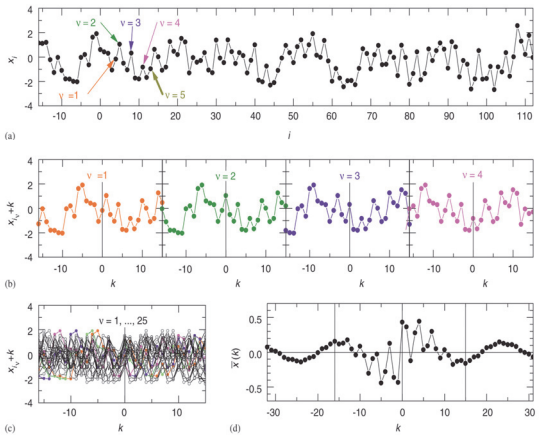


Figure 1: Illustration of the PRSA technique (Bauer et al., 2006b). (a) Anchor points are selected from the original signal x_i; here increase events are selected according to Equation 1. (b) Windows of length 2L are defined around each anchor point, here are shown the first four anchor points. (c) The surroundings of many anchor points (all located in the centre) are shown on top of each other. (d) The PRSA curve x_k resulting from averaging over all surroundings is shown.

$$x_i < x_{i-1} \tag{2}$$

$$\frac{1}{T}\sum_{j=0}^{T-1} x_{i+j} > \frac{1}{T}\sum_{j=1}^{T} x_{i-j} \tag{3}$$

$$\frac{1}{T}\sum_{j=0}^{T-1} x_{i+j} < \frac{1}{T}\sum_{j=1}^{T} x_{i-j} \tag{4}$$

We have applied Equations (1) and (2) to see the beat-to-beat response and (3) and (4) to visualize the 5 seconds (on average 14 beats) response.

Typically half of all points of the signal will be APs by these definitions. The parameter T sets an upper frequency limit for the detection of periodicities, because taking a mean over T samples is equal to applying a low-pass filter. The capability of resetting of this method comes from the fact that when we fix the AP in the increasing (decreasing) point, they will be in the phase of the steepest ascent (decent), which means when the phase of the oscillation is close to 0 (π). Thanks to this process we can extract the phase information of the oscillations from the signal itself (Bauer et al., 2006b). Heart rate accelerations and decelerations of more than 25% are excluded to suppress errors due to artifacts.

Afterwards, windows of length 2L, in this case L=100 samples, are defined around each AP. APs where no full surroundings of this length are available are excluded from the analysis. Since most of the APs are closer than 2L, most of the windows will overlap. It is important to make a proper choice for the parameter L; it should be larger than the period of the slowest oscillation that one wants to detect.

Lastly, the windows are aligned at the AP and the PRSA curve x_k is obtained by averaging the aligned windows. Thanks to this average, components that are not phase synchronized with the AP, will have zero mean and thus they will cancel out; instead, the events that have a fixed phase relationship with the AP in all the 2L windows will have the same pattern and thus will be kept in the average.

From each signal, the average was subtracted to highlight the variation around the mean and to facilitate the comparison between signals with different means.

2.3 Measures for the Quantification of PRSA Curves

For each HR signal, 4 PRSA curves x_k were calculated using Equations (1) to (4), with T=14 for Equations (3) and (4).

In x_k the central peak retains the information of all the quasi-periodicities of the HR tracks. Depending on the criteria for the selection of the AP, the central spike will quantify the mean capacity of the ANS to accelerate or decelerate the HR.

For the curves obtained with Equations (1) and (3), the following parameters were calculated:

- AAC: the Average Acceleration Capacity is the subtraction of the average of the signal after the AP from the average of the signal before the AP (Huhn et al., 2011);
- AC: the Acceleration Capacity is defined as the change around the anchor point that corresponds to computing the AAC for just 3 points before and after the AP (Bauer et al., 2006);
- SLOPE_A: the slope of the straight line connecting the point before and after the central anchor point is derived.

The same parameters were extracted for the curves obtained using Equations (2) and (4), taking into account the deceleration (respectively ADC, DC, SLOPE_D).

2.4 Time Domain HRV Measures

To validate the results obtained with PRSA, 5 well-known HRV time domain parameters were computed (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996):

- MeanNN: mean interval between consecutive QRS complexes (called NN intervals, i.e. all intervals between adjacent QRS complexes, obtained from sinus node depolarizations);
- SDNN: standard deviation of the NN intervals, i.e. the square root of the variance. SDNN is a measure for cyclic components that are present during the recordings;
- RMSSD: the square root of the mean squared differences of successive NN intervals. This measure quantifies parasympathetic modulation;
- pNN25: the percentage of NN intervals that differ more than 25 ms with respect to the preceding NN intervals, compared to the total number of NN intervals. This is also a measure for parasympathetic activity;
- SDSD: standard deviation of the differences between successive NN intervals. SDSD presents short-term variations and is highly correlated with RMSSD and pNN25.

3 RESULTS AND DISCUSSION

3.1 PRSA Curves

Figure 2 presents the mean PRSA curves for heart rate acceleration in beat-to-beat analysis. In Figure 3, the mean PRSA curves for heart rate decelerations in 14 beats analysis are shown. Both figures clearly show how the PRSA curves of term babies have larger amplitudes for all the experiments. In addition, beat-to-beat curves of terms are more unstable and unpredictable, whereas the signals of preterms show a smoother behaviour, indicating less variation in their HR. The curves obtained from prematurely born babies that reached a term PMA show a limited capacity of variation with respect to term babies of their age.

Figures 4 and 5 and Table 1 show the values of all the parameters compared among 12 patients for 14 beats analysis and Figures 6 and 7 and Table 2 for beat-to-beat.

In both experiments, it is observable that AAC and ADC are not suited parameters to describe the curve, since the difference between the 3 populations is minimal. This can be explained by the fact that in beat-to-beat and 14 beats analyses most of the length of the 2L window contains information not directly related to the instantaneous acceleration or deceleration capability of the HR. For this specific reason, parameters, which take into account the entire length of the signal, are considered irrelevant for this type of study.

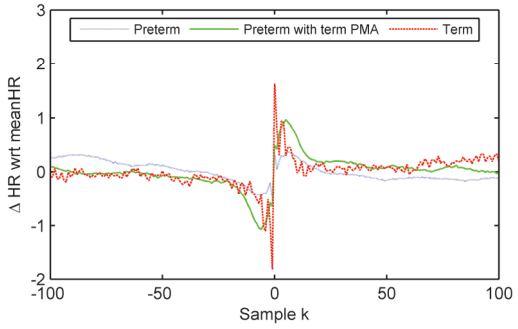


Figure 2: Mean PRSA curves for acceleration in beat-to-beat analysis. Premature infants are shown in blue, preterm with term PMA in green, term babies in red.

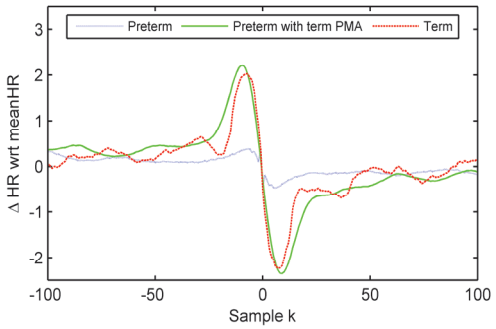


Figure 3: Mean PRSA curve for deceleration in 14 beats analysis. Premature infants are shown in blue, preterm with term PMA in green, term babies in red.

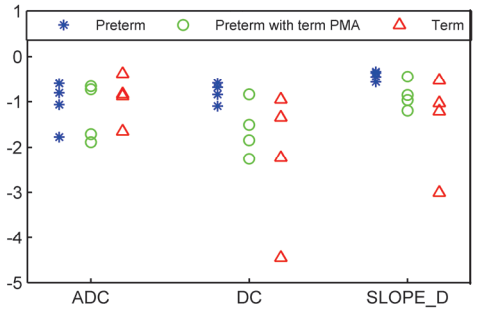


Figure 4: PRSA parameters related to deceleration for 14 beats analysis. Premature infants are shown in blue, preterm with term PMA in green, term babies in red.

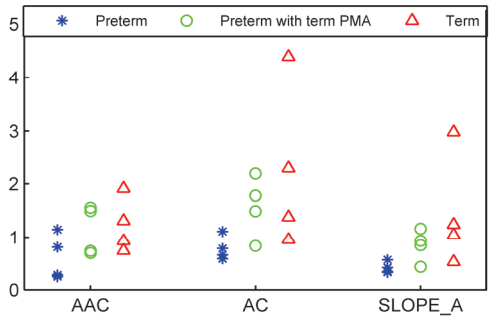


Figure 5: PRSA parameters related to acceleration for 14 beats analysis. Premature infants are shown in blue, preterm with term PMA in green, term babies in red.

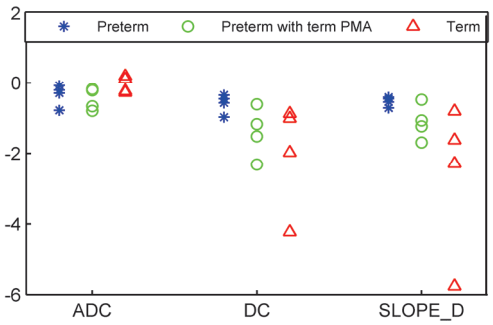


Figure 6: PRSA parameters related to deceleration for beat-to-beat analysis. Premature infants are shown in blue, preterm with term PMA in green, term babies in red.

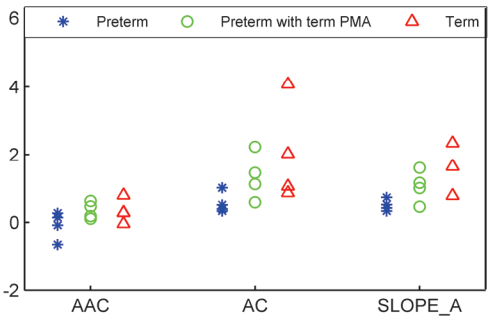


Figure 7: PRSA parameters related to acceleration for beat-to-beat analysis. Premature infants are shown in blue, preterm with term PMA in green, term babies in red.

On the contrary, SLOPE_A and SLOPE_D, and AC and DC reveal to be valuable parameters; they describe to which extent the heart is capable of increasing or decreasing its beating rate, taking this information from the central amplitude on the y-axis. At the same time, they take into account the velocity with which the heart manages to reach the required beating rate in response to external factors, weighing the time information from the x-axis.

Table 1: Mean (± standard deviation) PRSA parameters in 14 beats analysis.

14 Beats	Preterm	Preterm born with term PMA	Term
AC	0.79 ± 0.23	1.58 ± 0.57	2.26 ± 1.55
SLOPE_A	0.42 ± 0.11	0.84 ± 0.30	1.45 ± 1.07
DC	- 0.80 ± 0.22	- 1.61 ± 0.60	- 1.57 ± 2.42
SLOPE_D	- 0.26 ± 0.40	- 0.86 ± 0.32	- 1.44 ± 1.08

Table 2: Mean (± standard deviation) PRSA parameters in beat-to-beat analysis.

BTB	Preterm	Preterm born with term PMA	Term
AC	0.57 ± 0.35	1.35 ± 1.53	2.01 ± 1.47
SLOPE_A	0.50 ± 0.17	1.06 ± 0.47	2.59 ± 2.09
DC	- 0.59 ± 0.28	- 0.82 ± 0.32	- 2.02 ± 1.55
SLOPE_D	- 0.53 ± 0.14	- 1.12 ± 0.50	- 2.62 ± 2.18

Table 3: Mean (± standard deviation) time domain HRV parameters for beat-to-beat analysis.

Patients	meanNN (ms)	SDNN (ms)	RMSSD (ms)	pNN25 (%)	SDSD (ms)
Preterm	408.57 ± 48.65	19.45 ± 8.93	4.72 ± 6.42	0.39 ± 0.47	3.92 ± 6.39
Preterm born with term PMA	397.51 ± 54.33	18.54 ± 11.80	7.06 ± 2.37	0.36 ± 0.60	5.92 ± 2.51
Term babies	563.82 ± 134.92	44.55 ± 23.68	28.90 ± 25.09	19.89 ± 25.63	21.24 ± 17.96

For all the cases we analyzed, premature values, taken as absolute, were smaller than the ones from term babies. Preterm born babies with a term PMA, although they have the same PMA as the term babies, do not show similar characteristics, but behave between terms and preterms.

This fact is consistent with our primary hypothesis: lower values for these parameters indicate a reduced capability to respond to stimuli properly and in time, showing how a premature nervous system is less efficient and more at risk.

3.2 Comparison with Time Domain HRV Parameters

In Table 3, the mean time domain HRV parameters for each group of babies, are listed.

The heart rate of prematurely born babies is higher than the one of control subjects. It is also possible to see that the SDNN of preterms is lower than for the term babies. This is an indication of a more fixed heart rate, meaning that premature babies react slower to acute situations than the normal subjects. Another important observation is that RMSSD, pNN25 and SDSD, all markers for parasympathetic activity, are clearly reduced in prematurely born infants. This proves again that prematurity strongly reduces the development of the ANS. Moreover, preterm born babies with a term PMA show that the development of their ANS has not yet reached the same maturity as the term born babies. With these results, it is possible to confirm the results obtained with PRSA, where it is observed that the premature babies present a more fixed heart rate and a slower reaction to acute situations.

4 CONCLUSIONS

The aim of this investigation was to analyze the development of the ANS of full-term, prematurely born that reach term PMA and preterm babies by means of a computational analysis of HR recordings using the PRSA technique. A set of parameters

capable of describing the PRSA curves was defined.

HR was chosen as an indicative parameter of neurological development because its variability is regulated primarily by the ANS. Additionally, it can be taken from the ECG, which needs fewer electrodes than other techniques, such as electroencephalography.

The PRSA method was selected because it is proficient in condensing the signal into a shorter sequence, keeping any relevant quasi-periodicities but cancelling out all non-stationarities, artifacts, and noise. Moreover, it is a very straightforward algorithm which does not require a long preprocessing of the raw data.

In order to achieve the goals of this work, two types of PRSA investigations were developed in parallel: the first looked at the acceleration and deceleration on a beat-to-beat scale, the second one on a 14 beats scale. This separation is due to the fact that the two branches of the ANS, the sympathetic and parasympathetic have shown to have different time responses to external factors.

To quantify the difference among three groups of babies, a few parameters were implemented: AAC, ADC, SLOPE_A, SLOPE_D, AC and DC.

The last four revealed to be useful in PRSA interpretation, since they are able to interpret to which extent the heart is capable to increase or decrease its beating rhythm from one beat to the next one and how long it takes for this process to happen. This is possible thanks to an analysis that focuses on the beats just before and after the anchor point, which identifies the moment of increase/decrease of the signal. These parameters can be considered a relevant first screening method to have a rapid idea of the neurological condition of the patients, indicating where it is necessary to run further investigations.

The findings based on the PRSA technique were also compared and validated using traditional time domain HRV parameters. PRSA parameters proved to be consistent with the traditional ones, having the advantage of being less influenced by the noise or by physiologic regulatory events and thus are more robust and trustable. Additionally, the parameters proposed provide complex information in one number, taking into account the maximum range of HRV and the time required for the heart to reached the necessary HR. Moreover the possibility of varying the two parameters L and T and the criterion of choice of the AP, make this technique extremely versatile.

To conclude, the PRSA technique revealed to be an innovative and promising approach. Nonetheless it is necessary to confirm our conclusion on a larger population that will allow us to conduct statistical analysis and to define threshold values for the implemented parameters to distinct healthy and underdeveloped infants.

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