PHASE-RECTIFIED SIGNAL AVERAGING FOR THE QUANTIFICATION OF THE INFLUENCE OF PRENATAL ANXIETY ON HEART RATE VARIABILITY OF BABIES

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Abstract: The autonomic nervous system (ANS) modulates heartbeat intervals responding to inputs from its different branches, resulting in periodicities that occur on different time scales. Internal and external perturbations are continuously interrupting the periodic behavior, making the heartbeat intervals quasi-periodic. Phase-rectified signal averaging (PRSA) is a technique to detect those quasi-periodicities in noisy, non-stationary signals, like tachograms. The method compresses the tachogram in shorter curves based on internal information, and provides information on the deceleration and acceleration capacity of the heart. In this study, the PRSA technique is investigated as a novel signal processing technique for the analysis of heart rate variability (HRV) of babies. In this way, the effect of stress and anxiety during pregnancy on the ANS of the baby is analyzed. First, the PRSA curves are obtained for each baby and different measures that characterize these curves are defined. Next, these measures are linked to the anxiety level of their mothers during pregnancy. Only little influence of the anxiety level of the mother on the HRV of the baby is found.

1 INTRODUCTION

Stress and anxiety during pregnancy can lead to a less optimal development of the fetus, which can result in cognitive, emotional and behavioral problems in later life (O'Connor et al., 2003; Van den Bergh and Marcoen, 2004). Prenatal stress may also cause infants to suffer from a less mature autonomic nervous system (ANS) and an increased sensibility to stress (Van den Bergh et al., 2005). The activity of the ANS can be evaluated based on the variability of the heart rate, which is modulated by the interacting sympathetic and parasympathetic branches. To assess heart rate variability (HRV), the R peaks from the electrocardiogram (ECG) are detected and the intervals between successive peaks (RR intervals) are plotted in time, resulting in a tachogram. Based on this tachogram, several measures that quantify HRV are defined. By linking these HRV measures of the babies to the anxiety level of the mothers, the influence of prenatal anxiety on the ANS of the babies can be examined. This study is part of a larger project that aims at investigating the relation between stress and anxiety during pregnancy and the development and outcome of the baby. In a previous phase, the relation between the anxiety and the ANS of the pregnant women was analyzed (Taelman et al., 2010).

The ANS modulates the heart rate by continuously reacting to the inputs of the heart, lungs and blood vessels. These heart rate modulations due to intrinsic regulation processes occur on different time scales, which can be evaluated with phase-rectified signal averaging (PRSA). PRSA is a technique that detects quasi-periodicities in non-stationary signals, like the tachogram (Bauer et al., 2006b). It compresses the tachogram into a shorter sequence, keeping all relevant quasi-periodicities but eliminating non-stationarities, artifacts and noise. The resulting

PRSA curve characterizes the deceleration and acceleration capacity of the heart.

This paper focuses on the relevance of PRSA as a technique to measure heart rate variability. However, as other measures, defined in both the time and frequency domain, are generally used to quantify HRV (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996), we will briefly compare the most commonly used time domain HRV measures with the PRSA technique as well.

2 DATA

The data for this study have been measured at Tilburg University as a part of the EuroSTRESS project that investigates the influence of stress and anxiety during pregnancy on the cardiorespiratory system of the women and on the development of the baby. The State Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) is used as a psychological measure to quantify the anxiety during the first trimester of the pregnancy. Based on the STAI score, subjects belong to a low (STAI $\leq$ 28), moderate (28 $<$ STAI $<$ 40) or high (STAI $\geq$ 40) anxiety group. To assess the development of the baby, the electrocardiogram and electroencephalogram of the baby have been recorded at two ages. During the acquisition, an auditory oddball paradigm was presented. This paradigm consists of five series of stimuli, in which a frequent stimulus (1000 Hz tone) was randomly alternated with three different deviant stimuli. The sampling frequency is 512 Hz; an ECG signal during one stimulus sequence has a length of about 150 s. 76 babies of 2 to 4 months old are included in the study.

3 METHODS

The basic principle of the PRSA technique consists in defining anchor points, selecting windows around these anchor points, aligning the windows, and averaging over all surroundings. Next, measures are chosen to describe the resulting PRSA curves. In order to interpret the PRSA measures, some traditional HRV measures are calculated to make the comparison. The results are statistically evaluated using the Spearman's correlation coefficient and the Wilcoxon rank sum test.

3.1 Description of the PRSA Technique

Figure 1 outlines the basic steps of the PRSA technique, starting from the tachogram (Kantelhardt et al., 2007). In the first step, anchor points are selected according to a certain property in the tachogram x_i. Possible selection criteria are based on an increase and decrease of a sample with respect to the previous sample. The general definition of anchor points that is used in this study, compares averages of a period of T values of the tachogram:

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

or

$$\frac{1}{T}\sum_{j=0}^{T-1} x_{i+j} < \frac{1}{T}\sum_{j=1}^{T} x_{i-j} \tag{2}$$

The parameter T sets an upper frequency limit for the periodicities that can be detected and functions as a low pass filter. For $T = 1$, no filter is applied; all increases or decreases in the signal are selected as anchor points. In Figure 1, all increase events are defined as anchor points, according to Equation (1) with $T = 1$.

In the second step, windows (surroundings) of length $2L$ are defined around each anchor point. The parameter L should exceed the period of the slowest oscillation that is of interest.

Finally, the surroundings of all anchor points are aligned to each other and the PRSA curve $\bar{x}_k$ is obtained by averaging over all windows. With this averaging procedure, non-periodic components that are not in phase with the anchor points are cancelled out, leaving only periodicities and quasi-periodicities that have a fixed phase relationship with the anchor points. In this work, the symbols $PRSA_{\nearrow}$ and $PRSA_{\searrow}$ are used to indicate PRSA curves based on increases or decreases in the tachogram.

The center of the PRSA curve $\bar{x}_0$ is the average of the tachogram at all anchor points. The measures defined to quantify the curve, use this central point as reference. Therefore, a recalibration step shifts the curve such that the amplitude of $\bar{x}_0$ equals 0 ms.

3.2 Measures for Quantification of the PRSA Curve

In $\bar{x}_k$ all periodicities are superposed; the central peak of the PRSA curve contains the contributions from all the (quasi-)periodicities of the original tachogram. The deflection at the center of the PRSA curve depends on the definition of anchor points. For Equation (1), the central spike quantifies the average capacity

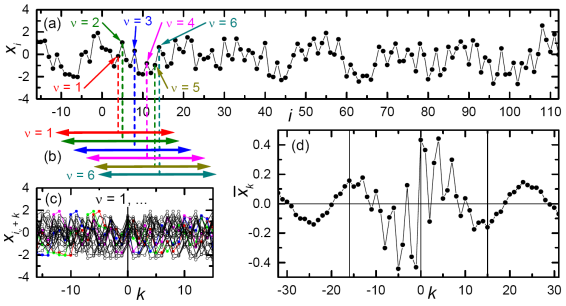


Figure 1: Illustration of the PRSA technique (Kantelhardt et al., 2007). (a) Anchor points are selected, based on increases in the tachogram; (b) windows are defined around each anchor points; (c) all anchor points are moved on top of each other, resulting in the alignment of all windows; (d) the phase-rectified signal average $\bar{x}_k$ is obtained by averaging over all windows.

of the ANS to decelerate the heartbeat (deceleration capacity DC). DC [ms] is calculated from four points around the center of $PRSA_{\nearrow}$, as shown in Figure 2 and Equation (3), and proved its use as a better predictor of mortality after myocardial infarction than other traditional HRV measures (Bauer et al., 2006a):

$$DC = |\bar{x}_0 + \bar{x}_1 - \bar{x}_{-1} - \bar{x}_{-2}|/4 \qquad (3)$$

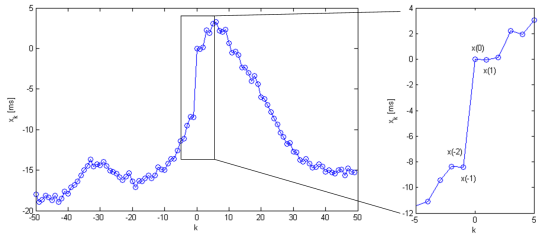


Figure 2: Illustration of the calculation of measure DC for $PRSA_{\nearrow}$ and $T = 1$ for the tachogram of a random baby of 2 months old.

For the definition described in Equation (2), the acceleration capacity (AC) is used to quantify the central deflection of $PRSA_{\searrow}$.

Observation of the PRSA curves showed that the curves of different babies not only differ from each other in values for DC and AC. Also the amplitude, oscillations and morphology for the whole curve vary between different subjects. In this study, additional measures are selected to describe the PRSA curve as precisely as possible. In this way, differences in curves between babies can be quantified and analyzed to examine the link with the STAI score of the mothers.

- Peak-to-peak: distance [samples] and difference in amplitude [ms] between the first peak before and the first peak after the center of the curve;
- Area-Under-Curve (AUC) [ms^2]: area under the PRSA curve $\bar{x}_k$ in the predefined intervals $k = [-20:0]$ and $k = [0:20]$;
- Skewness [-]: measure for the lack of symmetry of the distribution of the whole PRSA curve. Zero skewness indicates a symmetry around the mean. Positive or negative skewness indicates a right or left tail, respectively.
- Excess kurtosis [-]: measure for the 'peakedness' of the distribution of the whole PRSA curve. Negative values indicate flatness, while positive values indicate a more peaked distribution.

3.3 Time Domain Measures of HRV

In addition to the analysis of the PRSA curves, some traditional time domain measures for HRV are computed (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996):

- SDNN [ms]: standard deviation of the RR intervals. This measure indicates which cyclic components are present during the recordings;
- RMSSD [ms]: root mean square of successive RR differences. RMSSD is a measure of parasympathetic modulation;
- pNN25 [%]: the percentage of RR interval differences that are greater than 25 ms. Like RMSSD, pNN25 quantifies parasympathetic activity.

3.4 Statistical Analysis

The correlations between the STAI score of the mothers and the PRSA and HRV measures for all infants, are calculated using Spearman's correlation coefficient. This method aims at detecting a monotonic relation between two distributions. In order to interpret and compare the defined PRSA measures, the correlation between the PRSA measures and the time domain HRV measures are computed as well. The Wilcoxon rank sum test is used to compare the high anxiety group and the low anxiety group. It is a non-parametric test to check whether two data sets are coming from the same distribution. The significance level for rejecting the null hypothesis is $p = 0.05$.

4 RESULTS AND DISCUSSION

Four PRSA curves are obtained for each tachogram for surroundings of length $2L = 100$ samples, based on the four definitions used in this study: anchor

Table 1: Mean ± standard deviation of kurtosis for all PRSA curves, divided in three anxiety groups based on the STAI score of the mother (low, moderate and high anxiety groups). n is the number of babies in the anxiety group; ρ is the Spearman correlation coefficient and p is its corresponding p-value; p_{L-H} is the resulting p-value for the comparison between babies of low and highly anxious women.

		Low ($n=21$)	Mod. ($n=41$)	High ($n=14$)	ρ	p	p_{L-H}
$T=1$	$PRSA_{\nearrow}$	-0.50 ± 0.93	-0.23 ± 0.65	-0.16 ± 0.75	0.214	0.078	0.022
$T=1$	$PRSA_{\searrow}$	-0.76 ± 0.84	-0.40 ± 0.82	-0.47 ± 0.68	0.120	0.326	0.022
$T=10$	$PRSA_{\nearrow}$	-1.03 ± 0.28	-0.61 ± 0.51	-0.66 ± 0.33	0.268	0.026	<0.001
$T=10$	$PRSA_{\searrow}$	-0.99 ± 0.41	-0.75 ± 0.41	-0.72 ± 0.41	0.186	0.127	0.034

points linked to both increases and decreases for both $T=1$ and $T=10$. For each baby, the ECG was recorded during five stimuli sequences. The PRSA measures calculated for the five ECG signals are averaged for each baby.

As mentioned before, Figure 2 shows the PRSA curve of one baby, based on anchor points linked to all increase events in the tachogram ($T=1$). Figure 3 shows the PRSA curve for the same baby, according to $T=10$. In this way, a much smoother PRSA curve is obtained, compared to Figure 2. Also the absolute values of the amplitudes of the positive peak for $k>0$ and negative peak for $k<0$ are higher. This is because the parameter T functions as a low pass filter, only selecting anchor points by comparing series of T samples. One sudden increase in a series of decrease events will not be selected; only average increases in the tachogram will give rise to anchor points.

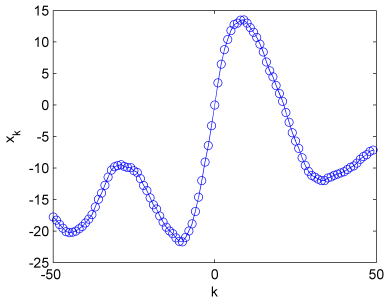


Figure 3: $PRSA_{\nearrow}$ curve ($T=1$) for the tachogram of a random baby of 2 months old.

4.1 Influence of Prenatal Anxiety on PRSA Measures of Babies

The defined PRSA measures are linked to the STAI score to assess the influence of prenatal anxiety of the pregnant women on the ANS of their babies. Significant differences between the anxiety groups are only found for the measure kurtosis for all four definitions of PRSA curves. Table 1 shows all statistically significant results. Babies with highly anxious mothers show higher kurtosis (but still negative) than babies with lowly anxious mothers. Kurtosis measures the degree of peakedness of the probability distribution of a variable. A distribution with negative kurtosis has a wider peak and is said to be flat. The lowest p-value ($p_{L-H}=9,58e^{-4}$) is found for the PRSA curve corresponding to increases in the average of 10 consecutive RR intervals ($PRSA_{\nearrow}$ and $T=10$). The corresponding boxplots are shown in Figure 4.

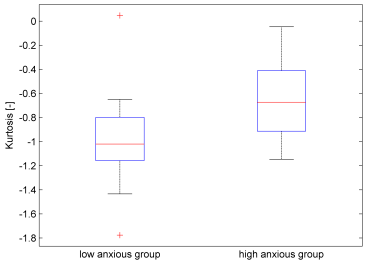


Figure 4: Boxplot for kurtosis [-] ($PRSA_{\nearrow}$ and $T=10$).

Besides this result, some remarkable but statistically not significant results are also presented. DC and AC quantify the central part of the PRSA curve around increase and decrease events respectively. A lower value for these two measures for babies of highly anxious mothers was observed for all four PRSA curves, though statistically not significant as mentioned before. Lower values indicate a reduced capacity of the ANS to quickly adjust the heartbeat.

One remark has to be made; the measure of anxiety used in this study, is based on the state anxiety in the first trimester of the pregnancy. This type of anxiety manifests itself as a transitory, emotional state. The trait anxiety on the other hand, is a relatively stable aspect of the personality. By using this form of anxiety to quantify the stress and anxiety level of the mothers instead of the state anxiety measured at one moment in time, the analysis of the effect of prenatal anxiety on the babies might improve.

4.2 Link of PRSA with Time Domain HRV Measures

In order to link the defined PRSA measures with the traditional HRV measures, the correlations between

Table 2: Spearman correlation coefficients between kurtosis of the PRSA curves and the time domain HRV measures ($* : p < 0.05, \dagger : p < 0.005, \ddagger : p < 0.001$).

		SDNN	RMSSD	pNN25
$T = 1$	$PRSA\nearrow$	-0.006	0.328 †	0.390 ‡
$T = 1$	$PRSA\searrow$	-0.068	0.371 †	0.451 ‡
$T = 10$	$PRSA\nearrow$	-0.015	0.170	0.214
$T = 10$	$PRSA\searrow$	0.097	0.279 $*$	0.342 †

PRSA and some time domain HRV measures are computed. All PRSA measures, except for skewness, show significant correlations with SDNN, RMSSD and pNN25. However, we will focus on the existing correlations of kurtosis of the PRSA curves as this measure showed to differ significantly between anxiety groups in the previous section and it is not straightforward to interpret these differences. Table 2 shows the correlation coefficients between the kurtosis of the PRSA curves and the time domain measures. Positive correlations are found between kurtosis and RMSSD and pNN25. Both of these time domain measures are linked with parasympathetic modulation, suggesting that the kurtosis of the PRSA curves might be related with the parasympathetic activity as well. However, future research must focus on the link between the defined PRSA measures and the ongoing physiological processes. Nevertheless, we want to stress that the defined PRSA measures are useful as kurtosis is able to distinguish between the effect of high and low anxiety during pregnancy on the ANS of the babies. In our study this was not possible with the traditional HRV measures.

5 CONCLUSION

Quasi-periodicities in the human heart rate reflect the different regulation processes of the ANS. The PRSA method is a suited technique for detection of quasi-periodicities in non-stationary data like the tachogram. Moreover, PRSA offers the possibility to study the deceleration and acceleration capacity of the heart, which might provide more insights into cardiac autonomic regulation processes.

The influence of the stress and anxiety of pregnant mothers, quantified by the STAI score, on the HRV is investigated by evaluating the PRSA curves. Only few significant results are found, all corresponding to the kurtosis. Although kurtosis seems to differ significantly between babies with low and highly anxious mothers, the interpretation of this measure is unclear.

The influence of the state anxiety of mothers on the HRV of babies, using the PRSA technique, is rather small. Nevertheless, PRSA is a promising signal processing tool for assessing information about the capacity of the ANS to quickly adjust its heart rate. A suggestion of further reseach has been made: by using a different psychological measure for stress and anxiety, better and more reliable results may be found.

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The scientific responsibility is assumed by its authors.

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