Coupling of Heart Rate and Systolic Blood Pressure in Hypertensive Pregnancy

A. Voss; C. Fischer; R. Schroeder
Department of Medical Engineering and Biotechnology, University of Applied Sciences Jena, Germany

1. Introduction
Hypertensive pregnancy disorders are leading causes of maternal and fetal morbidity and mortality and affect 6% to 8% of all pregnancies [1]. The 'National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy' (NHBPEP) classifies hypertension occurring during pregnancy based on the following conditions: chronic hypertension (CH), gestational hypertension (GH) and pre-eclampsia (PE) [1, 2].

During the past few decades, several studies on heart rate (HR) and blood pressure (BP) variability have shown that non-linear methods provide additional diagnostic and prognostic information, representing a useful complement to traditional time- and frequency domain analyses [3].

One of these methods, the Segmented Poincaré plot Analysis (SPPA), was first introduced by Voss et al. [4]. This method overcomes several limitations of PPA, i.e. the high correlation between PPA indices and linear parameters [5] and captures the nonlinear characteristics of a time series.

The successful prediction of the presence of hypertensive pregnancy disorders has already been proven by Voss et al. [6] by applying the bivariate Joint Symbolic Dynamics (JSD) method [7]. Analyzing interactions of HR and BP, he showed that the cardiovascular regulatory system changed considerably, depending on the type of hypertensive disorder. These analyses led to a significant differentiation between chronic or GH and PE.

The aim of this study has been to investigate the autonomic regulation by analyzing the interaction between HR and systolic blood pressure (SBP) by applying a novel method of nonlinear coupling analysis: the bivariate SPPA (BSPPA). It is assumed that SPPA permits an improved assessment of cardiovascular interaction which provides new insights into the role of autonomic regulation and improves the prediction accuracy of hypertensive pregnancy disorders.

2. Methods
2.1 Patients
The classification of hypertensive disorders was performed according to the NHBPEP [1].

For this study, we enrolled 35 pregnant women with hypertensive disorder from the Department of Obstetrics at the University Hospital Leipzig. All women had a...
comparable HR and SBP, measured by matching the mean beat-to-beat intervals (BBI) and their mean SBP. Nine of them suffered from CH (mean age = 31.2 ± 5.5 years, range: 21–28 years), 9 from GH (mean age = 28.7 ± 4.6 years, range: 19–34 years) and 17 developed a PE during pregnancy (mean age = 26.8 ± 6.2 years, range: 19–38 years).

The investigation conforms to the principles outlined in the Declaration of Helsinki. Approval from local ethics committee and the informed consent of all subjects were obtained before participation in this study.

### 2.2 Signal Acquisition and Preparation

Thirty minutes of continuous blood pressure (NIBP, fs = 200 Hz, resolution = 0.1 mmHg) was recorded in supine position during the late morning hours at University Hospital Leipzig. NIBP was measured on the left middle finger applying the noninvasive Portapres M2 blood pressure monitor (TNO-TPD, Amsterdam, Netherlands [8]).

The time series of beat-to-beat intervals (BBI) and systolic blood pressure amplitudes (SBP) were extracted using the ‘Beat-Fast’ pattern recognition software package (TNO Biomedical Instrumentation, The Netherlands). Ectopic beats and other disturbances or artifacts were detected and replaced by interpolated “normal” heartbeats using an adaptive variance estimation algorithm [9].

### 2.3 Bivariate Segmented Poincaré plot analysis (BSPPA)

The SPPA method is an enhanced pseudo phase space quantification method based on the traditional Poincaré plot analysis (PPA) by Babloyantz et al. [10] who first applied PPA for heart rate variability (HRV) analysis. To analyze couplings between two different time series, the SPPA method was adopted by determining phase-space (BSPPA) instead of pseudophase-space. Therefore, interactions between BBI and its temporal enclosed SBP time series were investigated.

BSPPA can be computed as follows:

1) The traditional PPA (Fig. 1(a)) was performed by calculating standard deviations of SBP (SD1) and BBI (SD2) time series by Equations 1 and 2:

\[
SD1 = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (SBP_i - \overline{SBP})^2}
\]

\[
SD2 = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (BBI_i - \overline{BBI})^2}
\]

2) A grid of 12 × 12 rectangles is drawn into the plot based on the mean value of BBI and SBP, respectively. The size of each rectangle (height, width) is adapted to SD1 and SD2 (Figure 1b).

![Figure 1 BSPPA procedure: a) traditional PPA calculating SD1 and SD2; b) segmentation of the plot and calculation of row(i) and column(j) percentages as well as row(i)_left/right and column(j)_bottom/top percentages](image)
Table 1  BSPPA – Most significant results of the group Tests I–III including median [%] and interquartile range (lower quartile (0.25) – upper quartile (0.75)); SENS [%] – sensitivity, SPEC [%] – specificity, AUC [%] – area under ROC curve, Mann-Whitney U-test: ** – highly significant (p < 0.01), * – significant (0.01 ≤ p ≤ 0.05); a – from KS-test; marked indices present the best results for multivariate ROC.

<table>
<thead>
<tr>
<th>Index</th>
<th>Median (lower quartile – upper quartile)</th>
<th>SENS</th>
<th>SPEC</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>row9_right</strong></td>
<td>0.05 (0.00–0.38)</td>
<td>0.47 (0.12–0.85)</td>
<td>94.1</td>
<td>50</td>
</tr>
<tr>
<td><strong>row2</strong></td>
<td>0.05 (0.00–0.09)</td>
<td>0.00 (0.00–0.00)</td>
<td>88.2</td>
<td>66.7</td>
</tr>
<tr>
<td><strong>row3_left</strong></td>
<td>0.21 (0.06–0.32)</td>
<td>0.00 (0.00–0.17)</td>
<td>82.4</td>
<td>55.6</td>
</tr>
<tr>
<td><strong>row5_left</strong></td>
<td>5.61 (4.59–6.61)</td>
<td>6.61 (5.92–8.47)</td>
<td>88.2</td>
<td>55.6</td>
</tr>
<tr>
<td><strong>row3</strong></td>
<td>0.46 (0.10–1.10)</td>
<td>0.10 (0.00–0.33)</td>
<td>94.1</td>
<td>55.6</td>
</tr>
<tr>
<td><strong>row4</strong></td>
<td>3.47 (2.06–4.02)</td>
<td>2.50 (1.43–3.18)</td>
<td>88.2</td>
<td>50</td>
</tr>
<tr>
<td><strong>row5</strong></td>
<td>11.31 (9.73–12.96)</td>
<td>13.91 (12.22–14.72)</td>
<td>64.7</td>
<td>83.3</td>
</tr>
<tr>
<td><strong>row6</strong></td>
<td>28.47 (25.30–33.11)</td>
<td>32.41 (29.77–34.47)</td>
<td>76.5</td>
<td>66.7</td>
</tr>
<tr>
<td><strong>row7</strong></td>
<td>42.51 (34.39–45.14)</td>
<td>35.88 (31.01–39.84)</td>
<td>94.1</td>
<td>55.6</td>
</tr>
<tr>
<td><strong>row9</strong></td>
<td>0.33 (0.00–1.08)</td>
<td>0.91 (0.41–1.91)</td>
<td>100</td>
<td>33.3</td>
</tr>
</tbody>
</table>

Test II: chronic hypertension vs. pre-eclampsia

<table>
<thead>
<tr>
<th>Index</th>
<th>Median (lower quartile – upper quartile)</th>
<th>SENS</th>
<th>SPEC</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>row5_left</strong></td>
<td>5.30 (4.51–6.18)</td>
<td>6.61 (5.92–8.47)</td>
<td>52.9</td>
<td>100</td>
</tr>
<tr>
<td><strong>row5</strong></td>
<td>11.27 (9.10–12.69)</td>
<td>2.50 (1.43–3.18)</td>
<td>88.2</td>
<td>66.7</td>
</tr>
<tr>
<td><strong>row3_left</strong></td>
<td>0.25 (0.11–0.54)</td>
<td>0.00 (0.00–0.17)</td>
<td>82.4</td>
<td>77.8</td>
</tr>
<tr>
<td><strong>row9_right</strong></td>
<td>0.03 (0.00–0.31)</td>
<td>0.47 (0.12–0.85)</td>
<td>94.1</td>
<td>66.7</td>
</tr>
<tr>
<td><strong>row3</strong></td>
<td>0.75 (0.17–1.27)</td>
<td>0.10 (0.00–0.33)</td>
<td>100</td>
<td>55.6</td>
</tr>
</tbody>
</table>

Test III: gestational hypertension vs. pre-eclampsia

<table>
<thead>
<tr>
<th>Index</th>
<th>Median (lower quartile – upper quartile)</th>
<th>SENS</th>
<th>SPEC</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>row2_right</strong></td>
<td>0.03 (0.00–0.06)</td>
<td>0.00 (0.00–0.00)</td>
<td>94.1</td>
<td>55.6</td>
</tr>
<tr>
<td><strong>row7_right</strong></td>
<td>22.54 (17.40–24.74)</td>
<td>18.21 (15.55–21.57)</td>
<td>100</td>
<td>44.4</td>
</tr>
<tr>
<td><strong>column6_top</strong></td>
<td>14.07 (10.91–17.97)</td>
<td>17.63 (15.14–20.39)</td>
<td>76.5</td>
<td>77.8</td>
</tr>
<tr>
<td><strong>row2</strong></td>
<td>0.03 (0.00–0.10)</td>
<td>0.00 (0.00–0.00)</td>
<td>88.2</td>
<td>66.7</td>
</tr>
<tr>
<td><strong>row6</strong></td>
<td>28.33 (22.85–31.66)</td>
<td>32.41 (29.77–34.47)</td>
<td>76.5</td>
<td>77.8</td>
</tr>
<tr>
<td><strong>row7</strong></td>
<td>42.46 (36.07–46.21)</td>
<td>35.88 (31.01–39.84)</td>
<td>88.2</td>
<td>66.7</td>
</tr>
</tbody>
</table>

3) The number of points within each rectangle (Mij), related to the total number of points (N), was counted to obtain the single percentages (percentage of occurrence p(ij)). Based on these single percentages, all row(i) and column(j) (►Eqs. 3 and 4) percentages were calculated by summation of the related single percentages to get the BSPPA values. Additionally, a novel segmentation algorithm was performed to calculate further BSPPA values summing up single percentages on the left (i = 1 – 6) or the right (j = 7 – 12) part of the plot regarding the rows as well as on the top (i = 1 – 6) or bottom (i = 7 – 12) of the plot regarding the columns (►Eqs. 5 and 6). Therefore, the low-moderate BBI (row(i)_left), the moderate-high BBI (row(i)_right), the low-moderate SBP (column(j)_bottom) and the moderate-high SBP (column(j)_top) are calculated (►Figure 1b):

\[ row(i) = \sum_{j=1}^{12} p_{ij} \]  
\[ column(j) = \sum_{i=1}^{12} p_{ij} \]  
\[ row(i)_left(right) = \sum_{j=11}^{12} p_{ij} \]  
\[ column(j)_top(bottom) = \sum_{i=1}^{6} p_{ij} \]

2.4 Statistics

The nonparametric Mann-Whitney U test (SPSS Statistics 17) was used to measure the statistical difference in BSPPA indices between the two patient groups. Two levels of significance were considered prior to the presentation of the results: significant indices (0.01 ≤ p < 0.05) and highly significant indices (p < 0.01). A precondition for the MW-test is a similar distribution shape in both groups tested by Kolmogorov-Smirnov test (KS-test, p < 0.05). For BSPPA indices with significant different shapes of distributions the p-value of the KS-test is provided.

The following group tests were performed:

- Test I: chronic and gestational hypertension vs. pre-eclampsia
- Test II: chronic hypertension vs. pre-eclampsia
- Test III: gestational hypertension vs. pre-eclampsia

The Receiver Operating Characteristic (ROC) curves together with estimations for the area under the ROC curve (AUC) were computed for each single index (univariate) as well as for index sets consisting of two indices (multivariate). Therefore, a discriminant analysis with two indices was performed first yielding a discriminant function which served as a starting basis for the ROC analysis. The sensitivity (SENS) and specificity (SPEC) were estimated from the nearest point to 1 on the horizontal axis of each ROC.

3. Results

Group tests (Test I–III) were performed to investigate cardiovascular couplings of BBI time series and SBP differentiating between various hypertensive pregnancy disorders, especially for those women who developed a PE.

Several indices revealed significances, whereby the most important ones are summarized in ►Table 1. Highly significant (p < 0.01) results could be shown for test I (row9_right), test II (row5_left and row5) and test III (row2_right).


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Figure 2 highlights those regions for each group of patients where couplings mainly occurred.

For multivariate risk stratification all uncorrelated (Pearson’s correlation coefficient < 0.4) significant BSPPA indices were applied. The ROC curves were calculated for every set of indices to determine the optimal set of indices characterized by the highest AUC value for each group test. The following optimal sets were determined:

- Test I: row3_left and row4; AUC = 78.4%; SENS = 100%; SPEC = 66.7%
- Test II: row9_right and row5; AUC = 90.8%; SENS = 100%; SPEC = 77.8%
- Test III: row2_right and row7_right; AUC = 86.3%; SENS = 82.4%; SPEC = 77.8%.

4. Discussion

The aim of this study was to quantify couplings between HR and SBP for improved risk stratification in hypertensive pregnancy disorders. One major task was to discriminate autonomic cardiovascular regulation in pregnant women with PE from women with other hypertensive pregnancy disorders. We applied BSPPA, based on the recently introduced univariate SPPA, to investigate coupling between BBI and SBP time series. When evaluating these couplings, it is advisable to observe specific regions of the cloud of points as well as total row and column percentages. For this type of observation, two segmentation algorithms were introduced: a) the summation of all single percentages (1–12) of one row or column; and b) the summation of half of them (1–6 or 7–12) for a more detailed segmentation.

It was shown that the alterations of interactions between the BBI and SBP time series differ significantly in all investigated hypertensive groups. This finding might be a sign of partly different regulatory mechanisms within the separate groups. The best discrimination power of Test I, related to chronic and GH pregnancies compared to PE, was achieved in the right part of row9 related to high BBI following very low SBP. The results of Test II differentiating between CH and PE applying row5 as well as its left part (row5_left) reflected the percentage of low BBI following (very) high SBP. For the group test pertaining to GH vs. PE, the index row2_right significantly decreased in PE, indicating that the percentage of regulation patterns in which high BBI’s follow high SBP’s was found more often in GH than in the condition of PE. However, statistical results where no points were counted (e.g. row2_right) should be interpreted with caution. Therefore, we estimated alternatively for test III the set consisting of column6_top and row7 (AUC = 80.4%; SENS = 70.6%; SPEC = 77.8%) where both indices have points.

In this study, we applied BSPPA for the first time when analyzing interactions between BBI and SBP time series. In Voss et al. (6) it was successfully shown that JSD is effective not only in demonstrating differences in the autonomic regulation between normal pregnancies and PE, but also between chronic and GH disorders and PE. In particular, the test comparing GH and PE reveals high significances in several indices. Therefore this test could contribute significantly in obtaining a more differential diagnosis for pregnant women. Since there is a better perinatal outcome of CH and GH and their postnatal reversibility of the alterations as compared to the outcome of PE, the early diagnosis of the PE disorder is fundamental in the field of obstetrics. The present study confirms the results of Voss et al. [6] which discriminated between all investigated hypertensions. In addition, we improved these results discriminating CH and PE by calculating row5 as well as row5_left.

In a previous study we could demonstrate [11] that the assessment of baroreflex sensitivity can reveal early indicators for the development of pathologic conditions, for example hypertensive disorders which lead to serious maternal and prenatal complications. However, we were not able to differ between chronic and/or GH and PE. In this study, we could discriminate between the varying hypertension disorders and PE by coupling the analysis of SBP and BBI time series.

In a graphical presentation (Figure 2), we showed the regions of different couplings and found different behavior between CH and GH as well as for PE. CH is not located within the baroreflex region. However, GH as well as PE showed various couplings in the baroreflex region. This can be caused by the diseases’ origin, whereby the condition of CH is not caused by pregnancy.

To summarize, BSPPA is able to indicate specific parts of the Poincaré plot and...
therefore give more detailed information about autonomic regulations in hypertension and PE. Based on the results of this exploratory study we speculate that the BSPPA method could be a potential tool to assess the autonomic regulation in hypertensive pregnant women and could contribute to an improved medical care for mother and child. However, further studies are needed to demonstrate whether this approach can be established as a standard diagnostic tool during the early stages of hypertensive pregnancy. Therefore, it is also necessary to overcome the limitation of this study which is the deviation of the BBI from blood pressure curves leading together with the low sampling frequency of 200 Hz to less precise estimations of the BBI. Furthermore, more specific studies need to be done to investigate the influence of the baroreflex on gestational age-related changes such as GH and PE.

5. Conclusions

With the new BSPPA we investigated for the first time interactions between BBI and SBP time series. BSPPA quantifies specific parts of the Poincaré plot and gives more detailed information about autonomic regulations in hypertension disorders and especially in PE. This study improves the assessment of autonomic regulation by analyzing the BBI and SBP time series. It can also be used to predict the outcome of hypertensive pregnancy disorders such as PE. Consequently, BSPPA could contribute to improve medical care for mother and child.

Acknowledgments

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References