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2011 Physiol. Meas. 32 1611

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Advanced Poincaré plot analysis differentiates between hypertensive pregnancy disorders

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Received 7 June 2011, accepted for publication 9 August 2011
Published 6 September 2011
Online at stacks.iop.org/PM/32/1611

Abstract

Hypertensive pregnancy disorders affect 6% to 8% of all pregnancies and can result in severe complications for the mother and the foetus of which pre-eclampsia (PE) has the worst perinatal outcome. Several studies suggested that the autonomic nervous system plays an important role in the process of developing hypertensive pregnancy disorders, especially PE. The aim of this retrospective study was to investigate whether women with PE could be differentiated from women with various other hypertensive pregnancy disorders, by employing an enhanced Poincaré plot analysis (PPA), the segmented Poincaré plot analysis (SPPA), to their beat-to-beat interval and blood pressure signals. Sixty-nine pregnant women with hypertensive disorders (29 PE, 40 with chronic or gestational hypertension) were included. The SPPA as well as the traditional PPA found significant differences between PE and other hypertensive disorders of diastolic blood pressure (p < 0.001 versus p < 0.001) but only the SPPA method revealed significant differences (p < 0.001) also of the systolic blood pressure. Further on, linear discrimination analysis demonstrated that indices derived from SPPA are more suitable for differentiation between chronic and gestational hypertension and PE than those from traditional PPA (area under the ROC curve 0.85 versus 0.69). Therefore this procedure could contribute to the differential diagnosis of hypertensive pregnancy disorders.
Keywords: pregnancy, pre-eclampsia, hypertension, blood pressure variability, segmented Poincaré plot analysis, cardiovascular regulation

1. Introduction

Hypertensive disorders during pregnancy are a leading cause of maternal and foetal morbidity and mortality and affect 6% to 8% of all pregnancies (NHBPEP 2000). The ‘National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy’ classifies hypertension in pregnancy to one of four conditions: (1) chronic hypertension (CH), (2) gestational hypertension (GH), (3) CH with superimposed pre-eclampsia (PE) which is not included in this study and (4) PE (Zamorski and Green 2001, NHBPEP 2000, Leeman and Fontaine 2008).

CH is defined as a blood pressure of more than 140/90 mmHg on two measurements before the 20th week of gestation or persisting beyond 12 weeks after delivery. GH describes the development of hypertension after 20 weeks of gestation without proteinuria whereas PE is a multisystem disorder characterized by hypertension in combination with proteinuria in the second half of pregnancy (NHBPEP 2000, Zamorski and Green 2001, Leeman and Fontaine 2008). Although the aetiology of PE is not yet fully understood it is well established that PE is accompanied by low circulating blood volume and an increase in peripheral vascular resistance (Roberts and Redman 1993, Borghi et al. 2011). It is associated with a disturbed placental development followed by endothelial dysfunction and can result in severe complications for the mother such as cerebral haemorrhage, lung oedema or liver haemorrhage and rupture. For the foetus, intrauterine growth restriction and preterm birth are possible consequences leading to a high risk of infant mortality or morbidity (VanWijk et al. 2000, NHBPEP 2000).

Several studies suggest that the autonomic nervous system plays an important role in the process of developing hypertensive pregnancy disorders, especially PE. A sympathetic overactivity in women with GH (Greenwood et al. 1998) and PE (Schobel et al. 1996) compared to normal pregnant and hypertensive non-pregnant women has been proven using the technique of microneurography.

It is well known that maternal autonomic cardiovascular control is strongly affected by pregnancy (Hermida et al. 1997). Voss et al. (2000) reported significant differences in heart rate variability (HRV) and spontaneous baroreflex sensitivity (BRS) between non-pregnant and normal pregnant women applying standard linear as well as nonlinear parameters. Furthermore, it was shown that the differences in HRV and BRS depend on the stage of gestation (Voss et al. 2000).

Faber et al. (2004) demonstrated that HRV and blood pressure variability (BPV) reveal significant alterations during the development of hypertensive disorders.

The Poincaré plot analysis (PPA) provides a visual tool to characterize the complex nature of time series fluctuations (Kamen and Tonkin 1995). Parameters from PPA were shown to be powerful predictors of postoperative ischemia (Laitio et al. 2002). However the traditional PPA parameters lose most of the nonlinear information contained in a time series (Brennan et al. 2002, Karmakar et al. 2009, Guzik et al. 2007). Therefore, we recently introduced an improvement to PPA, the segmented PPA (SPPA), which involves two main procedures: rotating the cloud of points and segmenting the plot into a defined number of rectangles (Voss et al. 2010). This method overcomes one of the previously mentioned limitations, i.e. the high correlation between PPA indices and linear parameters (Brennan et al. 2002, Guzik et al. 2007), and captures the nonlinear characteristics of a time series. For example, SPPA indices derived
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Table 1. Number of patients, mean, range and standard deviation (std) of age (in years) and week of gestation (gw) for each group.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Mean ± std age</th>
<th>Range age</th>
<th>Mean ± std gw</th>
<th>Range gw</th>
</tr>
</thead>
<tbody>
<tr>
<td>oHY</td>
<td>40</td>
<td>28.6 ± 5.0</td>
<td>19–38</td>
<td>32.9 ± 5.8</td>
<td>20–41</td>
</tr>
<tr>
<td>PE</td>
<td>29</td>
<td>27.7 ± 5.4</td>
<td>19–38</td>
<td>32.2 ± 4.1</td>
<td>25–39</td>
</tr>
</tbody>
</table>

from beat-to-beat interval time series were able to discriminate between low and high risk patients with dilated cardiomyopathy, which was not possible when applying traditional PPA (Voss et al 2010).

The aim of this study was to investigate whether women with PE, who have the worst perinatal outcome (VanWijk et al 2000) could be differentiated from women with various other hypertensive pregnancy disorders, by employing the SPPA technique to their beat-to-beat interval and for the first time to blood pressure signals.

2. Materials and methods

2.1. Data

In this study 69 pregnant women with hypertensive disorders (mean age 28.2 years, range 19–38 years, standard deviation 5.2 years) were included. Twenty-nine women suffered from PE. Forty women suffered from a hypertensive disorder other than PE (oHY), of which 18 had CH and 22 women had GH. Further details are provided in table 1.

The investigation conforms to the principles outlined in the Declaration of Helsinki. Local ethics committee approval and informed consent of all subjects were provided.

2.2. Signal acquisition and pre-processing

Continuous blood pressure was recorded for 30 min in the supine position during the late morning hours, at a sampling frequency of 200 Hz and a resolution of 0.1 mmHg (Portapres, TNO Biomedical Instrumentation).

From these recordings, time series of pulse intervals (beat-to-beat intervals BBI), and systolic and diastolic blood pressure (SBP, DBP) were extracted. Ectopic beats, calibration intervals in SBP and DBP and other disturbances were excluded and interpolated by an adaptive variance estimation algorithm, considering the variance within the time series just before and directly after the event.

2.3. Signal analyzing methods

2.3.1. Poincaré plot analysis. The PPA is a technique used to assess the heartbeat dynamics and based on simplified phase-space embedding. Usually, Poincaré plots are applied for a two-dimensional graphical and quantitative representation, where BBI_n is plotted against BBI_{n-1}. Typically, the Poincaré plot displays an elongated cloud of points oriented along the line of identity. An ellipse is usually fitted to the cloud of points to characterize its shape. The centre of the ellipse represents the mean value of all BBIs. Most commonly, three indices are calculated from this ellipse: the standard deviation of the short-term BBI variability (axis vertical to the line of identity, SD1), the standard deviation of the long-term BBI variability (axis along the line of identity, SD2) and the ratio SD1/SD2 (Kamen and Tonkin 1995, Brennan et al 2002).
The calculation of SD1 and SD2 is performed using equations (1) and (2), where VAR is the variance, $BBI_n$ is the beat-to-beat interval time series with $n = 1, \ldots, N-1$ ($N$ is the length of time series) and $BBI_{n+1}$ is the same time series shifted by a lag of $\tau = 1$ (Lerma et al 2003, Kamen and Tonkin 1995):

$$SD1 = \sqrt{VAR \left( \frac{BBI_n - BBI_{n+1}}{\sqrt{2}} \right)},$$  \hspace{1cm} (1)

$$SD2 = \sqrt{VAR \left( \frac{BBI_n + BBI_{n+1}}{\sqrt{2}} \right)}.$$ \hspace{1cm} (2)

Furthermore, the ratio $SD1/SD2$ is calculated. These indices are similarly determined for SBP and DBP time series.

2.3.2. Segmented Poincaré plot analysis. To retain nonlinear features of a system when applying PPA an enhanced pseudo-phase-space quantification method was introduced—the segmented Poincaré plot analysis (SPPA) (Voss et al 2010).

The SPPA procedure includes the following four procedures (figure 1).
The indices SD1 and SD2 (equations (1) and (2)) are calculated according to traditional PPA (figure 1(a)).

The cloud of points is rotated by an angle of $\alpha = 45^\circ$ around the centre of the cloud (figure 1(b)).

A grid of $12 \times 12$ rectangles is fitted to the cloud starting from the centre of the plot where the size of each rectangle is adapted to SD1 (height) and SD2 (width) (figure 1(c)).

For estimating single probabilities ($p_{ij}$) the number of points within every rectangle is counted and normalized by the total number of points. Based on these single probabilities all row ($i$) and column ($j$) probabilities are calculated by summation of the related single probabilities (equations (3) and (4)):

$$ p_{ri} = \sum_{j=1}^{12} p_{ij}, \quad (3) $$

$$ p_{lj} = \sum_{i=1}^{12} p_{ij}. \quad (4) $$

2.4. Statistics

Results were reported as group means and standard deviations. To test for significant differences between the PE and oHY groups we applied the Mann–Whitney-U-test (MW-test). The level of significance was set to $p < 0.05$ for all PPA derived indices. Due to the problem of multiple testing the significance level for SPPA indices was set to $p < 0.001$. A precondition for the MW-test is a similar distribution shape in both groups. This was tested with the Kolmogorov–Smirnov test (KS-test) for two samples with a significance level of $p < 0.05$. For parameters with a significant difference in shape of the distribution the $p$-value of the KS-test is provided.

To discriminate between patients with PE and patients with other hypertensive disorders linear discriminant function analysis (LDA) was performed including all highly significant PPA ($p < 0.01$) and SPPA ($p < 0.001$) indices. The performance of each index was assessed by estimating the area under the receiver-operating-characteristic (ROC) curve. Parameters achieving an area under the ROC curve above 0.75 were combined in sets of two or three and enrolled in LDA again to determine the optimal parameter set for classification.

3. Results

3.1. Univariate significance of parameters

Time domain analysis (mean and standard deviation of BBI) revealed highly significant differences only in the mean values but not in the standard deviations of all three time series (see also table 2).

Of PPA parameters SD1/SD2 revealed significant differences between both groups in BBI, SBP and DBP time series. In the DBP time series the parameter SD1 showed additional significant alterations. To overcome the limitations through multiple testing and small group sizes only the highly significant parameter DPB_SD1/SD2 was enrolled in further analysis. Table 3 presents the indices from PPA with $p$-values, means and standard deviations for both groups.

The SPPA of BBI time series did not reveal any significantly altered areas in the Poincaré plot.
Applying the SPPA method to SBP time series showed several altered regions in the plot in PE compared to oHY. In particular, columns 4, 6, 7, 9 and 10 (see also figure 1(c)) identified highly significant modifications. Also the SPPA of DBP time series indicated differences in row 3 of the rotated cloud.

Table 4 presents \( p \)-values, means and standard deviations (in %) of parameters for both groups.

### 3.2. Linear discriminant function analysis

To compare the strength of discrimination between PPA and SPPA, LDA was performed with each single highly significant parameter. The only highly significant parameter from PPA
was DBP_SD1/SD2 and achieved an area under the ROC curve of 0.687 (figure 4(a)). In contrast, univariate LDA of highly significant SPPA parameters revealed five parameters that achieved a ROC value above 0.75, of which the parameter SBP_column7 turned out to have the most discriminative power (area under the ROC curve of 0.781). The optimal parameter set containing two parameters consisted of SBP_column7 and SBP_column10 (see also figure 3) and improved the ROC value to 0.836. The best result was achieved through adding the parameter DBP_row3 (area under the ROC curve of 0.847, figure 4(b)). Results of LDA are summarized in table 5.

4. Discussion

The aim of this study was to investigate whether women with PE could be differentiated from women with other hypertensive pregnancy disorders through assessing individual autonomic cardiovascular regulation. We therefore applied the recently developed SPPA method for the first time on blood pressure time series and compared the results to those obtained with PPA. The SPPA is known to capture nonlinear features of a time series in contrast to traditional PPA (Voss et al 2010). Both methods, the PPA and SPPA, revealed major alterations in blood pressure time series, but not in heart rate oscillations despite the difference in mean values of BBI. These results support those of Faber et al (2004) who applied HRV analysis to these patient groups too and did not find significant differences between CH, GH and PE.

The parameter DBP_SD1/SD2 derived from PPA reflects the ratio between standard deviations of short-term variability and long-term variability of DBP. This ratio is increased in patients with PE due to a more pronounced increase in SD1 than in SD2, indicating higher variability in short-term regulation of DBP. Similar conclusions have been drawn by Malberg et al (2007) and Walther et al (2006). These studies achieved an increase in the prediction of PE to 70% by combining analysis of HRV, BPV and BRS with the standard examination of uterine perfusion by Doppler sonography several weeks before clinical manifestation. An elevated high frequency component of DBP was present in those women with abnormal uterine perfusion who later on developed a PE. However, the results are not completely comparable with our current findings since the reference groups in those studies also included pregnancies with normal outcome and intrauterine growth retardation but not patients with CH. Another study by Riedl et al (2010) analyzed the coupling between respiration, blood pressure and heart

<table>
<thead>
<tr>
<th>Parameter/parameter set</th>
<th>Area under ROC curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP_SD1/SD2</td>
<td>0.687</td>
</tr>
<tr>
<td>SBP_column7</td>
<td>0.781</td>
</tr>
<tr>
<td>SBP_column10</td>
<td>0.774</td>
</tr>
<tr>
<td>SBP_column6</td>
<td>0.771</td>
</tr>
<tr>
<td>DBP_row3</td>
<td>0.752</td>
</tr>
<tr>
<td>SBP_column4</td>
<td>0.751</td>
</tr>
<tr>
<td>SBP_column10, SBP_column7</td>
<td>0.836 (0.842a, 0.842b)</td>
</tr>
<tr>
<td>SBP_column10, SBP_column7, DBP_row3</td>
<td>0.847 (0.868a, 0.854b)</td>
</tr>
</tbody>
</table>

aSubgroup with adjusted mean SBP.
bSubgroup with adjusted gestational week.
rate of healthy pregnant women and subjects suffering from PE. They found a similar coupling structure in both groups, although the respiratory influence on the DBP was significantly increased in PE patients. Additionally the form of respiratory influence on heart rate showed significant changes.

The decrease of parameter DBP_row3 in patients with PE also reflects an altered distribution of DBP oscillations. Row 3 is located on the outer regions of the cloud (range: mean+3*SD1–mean+4*SD1) and indicates rapidly increased short-term variability of DBP. These sporadic maximum values are more seldom in patients with PE compared to CH and GH although the basic short-term variance is elevated which is indicated by a raised SD1.

Highly significant differences (p < 0.001) in SBP time series could only be revealed with SPPA. An example of the systolic SPPA plot for a patient of each group is provided in figure 3. The increase of probability in column 7 (range: mean–mean+SD2), which accounts for the centre of cloud of points and its decrease in column 10 (range: mean+3*SD2–mean+4*SD2), which is located at the outer bounds indicates a reduction of long-term variability in PE compared to the other hypertensive disorders. The basic long-term variance as represented by SBP_SD2 derived from PPA was not significantly altered. Further, haemodynamic and neurohumoral differences between both groups might cause the altered regulatory pattern. Decrease in cardiac output and elevated peripheral vascular resistance are features characteristic of PE but not of GH and CH (Roberts and Redman 1993, Borghi et al 2011). In particular the high vascular resistance might be associated with reduced variability in SBP shown in this study. Borghi et al (2011) also found significantly elevated plasma levels of atrial and brain natriuretic
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Figure 3. SPPA plots of SBP of a patient with CH (top), with GH (middle) and with PE (bottom); dark rectangles: more than 5% of all SBP pairs are located within this rectangle; light rectangles: less than 5% of all SBP pairs are located within this rectangle; highly significant columns 7 and 10 are marked by a frame.

(This figure is in colour only in the electronic version)
peptide in PE, both being humoral factors that are involved in blood pressure regulation and associated with cardiac overload.

Linear discrimination analysis demonstrated that indices derived from SPPA achieved a greater area under the ROC curve than those from traditional PPA. The SPPA parameter SBP_column7 exceeded the best PPA parameter DBP_SD1/SD2 by approximately 10% (0.78 versus 0.69). The combination of two and three SPPA parameters improved the results even further (see also figure 4).

To avoid any bias in the results caused by significantly different mean blood pressure levels, the parameter sets were applied to a subgroup of patients with reduced mean values, which lead to an area under the ROC curve of 0.842 for the two-parameter set and 0.868 for the three-parameter set. This indicates that our results are independent from mean SBP and DBP.

Further, a subgroup of patients that was matched for the gestational week was analyzed. Areas under the ROC curve were 0.842 and 0.854 for the two- and three-parameter sets, respectively, also emphasizing the robustness of this parameter set.

A limitation of this study is the low sample frequency of 200 Hz of blood pressure time series that could lead to imprecision in length of BBI intervals which are extracted from the blood pressure signal. For further studies data recording is expanded with a separate ECG channel for BBI time series determination. Further on, we did not control for the effect of anti-hypertensive medication, which is indicated by the lower mean values of SBP and DBP in CH and GH compared to patients with PE. However, this treatment cannot be interrupted and our data therefore reflects the real clinical situation. Since both methods PPA and SPPA are applied to the same data set, the comparative results are not biased through the influence of medication. Notwithstanding this limit, however, the results presented in this study represent a further step towards a deeper understanding of the possible different features of autonomic cardiovascular regulation in different forms of hypertension in pregnant women. It confirms the hypothesis that GH is not a preliminary stage of PE but that both diseases have their own regulatory mechanisms. It also underlines once more the usefulness of SPPA analysis of
short-term BPV, which may offer a more detailed insight into cardiovascular control mechanisms in future studies.

5. Conclusions

Patterns of systolic and diastolic BPV differ significantly between hypertensive pregnancy disorders, and therefore, reflect altered mechanisms of blood pressure regulation. This study showed that SPPA is also a potential technique for analyzing blood pressure time series and that indices from SPPA allow differentiation between CH and GH from PE. The SPPA method provides more detailed information on alterations of the SBP than the traditional PPA. Therefore this procedure could contribute to the differential diagnosis of hypertensive pregnancy disorders.

Acknowledgments

This study was partly supported by a grant from the University of Applied Sciences Jena and by the Deutsche Forschungsgemeinschaft DFG (Vo505/8-2). All authors hereby disclose any and all commercial associations that might pose a conflict of interest in connection with the manuscript.

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