Three-dimensional segmented Poincare plot analysis - a new approach of cardiovascular and cardiorespiratory regulation analysis

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Abstract— **Hypertensive pregnancy disorders affect 6 to 8 percent of all pregnancies which can cause severe complications for the mother and the fetus. The aim of this study was to develop a new method suitable for a three dimensional coupling analysis. Therefore, the three-dimensional segmented Poincaré plot analysis (SPPA3) is introduced that represents the Poincare analysis based on a cubic box model representation. The box representing the three dimensional phase space is (based on the SPPA method) subdivided into 12x12x12 equal cubelets according to the predefined range of signals and all single probabilities of occurring points in a specific cubelet related to the total number of points are calculated. From 10 healthy non-pregnant women, 66 healthy pregnant women and 56 hypertensive pregnant women suffering from chronic hypertension, gestational hypertension and preeclampsia, 30 minutes of beat-to-beat intervals (BBI), noninvasive blood pressure and respiration (RESP) were continuously recorded and analyzed. Couplings between the different signals were analyzed. The ability of SPPA3 for a screening could be confirmed by multivariate discriminant analysis differentiating between all pregnant woman and preeclampsia (index BBI3_SBP9_RESP6/ BBI8_SBP11_RESP4 leads to an area under the ROC curve of AUC=91.2%). In conclusion, SPPA3 could be a useful method for enhanced risk stratification in pregnant women.**

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 in pregnancy to several conditions: (1) chronic hypertension predating pregnancy; (2) preeclampsia as a serious, systemic syndrome of elevated blood pressure, proteinuria and other findings; (3) chronic hypertension with superimposed preeclampsia which is not included in this study; and (4) pregnancy induced hypertension, or gestational hypertension of pregnancy [1, 2].

In recent years several studies have demonstrated that nonlinear methods provide additional diagnostic and prognostic information representing a useful complement to traditional time- and frequency domain analyses [3, 4]. Therefore, Voss et al. [5] introduced the segmented Poincaré plot analysis (SPPA) method which constitutes an enhancement of the traditional Poincaré plot analysis (PPA). The SPPA method captures the nonlinear characteristics of a time series and, therefore, overcomes several limitations of traditional PPA method, i.e. the high correlation between the PPA indices and linear parameters [6].

Voss et al. [7] already proved the prediction of hypertensive pregnancy disorders applying the bivariate Joint Symbolic Dynamics (JSD) method introduced by Baumert et al. [8]. As one result, they showed that the cardiovascular regulatory system was changed considerably depending on the type of hypertensive disorder leading to a significant differentiation between chronic or pregnancy induced hypertension and preeclampsia by analyzing couplings between heart rate and blood pressure time series. However, the influences of normal pregnancy and pregnancy disorders on the cardiorespiratory system were not considered.

Therefore, the aim of this study was to establish a new method for investigating couplings between the subsystems of cardiovascular and cardiorespiratory autonomic regulation. That is why we have investigated time series of beat-to-beat intervals (BBI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and respiration rate (RESP) applying the three-dimensional segmented Poincaré plot analysis (SPPA3).

METHODS

A. Patients

The classification of the hypertensive disorders was performed according to the guidelines of the 'National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy' [1].

In this study, we enrolled data from 112 pregnant women (mean age 28 years, range 19-38 years, standard deviation (SD) 5.1 years) from the university hospitals of Berlin and Jena. 66 of them had normal pregnancies (PREG; mean age 28.1 years, range 20-38 years, SD 4.9 years), 13 suffered from chronic hypertension (CH; mean age 28.6 years, range 20-36 years, SD 5.2 years), 14 from pregnancy induced hypertension (PIH; mean age 27.5 years, range 19-34 years, SD 5.1 years) and 19 developed a preeclampsia (PE; mean age 27.6 years, range 15-38 years, SD 6 years). For more details see table I.

As a control group, 10 age-matched healthy women (CON; mean age 26.9 years, range 24-32 years, SD 2.6 years) from the Department of Medical Engineering and

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Biotechnology, University of Applied Sciences Jena were investigated. None of these controls had a cardiovascular or renal disease or took medications with cardiovascular effects.

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

TABLE I. DATA OF PREGNANT WOMEN AND CONTROLS (NON-PREGNANT WOMEN AS CONTROLS – CON, NORMAL PREGNANCIES – PREG, CHRONIC HYPERTENSION –CH, PREGNANCY INDUCED HYPERTENSION – PIH, PREECLAMPSIA - PE)

Group	Number	Age – mean ± SD [years]	Week of gestation		
			Mean	*Range*	*SD*
CON	10	26.9 ± 2.6	-	-	-
PREG	66	28.1 ± 4.9	34	19-40	4.7
CH	13	28.6 ± 5.2	30	20-39	6.7
PIH	14	27.5 ± 5.1	35	27-39	3.5
PE	19	27.6 ± 6.0	32	25-39	3.9
CH+PIH	27	28.0 ± 5.1	33	20-39	5.6
CH+PIH+PE	46	27.9 ± 5.4	32	20-39	4.9
PREG +CH+PIH	93	28.1 ± 4.9	33	19-40	5.0

TABLE II. DEFINITION OF THE CUBELET DIMENSION

Signal	Size of a single cubelet	Range of axis	
		min	*max*
BBI	75 ms	400 ms	1300 ms
SBP	13 mmHg	50 mmHg	206 mmHg
DBP	9 mmHg	22 mmHg	130 mmHg
RESP	1.25 s	0.5 s	15 s

B. Signal acquisition and preparation

Thirty minutes of continuous blood pressure (NIBP, fs = 200 Hz, resolution = 0.1 mmHg) and breathing intervals (via respiration belt - RESP) were recorded in supine position during the late morning hours. NIBP was measured on the left middle finger applying the noninvasive Portapres M2 blood pressure monitor (TNO-TPD, Amsterdam, Netherlands [9]).

The time series of beat-to-beat intervals (BBI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were extracted using the 'BeatFast' pattern recognition software package (TNO Biomedical Instrumentation, The Netherlands). The maxima of the respiratory curve were detected to get the respiratory frequency (breathing cycle length). Ectopic beats 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 [10].

C. Three-dimensional segmented Poincaré plot analysis (SPPA3)

The new three-dimensional SPPA3 method is a multivariate analysis technique based on the SPPA method introduced by Voss et al. [5]. Therefore, the SPPA3 determines both couplings between two (BBI and NIBP or RESP and NIBP) and three (BBI, NIBP and RESP) different systems represented by the time series of BBI(i+1), systolic/diastolic NIBP(i) and interpolated RESP(i) and plotted against each other within a cubic box model. Then, the cubic box model is subdivided into equal 12 x 12 x 12 cubelets for a total number of N=1728 cubelets (Fig.1) based on the standard SPPA [5].

This 3D cubic box model represents the basic model with regard to all patients. The chosen limits for a single cubelet are based on typical physiological scales (Table II). For each cubelet the probability of occurrence (Prob) of data points is calculated as:

$$\text{Prob}(Xr,Yc,Zd)/N$$
$$\text{with } r,c,d=1..12$$
$$\text{(r - row, c - column, d - depth).}$$

X represents the axis of the first signal (e.g. BBI), Y that of the second signal (e.g. SBP/DBP) and Z the axis of the third signal (e.g. RESP). Therefore, the index of each cubelet is generally defined as following:

$$Xr\_Yc\_Zd$$
(e.g. BBI1_SBP4_RESP2)

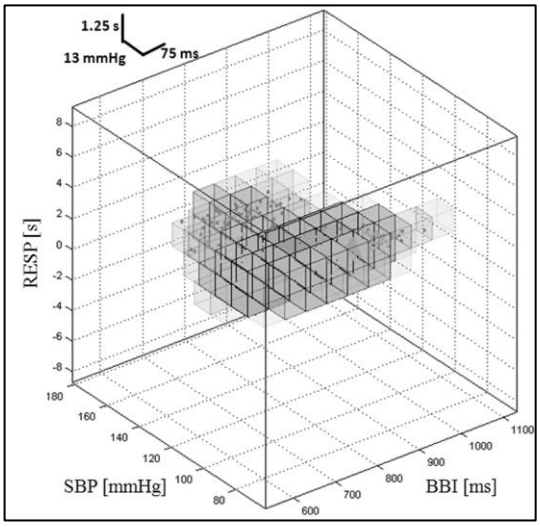

Figure 1. Example of a cubic box model of the SPPA3 investigating BBI, SBP and RESP from a healthy pregnant woman

D. Statistical Tests

The Mann-Whitney U-test was performed to figure out significant ($p < 0.05$) and highly significant ($p < 0.01$) parameters differentiating between all investigated groups of patients and for all kinds of coupling systems. Because of the high number of considered variables (1728) the Bonferroni criterion was applied ($p<0.00003$). The Receiver Operating Characteristic curves (ROC) were computed for each single index (univariate) as well as and for index sets consisting of two indices (multivariate). To validate a specific method, the performance of each index was assessed by estimating the area under the ROC curve (AUC) by applying discriminant analysis.

RESULTS

This study investigates the ability of SPPA3 to differentiate between non-pregnant and healthy pregnant

women as well as between hypertension pregnancy disorders and preeclampsia. For a first evaluation of the SPPA3 method the number of highly significant indices for each coupling system and all kind of group tests are shown within table III.

TABLE III. NUMBER OF SIGNIFICANT CUBLETS (P<0.01) FOR THE SPPA3 APPLYING COUPLINGS BETWEEN TWO AND THREE SYSTEMS

couplings	CON-PREG	PREG-CH	PREG-PIH	PREG-PE	CH-PIH	CH-PE	PIH-PE	CH+PIH-PE	PREG+CH+PIH-PE	PREG-CH+PIH+PE
Couplings between three systems										
BBI_DBP_RESP	112	0	20	110	3	21	15	39	109	46
BBI_SBP_RESP	128	4	29	143	1	25	45	55	130	112
Couplings between two systems										
BBI_SBP_DBP	105	17	21	94	6	23	26	38	94	59
SBP_DBP_RESP	61	18	11	83	9	24	14	26	73	63

Nearly all coupling tests including signals from the three different systems (BBI, DBP/SBP, RESP) revealed highest number especially for CON and PREG as well as for the group tests differentiating hypertension pregnancy disorders and PE (CH+PIH vs. PE and PREG+CH+PIH vs. PE).

A closer look at the most for medical purposes important group tests are shown within Tables IV-VII. Here, the top five of the highest significant indices of each group test and are presented.

TABLE IV: TOP FIVE SIGNIFICANCES ANALYZING THE COUPLINGS BETWEEN 3 DIFFERENT SYSTEMS (BBI, DBP AND RESP) FOR THE GROUP TESTS PREGNANT VS. NON-PREGNANT WOMEN (CON-PREG), HYPERTENSION PREGNANCY DISORDERS VS. PE (CH+GH-PE) AND ALL PREGNANT WOMEN VS. PE (PREG+CH+GH-PE); † - P<0.05; * - P<0.01; ** - P<0.00003 (BONFERRONI); NS – NOT SIGNIFICANT

Index	CON vs. PREG	CH+GH vs. PE	PREG+CH+GH vs. PE
BBI6_DBP11_RESP5	0.005*	2.19E-4*	4.34E-4*
BBI6_DBP11_RESP4	0.001*	7.99E-4*	0.005*
BBI6_DBP10_RESP6	0.002*	2.99E-4*	0.002*
BBI2_DBP9_RESP5	NS	0.002*	2.98E-08**
BBI3_DBP9_RESP7	NS	0.001*	3.04E-07**
BBI3_DBP9_RESP6	NS	0.002*	2.48E-07**
BBI3_DBP8_RESP7	NS	0.002*	7.66E-07**
BBI4_DBP8_RESP7	NS	6.50E-4*	3.67E-06**
BBI3_DBP6_RESP10	NS	7.44E-4*	3.20E-08**
BBI10_DBP6_RESP10	4.35E-11**	NS	NS
BBI3_DBP5_RESP10	NS	0.005*	4.73E-07**
BBI10_DBP5_RESP11	2.62E-14**	NS	NS
BBI10_DBP4_RESP12	1.49E-12**	NS	NS
BBI10_DBP4_RESP11	1.49E-12**	NS	NS
BBI10_DBP3_RESP12	1.49E-12**	NS	NS

Tables IV and V show most significant indices as a result of investigating the coupling between three time series.

Investigating the coupling between BBI, DBP and RESP (Table IV), the best results could be revealed for the index BBI2_DBP9_RESP5 (p=2.98*10-8) differentiating between PE and all other pregnant women (PREG, CH and GH). The best set of indices from multivariate discriminant analysis were BBI2_DBP10_RESP6 and BBI3_DBP8_RESP8 (AUC=82.9%).

The best results investigating the coupling between BBI, SBP and RESP (Table V) were achieved with BBI3_SBP8_RESP7 ($p=1.31*10^{-10}$) as single univariate index and the best set of indices were the combination of BBI3_SBP9_RESP6 and BBI8_SBP11_RESP4 (AUC=91.2%).

Tables VI and VII show most significant indices as a result of investigating the coupling between two time series. Here we considered only the couplings between the systems BBI and NIBP as well as RESP and NIBP.

TABLE V: TOP FIVE SIGNIFICANCES ANALYZING THE COUPLINGS BETWEEN 3 DIFFERENT SYSTEMS (BBI, SBP AND RESP) FOR THE GROUP TESTS PREGNANT VS. NON-PREGNANT WOMEN (CON-PREG), HYPERTENSION PREGNANCY DISORDERS VS. PE (CH+GH-PE) AND ALL PREGNANT WOMEN VS. PE (PREG+CH+GH-PE); † - P<0.05; * - P<0.01; ** - P<0.00003 (BONFERRONI); NS – NOT SIGNIFICANT

Index	CON vs. PREG	CH+GH vs. PE	PREG+CH+GH vs. PE
BBI6_SBP11_RESP5	0.018†	8.66E-5*	0.004*
BBI8_SBP11_RESP4	5.65E-4*	7.28E-5*	6.51E-06**
BBI2_SBP10_RESP5	NS	0.003*	5.60E-10**
BBI8_SBP10_RESP5	2.03E-4*	8.37E-5*	3.75E-06**
BBI2_SBP9_RESP6	NS	9.66E-4*	3.69E-10**
BBI3_SBP9_RESP7	NS	8.40E-4*	3.39E-10**
BBI3_SBP9_RESP6	NS	6.79E-5*	1.72E-10**
BBI3_SBP8_RESP7	NS	2.57E-4*	1.31E-10**
BBI4_SBP8_RESP7	NS	9.75E-5*	7.85E-08**
BBI2_SBP6_RESP10	NS	7.44E-4*	1.81E-09**
BBI10_SBP6_RESP10	7.69E-11**	NS	NS
BBI10_SBP5_RESP11	5.28E-11**	NS	NS
BBI10_SBP4_RESP11	7.69E-11**	NS	NS
BBI8_SBP3_RESP1	8.57E-10**	NS	NS
BBI10_SBP3_RESP12	1.49E-12**	NS	NS

TABLE VI: TOP FIVE SIGNIFICANCES ANALYZING THE COUPLINGS BETWEEN 2 DIFFERENT SYSTEMS: BBI AND NIBP (SBP AND DBP) FOR THE GROUP TESTS PREGNANT VS. NON-PREGNANT WOMEN (CON-PREG), HYPERTENSION PREGNANCY DISORDERS VS. PE (CH+GH-PE) AND ALL PREGNANT WOMEN VS. PE (PREG+CH+GH-PE); † - P<0.05; * - P<0.01; ** - P<0.00003 (BONFERRONI); NS – NOT SIGNIFICANT

Index	CON vs. PREG	CH+GH vs. PE	PREG+CH+GH vs. PE
BBI6_SBP11_DBP8	0.011†	9.16E-5*	0.007*
BBI8_SBP11_DBP7	0.003*	2.70E-4*	6.93E-5*
BBI2_SBP10_DBP12	NS	0.007*	2.51E-07**
BBI6_SBP10_DBP9	0.004*	3.98E-4*	0.005*
BBI7_SBP10_DBP9	0.002*	1.85E-4*	7.85E-5*
BBI8_SBP10_DBP8	0.00*	3.16E-5*	7.79E-06**
BBI1_SBP9_DBP2	NS	7.44E-4*	2.76E-07**
BBI1_SBP9_DBP1	NS	0.003*	1.71E-08**
BBI1_SBP8_DBP2	NS	0.002*	3.06E-09**
BBI2_SBP8_DBP1	NS	8.93E-4*	1.04E-07**
BBI10_SBP6_DBP9	1.49E-12**	NS	NS
BBI10_SBP5_DBP10	2.62E-14**	NS	NS
BBI10_SBP4_DBP11	1.49E-12**	NS	NS
BBI9_SBP3_DBP12	1.49E-12**	NS	NS
BBI10_SBP3_DBP12	1.49E-12**	NS	NS

TABLE VII: TOP FIVE SIGNIFICANCES ANALYZING THE COUPLINGS BETWEEN 2 DIFFERENT SYSTEMS: NIBP (SBP AND DBP) AND RESP FOR THE GROUP TESTS PREGNANT VS. NON-PREGNANT WOMEN (CON-PREG), HYPERTENSION PREGNANCY DISORDERS VS. PE (CH+GH-PE) AND ALL PREGNANT WOMEN VS. PE (PREG+CH+GH-PE); † - P<0.05; * - P<0.01; ** - P<0.00003 (BONFERRONI); NS – NOT SIGNIFICANT

Index	CON vs. PREG	CH+GH vs. PE	PREG+CH+GH vs. PE
SBP11_DBP11_RESP5	7.69E-11**	NS	NS
SBP10_DBP10_RESP7	3.64E-09**	NS	NS
SBP10_DBP10_RESP6	2.02E-12**	NS	NS
SBP11_DBP10_RESP6	3.64E-09**	NS	NS
SBP10_DBP9_RESP7	4.30E-09**	NS	NS
SBP7_DBP8_RESP7	4.92E-5*	5.78E-5*	9.82E-07**
SBP6_DBP7_RESP9	7.20E-4*	2.41E-4*	1.87E-5**
SBP4_DBP3_RESP12	NS	4.67E-4*	5.80E-09**
SBP2_DBP2_RESP12	NS	9.10E-5*	5.89E-12**
SBP2_DBP2_RESP1	NS	1.15E-4*	1.33E-11**
SBP3_DBP2_RESP12	NS	0.002*	2.20E-09**
SBP3_DBP2_RESP2	NS	0.004*	1.03E-08**
SBP3_DBP2_RESP1	NS	0.005*	2.10E-08**
SBP1_DBP1_RESP2	NS	0.002*	2.98E-08**
SBP3_DBP1_RESP12	NS	0.006*	3.30E-08**

The coupling analysis of BBI and NIBP (Table VI) revealed the best results for the index BBI1_SBP8_DBP2 ($p=3.06*10^{-9}$) from group test PREG, CH, GH vs. PE. The best set of indices for multivariate discriminant analysis was presented for BBI2_SBP7_DBP2 and BBI3_SBP8_DBP12 (AUC=87.9%).

The best result from coupling analysis of NIBP and RESP (Table VII) was achieved for SBP2_DBP2_RESP12 ($p=5.89*10^{-12}$) and the best set of indices with SBP3_DBP9_RESP6 and SBP8_DBP11_RESP4 for the group test PREG, CH, GH vs. PE (AUC=90.8%).

DISCUSSION

In this study, we introduced the new SPPA3 method which is a dimensional enhancement of the 1D SPPA [5]. Hereby, SPPA3 analyzes the three dimensional phase space retaining nonlinear features of the systems' dynamics.

A cubic box model with equal dimension for each patient was chosen subdivided into 12x12x12 equal cubelets. For each cubelet the relative probability of occurrence of the included points is calculated.

First of all, it could be demonstrated that SPPA3 is suitable for analyzing both 2 and 3 different systems. In all tests highly significant differences between the selected groups could be found. Differentiating between pregnant and non-pregnant women the combination with diastolic blood pressure (BBI, DBP AND RESP) revealed higher significances than that with systolic blood pressure (BBI, SBP AND RESP). The opposite result was found when differentiating the coupling between preeclamptic and all other pregnant women. This is in accordance with Riedl et al. [4] who analyzed the coupling between respiration, blood pressure and heart rate of PREG and PE. He found that the respiratory influence on the diastolic blood pressure was significantly increased in PE patients.

The best differentiation between the selected groups was found when analyzing the coupling of three different signals representing the cardiovascular and the cardiorespiratory systems (BBI, NIBP and RESP).

Seeck et al. [11] applied SPPA to differentiate between women with hypertension pregnancy disorders and PE investigating BBI and NIBP signals. Linear discrimination analysis leads to an area under the ROC curve of 84.2% for the two-parameter set. In our study this was increased to 91.2% applying SPPA3.

Limitations of this study are, on the one side, the low sampling frequency of 200 Hz of blood pressure time series that could lead to lower precision in estimating BBI intervals which are extracted from the blood pressure signal. In further studies the BBIs should be extracted directly from the ECG. On the other side especially the probability of occurrence of points in the cubelets close to the edge are often zero, leading to diagonals in the ROC curves.

Further studies should clarify the influence of obesity on autonomic control and blood pressure and provide information about the physiological background of impaired couplings caused by hypertensive pregnancy disorders.

In conclusion, SPPA3 demonstrates a useful application to analyze couplings between 3 different time series that was demonstrated by the group test between healthy non-pregnant vs. pregnant women and for risk stratification in pregnant women suffering from preeclampsia.

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