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ORIGINAL ARTICLE

Baroreflex sensitivity, heart rate, and blood pressure variability in hypertensive pregnancy disorders

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Hypertensive pregnancy disorders are a leading cause of perinatal and maternal morbidity and mortality. Heart rate variability (HRV), blood pressure variability (BPV), and baroreflex sensitivity (BRS) are relevant predictors of cardiovascular risk in humans. The aim of the study was to evaluate whether HRV, BPV, and BRS differ between distinct hypertensive pregnancy disorders. Continuous heart rate and blood pressure recordings were performed in 80 healthy pregnant women as controls (CON), 19 with chronic hypertension (CH), 18 with pregnancy-induced hypertension (PIH), and 44 with pre-eclampsia (PE). The data were assessed by time and frequency domain analysis, nonlinear dynamics, and BRS. BPV is markedly altered in all three groups with hypertensive disorders compared to healthy pregnancies, whereby changes were most pronounced in PE patients. Interestingly, this increase in PE patients did not lead to elevated spontaneous baroreflex events, while BPV changes in both the other hypertensive groups were paralleled by alterations in baroreflex parameters. The HRV is unaltered in CH and PE but significantly impaired in PIH. We conclude that parameters of the HRV, BPV, and BRS differ between various hypertensive pregnancy disorders. Thus, distinct clinical manifestations of hypertension in pregnancy have different pathophysiological, regulatory, and compensatory mechanisms.
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Introduction

In pregnancies with hypertensive disorders, the blood pressure and vascular resistance are increased, blood volume is smaller, and blood pressure and heart rate responses to various provocations are changed compared to those of normotensive pregnant women.[1,2] The aetiology of this maladaptation of the cardiovascular system to pregnancy is unknown, but two mechanisms, the immune maladaptation and the genetic imprinting, have been discussed.[3,4] A new report of the 'Working Group on High Blood Pressure in Pregnancy'[5] classified the relevant hypertensive pregnancy disorders in chronic hypertension (CH), pregnancy-induced hypertension (PIH), and pre-eclampsia/eclampsia (PE), whereby it is discussed whether PE is PIH plus proteinuria or is characterized by its own aetiology. In the pathogenesis of hypertensive disorders in pregnancies, especially in PE, the shallow endovascular cytotrophoblast invasion in the spiral arteries[6] and the following systemic endothelial cell dysfunction of the pregnant women are two key features.[3,5] Until the pathogenesis is well defined, prevention of this group of disorders in pregnancy remains unlikely.[7]

Heart rate and blood pressure variability (HRV and BPV) are generated by the rhythmic actions of cardiovascular hormones and neuronal pathways on effector organs such as the heart, kidneys, and vessels. The analysis of HRV, BPV, and baroreflex sensitivity (BRS) is a noninvasive diagnostic tool that provides important prognostic information in cardiology concerning individual risk after acute myocardial infarction.[8,9] Whereas HRV and BRS are reduced in pregnancy in comparison with the nonpregnant status, BPV seems to be unaffected.[1,10–12] Our research group showed first that

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HRV, BPV, and BRS are not changed in the second and third trimester in normal pregnancy.[10] In PIH and PE, an increased HRV and BPV,[13–16] and a decreased BRS[12] were described compared to healthy pregnant women, whereas other groups described no differences in those variability parameters in pre-eclamptic pregnancies.[17]

The purpose of this study was to evaluate whether HRV, BPV, and BRS are different between various hypertensive disorders and in comparison to normal pregnancies. This should lead to a better understanding of the cardiovascular regulation under these probably different pathophysiological conditions. The paper should clarify whether variability parameters and BRS could be useful to distinguish between different hypertensive disorders and might be of predictive relevance.

Methods

Subjects

In this cross-sectional study, 80 healthy pregnant women (=Control, CON), 19 pregnant women with CH, 18 women with PIH and 44 women with PE were recruited from the Department of Obstetrics and Gynecology, University of Leipzig, between June 2000 and December 2002. All diagnoses at admission were confirmed 6 weeks after delivery. The classification of the hypertensive disorders is according to the 'National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy'.[5] The investigation conforms with the principles outlined in the Declaration of Helsinki. Local ethics committee approval and informed consent of all subjects have been provided.

Data acquisition and preprocessing

To analyse HRV, BPV, and BRS, synchronously high-resolution ECG (1600 Hz) and noninvasive continuous blood pressure were recorded via finger cuff (100 Hz, PORTAPRES device Model 2, BMI-TNO, Amsterdam, The Netherlands).

All measurements were performed over 30 min under standardized resting conditions between 0800 and 1200 hours as described by Voss *et al*.[10] From the ECG recordings, time series of beat-to-beat intervals (BBI) were extracted to analyse HRV. From the PORTAPRES recordings, time series of systolic beat-to-beat pressure values were extracted to analyse BPV and BRS. All time series were filtered to exclude ventricular premature beats and artefacts.

Heart rate and blood pressure variability analysis

The parameters of time domain and frequency domain were calculated regarding HRV task force standards as described before.[18] For spectral analysis, the time series were linearly interpolated by equidistant 500 ms samples. The power density spectra were estimated using the fast Fourier transform. To avoid leakage effects a Blackman–Harris window function was applied.

Symbolic dynamics, as a nonlinear approach to investigate a system's complexity, facilitates the analysis of dynamic aspects of HRV.[19] The concept of symbolic dynamics is based on a coarse graining of the dynamics. The difference between each BBI/systolic blood pressure and mean BBI/systolic blood pressure is transformed into an alphabet of four symbols (0,1,2,3). Symbols '0' and '2' reflect low deviation (decrease or increase) from mean BBI/systolic blood pressure, whereas '1' and '3' reflect a stronger deviation (decrease or increase over a predefined limit). Subsequently, the symbol string is transformed to words (bins) of three successive symbols. The distribution of word types reflects some nonlinear properties of HRV/BPV. For detailed information see Voss *et al*.[19] From this symbolic dynamics, the following parameter was calculated: WPSUM13: words that contain only symbols '1' and '3' reflecting high variability. Using a modified symbol transformation BBI differences less than 20 ms/systolic blood pressure differences less than 5 mmHg were coded as '0' and otherwise as '1'. In this way a further parameter was obtained. PLVAR20 /bPLVAR5: words of length 6 that contain only '0' reflecting a low variability.

BRS analysis

The applied method of BRS estimation involves a scanning of the beat-to-beat series of systolic blood pressure to identify a 'sequence', that is a series of three heart beats in which a monotonic increase (or decrease) of systolic pressure is followed by a monotonic increase (or decrease) of BBI, that is the time intervals between the instants of occurrence of consecutive systolic peaks. The slope of the regression line between BBI and systolic pressure values of each sequence gives a local estimate of the BRS. Using the dual sequence method[20] two kinds of BBI responses were analysed:

- bradycardiac fluctuations (an increase in SBP causes an increase in BBI); and
- tachycardiac fluctuations (a decrease in SBP causes a decrease in BBI).

The main parameters analysed in the study are described in Table 1.

Statistics

The nonparametric Kruskal–Wallis test (K–W-t) with Bonferroni–Holm correction was used to test whether there are significant differences in variables within the four investigated groups. Subsequently, the nonparametric *U*-test was applied for specific group comparisons with Bonferroni–Holm

Table 1 Definitions of standard HRV/BPV parameters according to the HRV Task Force[5] and additionally of computed nonlinear parameters of symbolic dynamics as well as of baroreceptor reflex

Variables HRV/BPV	*Unit*	*Description*
Time domain		
meanNN/smeanNN/dmeanNN	ms/mmHg	Mean BBI/systolic/diastolic blood pressure
SDNN/bSDNN	ms/mmHg	Standard deviation of all BBI/systolic blood pressure values
RMSSD/bRMSSD	ms/mmHg	Square root of the mean of the sum of all squares of differences between adjacent BBI/systolic blood pressure values
Frequency domain		
VLF/bVLF	s^2/$mmHg^2$	Power of BBI/systolic blood pressure time series in the very LF range (0.003–0.04 Hz)
LF/bLF	s^2/$mmHg^2$	Power of BBI/systolic blood pressure time series in the LF range (0.04–0.15 Hz)
HF/bHF	s^2/$mmHg^2$	Power of BBI/systolic blood pressure time series in the HF range (0.15–0.4 Hz)
LFn/bLFn	n.u.	LF power of BBI/systolic blood pressure time series in normalized units; LF/(Total Power-VLF) × 100
LF/HF/bLF/HF	n.u.	Ratio LF/HF of BBI/systolic blood pressure time series
Symbolic dynamics		
WPSUM13/bWPSUM13	n.u.	Portion of high-variability patterns in the BBI/systolic blood pressure time series
PLVAR20/bPLVAR5	n.u.	Portion of low-variability patterns in the BBI time series (<20 ms) and systolic blood pressure time series (<5 mmHg), respectively
Variables baroreflex		
all_brady	N	Number of bradycardiac baroreflex fluctuations with a slope between 2.5 and 5 ms/mmHg
brady_2.5-5	N	Number of bradycardiac baroreflex fluctuations with a slope less than 50 ms/mmHg
brady_slope	ms/mmHg	Slope of the regression line between all bradycardiac baroreflex fluctuations
all_tachy	N	Number of tachycardiac baroreflex fluctuations with a slope less than 50 ms/mmHg
tachy_2.5-5	N	Number of tachycardiac baroreflex fluctuations with a slope between 2.5 and 5 ms/mmHg
tachy_slope	ms/mmHg	Slope of the regression line between all tachycardiac baroreflex fluctuations

correction using the number of parameters significant in K–W-t. The significance level P was set at $P<0.05$.

The analysis included seven different tests:

K–W-t:
differences within CON, CH, PIH and PE;
U-test 1:
influence of CH (CON *vs* CH);
U-test 2:
influence of PIH (CON *vs* PIH);
U-test 3:
influence of PE (CON *vs* PE);
U-test 4:
difference between CH and PIH (CH *vs* PIH);
U-test 5:
difference between CH and PE (CH *vs* PE); and
U-test 6:
difference between PIH and PE (PIH *vs* PE).

Results

Clinical data

The clinical data are summarized in Table 2. While there are no differences for maternal age, gravity, and parity, the gestational week at delivery and birth weight are significantly lower in the PE group. However, the gestational week when the measurement was performed did not show variation between the four groups investigated.

Blood pressure variability

The mean blood pressure was significantly elevated in all three hypertensive disorders compared to controls (CON: 86 (81–94); CH; 93 (87–109); PIH: 94 (80–108); PE: 110 (95–125) mmHg). BPV is markedly altered in all three groups with hypertensive disorders compared to healthy pregnancies, whereby changes were most pronounced in PE patients. Compared to the controls all hypertensive disorders were characterized by an increase in the BPV parameter RMSSD (Table 3), but SDNN was unaltered in PIH.

Patients with PIH and PE were additionally characterized by a significant increase in the low-frequency (LF) parameter compared to the controls, whereas the high-frequency (HF) parameter was elevated in all three groups. The nonlinear parameter PLVAR5 was significantly decreased in all hypertensive patient collectives; WPSUM13 was altered only in pre-eclamptic patients.

However, the comparison of the hypertensive groups demonstrated that there is no single parameter of BPV able to distinguish among all groups. Importantly, PIH and CH can be distinguished by the two independent parameters LF/P and WPSUM13.

Table 2 Clinical parameters of control pregnancies (CON), pregnancies with CH, PIH, and PE as medians and interquartile ranges, K–W-t and *U*-test results

Parameter	*CON* (N = *80*)	*CH* (N = *19*)	*PIH* (N = *18*)	*PE* (N = *44*)	*K–W-t*	*CON CH*	*CON PIH*	*CON PE*	*CH PIH*	*CH PE*	*PIH PE*
Maternal age	28 (24–31)	27 (24–32)	30 (27–33)	27 (22–31)	NS	NS	NS	NS	NS	NS	NS
Gravity	2 (1–2)	1 (1–3)	1 (1–3)	1 (1–2)	NS	NS	NS	NS	NS	NS	NS
Parity	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–0)	NS	NS	NS	*	NS	NS	NS
Week of delivery	39 (38–40)	39 (37–40)	39 (38–40)	34 (31–37)	***	NS	NS	***	NS	***	***
Birth weight (g)	3245 (2973–3623)	2945 (2180–3420)	3235 (2695–3560)	1840 (1315–2560)	***	*	NS	***	*	***	***
Hypotrophy (%)	0	37	11	34	—	—	—	—	—	—	—
C section (%)	25	42	33	75	—	—	—	—	—	—	—
Week of measurement	35 (32–37)	34 (25–38)	36 (31–37)	32 (30–36)	NS	NS	NS	*	NS	NS	NS

NS = not significant; * = $P<0.05$; *** = $P<0.001$.

Table 3 Statistical analysis for parameters of BPV presented as median and interquartile ranges in control pregnancies (CON), pregnancies with CH, PIH, and PE

	CON	*CH*	*PIH*	*PE*	*K–W-t*	*CON CH*	*CON PIH*	*CON PE*	*CH PIH*	*CH PE*	PIH *PE*
SmeanNN	117 (111–130)	131 (122–148)	129 (118–142)	154 (131–168)	***	**	*	***	NS	**	**
DmeanNN	70 (65–79)	73 (69–89)	76 (61–88)	86 (76–100)	***	*	NS	***	NS	*	*
SDNN	8 (7–9)	9 (8–11)	9 (7–11)	9 (8–10)	*	**	NS	*	NS	NS	NS
RMSSD	2.5 (2.1–2.8)	3.1 (2.5–3.4)	2.9 (2.3–3.4)	3.1 (2.8–3.6)	***	**	*	***	NS	NS	NS
VLF	15 (10–23)	23 (12–30)	19 (14–33)	17 (8–23)	NS	NS	NS	NS	NS	NS	NS
LF	6 (4–8)	9 (5–12)	13 (6–17)	10 (5–16)	***	NS	**	**	NS	NS	NS
HF	1.0 (0.7–1.5)	1.5 (0.9–2.4)	1.8 (0.8–2.9)	1.3 (0.8–2.4)	**	*	*	*	NS	NS	NS
LF/HF	6.0 (4.3–8.0)	6.5 (2.7–10.3)	7.0 (4.9–11.5)	6.7 (3.9–10.5)	NS	NS	NS	NS	NS	NS	NS
LFn	0.86 (0.81–0.89)	0.87 (0.73–0.91)	0.87 (0.83–0.92)	0.87 (0.80–0.91)	NS	NS	NS	NS	NS	NS	NS
LF/p	0.19 (0.16–0.24)	0.20 (0.14–0.23)	0.25 (0.17–0.33)	0.26 (0.20–0.36)	**	NS	*	***	NS	**	NS
WPSUM13	0.30 (0.25–0.37)	0.34 (0.22–0.45)	0.32 (0.18–0.44)	0.25 (0.16–0.34)	*	NS	NS	*	NS	*	NS
PLVAR5	0.72 (0.61–0.85)	0.59 (0.35–0.75)	0.62 (0.44–0.79)	0.50 (0.36–0.66)	***	**	*	***	NS	NS	NS

Results of the K–W-t for subjects analysis and *U*-test for group comparisons (NS = not significant; * = $P<0.05$; ** = $P<0.01$; *** = $P<0.001$).

BRS

While the number of all spontaneous tachycardiac and bradycardiac events was unchanged in all patient groups (0–50), PIH and CH showed a significant increase in the number of tachycardiac and bradycardiac events between 2.5 and 5. Consequently, patients with CH and PIH showed a decreased baroreflex slope (brady_slope and tachy_slope), whereas it was unaltered in PE patients. Moreover, neither the tachycardiac and bradycardiac slopes nor the number of events differed among the three hypertensive disorders (Table 4).

HRV

The mean BBI was unchanged between controls and the hypertensive groups of CH and PE but reduced in PIH women (Table 5), leading to a significant difference between PIH and CH. Since in PE the BBI increased without reaching significance in comparison to controls, the difference between PE and PIH consequently showed a high significant difference. Correlating with impaired tachycardiac and bradycardiac slopes, the SDNN was also restricted in PIH patients.

Importantly, all other HRV parameters, frequency and nonlinear parameters did not alter between controls and hypertensive disorders and also among the three hypertensive disorders themselves.

Discussion

HRV and BPV have been shown to be relevant predictors for the mortality of patients with cardiovascular disorders.[8,9] In order to evaluate HRV and BPV as a diagnostic tool for different hypertensive pregnancy disorders, we started with this pilot study to examine whether variability parameters are different in various hypertensive diseases.

Others and we could demonstrate that BPV is not significantly altered in healthy normotensive pregnancies compared to nonpregnant women.[10,21] Our current analysis of BPV demonstrates that all three investigated hypertensive pregnancy disorders are characterized by an increase in blood pressure, but the alterations of BPV differ significantly between these groups. Interestingly, both the parasympathetic (HF) and sympathetic activity (LF) is elevated in all three disorders, indicating an activated

Table 4 Statistical analysis for parameters of BRS presented as median and interquartile ranges in control pregnancies (CON), pregnancies with CH, PIH, and PE

	CON	*CH*	*PIH*	*PE*	*K–W-t*	*CON CH*	*CON PIH*	*CON PE*	*CH PIH*	*CH PE*	*PIH PE*
all_brady	57 (36–75)	57 (40–80)	69 (36–78)	54 (37–87)	NS	NS	NS	NS	NS	NS	NS
brady_slope	7.8 (6.2–10.2)	6.4 (5.3–7.8)	6.0 (4.7–8.1)	6.7 (5.6–8.8)	**	*	*	NS	NS	NS	NS
all_tachy	54 (35–82)	60 (45–88)	53 (41–93)	53 (37–83)	NS	NS	NS	NS	NS	NS	NS
tachy_slope	6.9 (5.7–9.6)	6.0 (5.2)	5.4 (4.2–6.8)	6.4 (4.9–9.3)	*	*	**	NS	NS	NS	NS
brady_2.5-5	11 (6–18)	20 (13–29)	20 (10–26)	16 (8–25)	**	**	*	*	N.S	NS	NS
tachy_2.5-5	10 (4–19)	22 (10–33)	23 (13–34)	15 (5–29)	**	**	**	NS	NS	NS	NS

Results of the K–W-t for subjects analysis and *U*-test for group comparisons (NS = not significant; * = $P<0.05$; ** = $P<0.01$).

Table 5 Statistical analysis for parameters of HRV presented as median and interquartile ranges in control pregnancies (CON), pregnancies with CH, PIH, and PE

	CON	*CH*	*PIH*	*PE*	*K–W-t*	*CON CH*	*CON PIH*	*CON PE*	*CH PIH*	*CH PE*	*PIH PE*
MeanNN	673 (612–670)	658 (613–699)	614 (560–656)	727 (628–796)	**	NS	*	NS	NS	*	**
SDNN	44 (31–53)	37 (28–42)	33 (28–42)	43 (29–51)	NS	NS	*	NS	NS	NS	NS
RMSSD	16 (10–24)	14 (12–24)	16 (8–19)	18 (12–28)	NS	NS	NS	NS	NS	NS	NS
VLF	0.27 (0.17–0.49)	0.25 (0.11–0.37)	0.22 (0.14–0.37)	0.26 (0.17–0.45)	NS	NS	NS	NS	NS	NS	NS
LF	0.15 (0.10–0.20)	0.16 (0.06–0.22)	0.14 (0.11–0.20)	0.16 (0.07–0.25)	NS	NS	NS	NS	NS	NS	NS
HF	0.06 (0.03–0.13)	0.05 (0.03–0.09)	0.06 (0.02–0.09)	0.05 (0.02–0.10)	NS	NS	NS	NS	NS	NS	NS
LF/HF	2.5 (1.7–3.5)	2.5 (1.6–3.0)	3.2 (1.8–6.0)	2.4 (1.5–5.2)	NS	NS	NS	NS	NS	NS	NS
LFn	0.72 (0.63–0.78)	0.71 (0.61–0.75)	0.76 (0.64–0.85)	0.70 (0.59–0.84)	NS	NS	NS	NS	NS	NS	NS
WPSUM13	0.22 (0.16–0.32)	0.20 (0.09–0.26)	0.21 (0.13–0.36)	0.20 (0.09–0.32)	NS	NS	NS	NS	NS	NS	NS
PLVAR20	0.38 (0.12–0.79)	0.52 (0.17–0.67)	0.40 (0.19–0.89)	0.22 (0.03–0.63)	NS	NS	NS	NS	NS	NS	NS

Results of the (K–W-t) for subjects analysis and *U*-test for group comparisons (NS = not significant; * = $P<0.05$; ** = $P<0.01$).

autonomic system. However, PE patients show the most pronounced increase in BPV compared to normotensive pregnant women, which is illustrated, for example, by a shift in the linear frequency domains as also demonstrated for PIH.

Consequently, the increased BPV in PIH and the less stimulated one in CH cause a rise in BRS that is characterized by an increase in baroreceptor activity with a slope between 2.5 and 5, and consequently to a decrease in tachycardiac and bradycardiac slopes. In contrast, the sensitivity and the number of reflex events are unchanged in PE compared to healthy pregnant women, although these patients showed the most alterations in BPV. However, it should be at least mentioned that healthy normotensive pregnancies are characterized by a significant reduction of baroreflex events[10,22] that could be explained by an increase in baroreflex threshold. Thus, it cannot be distinguished whether the discovered increase in baroreflex events in PIH is caused exclusively by an increased BPV or at least partly by a threshold shift. But importantly, our data clearly demonstrate that the unaltered number of baroreflexes by dramatic increased BPV in PE patients is mediated by an increase in the threshold for baroreflex events.

We did not find any HRV differences between the hypertensive groups and the control when only nonlinear time domains and frequency parameters are taken into consideration. However, SDNN as a time domain parameter is at least partly altered. The decreased SDNN in PIH reflects an impaired HRV in these patients. The fact that parameters of symbolic dynamics as WPSUM13 and PLVAR20 are unaltered in all three investigated hypertensive disorders is important, as symbolic dynamics is an approach to investigate complex nonlinear systems, facilitating HRV dynamics,[19,23] but might be caused by the short-term HRV analysis about only 30 min. Regarding the complexity of the total system of sinus node activity modulation, a more predominant nonlinear characteristic would be assumed.[23]

The BPV data implicate an activated autonomic system for all the three hypertensive disorders. That this activation does not cause HRV changes implicates a general activation of the sympathicus during pregnancy as demonstrated by our group recently.[10] The general increase in heart rate does not allow a further sympathetic stimulation in the pathophysiological status.

In summary, the increase of blood pressure in PE seems to be caused by an increased sympathetic activity without pathological alterations of HRV caused by an increase in baroreflex threshold leading to a normal number of baroreflex events by increased blood pressure fluctuations. In contrast, in individuals with PIH and CH the increased BPV correlates with elevated baroreflex events. Thus, similar alterations can be observed between pregnancies with CH or PIH, although the pathogenesis is very different.

Since the better perinatal outcome of PIH and CH pregnancies and their postnatal reversibility of the alterations compared to PE that is defined as a multisystem disorder due to a disturbed placental development followed by endothelial dysfunction and severe complications,[5,24] it should be firstly concluded that the impaired HRV in PIH is not as negative as discussed for patients with cardiovascular diseases.[8,9] Secondly, the depressed baroreflex sensitivity in PE patients as indicated by increased BPV, but a normal number of baroreflex events compared to controls, could have a negative impact for the perinatal outcome.

We are the first to show that various hypertensive disorders in pregnancy are different in BPV, BRS, and HRV, indicating that all three investigated hypertensive disorders (CH, PIH, and PE) have, at least, partly different regulatory mechanisms. Further studies have to demonstrate the predictive value of these parameters and its applicability as an ambulatory test to distinguish between different hypertensive disorders in pregnancy.

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