Original Article

Longitudinal Analysis of Heart Rate Variability in Chronic Hypertensive Pregnancy

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In the US, it is currently estimated that 3% of pregnant women have chronic hypertension, or more than 100,000 pregnant women each year. The aim of our study was to investigate the adaptation of autonomic control during pregnancy based on heart rate variability analysis and to determine whether chronic hypertension during pregnancy has an impact on this adaptation. Sixteen pregnant women with chronic hypertension (CH group; mean age, 30 years; range, 25–33 years) and 35 healthy pregnant women serving as controls (CON group; mean age, 28 years; range, 24–30 years) were recruited for this longitudinal study. Beginning at the 20th week of pregnancy, the women were monitored every 4th week until delivery. For the analysis of heart rate variability, Portapres signals (200 Hz) were recorded for 30 min under resting conditions. Women in the CH group had significantly elevated blood pressure compared to controls (CON, 111 mmHg [105–132]; CH, 140 mmHg [132–148]; $p<0.001$). An increased heart rate was found in both groups during the second half of pregnancy. Consequently, decreased heart rate variability was observed, but was more pronounced in the CON group. There was a shift in the frequency bands indicated by an elevation of the low-to-high frequency ratio (LF/HF) in both groups due to a decrease in HF, and thus a significant increase in LFn (LF power in normalized units). However, VLF (power of very low frequency range) increased exclusively in the CON pregnancies. Our data showed no significant difference in heart rate variability between the subjects of the CH and CON groups. Longitudinal variations were detectable in normal pregnancies and also, albeit to a lesser degree, in chronic hypertensive pregnant women. Thus, our data indicate that patients with long-term hypertension are still able to respond to the physiological changes occurring during pregnancy. (*Hypertens Res* 2005; 28: 113–118)

***Key Words*: heart rate variability, normotensive pregnancy, chronic hypertensive pregnancy**

Introduction

The analysis of heart rate variability (HRV), blood pressure variability (BPV), and baroreflex sensitivity (BRS) has become a powerful tool for the assessment of autonomic control. HRV, BPV, and BRS measurements have proven to be independent predictors for sudden cardiac death after acute myocardial infarction, chronic heart failure, or dilated cardiomyopathy (*1–3*). However, the underlying regulatory mechanisms are still poorly understood. Short-term blood pressure regulation is mainly accomplished by neural sympathetic- and parasympathetic-mediated cardiac baroreflexes and peripheral vessel resistance, whereas long-term regulation is achieved by hormonal pathways as well as other systems such as the renin-angiotensin-system (*4*). Although HRV analysis

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Table 1. Clinical Parameters of Control Pregnancies (CON) and Pregnancies with Chronic Hypertension (CH) as Medians and Interquartile Ranges, Mann-Whitney *U*-Test or the χ^2 Test for Equality of Proportions

Parameter	CON (N=35)	CH (N=16)	p
Maternal age (years)	28 (24–30)	30 (25–33)	n.s.
Parity	0 (0–1)	0 (0–2)	n.s.
Gravity	2 (1–3)	2 (1–4)	n.s.
Week of delivery	39 (39–40)	39 (37–40)	n.s.
Birth weight (g)	3,430 (3,100–3,660)	2,795 (2,215–3,435)	*
Rate of section (%)	29	44	n.s.
Hypotrophy (%)	0	44	*

n.s., not significant; *$p<0.05$.

was initially developed for risk stratification in cardiology (*1–3*), the field of clinical application has broadened in recent years. For example, variability analysis is suitable for quantifying pregnancy-induced adaptations of autonomic control. Several studies have reported reductions in parasympathetic tone and BRS in normotensive pregnant women during the 2nd and 3rd trimester (*5–7*). Women with chronic hypertension have an increased risk for superimposed preeclampsia and abruption placentae as well as for life-threatening maternal complications such as pulmonary oedema, hypertensive encephalopathy, retinopathy, cerebral hemorrhage, and acute renal failure. Moreover, the fetal and neonatal complications are increased in women with chronic hypertension (*8*).

The impact of chronic hypertension on autonomic control has been investigated in several studies. For example, it has been shown that essential hypertension leads to a reduction in HRV depending on the degree of severity (*9–11*). However, to the best of our knowledge, the impact of chronic hypertension on pregnancy-induced autonomic adaptation has not yet been investigated. Thus, the aim of this study was to investigate the adaptation of autonomic control during pregnancy without gestation-related complications based on HRV analysis, and to determine whether chronic hypertension during pregnancy has an impact on this adaptation.

Methods

Subjects

In this longitudinal study, 35 healthy pregnant women (CON group; age: 28 [24–30] years) and 16 pregnant women with chronic hypertension (CH group; age: 30 [25–33] years) were recruited from the Department of Obstetrics and Gynecology, University of Leipzig, between June 2000 and December 2002. Gravidity and parity of single pregnancies were comparable between the two groups (Table 1). The health status of the CON subjects was confirmed by history and ultrasound examination in the first trimester. Patients with CH were classified by the definition of the ISSHP (task force) (*12*). Briefly, these patients were characterized by mild or moderate (stage 1 or 2) essential hypertension (diastolic blood pressure less than 110 mmHg or systolic blood pressure less than 180 mmHg), comparable to the low-risk group as defined by Sibai (*8*).

Beginning around the 20th week of pregnancy, women were monitored every 4th week until delivery and underwent at least three measurements to be included in this study. In addition to ECG recording, women were examined by ultrasound sonography. None of the CON subjects developed a hypertensive disorder or any other gestation-related disease. Consequently, no drugs were administered. CH patients were receiving different blood pressure-lowering treatments, *i.e.*, α-methyldopa (n=8), hydralazine (n=3), or β-receptor blockers (n=5). Antihypertensive medications being taken before pregnancy were continued at a fixed dose throughout the study period. CH patients were excluded if they had a preexisting disease influencing autonomic function, such as diabetes, or if they developed a gestation-related disease (*e.g.*, super-imposed hypertension [stage 3], abruptio placentae, or super-imposed preeclampsia) or postpartum complications such as pulmonary edema, renal failure, or hypertensive encephalopathy. This investigation conforms to the principles outlined in the Declaration of Helsinki, and was approved by the ethics committee of our institution. All subjects gave their informed written consent to participate.

Data Acquisition and Preprocessing

To analyze HRV, Portapres signals (200 Hz) were recorded. All measurements were performed over 30 min under standardized resting conditions between 8 AM and 12 AM as described by Voss *et al*. (*5*). From these 30-min recordings, time series of beat-to-beat intervals (BBI) were extracted to analyze HRV. All time series were filtered to exclude ventricular premature beats and artifacts (*13*).

HRV Analysis

The parameters of time domain and frequency domain were calculated from the complete recordings regarding HRV task force standards as described previously (*14*). For spectral analysis, the time series were linearly interpolated by equidis-

Table 2. Definitions of Heart Rate Variability Parameters According to the HRV Task Force (*14*) as Well as of Symbolic Dynamic Parameters

	Unit	Description
Time domain		
meanNN	ms	Mean BBI blood pressure
SDNN	ms	SD of all BBI values
RMSSD	ms	The square root of the mean of the sum of all squares of differences between adjacent BBI values
Frequency domain		
VLF	s^2	Power of BBI time series in the very low frequency range (0.003–0.04 Hz)
LF	s^2	Power of BBI time series in the low frequency range (0.04–0.15 Hz)
HF	s^2	Power of BBI time series in the high frequency range (0.15–0.4 Hz)
LFn	n.u.	LF power of BBI time series in normalized units; LF/(total power −VLF)
LF/HF	n.u.	Ratio LF/HF of BBI time series
Symbolic dynamics		
WPSUM13	n.u.	Portion of high variability patterns in the BBI time series
PLVAR20	n.u.	Probability of intermittently low variability (successive BBI differences <20 ms)

BBI, beat-to-beat interval.

tant 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 dynamical aspects of short-term HRV series (*13*, *15*) in cases where other nonlinear methods are not applicable (*16*, *17*). The concept of symbolic dynamics is based on a coarse-graining of the dynamics. The difference between each BBI and mean BBI is transformed into an alphabet of 4 symbols (0, 1, 2, 3). Symbols 0 and 2 reflect low deviations (decrease or increase) from mean BBI, whereas 1 and 3 reflect stronger deviations (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 certain nonlinear properties of HRV. From this symbolic dynamics, we calculated the parameter WPSUM13 (see Table 2) (*18*), which consists of those words that contain only the symbols reflecting high variability, *i.e.*, 1 and 3.

Using a modified symbol transformation, successive BBI differences less than 20 ms were coded as 0 and those greater than 20 ms as 1. In this way a further parameter was obtained: PLVAR20, defined as the percentage of length-6-words that contain only 0, reflecting a low variability (see Table 2).

Statistics

To assess pregnancy-induced changes of autonomic control, we formed five groups with respect to the monthly interval of monitoring:

18–22 wG: 20th week of gestation (wG), including 27 CON and 10 CH measurements;

23–26 wG: 24th wG, including 33 CON and 14 CH measurements;

27–30 wG: 28th wG, including 34 CON and 16 CH measurements;

31–34 wG: 32nd wG, including 29 CON and 13 CH measurements; and

35 wG–end: 37th wG, including 27 CON and 12 CH measurements.

The non-parametric Kruskal-Wallis-Test was applied to the CON as well as the CH subjects to test whether the parameters changed significantly during the investigated intervals of gestation. Although the Friedman-Test seems to be more appropriate to test for longitudinal parameter changes, we decided to apply the Kruskal-Wallis test, because we were more interested in intra-group differences than intra-subject changes. Furthermore, the non-parametric Mann-Whitney *U*-test was used for interval-based as well as for the clinical parameter comparisons between the CON and CH groups. To test for equality of proportions and independence, the χ^2 test for equality of proportions for independent samples was applied. Values of $p<0.05$ were considered to indicate statistical significance, and group summaries were presented as medians (interquartile range).

Results

Patient Characteristics

Maternal age, parity, and gravity did not differ between the CON and CH subjects. The birth weight was lower in the chronic hypertensive pregnancies, and the number of newborns with hypotrophy and the rate of Cesarean sections were increased (Table 1).

Heart-Rate Variability

In the HRV analysis, an increase in heart rate (=decreased meanNN) was seen during the second half of pregnancy in

Table 3. Parameters Heart Rate Variability (HRV) Presented as Median and Interquartile Ranges in Control Pregnancies (CON) and Pregnancies with Chronic Hypertension (CH)

Parameter	18–22 wG	23–26 wG	27–30 wG	31–34 wG	35 wG–end	KW-test
	CON: *N*=27 CH: *N*=10	CON: *N*=33 CH: *N*=14	CON: *N*=34 CH: *N*=16	CON: *N*=29 CH: *N*=13	CON: *N*=27 CH: *N*=12	
CON						
meanNN	725 (678–771)	689 (639–744)	677 (606–734)	633 (596–670)	663 (576–691)	0.00003
SDNN	36 (31–43)	36 (27–44)	36 (31–48)	39 (29–47)	44 (33–49)	n.s.
RMSSD	18 (14–28)	20 (10–24)	14 (11–19)	13 (8–19)	13 (9–20)	0.01
VLF	174 (131–258)	161 (122–258)	245 (155–300)	247 (200–414)	369 (233–573)	0.0001
LF	110 (85–178)	93 (59–162)	112 (77–156)	105 (75–210)	134 (106–185)	n.s.
HF	76 (41–181)	57 (28–167)	53 (35–93)	46 (23–97)	49 (30–127)	n.s.
LF/HF	1.3 (0.8–2.2)	1.4 (0.9–2.4)	2.1 (1.4–3.2)	2.5 (1.9–4.2)*	2.7 (2.0–3.5)	0.0006
LFn	0.56 (0.45–0.69)	0.58 (0.48–0.70)	0.68 (0.58–0.76)	0.71 (0.65–0.81)*	0.73 (0.67–0.78)	0.0006
WPSUM13	0.14 (0.08–0.17)	0.15 (0.09–0.21)	0.20 (0.14–0.33)*	0.24 (0.16–0.36)	0.30 (0.22–0.44)	0.000003
PLVAR20	0.22 (0.03–0.50)	0.15 (0.07–0.78)	0.44 (0.21–0.69)	0.53 (0.32–0.89)	0.59 (0.15–0.88)	0.0009
CH						
meanNN	757 (665–806)	677 (631–748)	662 (601–729)	631 (584–694)	661 (625–703)	0.06
SDNN	37 (30–47)	32 (25–47)	30 (27–39)	36 (22–45)	36 (31–44)	n.s.
RMSSD	23 (13–35)	14 (11–24)	14 (9–21)	12 (8–15)	14 (11–21)	0.08
VLF	201 (96–309)	202 (136–314)	188 (144–266)	205 (122–376)	274 (133–366)	n.s.
LF	109 (89–237)	106 (78–209)	120 (70–155)	123 (75–182)	180 (100–227)	n.s.
HF	91 (36–184)	49 (26–89)	45 (25–81)	24 (17–44)	65 (24–77)	n.s.
LF/HF	2.3 (0.7–2.7)	2.9 (1.0–4.0)	2.5 (1.7–4.0)	4.3 (3.2–6.5)*	2.8 (2.5–6.3)	0.003
LFn	0.70 (0.40–0.73)	0.74 (0.50–0.80)	0.71 (0.63–0.80)	0.81 (0.76–0.87)*	0.74 (0.72–0.86)	0.003
WPSUM13	0.13 (0.09–0.15)	0.13 (0.07–0.19)	0.12 (0.09–0.23)*	0.18 (0.10–0.28)	0.20 (0.14–0.27)	n.s.
PLVAR20	0.17 (0.02–0.56)	0.49 (0.14–0.72)	0.49 (0.13–0.87)	0.68 (0.57–0.89)	0.51 (0.31–0.76)	0.04

Results of the Kruskal-Wallis-Test (KW-test; n.s., not significant) for subjects analysis and *U*-test for group comparisons (*$p<0.05$).

both groups, but was more pronounced in the CON group. The analysis of linear HRV parameters revealed a decrease in both groups as indicated by a reduced RMSSD (Table 3, Fig. 1C).

There was a shift in the frequency bands during the second half of pregnancy. While the low-to-high frequency ratio (LF/HF) was elevated in both groups due to a slight decrease in HF, as was also illustrated by the significantly increased LFn, VLF was increased exclusively in the CON subjects (Table 3, Fig. 1A).

In the analysis of nonlinear parameters, PLVAR20 was higher in both groups, whereas WPSUM13 continuously increased only in the CON group (Fig. 1B), which reflects the higher dynamics in normal pregnancies. Furthermore, there were few significant inter-group differences: in the 27–30 wG subjects, there was a significant difference in the non-linear parameter WPSUM13, and in the 31–34 wG group, there were significant differences in the frequency domain parameters LF/HF and LFn.

Although longitudinal differences occurred earlier in the CH than the CON group (approximately 4-week shift: 23–26 wG *vs.* 27–30 wG) as indicated for example for the decrease of the linear parameter RMSSD and the increase of the non-linear parameter PLVAR20 (Fig. 1C and D), this difference did not reach the level of statistical significance for single parameters.

Discussion

In previous studies, we demonstrated that the parameter domains of HRV, BPV and BRS in the second half of normal pregnancy show a high degree of stability in relation to maternal and gestational age (*5*). Thus, we concluded that this method could be a useful tool to detect pathophysiological changes, particularly in hypertensive pregnancy disorders. Recently, we analyzed various hypertensive disorders in a cross-sectional study after clinical diagnosis (CH, pregnancy-induced hypertension [PIH], and preeclampsia [PE]) and found differences in BPV and HRV in the last weeks of pregnancy, indicating that CH, PIH and PE have at least some different regulatory mechanisms (*19*). This paper was also the first to investigate BRS in pregnancy disorders, demonstrating that increased BPV correlates with elevated baroreflex events in individuals with CH.

Hermida *et al*. first described alterations of circadian variability in longitudinal-measured pregnancies with PE (*20*). However, no data were available on possible differences in

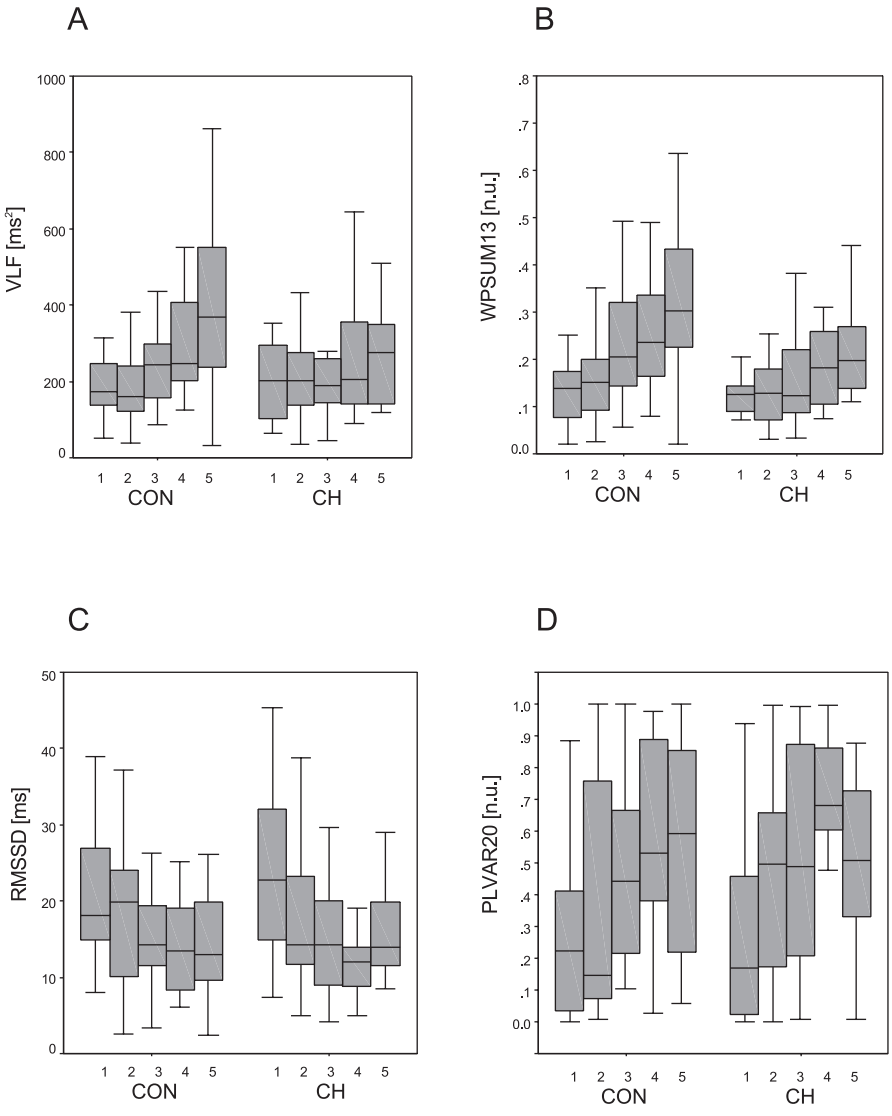

Fig. 1. *Box plot analysis of the HRV parameters VLF (A) and WPSUM13 (B) as well as RMSSD (C) and PLVAR20 (D). The five data bars reflect the following intervals of monitoring: 1: 18–22 wG; 2: 23–26 wG; 3: 27–30 wG; 4: 31–34 wG; 5: 35 wG–end. CON, controls/healthy pregnancies; CH, pregnancies with chronic hypertension.*

cardiovascular regulation in pregnancies with chronic hypertension compared to normal pregnancies. Thus, the aim of our first longitudinal study was to determine whether HRV is also regulated differently in pregnancies with chronic hypertension.

In the HRV analysis, an increase in heart rate and a consequently decreased HRV were found during the second half of pregnancy in both groups, but the increase was more pronounced in CON, which agrees with earlier studies investigating heart rate in healthy pregnancies (*21*). The increase in heart rate results from an increased cardiac output as a consequence of the elevated blood volume. The decreased HRV, as illustrated for example by RMSSD und PLVAR20, reflects the reduced respiratory sinus arrhythmia (RSA) in the second and third trimester due to restricted breathing depth. This HRV suppression is primary because both groups demonstrate these alterations.

Interestingly, although the unaltered SDNN would implicate that the HRV was unchanged in both groups, the introduction of a more complex analysis using a time- and frequency-domain as well as non-linear parameters revealed highly significant longitudinal differences. For example, there was a shift in the frequency bands during the second half of pregnancy: while LF/HF was elevated in both groups due to a slight decrease in HF, VLF increased exclusively in the CON subjects (Table 3, Fig. 1). This missing VLF increase in patients with CH could be a consequence of an impaired ability to adapt to pregnancy-controlled regulation. Although we

cannot exclude the possibility that the antihypertensive drugs had an impact on the variability parameters, such an effect would seem to be limited, since the CH patients were taking the same medications as prior to the pregnancy. Since chronic hypertension itself can be caused by one or more underlying disorders, such as renal disease (glomerulonephritis, interstitial nephritis, polycystic kidneys, renal artery stenosis), collagen vascular disease (lupus, scleroderma), endocrine disorders (diabetes mellitus with vascular involvement, pheochromocytoma, thyrotoxicosis, Cushing's disease, hyperaldosteronism), or coarctation of the aorta, impaired reactibility of the vasculature and restricted function of such end-organs as the heart and kidney have to be expected.

However, since most of the described longitudinal alterations in HRV can still be observed in chronic hypertensive pregnancies, although less markedly, these variability parameters seem to be predominantly regulated by pregnancy and not by pathophysiological alterations such as chronic hypertension. This is further supported by the fact that almost no significant differences were found in a comparison between the two groups at all time points, and suggests that patients with long-term hypertension are still able to respond to the physiological changes occurring during pregnancy.

References

1. Kleiger RE, Miller JP, Bigger JT, Moss AJ: Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; **59**: 256–262.
2. Tsuji H, Larson MG, Venditti FJ, *et al*: Impact on reduced heart rate variability on risk for cardiac events. *Circulation* 1996; **94**: 2850–2855.
3. Szabo BM, van Veldhuisen DJ, van der Veer N, Brouwer J, De Graeff PA, Crijns HJ: Prognostic value of heart rate variability in chronic congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol* 1997; **79**: 978–980.
4. Berntson GG, Bigger JT, Ckberg DL, *et al*: Heart rate variability: origins, methods, and interpretative caveats. *Psychophysiology* 1997; **34**: 623–648.
5. Voss A, Malberg H, Schumann A, *et al*: Baroreflex sensitivity, heart rate, and blood pressure variability in normal pregnancy. *Am J Hypertens* 2000; **13**: 1218–1225.
6. Kuo CD, Chen GY, Yang MJ, Lo HM, Tsai YS: Biphasic changes in autonomic nervous activity during pregnancy. *Br J Anaesth* 2000; **84**: 323–332.
7. Avery ND, Wolfe LA, Amara CE, Davies GA, McGrath MJ: Effects of human pregnancy on cardiac autonomic function above and below ventilatory threshold. *J Appl Physiol* 2001; **90**: 321–328.
8. Sibai BM: Chronic hypertension in pregnancy. *Obstet Gynecol* 2002; **100**: 369–377.
9. Guzzetti S, Piccaluga E, Casati R, *et al*: Sympathetic predominance in essential hypertension: a study employing spectral analysis of heart rate variability. *J Hypertens* 1988; **6**: 711–717.
10. Iwane M, Arita M, Tomimoto S, *et al*: Walking 10,000 steps/day or more reduces blood pressure and sympathetic nerve activity in mild essential hypertension. *Hypertens Res* 2000; **23**: 573–580.
11. Mussalo H, Vanninen E, Ikaheimo R, *et al*: Heart rate variability and its determinants in patients with severe or mild essential hypertension. *Clin Physiol* 2001; **21**: 594–604.
12. National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy: Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000; **183**: 1–22.
13. Wessel N, Voss A, Malberg H, *et al*: Nonlinear analysis of complex phenomena in cardiological data. *Herzschr Elektrophys* 2000; **11**: 159–173.
14. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996; **93**: 1043–1065.
15. Kurths J, Voss A, Witt A, Saparin P, Kleiner HJ, Wessel N: Quantitative analysis of heart rate variability. *Chaos* 1995; **5**: 88–94.
16. Pincus SM, Gladstone IM, Ehrenkranz RA: A regularity statistic for medical data analysis. *J Clin Monit* 1991; **7**: 335–345.
17. Iyengar N, Peng CK, Morin R, Goldberger AL, Lipsitz LA: Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics. *Am J Physiol* 1996; **271**: R1078–R1084.
18. Voss A, Kurths J, Kleiner HJ, *et al*: The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death. *Cardiovasc Res* 1996; **31**: 419–433.
19. Faber R, Baumert M, Stepan H, Voss A, Walther T: Baroreflex sensitivity, heart rate and blood pressure variability in hypertensive pregnancy disorders. *J Hum Hypertens* 2004; **18**: 135–137.
20. Hermida RC, Ayala DE, Mojon A, *et al*: Blood pressure patterns in normal pregnancy, gestational hypertension, and preeclampsia. *Hypertension* 2000; **36**: 149–158.
21. Stein PK, Hagley MT, Cole PL, Domitrovich PP, Kleiger RE, Rottman JN: Changes in 24-hour heart rate variability during normal pregnancy. *Am J Obstet Gynecol* 1999; **180**: 978–985.