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Increased Sympathetic Activity Present in Early Hypertensive Pregnancy is Not Lowered by Plasma Volume Expansion

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Objective: To evaluate whether sympathetic activity is increased in early-onset hypertensive pregnancy and whether this can be influenced by management with plasma volume expansion. *Methods:* The study group consisted of 74 subjects, of which 37 had early-onset hypertensive disorders of pregnancy (preeclampsia or gestational hypertension with fetal growth restriction), who were included at 24 to 34 weeks in a randomized controlled trial of management with (n = 18) or without (n = 19) plasma volume expansion. Heart rate and blood pressure variabilities, LF/HF ratio for heart rate, baroreflex sensitivity, and phase difference at low frequency (LF≈0.1 Hz) were calculated by spectral analysis from continuous heart rate and blood pressure recordings of the finger pulse wave (Portapres™, TNO). Measurements were performed at inclusion, after 20 to 40 hours and after 65 to 100 hours. The control group consisted of 29 women with a normal pregnancy and 8 women who had late-onset preeclampsia after 34 weeks. Controls were measured at 32 weeks. All controls had a normal blood pressures at that time. *Results:* LF variability of heart rate and blood pressure were significantly higher and baroreflex sensitivity was significantly lower in early-onset patients compared with normal controls. A significant trend towards higher LF variability of blood pressure and lower baroreflex sensitivity was found from normal controls to late-onset controls to early-onset patients. Parameters of sympathetic activity were not influenced by plasma volume expansion. *Conclusion:* Sympathetic activity was increased in early-onset hypertensive pregnancy. However, this was not affected by management with plasma volume expansion, suggesting that hypovolaemia in preeclampsia is a secondary phenomenon.

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INTRODUCTION

Hypertensive disorders of pregnancy are characterized by increased blood pressure, systemic vascular resistance, and reduced plasma volume (1,2). The vascular regulation by the autonomic nervous system has been implicated in the pathophysiology of the disorder. Higher sympathetic activity, measured by microneurography, has been reported in pregnancy induced hypertension and preeclampsia (3–5). Evidence on autonomic nervous system activity estimated by non-invasive methods are inconclusive, but in established pregnancy induced hypertension and preeclampsia an attenuation of parasympathetic influence and increase of the sympathetic influence of the autonomic nervous system, and a decrease in baroreflex control of heart rate have been shown (6–8). Sympathetic hyperactivity might already be present before the clinical presentation of the disorder (9).

In a state of reduced plasma volume, increased vasoconstriction is probably essential to secure blood flow to vital organs. Assuming an association between low plasma volume, vasoconstriction and high sympathetic activity, it could be hypothesized that plasma volume expansion would diminish sympathetic activity. Especially in a group of patients with early hypertension of pregnancy (*i.e.*, between 24 and 34 weeks of gestational age), reduction of sympathetic activity by plasma volume expansion may be an important target for therapy.

The first aim of this study was to compare sympathetic activity in subjects with a normal pregnancy, subjects who would later develop preeclampsia after 34 weeks and patients with clinical signs of early hypertensive disorders of pregnancy before 34 weeks. We hypothesized that sympathetic activity would be elevated in the pre-clinical stage, and still higher in patients with overt disease. The second aim was to evaluate the effect of management with plasma volume expansion on sympathetic activity in patients with overt disease. We hypothesized that management with plasma volume expansion would decrease sympathetic activity.

METHODS

Subjects and Protocol

All studies were performed in the Academic Medical Centre, the university hospital of the University of Amsterdam, The Netherlands. Subjects and patients gave written informed consent and all procedures were approved by the local medical ethics committee. The research group consisted of consecutively

recruited participants in a randomized controlled trial, that compared management strategies with or without plasma volume expansion (10, 11). This study included patients with a gestational age between 24 and 34 weeks and either severe preeclampsia, pregnancy induced hypertension with fetal growth restriction, hemolysis elevated liver enzymes low platelets (HELLP) or eclampsia(12–14). Recruitment for the present study was in 2001/2002 and was restricted to one of the participating centres. Severe preeclampsia was defined as a diastolic blood pressure of ≥110 mm Hg (measured auscultatory using Korotkoff 5), and proteinuria ≥0.3 g/24h (or 0.5 g/L or ≥++ dipstick); pregnancy induced hypertension as a diastolic blood pressure of ≥90 mm Hg (Korotkoff 5) measured on two occasions; foetal growth restriction as an estimated foetal weight below the 10^{th} centile; (14) HELLP-syndrome as a platelet count $<100 \times 10^9$/L and aspartate aminotransferase ≥70 U/L and lactate dehydrogenase ≥600 U/L or haptoglobin <0.4; eclampsia as generalized convulsions in pregnancy, not caused by epilepsy.

Patients who were allocated to the plasma volume expansion group received 250 mL HydroxyEthylStarch (HES) 6% (200/0.5) twice daily in 4 hours. Restricted amounts of NaCl 0.9% were infused with intravenous medication and in-between doses of HES. In both randomization groups antihypertensive medication strategies were logged and medications used were alpha-methyldopa, labetalol, ketanserine, nifedipine, and magnesium sulphate.

One control group consisted of women who remained normotensive (diastolic blood pressure <90 mm Hg) during pregnancy and delivered an infant with a birth weight $>10^{th}$ centile. A second control group consisted of women who developed preeclampsia (diastolic blood pressure ≥90 mm Hg and proteinuria ≥0.3 g/24 h or dipstick more than 1+) after 34 weeks of gestation. Both the normal control group and the late-onset control group had been recruited between June 1999 and February 2001, and had participated in a previously published longitudinal study of autonomic control before and during pregnancy (9). The measurements performed at 32 weeks were used as reference in this study. All women in both control groups had normal blood pressure at that time (diastolic blood pressure <90 mm Hg).

Measurement Procedure

Continuous heart rate and blood pressure registration was performed by non-invasive finger arterial pressure waveform registration of the left hand by Portapres™ (TNO/BMI Amsterdam, The Netherlands), as previously described (9). In summary, studies took place in a quiet room with an ambient temperature between 20 and 22 °C. An appropriate size finger cuff was applied at the middle finger, which was held at heart level, to avoid hydrostatic pressure influences. Portapres is a device for the measurement of finger

arterial blood pressure on a beat-to-beat basis, validated for continuous recordings by spectral analysis. At a stable signal the pressure registration was corrected for the pressure decay over the arm by the return to flow method. Data were collected after stabilization for a period of 10 minutes supine rest. In the early-onset group, the procedure was performed at admission (t0), and was repeated after 20 to 40 hours (t1) and after 65 to 100 hours (t2), unless the subject had delivered. In both control groups, a similar measurement procedure had been performed at 32 weeks.

Data Analysis

Data analysis was performed using the Beatfast program (TNO/BMI, Amsterdam, The Netherlands), as previously described (9). Continuous recordings of blood pressure and pulse interval during 10 minutes supine rest were quantified in the low frequency (LF, 0.04 to 0.15 Hz) and high frequency (HF, 0.15 to 0.4 Hz) bands by the Discrete Fourier transform algorithm (Matlab™). The HF oscillations of heart rate and blood pressure are mainly due to vagus nerve activity, and are linked with the breathing pattern. The LF oscillations of blood pressure are mediated by sympathetic activity and the LF oscillations of heart rate are baroreflex mediated by combined vagal and sympathetic activity (14). Sympathetic dominance of heart rate was estimated by dividing heart rate power in the LF-band by that in the HF-band (LF/HF ratio) (16, 17). From simultaneous spectral analysis of heart rate and blood pressure variability, a quantitative assessment of the overall sensitivity of the cardiac branch of the baroreflex was obtained. Baroreflex sensitivity (BRS) was quantified by α-index, which was computed as the square root of the ratio between the powers of the pulse interval (RRI) and systolic blood pressure (SBP) ($\alpha = \sqrt{[RRI_{power} / SBP_{power}]}$) for the LF-band; additionally, the phase difference between blood pressure and heart rate in the LF-band was computed. Modulation of vagus nerve activity causes changes in heart rate within the same or the next beat after a change in blood pressure, whereas sympathetically mediated changes in heart rate occur after 2 to 3 seconds. This reflex delay leads to a phase difference between blood pressure and heart rate oscillations. The larger the contribution of the sympathetic nervous system at a specific frequency, the larger the phase difference. We considered BRS and phase difference significant if coherence between blood pressure and heart rate oscillations exceeded 0.5 (18).

First, we compared baseline characteristics of the early-onset hypertensive patients on admission in the study with normal controls and late-onset controls. As heart rate significantly influences spectral analysis, the groups were matched for heart rate, with a maximum difference <10 bpm. Matching was at random by computer between early-onset patients and normal controls (1:1) and between late-onset controls and normal controls (1:3) (19). Second,

the intra-individual changes between the measurement at t0 and t1, and at t0 and t2 were compared between the early-onset patients treated with and those treated without plasma volume expansion. To examine possible interfering factors, we also analysed differences in clinical subgroups, as well as the influence of medication on outcome. Statistical analysis was performed with SPSS version 12. Values were expressed by median and range. Data between groups were compared by Kruskal-Wallis non-parametric tests and differences were considered statistically significant if $p < 0.05$.

RESULTS

Autonomic Regulation in Early-Onset Hypertensive Pregnancy and Controls

In total, 74 subjects underwent the procedures, 37 patients with early-onset hypertensive disorders of pregnancy, of whom 18 were treated with plasma volume expansion (trial treatment) and 19 without (trial control); 29 normal controls and 8 late-onset preeclampsia controls were also included. Baseline characteristics between groups were comparable, except for ethnicity with 24% non-Caucasian in the early-onset patients (Table 1). In this group, 11 patients had (H)ELLP-syndrome, 7 had severe preeclampsia and the remaining 19 patients had hypertension and foetal growth restriction. Diastolic and systolic blood pressures were by definition significantly higher in the early-onset patients group than in the normal control group or the late-onset control group. In both control groups, no subjects used medication. Five of the early-onset patients used MgSO4 and 14 used mono- or combination antihypertensive therapy: methyldopa ($n = 10$), nifedipine ($n = 7$), ketanserine ($n = 4$) or labetalol ($n = 3$) on admission.

The data were matched for heart rate as described in the methods, and as a result, 26 early-onset patients were matched with 26 normal controls, and 8 late-onset controls were matched with 24 normal controls (1:3) (Table 2). Three normal controls could not be matched due to differences in heart rate. Notwithstanding the matching procedure heart rate in early-onset patients group was lower than in both control groups. Total blood pressure variability and blood pressure variability in the LF-band were significantly higher in the early-onset patients group compared to both controls groups, and a significant trend towards higher values in the LF variability was found from normal controls to late-onset controls to early-onset patients (Figure 1-A). Heart rate variability in the LF-band was significantly higher in early-onset patients than in normal controls and non-significantly higher than in late-onset controls. Total heart rate variability and LF/HF ratio were non-significantly higher in early-onset patients compared to both control groups. The BRS was significantly lower in early-onset patients than in normal controls, and a

Table 1: Baseline characteristics at inclusion of normal controls, late-onset controls, and early-onset hypertensive patients.

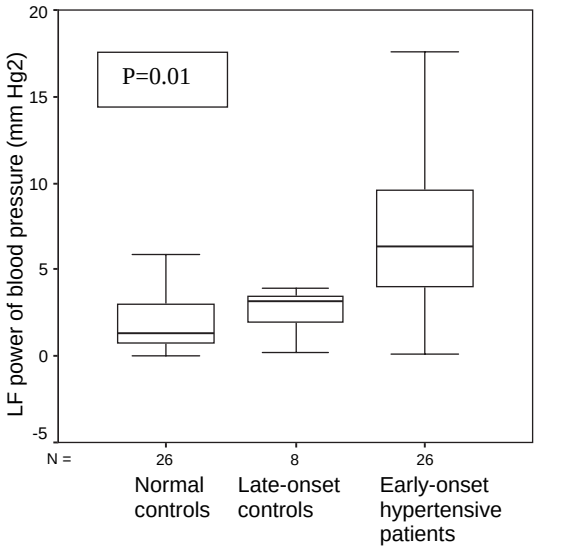
Variable	Normal Controls	Late-Onset Controls	Early-Onset Hypertensive Patients	Trial Treatment	Trial Control
Total subjects (n)	29	8	37	18 (49)	19 (51)
Age (years)	30 (22–39)	30 (24–30)	30 (20–40)	30 (20–38)	30 (20–40)
Gestational age (weeks^{days})	32^{0} (31^{3}–32^{4})	32^{0} (31^{3}–32^{4})	28^{5} (24^{2}–33^{5})	28^{6} (24^{2}–33^{5})	28^{5} (24^{6}–33^{2})
Pregestational weight (kg)	65 (48–125)	76 (58–84)	67 (49–130)	66 (50–130)	68 (49–91)
Nulliparous	16 (55)	2 (25)	27 (73)	14 (78)	13 (68)
Caucasian	29 (100)	8 (100)	28 (76)	12 (67)	16 (84)
Medication	0 (0)	0 (0)	19 (51)	8 (44)	11 (58)
Systolic blood pressure (mm Hg)	97 (80–123)	113 (104–150)	156 (123–221)	151 (125–221)	167 (124–195)
Diastolic blood pressure (mm Hg)	57 (39–73)	65 (57–93)	88 (66–109)	85 (70–109)	89 (66–106)
Heart rate (bpm)	85 (74–109)	84 (70–100)	72 (55–94)	75 (55–88)	70 (57–94)

Values are expressed as median (range) or numbers (percentage) as appropriate. The last two columns specify patients for randomized allocation to treatment with and without plasma volume expansion.

Table 2: Spectral analysis in normal controls, late-onset controls and early-onset hypertensive patients.

Variable	Normal Controls	Late-Onset Controls	Early-Onset Hypertensive Patients	Significance
Number	26	8	26	
Heart rate (bpm)	84 (74–98)	84 (70–100)	79 (67–94)	*
Systolic blood pressure (mm Hg)	98 (78–123)	113 (104–150)	150 (124–206)	* ^ †
Diastolic blood pressure (mm Hg)	57 (39–73)	67 (57–93)	88 (66–106)	* ^ †
Blood pressure variability				
Total power (mm Hg^2)	18 (3.4–81)	19 (7.4–36)	35 (4.3–132)	* ^
Low frequency power (mm Hg^2)	1.34 (0.01–16)	3.16 (0.2–3.9)	6.36 (0.09–55)	* ^
Heart rate variability				
Total power (ms^2)	810 (160–3,590)	695 (190–2,560)	1800 (500–8,510)	** ^^
Low frequency power (ms^2)	80 (4–1,560)	80 (30–370)	270 (11–1,150)	*
High frequency power (ms^2)	140 (3–1,060)	115 (40–1,240)	210 (0–3,220)	
LF/HF ratio	0.57 (0–9.6)	0.56 (0.07–1.6)	1.15 (0.03–14)	** ^^
Baroreflex sensitivity (ms/mm Hg)	8.5 (3.2–40.3)	6.7 (2.7–14)	4.7 (1.7–22)	*
LF phase difference (degree)	–70 (–108– –39)	–95 (–99– –47)	–80 (–119– –6)	** †

Values are expressed as median (range) or numbers as appropriate. LF; low frequency (0.04–0.15 Hz), HF; high frequency (0.15–0.4 Hz), Baroreflex sensitivity was quantified by α-index in the LF-band.
Significant difference between early-onset hypertensive patients and normal controls with * $p < 0.05$, ** $p < 0.1$.
Significant difference between early-onset hypertensive patients and late-onset controls with ^ $p < 0.05$, ^^ $p < 0.1$.
Significant difference between late-onset controls and normal controls with † $p < 0.05$ (9).



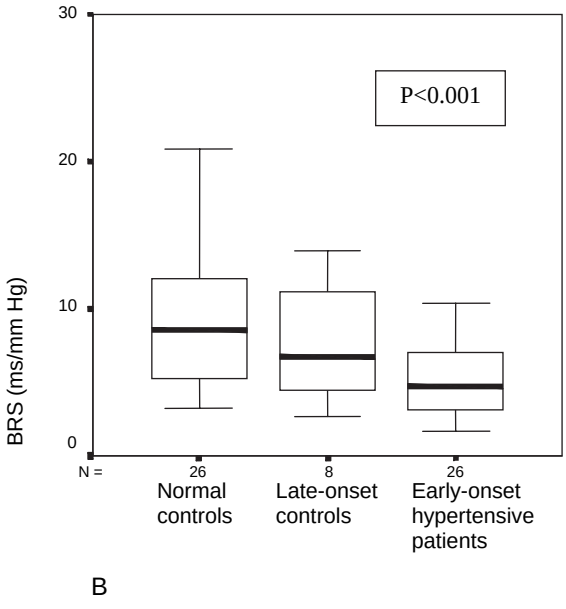


Figure 1: Sympathetic activity presented by Low Frequency (*LF*) blood pressure variability (*A*) and baroreflex sensitivity (*BRS*) (*B*) in normal pregnant controls, controls who developed late-onset preeclampsia (after 34 weeks), and early-onset hypertensive patients (before 34 weeks), All controls were measured at 32 weeks and were normotensive at that time. A significant trend towards higher values of sympathetic activity was found from normal controls to late-onset controls to early-onset hypertensive patients, presented by gradually higher LF-power and a gradually lower BRS ($p < 0.05$). Data are presented by boxplots, where the box represents 0.5 limits, the middle transverse bar the median, and the outer transverse bars the 0.95 limits. LF-power was calculated between 0.04 and 0.15 Hz.

significant trend towards lower values of BRS was found from normal controls to late-onset controls to early-onset patients (Figure 1-B). Phase difference in the LF-band was non-significantly larger in early-onset patients than in normal controls. Coherence in the LF-band was >0.5 in all groups. No differences in power, BRS or phase difference were found between early-onset patients with antihypertensive medication and those without medication.

Autonomic Regulation and Plasma Volume Expansion

Thirty-two early-onset patients were still pregnant at t1 (n = 15, n = 17) and 24 were still pregnant at t2 (n = 13, n = 11) (Table 3). The trial treatment group received significantly more fluid during the study period than the trial control group ($p < 0.001$). Median infused HES during the time period after the first measurement in the trial treatment group was 500 mL (range, 250 to 1,500 mL) at t1 and 2,000 mL (range, 250 to 3,000 mL) at t2, *versus* 0 mL (range 0 to 0 mL) at t1 and t2 in the trial control group. Hemoglobin levels were significantly lower at t2 in the trial treatment group than in the trial control group (difference 0.65 mmol/L). Heart rate and blood pressure did not show consistent differences. No significant differences were observed in intra-individual changes of the results of spectral analysis between t0 and t1 or t0 and t2. Furthermore, no differences were observed between the trial treatment and trial control group in specific subgroups (severe preeclampsia, HELLP-syndrome, pregnancy-induced hypertension with foetal growth restriction, with or without use of medication).

DISCUSSION

Our results suggest increased sympathetic activity in early onset hypertensive disorders of pregnancy, as both heart rate power and blood pressure power of the LF-band were significantly higher, and BRS was significantly lower in early-onset hypertensive patients compared to normal pregnant controls. Total heart rate variability, LF/HF ratio and LF phase difference were non-significantly higher. Furthermore, both LF blood pressure power and BRS demonstrated a significant trend to higher sympathetic activity from normal controls to late-onset controls to early-onset hypertensive patients. We observed no evidence to suggest that therapeutic plasma volume expansion had any effect on sympathetic activity.

Autonomic Regulation in Hypertensive Pregnancy

Higher blood pressure and heart rate variabilities in this study are partly consistent with data from Ekholm et al. (20), who suggested higher

Table 3: Intra-individual changes (Δ) between measurements at t0 (baseline), t1 (20 to 40 hours after inclusion) and t2 (65 to 100 hours after inclusion) in trial treatment and trial control group.

	t0-t1		t0-t2	
Variable	**Trial Treatment**	**Trial Control**	**Trial Treatment**	**Trial Control**
Number	15	17	13	11
Infused HES (mL)	500 (250–1,500)	0 (0–0)*	2,000 (500–3,000)	0 (0–0)*
ΔHemoglobin count (mmol/L)	N/A	N/A	–0.85 (–2.3–0.10)	–0.20 (–1.8–0.8)*
ΔHeart rate (bpm)	–2.7 (–21–23)	–0.89 (–23–9.6)	–6.3 (–23–19)	–1.6 (–23–5.2)
ΔSystolic blood pressure (mm Hg)	0.95 (–67–16)	0.1 (–32–21)	18 (–11–39)	–3.9 (–13–24)
ΔDiastolic blood pressure (mm Hg)	1.5 (–17–9.2)	1.1 (–11–19)	–2.3 (–8.0–6.7)	–0.78 (–6.2–9.0)
Blood pressure variability				
ΔTotal power (mm Hg^2)	11 (–33–52)	–0.68 (–12–40)	–45 (–102–0.99)	–31 (–125– –8.6)
ΔLow frequency power (mm Hg^2)	–0.95 (–31–10)	–0.64 (–38–15)	–0.71 (–7.1–9.1)	0.94 (–21–11)
Heart rate variability				
ΔTotal power (ms^2)	440 (–6900–5100)	–630 (–3900–1400)	1800 (–4700–7400)	1800 (–4600–8800)
ΔLow frequency power (ms^2)	170 (–1400–930)	–28 (–7000–360)	–90 (–1100–370)	13 (–3400–3800)
ΔHigh frequency power (ms^2)	54 (–3900–2600)	59 (–2800–1400)	58 (–1800–900)	–61 (–2600–4500)
ΔLF/HF ratio	–0.15 (–6.0–20)	–0.055 (–44–11)	–0.83 (–4.3–0.30)	–0.081 (–44–1.8)
ΔBaroreflex sensitivity (ms/mm Hg)	–0.34 (–7.3–8.6)	–0.18 (–1.8–5.7)	–0.66 (–7.0–1.8)	–0.15 (–5.4–107)
ΔLF phase difference (degree)	–5.8 (–58–140)	–0.089 (–62–46)	15 (15–160)	30.74 (–28–97)

LF: low frequency (0.04–0.15 Hz); HF: high frequency (0.15–0.4 Hz).
*Denotes a significant difference, $p < 0.05$.
N/A: not available.

sympathetic and parasympathetic activity in their population of late-onset pregnancy induced hypertension. They observed higher heart rate and blood pressure variabilities in both the LF and HF-band, with the greatest difference in the HF-band both for heart rate and blood pressure. In contrast, a study from Eneroth et al.(21) demonstrated lower heart rate variability in the HF-band, and found no differences in other heart rate and blood pressure variabilities. They considered this suggestive for lower parasympathetic control. The results from the present study are complementary to the above findings, as not only higher LF blood pressure and heart rate variabilities in early-onset patients were observed, but also a significant trend towards higher LF blood pressure variabilities from normal controls to late-onset controls to early-onset patients. These results are suggestive for higher sympathetic activity in patients with early-onset hypertensive pregnancies compared to normal pregnant women, and suggest a gradual increase in sympathetic activity during the development of hypertensive pregnancy. Facilitation of the sympathetic nervous system was also reported by Yang et al.(6) who found a higher LF/HF ratio in heart rate variability. Although there was no statistically significant difference in LF/HF ratio in our study ($p < 0.1$), higher values in early hypertensive pregnancy were found. Heart rate variability analysis has further shown conflicting results for sympathetic and parasympathetic activity(15, 21, 22). The inconsistency of previous data may be explained by methodological factors and selection of cases. The severe disease in this patient group with early-onset hypertensive disorders of pregnancy in comparison to other studies may explain the observed higher sympathetic activity.

The early-onset patients had a significantly higher blood pressure and lower heart rate than the both control groups. At lower heart rates, the vagal influence on heart rate is probably larger resulting in higher heart rate variability in the HF-band (23). However, this supposed vagal predominance was not accompanied by sympathetic withdrawal. Despite the lower heart rate in early-onset patients, all parameters of sympathetic activity were higher compared to both control groups, and baroreflex sensitivity of the LF-band was significantly lower in early-onset patients compared to normal controls. This implies that in these patients with hypertensive disorders of pregnancy higher sympathetic activity overrules vagal influences.

Analysis of heart rate and blood pressure variabilities combined provides a more detailed view on the regulatory mechanisms than heart rate variability alone, as a quantitative assessment of the baroreflex sensitivity can be obtained. BRS was significantly lower in early-onset patients compared with normal controls in our study, in accordance with Molino et al.(8) in their study on preeclamptic patients. The higher LF-phase difference found in this study, although not significant ($p < 0.1$), supports the findings on BRS, suggesting sympathetic dominance. Furthermore, the significant decrease in BRS from

normal controls to late-onset controls to early-onset patients suggests a gradually higher sympathetic activity from healthy pregnancy to disease. This also supports the results of Rang et al., (9) who showed in a longitudinal study that phase difference was progressively larger towards the end of pregnancy in patients who developed late-onset preeclampsia compared to patients who remained normotensive throughout pregnancy.

The results from this study are also compatible with the study by Schobel et al., (3) who analysed sympathetic activity to skeletal muscle vessels by microneurography, and found increased sympathetic activity in preeclampsia. However, some have argued that increased sympathetic outflow to skeletal muscle may not reflect sympathetic activity to other organs. The results of heart rate and blood pressure regulation in this study supports the presence of sympathetic hyperactivity at the systemic level.

Autonomic Regulation After Plasma Volume Expansion

We could not confirm the second hypothesis regarding an effect of therapeutic plasma volume expansion on sympathetic activity in patients with hypertensive disorders in early pregnancy. A number of controlled and randomized studies could observe an increased cardiac output and a reduced systemic vascular resistance as a result of plasma volume expansion (24–27). However, no study has described the duration of these effects. It may well be that strong homeostatic mechanisms (28) causing increased diuresis (24, 29), and endothelial leakage of fluids into the interstitial space neutralize long-term effects. The infused volume in the treatment group in this study was comparable to other studies of plasma volume expansion and a statistically significant decrease of hemoglobin count was observed in the plasma volume treatment group compared with the control group. It may be inferred that vasoconstriction and increased sympathetic activity may constitute the primary process rather than a constricted plasma volume.

To our knowledge, no literature of the effect of plasma volume expansion on sympathetic activity in hypertensive pregnancy exists for comparison with our data. In normal healthy subjects, stimulation of baroreceptors by atrial stretch and release of atrial natriuretic peptide in response to volume expansion, and the haemodilutory effect are important stimuli for a prompt and sustained suppression of renin release (30–32). One of these studies demonstrated that this effect from plasma volume expansion in normal healthy subjects was seen within 30 to 60 minutes, and that values returned to normal after 60 to 90 minutes. They suggested that a direct baroreflex-mediated inhibitory effect on sympathetic activity might be found after plasma volume expansion, with a prompt renin release inhibition. This relatively fast-acting mechanism may limit a lasting effect of plasma volume expansion. Therefore we cannot exclude that the plasma volume expansion in our study may have

had a short-term effect that went unnoticed at our measurement intervals. Follow-up studies with measurements during volume loading are currently underway to study these short-term effects. Similarly, we have no data in our research on alterations of hormonal parameters possibly influencing plasma volume. This might be an interesting line of future research.

Measurements were performed in clinical test circumstances. Many patients in the early-onset hypertensive group had symptoms and complaints due to severe preeclampsia. Antihypertensive treatment, which interferes with autonomic cardiovascular control, could not be withheld. Although medication may have influenced results, spectral analysis at baseline did not show differences between patients using medication and patients not using medication. Furthermore, medication was used equally in both randomization groups and a separate analysis of the patients without medication did not lead to different results.

In conclusion, our study provides evidence that sympathetic activity gradually increases during the development of disease. We also demonstrated that in hypertensive disorders of pregnancies clinically overt between 24 and 34 weeks of pregnancy, hyperactivity of the sympathetic nervous system is an important feature. Furthermore, treatment with plasma volume expansion did not cause long-term changes in sympathetic activity, suggesting that the hypovolemia in preeclampsia is a secondary phenomenon.

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