Non-invasive hemodynamic measurements early in pregnancy

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Serial assessment of cardiovascular control shows early signs of developing preeclampsia

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Abstract

**Purpose** To evaluate whether differences in autonomic cardiovascular control between normal pregnant women and women who develop pre-eclampsia later in pregnancy can be detected even before or early in pregnancy.

**Design** We studied 42 women, 21 multigravid with a history of pre-eclampsia and 21 primigravid, before pregnancy, at 6, 8, 12, 16, 20 and 32 weeks gestation and 15 weeks after delivery.

**Methods** The outcome of pregnancy was classified after delivery as normal pregnancy (NP group) or pre-eclampsia (PE group). Continuous heart rate and blood pressure were recorded by Portapres (TNO, Amsterdam, The Netherlands) during orthostatic stress, during rest in a supine and sitting position, and during paced breathing for periods of 1 minute at breathing frequencies of 6, 10 and 15 breaths / min. Baroreflex gain from heart rate and blood pressure variability and the phase angle between both signals at low (~0.1 Hz) and high frequency (respiratory rate) were analysed by spectral analysis.

**Results** Eight women were diagnosed with pre-eclampsia. Subgroups did not differ in age, weight or height. The PE group showed a significantly higher mean arterial pressure before and during pregnancy [analysis of viriance(ANOVA), $P = 0.001$], a significantly larger initial blood pressure drop to orthostatic stress before and in the first half of pregnancy (ANOVA, $P = 0.002$) and a significantly larger negative phase difference during supine rest at low frequency from 8 weeks onward (ANOVA $P = 0.003$).

**Conclusions** These findings are compatible with increased resting sympathetic activity and decreased circulating volume, already present before and early in pregnancy, in women who will later develop preeclampsia.
Introduction

Pre-eclampsia, defined as hypertension associated with proteinuria during pregnancy, is a multisystem disorder with unknown etiology. Hemodynamics of pre-eclampsia are characterized by low circulating volume and high vascular resistance [1; 2]. Normally, vascular tone is largely determined by the sympathetic nervous system, and increased sympathetic nerve activity has indeed been demonstrated in women with pre-eclampsia and pregnancy-induced hypertension by direct microneurography of post-synaptic sympathetic nerve fibers [3; 4]. These findings suggest that elevated blood pressure in pre-eclampsia may be partially mediated by increased sympathetic activity.

The association between the pathophysiology of pre-eclampsia and the autonomic nervous system has been made earlier. Many investigators have used a number of clinical non-invasive methods (i.e. isometric hand grip, cold pressor, orthostatic stress,Valsalva’s maneuver, deep breathing and spectral analysis of blood pressure and heart rate variability) in attempting to differentiate autonomic cardiovascular control in uncomplicated pregnancy from that in pre-eclampsia. Although small differences have been observed between normal pregnancy and pre-eclampsia in individual studies, on reviewing the results of these methods we demonstrated that the consistency between data is insufficient to discriminate between normal pregnancy and pre-eclampsia. The failure to demonstrate increased sympathetic activity, as observed by direct microneurography, might be due to methodological factors of the non-invasive studies. Most studies are cross-sectional or, if longitudinal, compare data in pregnancy with post-partum values. Only few studies performed measurements before the onset of disease and none did so before pregnancy. Moreover, most non-invasive test methods show large inter-individual variability [5].

Furthermore, most studies using spectral analysis were only applied to heart rate variability, since continuous blood pressure recordings were unavailable. Heart rate variability is, for the most part, the reflection of underlying blood pressure variability operating by way of the baroreflex [6]. Therefore, combined analysis of heart rate and blood pressure variability enables more detailed evaluation of the autonomic nervous system. It also provides the possibility for non-invasive assessment of the overall arterial pressure to heart rate baroreflex gain (BRS, index $\alpha$) and the phase spectrum. The phase angle between heart rate and blood pressure at specific frequency provides information on the time delay involved in sympathetic or parasympathetic activation through the baroreflex. When the phase angle is negative, the variation in blood pressure leads the variation in heart rate at the same frequency. This phase angle expresses the required time delay from blood pressure change to the ensuing change in heart rate where sympathetic contributions induce more delay (up to seconds), while vagal contributions are within
the same, or at most the next, heart beat [6; 7]. To our knowledge, the phase spectrum has never been investigated in pregnancy or pre-eclampsia. Presently, continuous heart rate and blood pressure measurements can be derived non-invasively by arterial pressure recordings at the finger. The aim of our study was to evaluate whether in a longitudinal study design before or early in pregnancy a difference could be detected in autonomic cardiovascular control between normal pregnant women and women, who develop pre-eclampsia later in pregnancy, by non-invasive measurement techniques.

Methods

Participants were recruited before they were pregnant by advertisement or from the outpatient clinic. Women with a history of preeclampsia before 34 weeks in their previous pregnancy or women who had never been pregnant were eligible. All women had a normal blood pressure at enrollment, when measured by conventional sphygmomanometry (diastolic blood pressure ≤ 90 mmHg). They all had a regular menstrual cycle and none of them was taking oral contraceptives. After written informed consent, all subjects underwent identical study protocols. The study was approved by the Medical Ethical Committee of our hospital.

Measurements were started before pregnancy during the first half (days 5 – 10) and second half (days 18 - 25) half of the menstrual cycle. Further measurements were performed at the gestational age of 6, 8, 12, 16, 20 and 32 weeks, with a maximum deviation of 4 days. Gestational age was confirmed by ultrasound measurement of the crown-rump length in the first trimester. All women had singleton pregnancies. Fifteen weeks (± 4) after delivery one final measurement was performed. According to pregnancy outcome women were stratified after delivery in two groups (i.e. normal pregnancy or pre-eclampsia). Preeclampsia was defined according to the definition of the ISSHP [8] by a diastolic blood pressure ≥90 mmHg after 20 weeks of gestation and proteinuria ≥0.3 g/24 h. Normal pregnancy was defined by a diastolic blood pressure less than 90 mmHg throughout pregnancy and a newborn weight ≥ 10th percentile, adjusted for maternal parity, weight, length and race [9].

For each subject, visits were scheduled on the same time of day. Studies took place in a quiet room with an ambient temperature between 20 and 22 °C. Subjects were advised to abstain from coffee or smoking from the night before the measurement. They were informed about the procedures involved and were instructed to empty their bladder prior to the start of testing. The actual protocol was begun after a test run to train the subject to perform the test maneuvers correctly.
Continuous heart rate and blood pressure registration

Non-invasive finger arterial pressure waveform registration by Portapres, Model 2 (TNO/BMI, Amsterdam, the Netherlands) was used for monitoring continuous heart rate and blood pressure. Portapres is a device for the measurement of finger arterial pressure on a beat-to-beat basis, according to the volume clamp method of Penaz [10; 11]. The use of continuous recordings of finger arterial blood pressure by this method has been validated for spectral analysis and for the orthostatic stress test [12; 13]. Blood pressure measurement by this method has been validated in pregnant women against conventional sphygmomanometry, following the AAMI and BHS protocol [14]. An appropriate size finger cuff was applied at the middle finger of the left hand and the cuffed finger was kept at heart level during the procedure by a sling, to avoid hydrostatic pressure influences. At a stable signal the pressure registration was corrected for the pressure decay over the arm by the Return to Flow method [15; 16]. The physiocal, a dynamic servo setpoint adjuster, was switched off during the transient phases of the maneuvers to ascertain a continuous recording, but was switched on between maneuvers. Data collection was started after a stable signal had been reached for 5 minutes during supine rest.

Cardiovascular reflex tests

There are basically two methods to test the function of the autonomic nervous system non-invasively. By analysis of spontaneous heart rate and blood pressure variability from continuous recordings of heart rate and blood pressure, or by cardiovascular reflex tests, where blood-pressure and heart rate responses to a variety of physiological stresses are analysed. We chose to use the orthostatic stress test and spectral analysis during rest and paced breathing, both in supine and sitting position.

Short-term adjustments to orthostatic stress can be distinguished in an initial reaction (first 30 s) and an early steady-state response (after 1-2 min standing). The orthostatic stress test provides information on the overall integrity of the baroreflex arc. The initial heart rate response is mainly vagally mediated and can be used as a measure of cardiac vagal integrity. Blood pressure maintenance in the early steady state depends predominantly on increased activity of the sympathetic system. The heart rate increase at that moment gives an indication of the decreased vagal and increased sympathetic eference to the sinus node [17-19].

Spectral analysis techniques were used to differentiate between low frequency (LF) (around 0.1 Hz) and high frequency (HF) (or respiratory, at 0.15 – 0.4 Hz) oscillations of heart rate and blood pressure, and to analyse the overall baroreflex sensitivity index and the phase spectrum at LF and HF.
The HF or respiratory oscillations are mainly due to vagus nerve activity since they nearly disappear following administration of high-dose atropine[6; 20; 21]. LF oscillations are due to LF oscillations of the blood pressure mediated by sympathetic activity and LF oscillations of heart rate mediated by combined vagal and sympathetic activity impinging on the sinus node[6; 7; 17]. From simultaneous spectral analysis of heart rate and blood pressure variabilities, a quantitative assessment of the overall gain of the baroreceptor mechanism can be obtained. This gain can be represented by the index (α), which can be computed as the square root of the ratio between the powers of the heart period and blood pressure (α = √ {RRI power / SBP power}) in correspondence to either LF or HF components. The amount of linear coupling between two signals in the frequency domain can be expressed by means of the coherence function. The index values become unreliable if the coherence is low. In the spectral smoothing that we used the coherence function had to be greater or equal to 0.5. The phase can be derived out of the angle difference between the two signals at the same frequency. Also the phase relationship only makes sense if coherence is sufficiently high (≥ 0.5) [6]. Respiratory rate and a change of posture have significant effects on measurements derived from spectral analysis of heart rate and blood pressure variability. Low respiratory frequencies (at or below 10 breaths/min) are associated with increases in HF variability. A change from supine to upright position is accompanied by an increase in LF variability[22; 23].

Study protocol
We recorded data for spectral analysis during rest in supine (10 min) and sitting (2 min) position at spontaneous breathing frequencies and during paced breathing for periods of 1 min at breathing frequencies of 6, 10 and 15 breaths/min, in both supine and sitting position [22; 23]. During paced breathing subjects were instructed not to force their breathing to prevent hyperventilation. The required frequencies were made audible and visible by a computer for guidance of the subject.

For the orthostatic stress test data were collected during 10 minutes supine rest, after which the subject was asked to rise in ~3 s and remain standing for 2 min [18]. The supine posture at gestational ages of 20 and 32 weeks was changed to 30° left lateral tilt for all subjects.

Data Analysis
Two-hundred hertz digitized pulswave blood pressure data were read out of the memory of the Portapres. These data were analyzed by the Beatfast program (TNO/BMI, Amsterdam, the Netherlands). From the orthostatic response the initial (during the first 30 s after standing up) and the steady-state response (reached after 1 min of standing) of the mean arterial pressure and heart rate were analyzed. The average estimates during 10 min supine rest prior to standing up were used as control values. The initial heart rate response was quantified by the initial heart rate increase (Δ HRmax) determined from the difference between the maximum heart rate (HRmax) and control. The initial
Cardiovascular control

blood pressure response was quantified as the lowest blood pressure value (minimum mean arterial pressure, \(\Delta MAP_{\text{min}}\)) immediately after standing up compared to control. The early steady-state heart rate and blood pressure were determined by the difference between values after 1 and 2 minutes standing and control. [17; 17-19]

For spectral analysis systolic blood pressure values and interbeat intervals were identified for each cardiac cycle. The pulse-interval signal and the systolic blood pressure signal were transformed to the frequency domain by the Fast Fourier transform algorithm. For each maneuver powers in the LF (0.04-0.15 Hz) and HF (0.15-0.40Hz) bands were computed for systolic blood pressure and pulse interval [17; 20; 21; 24; 25]. From the simultaneous analysis of systolic blood pressure and pulse interval variabilities, the baroreflex sensitivity index was derived as the square root of the ratios of the spectral powers of the pulse interval and systolic blood pressure in the LF and HF bandwidths. The phase was derived out of the angle difference between the two signals at LF and HF. The amount of linear coupling between the two signals in their frequency domain was expressed by means of the coherence function [7; 26].

Statistics
For each variable at each maneuver a repeated-measures analysis of viriance (ANOVA) was performed to determine differences over time between subgroups. A paired \(t\) test was performed to determine differences between subgroups at different periods.

We estimated that 20% of the study population would develop pre-eclampsia, resulting in a case–control ratio of 1:4. Forty women (eight cases, 32 controls) would enable the detection of a difference of over 10% of a parameter with a standard deviation of 10% at alpha 0.05 and beta 0.8 when tested one-sided. We assumed that 50% of the women who were recruited would become pregnant within 1 year and would complete all examinations.

Results

General data
Eighty-two women were enrolled before pregnancy. Forty-seven became pregnant within 1 year. Five experienced a miscarriage before 12 weeks gestational age. Forty-two women completed the study, 21 with a history of early preeclampsia and 21 during their first pregnancy. Of the 42 women participating in the study, four had pregnancies complicated by intra uterine growth retardation, but did not develop elevated blood pressure. Their data were excluded from the analysis. Eight women developed pre-eclampsia. In all the diagnosis was made after 32 weeks of gestation and all had mild pre-eclampsia (diastolic blood pressure < 110 mmHg). The women with normal
Fig 1. Heart rate (HR) serially in women with uncomplicated pregnancies (NP group) and women with pregnancies complicated by pre-eclampsia (PE group). Vertical bars represent 0.95 confidence limits. Measurements were performed in the first half of a normal menstrual cycle (PC1), in the second half of a normal menstrual cycle (PC2), at a gestational age of 6, 8, 12, 16, 20 and 32 weeks, and 3 months after delivery (PP).

Fig 2. Mean arterial pressure (MAP) serially in women with uncomplicated pregnancies (NP group) and women with pregnancies complicated by pre-eclampsia (PE group). Vertical bars represent 0.95 confidence limits. Measurements were performed in the first half of a normal menstrual cycle (PC1), in the second half of a normal menstrual cycle (PC2), at a gestational age of 6, 8, 12, 16, 20 and 32 weeks, and 3 months after delivery (PP). * Statistically significant difference at P < 0.05.

Fig 3. Initial blood pressure response (ΔMAPmin) to orthostatic stress serially in women with uncomplicated pregnancies (NP group) and women who developed pre-eclampsia (PE group). Vertical bars represent 0.95 confidence limits. Measurements were performed in the first half of a normal menstrual cycle (PC1), in the second half of a normal menstrual cycle (PC2), at a gestational age of 6, 8, 12, 16, 20 and 32 weeks, and 3 months after delivery (PP). * Statistically significant difference at P < 0.05.
Cardiovascular control

pregnancy (NP group) and the women, who developed pre-eclampsia (PE group) were similar regarding age, weight and body height (Table 1). Gestational age at delivery and neonatal birth weight in the PE group was significantly lower compared with the NP group (\( P = 0.007 \)). Resting heart rate was not different between subgroups (Fig. 1). The resting mean arterial pressure was significantly higher in PE group compared with the NP group, already before pregnancy (ANOVA, \( P = 0.001 \)) (Fig. 2).

<table>
<thead>
<tr>
<th>Table 1 Study group characteristics specified for women with an uneventful pregnancy and women who developed pre-eclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Pregnancy ( (n = 30) )</td>
</tr>
<tr>
<td>At intake, before pregnancy</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Primigravid (no)</td>
</tr>
<tr>
<td>Smoking (no)</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Body length (cm)</td>
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<tr>
<td>BSA (m(^2))</td>
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<tr>
<td>SBP (mmHg)</td>
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<tr>
<td>DBP (mmHg)</td>
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<tr>
<td>After delivery</td>
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<tr>
<td>Neonatal weight (g)</td>
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<tr>
<td>GA delivery (weeks)</td>
</tr>
</tbody>
</table>

Blood pressure measured by conventional sphygmomanometry. Diastolic blood pressure at Korotkov V. Values are presented as mean (standard deviation) or number (%). * Statistically significant difference at \( P < 0.05 \).

Orthostatic response

Heart rate and blood pressure response on orthostatic stress in normal pregnancy showed no changes when compared to the non-pregnant state. Heart rate response in the initial and steady state was not different in the PE group compared with the NP group. Before pregnancy and in early pregnancy, and at 16 and 20 weeks, \( \Delta MAP_{\text{min}} \) was significantly larger in the PE group compared with the NP group (ANOVA, \( P = 0.002 \)) (Fig. 3). The mean arterial pressure increase after 1 and 2 min of standing showed no differences between the NP and PE groups.

Spectral analysis

The total heart rate and blood pressure variability and heart rate and blood pressure variability at LF or HF during rest in the supine or sitting position or at paced breathing in the supine and sitting position was not influenced by pregnancy and showed no differences between subgroups. Baroreflex sensitivity index \( \alpha \) showed a significant decrease towards 32 weeks gestation, compared to the pre-pregnant state, during supine rest (ANOVA, \( P = 0.000 \)). This was similar for both subgroups. During rest in the
sitting position or at paced breathing in the supine or sitting position, baroreflex sensitivity index $\alpha$ was not influenced by pregnancy or pre-eclampsia. At supine rest the negative phase difference at the LF band was larger in the PE group compared with the NP group, with a gradual increase towards the third trimester of pregnancy. This difference was statistically significant at 8, 12, 20 and 32 weeks of gestation, but not at 16 weeks (ANOVA, $P = 0.003$) (Fig. 4). The exact data of the phase difference at rest are presented in Table 2. In the sitting position or during paced breathing at different frequencies the phase difference was comparable between the PE and NP groups.

Table 2  Phase difference in the supine position at low frequency in women with uncomplicated pregnancies (NP group) and women with pregnancies complicated by pre-eclampsia (PE group), measured in the first half of a normal menstrual cycle (PC1), the second half of a normal menstrual cycle (PC2), during gestation at 6, 8, 12, 16, 20 and 32 weeks, and 3 months postpartum

<table>
<thead>
<tr>
<th>GA (weeks)</th>
<th>NP Phase (deg)</th>
<th>PE Phase (deg)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pc. 1</td>
<td>-59 (15)</td>
<td>-65 (20)</td>
<td>0.4</td>
</tr>
<tr>
<td>Pc. 2</td>
<td>-60 (15)</td>
<td>-61 (22)</td>
<td>0.6</td>
</tr>
<tr>
<td>6</td>
<td>-63 (16)</td>
<td>-66 (19)</td>
<td>0.2</td>
</tr>
<tr>
<td>8</td>
<td>-64 (15)</td>
<td>-77 (18)</td>
<td>&lt; 0.04*</td>
</tr>
<tr>
<td>12</td>
<td>-61 (19)</td>
<td>-77 (22)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>16</td>
<td>-56 (22)</td>
<td>-62 (18)</td>
<td>0.9</td>
</tr>
<tr>
<td>20</td>
<td>-63 (30)</td>
<td>-79 (37)</td>
<td>&lt; 0.004*</td>
</tr>
<tr>
<td>32</td>
<td>-68 (41)</td>
<td>-92 (27)</td>
<td>&lt; 0.03*</td>
</tr>
<tr>
<td>pp</td>
<td>-59 (15)</td>
<td>-61 (17)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Data presented as mean (standard deviation), and P values of paired t test (analysis of variance, $P = 0.003$).
Discussion

Pre-eclampsia is a disease of unknown etiology, and early detection and prevention of the development of pre-eclampsia is not possible. Early prediction of women at high risk for pre-eclampsia could offer the opportunity to target care at those most likely to benefit and to evaluate or design preventive strategies more effectively.

We earlier reviewed non-invasive assessment of autonomic cardiovascular control in normal pregnancy and pre-eclampsia, and found that we mentioned that heart rate and blood pressure variability in women with pre-eclampsia, compared to healthy pregnant women, showed no differences or were inconsistent. A possible explanation was the cross-sectional study design of most non-invasive studies[5]. The present study refutes this explanation because, although we performed our study longitudinally, we could not demonstrate differences in heart rate and blood pressure variability with spectral analysis at different positions or breathing frequencies between pregnant and non-pregnant women, nor between NP and PE. The baroreflex sensitivity index $\alpha$ showed a small but statistically significant decrease towards the end of pregnancy compared to the pre-pregnant state, which is consistent with previous published data [27-29]. This change in the baroreflex sensitivity index $\alpha$ was similar in both groups. Molino et al.[28] observed a lower baroreflex sensitivity index $\alpha$ in pre-eclamptic women compared to healthy pregnant women. Our measurements were performed during the pre-clinical phase of pre-eclampsia, whereas Molino et al. examined women after the diagnosis of pre-eclampsia was made. This may explain differences in results, since in hypertensive conditions the baroreflex sensitivity is reset towards the elevated blood pressure[30].

To our knowledge, phase differences between heart rate and blood pressure have never been investigated before in pregnancy or pre-eclampsia. During supine rest, we observed a tendency to a larger negative phase difference at the LF band in the pre-eclamptic group compared to the normal pregnant group, with a gradual increase of difference towards the third trimester of pregnancy. These findings suggest a higher sympathetic activity during rest, increasing as pregnancy further develops. Vagal modulation acts much faster than sympathetic modulation[17]. At high frequency the phase difference between systolic pressure variability and pulse interval variability is around zero because for these frequencies the slow sympathetic system is not effective and only the vagal part of the baroreflex arc matters[7]. At low frequency, around 0.1 Hz, systolic blood pressure variability and pulse interval variability are due to the combined effect of the vagal and sympathetic baroreflex regulation of the cycle length. The negative phase difference at 0.1 Hz indicates that systolic blood pressure changes occur before the heart period changes. A larger phase difference indicates a larger influence of the slower sympathetic system[6; 7]. At 0.1 Hz, the blood pressure precedes the heart period by $\sim$60 °
in normal pregnant women at all test moments. This represents one-sixth of the cycle of 10 s, or 1.7 s. Such time delay is compatible with a baroreflex action, now mainly acting through the sympathetic nervous system. The time delay from the sympathetic nerve activation to the ensuing change in heart rate is known to take ~1-2 s [6]. In the PE group at ~8, 12 and 20 weeks gestational age, the larger phase difference is ~80° and at 32 weeks ~90°. This represents a time delay of more than 2 s (~2.2s and ~2.5s), the time needed for the sympathetic system. This larger phase difference in the PE group thus represents a larger contribution of the sympathetic system, which increases its activity towards the third trimester. We observed a larger phase difference at rest, but not during stimulation by the sitting position. Although resting sympathetic activity seems to be increased in PE, the sympathetic response to stimuli is similar compared with normal pregnancy. This is in accordance with the findings of Schobel et al. and Greenwood et al. [3; 4], who observed an increased sympathetic activity at rest in pre-eclamptic women by microneurography, but also did not observe a difference in sympathetic response on stimuli compared with normal pregnant women. A remarkable observation, which we cannot just discard as a chance finding, is that phase difference and mean arterial pressure were comparable between the NP and PE groups at 16 weeks, while before and after this time a statistically significant difference was observed. We have no ready explanation of this finding.

Our findings by spectral analysis agree with our observations on orthostatic stress. On orthostatic stress, we observed a larger initial blood pressure response in the first half of pregnancy in women who developed pre-eclampsia compared with normal pregnant women. Although control blood pressure values were higher in those preeclamptic women, this cannot entirely explain the larger initial blood pressure response. In the first 3 s after standing up, arterial blood pressure shows an increase due to the muscular compression of the vessels of the legs and an increase in abdominal pressure, causing a shift of blood towards the heart. This causes a reflex release of vasoconstrictor tone and a fall in blood pressure, followed by a sympathetically mediated vasoconstriction whereby blood pressure recovers and sometimes overshoots [31-33]. During the fall in blood pressure, mean arterial pressure is mainly preserved due to the pooled blood volume in the lungs [34]. When resting sympathetic activity is higher, the sensitivity to a decrease in vasoconstrictor tone will be increased. This increased sensitivity combined with a lower pooled blood volume might explain the larger blood pressure drop observed in women who developed pre-eclampsia. Pre-eclampsia is known to be characterized by a decreased cardiac output and circulating volume in the clinical phase of the disease. Our findings are compatible with a decreased circulating volume prior to the clinical onset of disease, as found by Spaanderman et al. [35]. On the contrary, when circulating volume is decreased in the pre-clinical phase of pre-eclampsia, we would expect total blood pressure variability to be increased. We observed no difference in
total blood pressure variability between subgroups. The observation that at 32 weeks, shortly before the clinical presentation of pre-eclampsia, the initial orthostatic blood pressure drop did not differ between the NP and PE groups seems also contradictory to the underfill hypothesis. It should be realized in this respect that a pregnant woman at 32 weeks is not able to rise quickly from the lying position and that therefore standing up takes more time. The blood volume shift, normally seen in the first 3 s, is therefore less pronounced and extends over a longer period. Therefore the reflex decrease of vasomotor tone will be less.

The initial blood pressure drop on standing has not been investigated previously in pregnant women. All studies of the orthostatic test investigated the blood pressure change after 30 s of standing, representing the blood pressure overshoot that showed no differences between normal pregnancy and pre-eclampsia [36; 37].

Our study provides evidence for an increased resting sympathetic activity and decreased circulating volume, already present in early pregnancy, in women who will develop pre-eclampsia compared to women who will have a normal pregnancy. In normal pregnancy blood pressure was decreased from the onset on with a second drop at the beginning of the second trimester, when secondary trophoblast invasion takes place and the resistance of the uterine-placental circulation diminishes [38; 39]. In women, who developed pre-eclampsia, this drop in blood pressure was only temporary at 16 weeks, when both the NP and PE groups had comparable blood pressure and resting sympathetic activity. Thereafter blood pressure and resting sympathetic activity increased again from 20 weeks of gestation onwards.

Since these differences were already present in early pregnancy, they might be useful for early identification of women at risk for pre-eclampsia.
References


Cardiovascular control


