Non-invasive hemodynamic measurements early in pregnancy

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Non – invasive assessment of autonomic cardiovascular control in normal human pregnancy and pregnancy associated hypertensive disorders; a review

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Abstract

**Purpose** Preeclampsia is a major complication of pregnancy. Although the disorder usually becomes apparent only in the third trimester of pregnancy, evidence is available that underlying pathophysiological abnormalities are already present early in pregnancy. The association between alterations in autonomic cardiovascular control and the development of hypertension in pregnancy has been investigated for some time. Non-invasive methods are especially of interest, since they have the advantage of minimal risk for the mother and the conceptus and enable repeated measurements during pregnancy. If non-invasive tests for autonomic cardiovascular control could demonstrate the increased sympathetic activity, as observed by microneurography than this method is a candidate for early identification of preeclampsia. Therefore, the literature on non-invasive testing of autonomic cardiovascular control in normal pregnancies and preeclampsia was summarized.

**Data identification and selection** Medline was searched and 36 articles on autonomic cardiovascular control in human pregnancy by non-invasive test methods were reviewed. For each test method, data of different studies were summarized to evaluate if the method could discriminate between healthy pregnancy and preeclampsia.

**Conclusion** Although small differences have been observed between normal pregnancy and preeclampsia in individual studies using non-invasive methods, the consistency in the available data is insufficient to discriminate between normal pregnancy and preeclampsia. The failure to demonstrate the increased sympathetic activity, as observed by direct microneurography, might be due to methodological factors of the non-invasive studies. Alternatively, sympathetic activity to resistance vessels in skeletal muscle may not be a proper reflection of autonomic cardiovascular control in pregnancy. Well-designed longitudinal research could be useful to test these suppositions.
Introduction

Preeclampsia, defined as hypertension associated with proteinuria, complicates up to 10% of all pregnancies. It is a major cause of maternal, fetal and neonatal morbidity and mortality. [1; 2] This common disease of pregnancy develops in the second half of pregnancy and resolves shortly after delivery. In this disease, the placenta plays an important role - only removal of the placenta cures the disorder. The clinical expression of the disease shows a large variability. Till now, there are no possibilities for prevention or treatment of this disorder and the underlying aetiology of preeclampsia is still unknown. Abundant studies are available concerning the pathophysiologic mechanisms of this disease. Although some dissimilarities exist between results, it is generally accepted that the disease is characterised by low circulating volume and high vascular resistance. [3; 4] This is the opposite of the haemodynamic changes that occur in normal pregnancy (Table 1). Haemodynamic changes in normal pregnancy show a decrease in mean arterial pressure and systemic vascular resistance and an increase in circulating volume, heart rate and cardiac output. The largest changes occur early in pregnancy, already before 8 weeks of gestational age.[5-7] It is uncertain if haemodynamic changes early in pregnancy are different between women, who develop preeclampsia, and women with a normal pregnancy. Although the amount of data on the haemodynamic changes before the clinical presentation of preeclampsia is limited, a higher cardiac output was observed early in pregnancy in women, who developed preeclampsia later in pregnancy compared to healthy pregnant women. [8; 9] The higher cardiac output in these women was, partly, based on a significantly higher heart rate. This has been regarded as an early sign of increased sympathetic activity. Vascular tone is largely determined by the activity of the sympathetic nervous system and Schobel et al [10] were the first to measure postganglionic action potentials in sympathetic-nerve fibers innervating blood vessels in the skeletal muscle in patients with preeclampsia. Mean sympathetic activity during rest appeared to be three times higher in preeclamptic women compared to healthy pregnant women, and two times higher compared to the hypertensive non-pregnant women. After delivery, the preeclamptic women showed an almost parallel decrease of mean arterial pressure and sympathetic nerve activity. Although Schobel et al found a higher sympathetic nerve activity in preeclampsia, they observed no difference in haemodynamic and sympathetic nerve responses to Valsalva’s manoeuvre and cold pressore test. Data

Table 1. Haemodynamic characteristics of normal pregnancy compared with non-pregnant women and of preeclampsia compared with normal pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>BP</th>
<th>CO</th>
<th>HR</th>
<th>SVR</th>
<th>Circ.vol</th>
<th>Symp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pregnancy vs non-pregnant</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>»</td>
</tr>
<tr>
<td>Preeclampsia vs normal pregnancy</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

↓: decreased; ↑: increased; †: strongly increased; w: not different; BP: blood pressure; CO: cardiac output; HR: heart rate; SVR: systemic vascular resistance; Circ.vol: circulating volume; Symp: sympathetic activity
of Schobel et al were later confirmed by Greenwood et al [11], who performed a similar study in women with pregnancy induced hypertension. These data could indicate that the increase in systemic vascular resistance, at least partly, is mediated by a marked increase in sympathetic vasoconstrictor activity in hypertensive pregnancies. [12]

Signs and symptoms of preeclampsia become apparent in a relatively late stage of pregnancy, usually in the third trimester. However, there is some evidence, that the underlying pathophysiological mechanism is already present before the clinical presentation of preeclampsia. [5; 8; 9] The increased sympathetic activity, observed in preeclampsia, may already be present before the clinical presentation of the disorder, before the blood pressure and vascular resistance start to rise.

Already a few decades before the observations of Schobel et al and Greenwood et al were published, the association between the development of hypertension in pregnancy and alterations in autonomic cardiovascular control was investigated. Different methods for the clinical assessment of autonomic cardiovascular control in humans have been used. Most studies were performed with non-invasive methods, which have the advantage of minimal risk for the mother and the conceptus and the possibility of repeated measurements during pregnancy.

We wondered if non-invasive methods for autonomic cardiovascular testing could demonstrate the increased sympathetic activity, as observed by microneurography. Secondly, we wondered if in early pregnancy one or more of these test methods could demonstrate differences in autonomic cardiovascular control between women, who would have a normal pregnancy and women, who would develop preeclampsia. Early detection of differences in autonomic cardiovascular control could give opportunities for screening. Therefore, in this review we summarize the literature, published on non-invasive testing of autonomic cardiovascular control in normal pregnancies and preeclampsia.

Cardiovascular reflex tests: What do they tell us.
There are basically two methods to test the function of the autonomic nervous system non-invasively. Analysis of spontaneous heart rate and blood pressure variability from continuous recordings of heart rate and blood pressure, or cardiovascular reflex tests, where blood-pressure and heart rate responses to a variety of physiological stresses are analysed.

Although non-invasive methods have the advantage in pregnancy of minimal risk for the mother and conceptus, the information they provide is limited due to the fact that autonomic regulation of blood pressure can be disturbed at several levels between the hypothalamus and the periphery. There are cortical, limbic, anterior, and posterior hypothalamic, midbrain and medullary centres, where the input from the carotid sinus
and other afferents can be integrated and where output by way of the vagus and sympathetic to heart and blood vessels may be co-ordinated.

Most of the classic cardiovascular reflex tests provide information of the overall integrity of the baroreflex arc. The autonomic nerves, as well as end-organ responsiveness and circulatory haemodynamics are involved and only indirect information about a complex cardiovascular reflex loop is obtained. (Table 2) The overall integrity of the baroreflex arc can be assessed by analysing the heart rate and blood pressure responses to orthostatic posture or Valsalva straining. Afferent and central integrity of the baroreflex arc can not be assessed directly. The common approach is to evaluate the integrity of the efferent pathways. If these are normal, the disturbance is supposed to be on the afferent or central site of the arterial baroreflex arc. The integrity of the efferent sympathetic and/ or parasympathetic pathways can be assessed by evaluation of heart rate or blood pressure responses to stimulation of these pathways with afferent stimuli other than blood pressure. For example, placing the hand in ice water or exercise, such as sustained handgrip are selective physiological stressors to test the efferent sympathetic pathways. Selective evaluation of efferent cardiac vagal pathways can be performed by the forced breathing manoeuvre. [13-15] Another method is spectral analysis of the heart period (RR interval) and systolic arterial pressure variabilities. This method provides indices of efferent parasympathetic and sympathetic neural regulation, and of the balance between parasympathetic and sympathetic cardiovascular modulation. [16]

The most frequently used methods for investigating autonomic cardiovascular control in pregnant women are the orthostatic stress test, Valsalva’s manoeuvre, the cold pressor test, the isometric handgrip test, the deep breathing test and power spectrum analysis.

**Methods**

First, Medline was searched, using the following keywords: pregnancy, preeclampsia, autonomic nervous system. Second, the reference lists of the retrieved articles were scanned for relevant articles, which had not been found by Medline. A total of 36 articles concerning autonomic cardiovascular control in human pregnancy by non-invasive test methods, were found and reviewed.

For each test method, the data from different studies was summarized. This was done for normal pregnancy and for preeclampsia. Then, per test-method, the consistency between data from different studies was considered. Results were defined inconsistent if less than 75% of the studies had comparable results in direction and magnitude. Finally, based on the summary of results and the consistency it was evaluated if the test method could identify differences in autonomic cardiovascular control between healthy
pregnant women and preeclamptic women and if the test method could be of any clinical use, for example, as an early screening method.

In this review, we restrict ourselves to a description of the test methods that are summarized in table 2.

### Table 2. Non-invasive test methods for autonomic function testing

<table>
<thead>
<tr>
<th>Test Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power spectrum analysis</td>
<td>Overall baroreflex sensitivity</td>
</tr>
<tr>
<td></td>
<td>Efferent sympathetic / parasympathetic control</td>
</tr>
<tr>
<td>Active standing (orthostatic stress test)</td>
<td>Overall baroreflex integrity</td>
</tr>
<tr>
<td>Valsalva’s manoeuvre</td>
<td>Overall baroreflex integrity</td>
</tr>
<tr>
<td>Cold pressor test</td>
<td>Efferent sympathetic pathway</td>
</tr>
<tr>
<td>Isometric handgrip test</td>
<td>Efferent sympathetic pathway</td>
</tr>
<tr>
<td>Deep breathing test</td>
<td>Efferent vagal pathway</td>
</tr>
</tbody>
</table>

A description of the test method is given, followed by a summary of the results in uncomplicated and hypertensive pregnancy. With each test method, a summary of the results for normal pregnant women compared to non-pregnant women and for preeclamptic women compared to normal pregnant women, is given. In these tables each different response variable is indicated as increased(↑), decreased(↓), not different(≈) or undetermined(?), compared with non-pregnant or healthy pregnant values. The variable is defined as undetermined if less than 75% consistency existed between data of different studies. It should be mentioned that between articles, a large variability in the definition of pregnancy induced hypertensive disorders was found. If necessary, corrections of the definitions according to standard ISSHP consensus were made [1]. Pregnancy induced hypertension was defined as an arterial blood pressure $\geq 140$ mmHg systolic blood pressure and / or $\geq 90$ mmHg diastolic blood pressure on two consecutive readings more than 4 h apart, after 20 weeks of gestational age, in women with a normal blood pressure before 20 weeks of gestational age. Preeclampsia was defined as pregnancy induced hypertension combined with proteinuria $\geq 300$ mg/24h. Also, large variability in the definitions of low and high frequency oscillations of blood pressure and heart rate were found and they were also adapted if necessary. We defined low frequency oscillations as oscillations between 0,04 – 0,15 Hz and high frequency oscillations as oscillations between 0,15 – 0,40 Hz.

### Testmethods

**Power Spectrum analysis.**

Cardiovascular fluctuations can be studied by a computer-oriented technique applied to continuous recordings of arterial blood pressure and heart rate. The frequency domain
method, based on spectral analysis of the recorded signal, provides basic information on the distribution of power (variance) as a function of frequency by way of the Fourier transform. This is a mathematical tool to decompose a signal into a spectrum of sinusoids that, when added together, will reconstitute the signal. [15; 17-19] The spectrum of variation of heart rate and blood pressure can be divided into three peaks. One at very low frequencies (VLF; below 0,04 Hz or one period per 20 sec), one at low frequencies (LF; around 0,1 Hz (0,04 – 0,15 Hz) or one period in 10s) and one around the respiratory rate at high frequencies (HF; mostly 0,25 Hz (0,15 – 0,4 Hz) or one period in 4s). The respiratory (HF) peak is mainly due to vagus nerve activity since it nearly disappears following administration of high-dose atropine. [20, 21] The 0,1 Hz (LF) peak is due to low frequency oscillations of blood pressure mediated by sympathetic activity and low frequency oscillations of heart rate mediated by combined vagal and sympathetic activity impinging on the sinus node. [15] [22] Still slower (VLF) variations are due to various regulatory mechanisms, such as chemoreception and temperature regulation. LF and HF variability may also be measured in normalised units, which represents the relative value of each power component in proportion to the total power minus the VLF component. The normalisation procedure is helpful in allowing comparisons between subjects characterised by large differences in total power or VLF noise. [18]

From simultaneous spectral analysis of heart rate (HRV) and blood pressure (BPV) variabilities, a quantitative assessment of the overall gain of the baroreceptor mechanisms can be obtained. This gain can be represented by the index ($\alpha$), which can be computed out of the square root of the ratio between the power of the heart period and the blood pressure power ($\sqrt{\text{RRI}_{\text{power}} / \text{SBP}_{\text{power}}}$) 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 and the coherence function has to be ≥ 0,5. [23, 24] Respiratory rate and a change in posture have a significant effect 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 an increase in high frequency oscillations. A change from supine to upright position is accompanied by an increase in low frequency oscillations. [25]

Results
Normal pregnant women show less high frequency heart rate variability in supine position and less low frequency heart rate variability in standing position compared to non-pregnant women. Blood pressure variability showed no differences or consistency between data of different studies was less than 75 %. The baroreflex sensitivity index was found to be decreased in supine position in normal pregnancy. (Table 3)

Compared with healthy pregnant women, data of women with preeclampsia showed no differences or consistency between data of different studies was less than 75 %, for heart rate and blood pressure variability. The baroreflex sensitivity index was found to
be more decreased in supine position, although these data are derived from only one author. (Table 4)

Orthostatic stress
After a total of 5-10 minutes of supine rest, the subject is instructed to stand up and remain in upright position for at least 2 min [40]. 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). Directly after standing up heart rate (HR) increases in 3 seconds due to an exercise reflex. The secondary, more gradual HR increase, within 5 s, results from the dual effect of cardiac vagal inhibition and sympathetic activation. The subsequent rapid decrease in HR is associated with the recovery of arterial pressure and is due to rapid vagal inhibition mediated through the baroreflex. The arterial blood pressure shows, directly after standing up, 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. This drop in blood pressure induces sympathetically mediated vasoconstriction, whereby blood pressure recovers and sometimes overshoots [41-44]. After around 1 min, circulatory readjustment has been reached [15; 40; 42; 44; 45].

Table 3. Power spectrum analysis in normal pregnancy compared with non-pregnant women.

<table>
<thead>
<tr>
<th></th>
<th>LF</th>
<th>HF</th>
<th>LF/HF</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRV, supine</td>
<td>?</td>
<td>↓</td>
<td>?</td>
<td>[26-34]</td>
</tr>
<tr>
<td>HRV, standing</td>
<td>↓</td>
<td>?</td>
<td>?</td>
<td>[28; 30; 31; 35]</td>
</tr>
<tr>
<td>BPV, supine</td>
<td>»</td>
<td>»</td>
<td>»</td>
<td>[28; 30; 32; 33; 35]</td>
</tr>
<tr>
<td>BPV, standing</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>[28; 30; 35]</td>
</tr>
<tr>
<td>BRS, supine</td>
<td>↓</td>
<td></td>
<td></td>
<td>[28; 30; 35]</td>
</tr>
<tr>
<td>BRS, standing</td>
<td></td>
<td></td>
<td></td>
<td>[28; 35; 39]</td>
</tr>
</tbody>
</table>

↓: lower; ↑: higher; ?: undetermined, consistency between data < 75%; ≈: no difference; LF, low frequency; HF, high frequency; LF/HF, low frequency-high frequency ratio, HRV, heart rate variability; BPV, blood pressure variability; BRS, baroreflex sensitivity.

Table 4. Power spectrum analysis in preeclampsia compared with normal pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>LF</th>
<th>HF</th>
<th>LF/HF</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRV, supine</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>[29; 32; 33; 35; 36; 38]</td>
</tr>
<tr>
<td>HRV, standing</td>
<td>»</td>
<td>»</td>
<td>»</td>
<td>[35]</td>
</tr>
<tr>
<td>BPV, supine</td>
<td>?</td>
<td>?</td>
<td>»</td>
<td>[32; 33; 35]</td>
</tr>
<tr>
<td>BPV, standing</td>
<td>»</td>
<td>»</td>
<td>»</td>
<td>[35]</td>
</tr>
<tr>
<td>BRS, supine</td>
<td>↓</td>
<td></td>
<td></td>
<td>[35]</td>
</tr>
<tr>
<td>BRS, standing</td>
<td></td>
<td></td>
<td></td>
<td>[35]</td>
</tr>
</tbody>
</table>

↓: lower; ↑: higher; ?: undetermined, consistency between data < 75%; ≈: no difference; LF, low frequency; HF, high frequency; LF/HF, low frequency-high frequency ratio, HRV, heart rate variability; BPV, blood pressure variability; BRS, baroreflex sensitivity.
The heart rate response to orthostatic stress during the initial reaction can be quantified by the initial heart rate increase ($\Delta HR_{\text{max}}$), determined from the difference between the maximum heart rate ($HR_{\text{max}}$) and control and by the relative bradycardia ($HR_{\text{max}} / HR_{\text{min}}$). The $\Delta HR_{\text{max}}$ and $HR_{\text{max}} / HR_{\text{min}}$ ratio are mainly vagally mediated and can be used as a measure of cardiac vagal integrity. Blood pressure maintenance after 1 and 2 minutes of standing (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 efferens to the sinus node.[15; 40]

Results

In the initial phase, in normal pregnant women the bradycardic response is diminished, compared to non-pregnant women. Preeclamptic women showed no differences in heart rate and blood pressure response compared to healthy pregnancy. (Table 5)

In the steady state, there is a higher diastolic blood pressure difference in normal pregnant women compared to non-pregnant women. Responses were similar for preeclamptic women compared to normal pregnant women. (Table 6)

Table 6. Steady state to orthostatic stress in normal pregnancy to non-pregnant women and in preeclampsia compared with normal pregnancy.

<table>
<thead>
<tr>
<th>Steady state</th>
<th>$\Delta$ SBP</th>
<th>$\Delta$ DBP</th>
<th>$\Delta$ HR</th>
<th>author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia vs. Normal pregnancy</td>
<td>»</td>
<td>»</td>
<td>?</td>
<td>[48-50]</td>
</tr>
</tbody>
</table>

$\downarrow$: lower; ↑: higher; ?: undetermined, consistency between data < 75%; »: no difference

$\Delta$ SBP, systolic blood pressure increase; $\Delta$ DBP, diastolic blood pressure increase; $\Delta$ HR, heart rate increase.

Valsalva’s manoeuvre

In Valsalva’s manoeuvre the intra thoracic and intra-abdominal pressures are increased abruptly by forced expiration against a resistance. By blowing through a mouthpiece with a small air leak, the subject maintains a prescribed airway pressure while closure of the glottis is prevented and pressure is transmitted to the chest. The increased intra-thoracic pressure causes a decrease of venous return to the right atrium, which leads to
a fall in arterial pressure. A serious fall in arterial pressure is prevented by a baroreflex-mediated vasoconstriction due to increased sympathetic activity. The heart rate shows an increase to preserve the cardiac output, which is mediated both by vagal withdrawal and increased sympathetic outflow to the sinus node. After the strain, the venous return increases abruptly and because the vascular bed is still constricted arterial pressure overshoots, causing a vagally mediated bradycardia [15; 51; 52]. The heart rate response caused by Valsalva’s manoeuvre can be quantified as the *tachycardia ratio* (expressed as the ratio between maximum heart rate during the strain and the mean heart rate 30-15 s before the strain) and the *Valsalva ratio* (expressed as the ratio between maximum heart rate and minimum heart rate) [51] [15] [46]. Arterial pressure elevations after release of Valsalva straining provide acceptable estimates of preceding sympathetic nerve responses and the integrity of arterial baroreceptor- sympathetic control mechanisms [52]. The *baroreflex sensitivity* (BRS) can be estimated by the change in interbeat-interval per unit change in systolic blood pressure (ms/mmHg) during the overshoot of blood pressure after straining (phase 4 of Valsalva’s manoeuvre) [53].

**Table 7.** Valsalva’s manoeuvre in normal pregnancy compared with non-pregnant women and in preeclampsia compared with normal pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>Valsalva’s ratio</th>
<th>Tachycardia ratio</th>
<th>author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pregnancy vs. Non-pregnancy</td>
<td>?</td>
<td>↑</td>
<td>[46; 47]</td>
</tr>
<tr>
<td>Preeclampsia vs. Normal pregnancy</td>
<td>»</td>
<td>»</td>
<td>[49; 50]</td>
</tr>
</tbody>
</table>

↓: lower; ↑: higher; ?: undetermined, consistency between data < 75%; »: no difference

**Results**

The tachycardia ratio is higher in pregnancy compared to non-pregnant values but the heart rate response to Vasalva’s straining is not influenced by preeclampsia. (Table 7).

**Isometric Handgrip**

During the isometric handgrip test, the subject squeezes a pressure gauging device with the dominant hand for 3 min using 30% of the predetermined maximum voluntary force. During isometric exercise, systolic and diastolic blood pressure and heart rate gradually increase and immediately after cessation of exercise blood pressure and heart rate fall abruptly to their basal levels [54]. Two mechanisms are responsible for the cardiovascular adjustments to static exercise. The increase in blood pressure occurs mainly via an increase in sympathetic activity to blood vessels due to activation of chemically sensitive muscle afferents (muscle metabo reflex). The increase in heart rate occurs mainly through a decrease in parasympathetic activity to the sinus node due to central command, but also via sympathetic activation through the muscle metabo reflex [55-57].
Chapter 2

Autonomic cardiovascular control; review

Results

The heart rate and blood pressure response to isometric exercise is not influenced by pregnancy or preeclampsia. (Table 8)

Table 8. Isometric hand grip test in normal pregnancy compared with non-pregnant women and in preeclampsia compared with normal pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>Δ SBP</th>
<th>Δ DBP</th>
<th>Δ HR</th>
<th>author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pregnancy vs. Non-pregnant</td>
<td>?</td>
<td>?</td>
<td>»</td>
<td>[47; 49; 58; 59]</td>
</tr>
<tr>
<td>Preeclampsia vs. Normal pregnancy</td>
<td>»</td>
<td>»</td>
<td>?</td>
<td>[46; 50; 59; 60]</td>
</tr>
</tbody>
</table>

↓: lower; ↑: higher; ?: undetermined, consistency between data < 75%; »: no difference

Δ SBP, systolic blood pressure change; Δ DBP, diastolic blood pressure change; Δ HR, heart rate response.

Cold Pressor Test

The Cold Pressor test is performed by immersing the subject’s hand to the wrist in ice water (0-4 °C) for 2 min [61; 62]. This elicits an instantaneous local and generalised vasoconstriction in the skin and the skeletal muscle, which is not only due to a direct effect of cold on the local skin vessels, but also to pain activating spinal cord and hypothalamic reflexes. The heart rate increases and shows a peak in the first 30 s and returns to control values during the second minute. Due to an increase in total peripheral resistance, arterial pressure increases with a maximum in the second minute of the test. The pressor response has shown a strong correlation with the increase of muscle sympathetic neural activity as measured by direct recordings of sympathetic neural activity. This indicates that activation of the sympathetic vasoconstrictor outflow to the skeletal muscle is an important component of the pressor response to this test. The increased heart rate is mediated by sympathetic activation rather than by parasympathetic withdrawal, since the heart rate increase can be abolished by β-Adrenergic blockade [62; 63].

Results

In normal pregnant women less change in systolic blood pressure to cold exposure than non-pregnant women has been observed. For preeclamptic women, data of blood pressure response to cold exposure were inconsistent. The heart rate response was not influenced by pregnancy or preeclampsia. (Table 9)

Table 9. Cold Pressor Test in normal pregnancy compared with non-pregnant women and in preeclampsia compared with normal pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>Δ SBP</th>
<th>Δ DBP</th>
<th>Δ HR</th>
<th>author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pregnancy vs. Non-pregnant</td>
<td>↓</td>
<td>»</td>
<td>»</td>
<td>[59]</td>
</tr>
<tr>
<td>Preeclampsia vs. Normal pregnancy</td>
<td>?</td>
<td>?</td>
<td>»</td>
<td>[59; 64]</td>
</tr>
</tbody>
</table>

↓: lower; ↑: higher; ?: undetermined, consistency between data < 75%; »: no difference

Δ SBP, systolic blood pressure change; Δ DBP, diastolic blood pressure change; Δ HR, heart rate response.
Deep Breathing Test
A subject is asked to breathe deeply and evenly at 6 breaths/min. This produces maximum variation in heart rate. Respiratory fluctuations in heart rate are likely to be mediated primarily by parasympathetic efferent pathways. The respiratory sinus arrhythmia can thus be used as a measure of cardiac vagal modulation [19; 65; 66]. The maximum and minimum heart rates during each breathing cycle are measured and the mean of the differences between the maximum and minimum instantaneous heart rates is calculated as the deep breathing difference.

Results
Deep breathing difference was not influenced by pregnancy or preeclampsia. (Table 10)

Table 10. Deep breathing test in normal pregnancy compared with non-pregnant women and in preeclampsia compared with normal pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>Deep Breathing Difference</th>
<th>author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pregnancy vs. Non-pregnant</td>
<td>»</td>
<td>[31; 33; 46; 47; 49; 50; 67]</td>
</tr>
<tr>
<td>Preeclampsia vs. Normal pregnancy</td>
<td>»</td>
<td>[33; 49; 50]</td>
</tr>
</tbody>
</table>

» no difference

Conclusion
Most information regarding autonomic cardiovascular control in normal pregnancy and preeclampsia has been obtained by non-invasive methods. Although small differences were observed between normal pregnancy and preeclampsia in individual studies, the consistency between data was insufficient to discriminate between normal pregnancy and preeclampsia. Only two studies could demonstrate an increased resting sympathetic activity in preeclampsia, using direct neurography [10; 11]. Remarkably, in this same study population, they did not observe any differences in haemodynamic and sympathetic activity response to isometric exercise, cold pressor test or Valsalva’s manoeuvre between normal pregnant and preeclamptic women [10; 11].

This discrepancy of results could be due to methodological factors of the non-invasive studies. Data in literature are not easy to compare due to the differences in definition of disease, study design and performance of the test methods. 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. The performance of the different cardiovascular tests is not uniform and standardised. An important factor could be the difference in blood pressure measurement methods. Most studies used the occlusive upper arm technique. With this discontinuous method, peak changes in blood pressure could easily be missed. For prop-
er analysis of the heart rate and blood pressure response to different stimuli, continuous blood pressure and heart rate recordings should be used. The method of continuous finger pressure waveform registration by Finapres provides opportunities for non-invasive beat-to-beat blood pressure registration [68]. The large inter-individual variability of non-invasive test methods might be an other explanation for the discrepancy between results of non-invasive and invasive methods. This implies that in transversal studies, the variation within subgroups may be so large that differences between groups may not be detected. The non-invasive test methods, that have been evaluated, may seem to be directed purely at efferent pathways, but they involve reflex arcs and hence central and afferent connections are involved as well. The similar test results between healthy and preeclamptic pregnant women does presume an intact reflex response and efferent pathway. The increased resting sympathetic activity demonstrated by microneurography in preeclampsia might be caused by a disturbance of central control, or a change off afferent sensitivity.

Afferent sensitivity could be changed due to a resetting of the baroreceptor sensitivity. A decreased baroreflex sensitivity in preeclamptic women compared to healthy pregnant women has been observed when using spectral analysis [35]. This is in accordance with the earlier findings of Wasserstrum et al [69], who calculated baroreflex sensitivity in women with preeclampsia from the heart rate increase in response to a hydralazine-induced fall in blood pressure. Essential hypertension in humans is also known to be characterized by increased sympathetic activity and a decreased baroreflex sensitivity. In all hypertensive conditions, the baroreflex is reset towards the elevated blood pressure. This implies that, rather than opposing the blood pressure elevation, this mechanism acts to maintain it. This reflex mechanism may participate in the sympathetic activation characterizing hypertension [70].

Finally, it should be mentioned that it could be disputed if the increased sympathetic activity, which was observed by microneurography, truly represents an overall increase of sympathetic activity in preeclamptic women. Microneurography measures the sympathetic outflow to the skeletal muscle. The sympathetic activity in the skeletal muscle may not reflect the sympathetic activity in other organs, such as the heart or the kidney’s. Unfortunately, measurement of the overall sympathetic activity, for example by measuring arterial catecholamines, is also known to be of limited value [71] [72]. Arterial plasma noradrenaline levels were demonstrated to be similar between preeclamptic and healthy pregnant women [73].

Furthermore, the observed increased sympathetic activity seems to be purely an increase in vasomotor tone. None of the authors observed a difference in heart rate between
healthy pregnant women and preeclamptic women. Increased sympathetic activity does not seem to act on the heart, were perhaps it is masked by vagal tone [74].

If the increased sympathetic activity, as observed by microneurography in preeclampsia, is not representative for the overall sympathetic vasomotor tone or is due to disturbed central command, then we may be conclude that non-invasive methods will not contribute to discriminate preeclampsia from normal pregnancy. On the other hand, if only methodological confounders explain the discrepancy between results, then these could be avoided by a longitudinal study design, starting before pregnancy, using a standardized protocol for test methods and continuous registration of blood-pressure and heart rate. Analysis of changes in baroreflex sensitivity serially in pregnancy by using non-invasive methods could be a field of interest that should be further explored.
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