Part III

Pathophysiological study
Hemodynamic changes in the second half of pregnancy: a longitudinal, non-invasive study with thoracic electrical bioimpedance

Summary

OBJECTIVE: Maternal cardiovascular adaptations to pregnancy are necessary for an adequate fetomaternal circulation. However, the time course of physiological hemodynamic changes during the second half of pregnancy remains unclear. Various methods, invasive and non-invasive, are described to measure these changes. The thoracic electrical bioimpedance technique (TEB) is a method which is especially suitable to measure hemodynamic changes over time. The aim of the study was to determine both individual and group trends of hemodynamic changes in healthy pregnant women during the second half of pregnancy by means of TEB. Outcome variables are heart rate (HR), stroke volume (SV), cardiac output (CO) and blood pressure.

DESIGN: Longitudinal study.

SETTING: Outpatient antenatal care clinic of university hospital.

POPULATION: A total of 22 healthy nonsmoking women with an uncomplicated singleton pregnancy and without pre-existing vascular disorders were invited.

METHODS: TEB and blood pressure measurements were performed at each regular visit from about 24 weeks of gestation through term age.

MAIN OUTCOME MEASURES: Trends were calculated with the random effects model.

RESULTS: Data obtained from 19 women were analyzed, with a median of eight (range 3-11) measurements. HR showed a linear increase ($P < .0005$) and a quadratic trend ($P < .0005$). SV decreased linearly ($P = .046$), without a quadratic course. CO remained stable over time.

CONCLUSION: During the second half of physiological pregnancy significant trends could be determined. An increase in HR, a decrease in SV, a stable CO and an increase in systolic and diastolic blood pressures were found.
Introduction

Maternal cardiovascular changes in pregnancy are necessary to facilitate adequate circulation. In hypertensive disorders of pregnancy, such as preeclampsia, these physiological hemodynamic adaptations tend to be seriously disturbed.\textsuperscript{1-3} Although the time course of physiological hemodynamic changes during the first trimester of pregnancy have been elucidated, changes during the second half of pregnancy remain unclear. Despite the large number of women studied during the second half of pregnancy, in most studies only 2 or 3 measurements were performed per woman, preventing determination of a precise time course of hemodynamic changes during this specifically important period.\textsuperscript{4-6}

Various methods are described to measure these changes. As early as 1915, Lindhard used the dye-dilution technique to determine cardiac output (CO).\textsuperscript{7} Since its introduction in 1970, the thermodilution technique has been the gold standard technique to measure hemodynamic changes.\textsuperscript{8} Due to its invasiveness this technique is neither applicable for longitudinal and comparative studies in healthy subjects nor in moderately ill women. More recent non-invasive techniques of determining hemodynamic changes are Doppler echocardiography\textsuperscript{9} and thoracic electrical bioimpedance (TEB). TEB, introduced by Kubicek\textsuperscript{10} in 1966, is especially suitable to measure hemodynamic changes over time.\textsuperscript{6,11} TEB has been validated in normal pregnancies.\textsuperscript{12-15} In recent years, adaptations have been made to improve this technique, including reduction of the number of electrodes and a change in the position. Furthermore, improvements in signal analysis have been made, for example, corrections for breathing and calculations from less cardiac cycles.

In this study, both individual and group hemodynamic changes have been investigated in healthy pregnant women from 24 weeks of gestation to term. An improved TEB technique was applied longitudinally for this purpose.

Methods

Study design

Participants were selected from the obstetric outpatient clinic of the VU University Medical Center, Amsterdam, The Netherlands, between June and November 2002. Healthy, nonsmoking women with an uncomplicated singleton pregnancy were enrolled between 22 and 26 weeks of gestation.

Exclusion criteria were pre-existing vascular disorders (e.g. hypertension and diabetes mellitus) or a medical history of hypertensive complications during pregnancy. Gestational age was determined by ultrasound dating in the first trimester. Written informed consent was obtained from all participants. The medical ethics committee of VU University Medical Center approved the study protocol.
Technique

The bioimpedance apparatus used (MFI 9404)\textsuperscript{16,17} was connected to the thorax by four electrodes: two transmitting and two recording electrodes. The transmitting electrodes were placed in the middle of the forehead and at the lateral iliac crest and transmitted an unnoticeable, harmless, electric alternating current of 350 $\mu$A at a frequency of 64 kHz through the body. The recording electrodes were placed at the thorax just above the left clavicle and in the mid-axillary line at the level of the xyphoid process. During each visit, the distance between the recording electrodes was measured and used as one of the parameters to calculate stroke volume (SV). Other parameters to calculate SV were the maximum change of the impedance during the cardiac cycle and its first derivative. CO was calculated as the product of SV and heart rate (HR). Heart function parameters were calculated off-line with a software package that allowed filtering to eliminate breathing artefacts, coherent averaging and manual selection of appropriate tracings. Full technical details have been previously described.\textsuperscript{11,12} For the algorithm, a Kubicek like algorithm was used, in which the specific resistivity of the blood was taken as constant.\textsuperscript{15}

Study procedures

The measurements were carried out by one researcher (A.R.) and were performed at the obstetrical ward of the outpatient clinic of the VU University Medical Center. Measurements were performed throughout pregnancy from 24 weeks of gestation, in combination with regular visits: one measurement every 3 weeks from 24 to 30 weeks, every 2 weeks from 30 to 36 weeks and weekly after 36 weeks. Blood pressure was measured during each visit (standard sphygmomanometer [aneroid], Korotkoff 5 for diastolic blood pressure [DBP]). No medications were used, except vitamin or folic acid supplementation. Measurements were carried out in the semirecumbent position to prevent supine hypotension syndrome and to assure that no asymmetrical distribution of blood influences the results. Instructions were given not to move or talk during the recording.

Data handling

All data handling and data storage was performed in accordance with the guiding rules for good clinical practice.

Statistical analysis

For each measurement, ten successive beats from the most stable part of the signal were chosen for analysis. HR was calculated from the electrocardiogram signal, which was also measured with the TEB technique. The random effects model (REM),\textsuperscript{18} a variant of the multiple regression model suitable for longitudinal data, was used for statistical analysis. We postulated a quadratic
trajectory with three parameters representing 1) onset level of the hemodynamic measure, 2) rate of change of the hemodynamic measure during pregnancy and 3) curvature or acceleration.

In the main model, each woman had an individual onset level, but women had the same rate of change and the same curvature. In subsequent analyses, both the onset level and rate of change were allowed to differ among women.

Statistical significance of the overall rate of change and curvature were assessed using the Z test. Individual onset levels and rates of change were estimated with the empirical Bayes method. Variability among individual onset levels and among rates of change were assessed with the likelihood ratio test. Association between the individual rates of change of two different hemodynamic measures was measured by Spearman’s rank correlation. Software packages MLwiN1.1 and STATA8.0 were used for the statistical analysis.

Results

Twenty-two women were enrolled in the study. Three women were excluded from analysis because of complications during pregnancy: one woman with fetomaternal transfusion (gestational age 320/7 weeks) and two women with a spontaneous preterm delivery (gestational age 300/7 and 306/7 weeks, respectively).

Baseline characteristics of the 19 remaining women, whose data were analyzed, are summarized in Table I. Throughout pregnancy 155 measurements were performed, with a median of eight per woman (range 3-11). Median gestational age at delivery was 39.6 weeks (range 37.0-42.1).

The REM being used to assess trends in hemodynamic parameters determined both curved and linear shaped trends and assessed their significance. The amount of decrease or increase is estimated from 24 weeks to 40 weeks of pregnancy: HR showed a significant increase of 7.2 (95% CI 3.5-10.9) beats per minute (P < .0005) and a significant curvature (P < .0005) and peaked between 35 and 36 weeks (Figure 1). SV decreased 4.3 mL (95% CI 0.1-8.6; P = .046; Figure 2). No significant trend was found in CO (P = .867 for rate of change, P = .207 for curvature; Figure 3). Systolic blood pressure (SBP) increased significantly (7.3 mm Hg; 95% CI 3.3-11.4; P < .0005; Figure 4). DBP showed a significant increase of 10.9 mm Hg (95% CI 8.6-13.3; P < .0005) and a significant curvature and attained the minimum value at about 26 weeks (P < .0005; Figure 5). The estimated time courses of HR, SV, DBP and SBP are presented in Table II.

The individual slopes varied significantly among individuals for HR (P = .041), SV (P = .011), and SBP (P = .025). No interindividual variation in slopes was found for CO. The individual slopes of SV and HR as calculated from the REM were negatively correlated (Spearman’s p = –0.67).
Discussion

This study elucidates the physiological time course of hemodynamic variables throughout pregnancy from 24 weeks of gestation. HR curves showed a clear increase and a curvature, with a peak value between 35 and 36 weeks. SV decreased significantly. Group and individual CO remained stable. As expected in our population with a physiologic course of pregnancy, there was a significant increase in SBP and DBP during this period.

Figure 1. Rate of change in HR as calculated from the REM: $HR = -30 + 7.1t - 0.10t^2$. Curvature $P < .0005$, increase $P < .0005$. bpm, beats per minute.

Figure 2. Rate of change in SV as calculated from the REM: $SV = 74 - 0.27t$, decrease $P = .046$.

Figure 3. Rate of change in CO as calculated from the REM: stable ($P = .867$).

Figure 4. Rate of change in SBP as calculated from the REM: $SBP = 103 + 0.46t$, increase $P < .0005$.

Figure 5. Rate of change in DBP as calculated with the REM: $DBP = 105 - 3.08t + 0.059t^2$. Curvature $P < .0005$, increase $P < .0005$. 
Our study provides three indications that support the finding that the average CO time course is unchanged. First, the average increase in HR and the decrease in SV were of the same magnitude. Second, the individual slopes of CO were not significantly different. Third, the correlation between the slopes of SV and HR being –0.67 shows that women with the largest increase of HR also have the largest decrease in SV. Apparently, maintenance of a stable CO is important during the period from 24 weeks of pregnancy through term. An unchanged CO was found in various studies. Desai et al. reported an unchanged CO from 28 to 31 weeks. Bosio et al. described a plateau in CO from 24 weeks followed by a small decrease closer to term. Others described a change in CO. Most authors agree on a rise in blood pressure near term. The increase in HR is in agreement with others, although individuals were measured in various positions and the increase was not the same in each study, sometimes even not significant. The parabolic time course in HR with a peak value between the 35th and 36th week, is in concurrence with others, where peak values were reached at 29-32 weeks, 32 weeks and 32-36 weeks. Other studies, however, reported a stable or a decreased HR.

Group SV decreases throughout pregnancy, which was comparable with the sometimes minimal and position-dependent decrease in several other reports. A parabolic

### Table I. Baseline characteristics of women

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>34 (31 – 40)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 (158 – 182)</td>
</tr>
<tr>
<td>Pre-pregnancy weight (kg)</td>
<td>66 (52 – 80)</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Gestational age† (weeks)</td>
<td>24.5 (20.3 – 27.0)</td>
</tr>
<tr>
<td>SBP† (mm Hg)</td>
<td>120 (100 – 130)</td>
</tr>
<tr>
<td>DBP† (mm Hg)</td>
<td>65 (55 – 75)</td>
</tr>
</tbody>
</table>

Values presented as medians and ranges or number and %. †At first measurement.

### Table II. Equations of estimated time courses of hemodynamic changes from 24 weeks of pregnancy through term as determined by the REM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>[ -30 \pm 21 + 7.1 \pm 1.4 \times t - 0.10 \pm 0.02 \times t^2 ]</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>[ 74 \pm 5.2 - 0.27 \pm 0.14 \times t ]</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>[ 103 \pm 4.6 + 0.46 \pm 0.13 \times t ]</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>[ 105 \pm 14 - 3.1 \pm 0.91 \times t + 0.059 \pm 0.01 \times t^2 ]</td>
</tr>
</tbody>
</table>

bpm, beats per minute; t = time in weeks. Standard error is given between brackets.
time course is also reported with a peak value at 31 and 36 weeks.\textsuperscript{25,26} In addition, distinct contradicting results are shown.\textsuperscript{5,20,23}

Discrepancies in literature are generally considered to be because of either individual patient factors or different maternal position\textsuperscript{5} rather than measurement error or different or inadequate measurement techniques.\textsuperscript{6,28} We propose another explanation: inadequate frequency and timing of sampling. Most well-performed studies measure changes during the entire pregnancy rather than changes in the latter half of pregnancy. Therefore, the description of the time course of the variables in late pregnancy is based on only two or three measurements per woman during the period from 24 weeks of gestation through term. This limits the determination of a precise time course of hemodynamic changes. In this study, the number of measurements per woman during this period was eight (median). This set up was chosen to facilitate this examination over time. A further factor is that in few studies, trends are presented only graphically, without reporting the amount of change and the significance, although absolute values are presented. Changes or trends in cardiovascular parameters and their significance are usually determined by comparing the mean value at a certain time point in pregnancy to a non-pregnant, an early gestation or a postpartum value. This indicates whether values during a specific period are significantly higher, lower or equal to such a value, but it is not possible to conclude that values are significantly increasing or decreasing during a certain period during pregnancy. Therefore, changes and the statistical significance of these changes during the period between 24 and 40 weeks of gestation are not fully considered. In contrast, by means of the REM, we were able to examine time trends and interindividual variation during the 24 to 40 weeks of gestation period. The model has several desirable features. There are no requirements with regard to the spacing and number of time points per woman. This also means that each woman is allowed to have a different onset time. Besides, the development of each woman during pregnancy is represented by an individual trajectory with well-interpretable parameters.

This study has several limitations. As thermodilution and not TEB is considered the gold standard technique for the measurement of SV and CO, our results can be disputed. Obviously, the use of thermodilution in uncomplicated pregnancies is unethical. In addition, TEB has been validated in normal pregnancy.\textsuperscript{12-15} Several authors\textsuperscript{13-15} report correlation coefficients of 0.77-0.94 of SV as measured with TEB compared with dye dilution and thermodilution in the left lateral, right lateral and supine positions. In a study comparing cardiac index as measured with TEB against the oxygen extraction technique in the left lateral, right lateral and supine positions, correlations of 0.915 and 0.863 were found respectively.\textsuperscript{12} However, in the supine and sitting positions considerable lower correlations (0.423 and 0.554) were measured.\textsuperscript{13-15} Although no explanation is found in literature for this effect, disturbed circulation in the supine position (supine hypotension) may contribute to this. In the semirecumbent position used, no circulatory
discomfort is experienced by pregnant women, so we feel it justified to use the TEB technique. The TEB technique used is based upon the principle that a current applied to the thorax causes a potential distribution at the skin, which is modulated by cardiac contraction. Bioimpedance devices are being used in medicine over the past 40 years, using currents up to 10 mA. No harmful effects have been reported yet. Our device is using only 0.35 mA. This current flows through the maternal thorax. As the fetus is mainly outside the measuring volume no harm is expected. Due to its non-invasiveness, easy use and patient friendliness, the technique is very suitable for the measurement of changes over time.\textsuperscript{6,11} In addition, no significant difference in change of SV during serial measurements was found between TEB and dye dilution.\textsuperscript{13,14} Furthermore, in contrast to echocardiography, TEB does not need to be carried out by a specialist and makes continuous registration possible. Another limitation to the study is the small number of subjects included, only 19 women. However, 155 measurements have been carried out to facilitate examination of changes over time by means of the longitudinal approach in which each woman is her own control. We did realize that a cross-sectional approach would have the advantage of better normal reference values and less influence of interindividual differences.

\section*{Conclusion}

Since deviation in hemodynamic adaptations throughout pregnancy may relate to serious complications, such as preeclampsia and hemolysis elevated liver enzymes low platelet count syndrome, knowledge of the time course of the adaptations is important. Using TEB, clear and significant trends can be determined. An increase in HR, a slight decrease in SV, a stable CO and an increase in blood pressure normally occur. Further studies are necessary to assess the value of TEB for early deviations in abnormally developing pregnancies.

\section*{Acknowledgements}

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Reference List


