The maternal circulation in early-onset hypertensive disorders of pregnancy; measurements with the thoracic electrical bioimpedance technique

Hypertension in Pregnancy; submitted
Summary

OBJECTIVE: To measure hemodynamic effects of plasma volume expansion in severe early-onset hypertensive disorders of pregnancy by means of thoracic electrical bioimpedance.

METHODS: Measurements were performed in 35 patients participating in a randomized controlled trial on management with (n=16) or without (n=19) plasma volume expansion between 24 - 34 weeks gestation and in 19 healthy low-risk pregnant women.

RESULTS: Plasma volume expansion did not influence maternal hemodynamic parameters, only a marginal decreased systemic vascular resistance (P = .06) was observed. The hypertension group and controls differed in heart rate (P < .001), cardiac output (P = .008) and systemic vascular resistance (P < .001).

CONCLUSION: Plasma volume expansion has no significant influence on hemodynamic parameters as measured with the bioimpedance technique.
Introduction

Hypertensive disorders of pregnancy are caused by a maladaptation of the maternal cardiovascular system to pregnancy.\textsuperscript{1,2} This adaptation has to occur early in pregnancy at the time of trophoblast invasion into the uterine spiral arteries. When adaptation fails, a hyperdynamic situation with a decreased cardiac output, increased systemic vascular resistance, reduced plasma volume and hypertension occurs later on in pregnancy.\textsuperscript{3-5} Plasma volume expansion to correct this hyperdynamic situation is applied in the management of hypertensive disorders of pregnancy, necessitating monitoring of the maternal circulation. Diverse methods (non-invasive and invasive) have been described,\textsuperscript{4,6,7} of which the thermodilution technique, an invasive method, is considered to be the gold standard.\textsuperscript{8} This invasive technique has several side effects, due to the use of a pulmonary artery catheter and has to be performed in an Intensive Care Unit. A non-invasive method with the possibility of bedside measurements is preferable in critically ill patients. Thoracic electrical bioimpedance, a non-invasive technique, is easy to perform and relatively low-cost. The technique has been validated for the measurement of cardiovascular parameters throughout pregnancy\textsuperscript{6,9} and for the measurement of cardiac output in preeclampsia.\textsuperscript{10} The bioimpedance technique has recently been used to examine individual and group hemodynamics in the second half of uncomplicated pregnancies by a variant of multiple regression analysis (random effects model).\textsuperscript{11}

In the current prospective study the effect of plasma volume expansion on cardiovascular parameters was measured with thoracic electrical bioimpedance in severe hypertensive disorders of pregnancy. We hypothesized that plasma volume expansion increases cardiac output and decreases systemic vascular resistance.

Methods

Study population

The study was performed at the Department of Obstetrics of the VU University Medical Center in Amsterdam, The Netherlands, between 2000 and 2003. Subjects in the present study consisted of participants in a randomized controlled clinical trial, comparing two management strategies in severe hypertensive disorders of pregnancy; i.e. preeclampsia, hemolysis elevated liver enzymes low platelets (HELLP) syndrome, pregnancy induced hypertension with fetal growth restriction or eclampsia; Table 1.\textsuperscript{12-14} Seven patients (20%) fulfilled the criteria for HELLP syndrome, 18 patients (51%) had severe preeclampsia and 16 patients (46%) were diagnosed with fetal growth restriction. Patients were enrolled at a gestational age between 24 and 34 completed weeks and were allocated to a management strategy with or without plasma volume
expansion (PVE).\textsuperscript{15,16} Patients in the hypertension with PVE group received 250 mL HydroxyEthylStarch (HES) 6\% (200/0.5) twice daily in 4 hours. Restricted amounts of NaCl 0.9\% were given with intravenous medication and in-between doses of HES. The amount of administered intravenous fluid a day was, per protocol, significantly higher in the hypertension with PVE group (median 46 mL \textit{versus} 863 mL; \( P < .001 \)) as was the amount of total administered fluid intravenously during the study period (median 401 mL \textit{versus} 9113 mL; \( P < .001 \)). A protocol for antihypertensive medication was performed in both groups. Medications used were \( \alpha \)-methyldopa, labetalol, nifedipine, ketanserine, and magnesium sulphate.

The control group consisted of patients selected from the low-risk population of the obstetric outpatient clinic of the VU University Medical Center, between June and November 2002. They were all healthy, non-smoking women with an uncomplicated singleton pregnancy. Subjects were enrolled between 22 and 26 weeks gestation.\textsuperscript{11} Exclusion criteria were pre-existing vascular disorders (e.g. hypertension, diabetes mellitus), or a medical history of hypertensive complications during pregnancy.

In all groups gestational age was verified by ultrasound dating scan in the first trimester. Written informed consent was obtained from all patients and study procedures were approved by the VUmc medical ethics committee.

\textbf{Technique}

The thoracic electrical bioimpedance technique used, is based upon the principle that a current, injected in the thorax, causes a potential distribution at the skin, which is modulated by cardiac contraction. Heart function parameters were assessed from the synchronic changes caused by cardiac contraction. The bioimpedance apparatus used (MFI 9404)\textsuperscript{17,18} was connected to the thorax by 4 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 microamperes at a frequency of 64 kHz through the body. The recording electrodes were placed at the thorax just above the left clavicle.

<table>
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<tr>
<th>Inclusion diagnosis</th>
<th>Definition</th>
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<tr>
<td>Severe preeclampsia\textsuperscript{13}</td>
<td>diastolic blood pressure ( \geq 110 \text{ mm Hg} ) and proteinuria ( \geq 0.3 \text{ grams/24 hours} )</td>
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<tr>
<td>HELLP syndrome\textsuperscript{12}</td>
<td>platelet count (&lt; 100 * 10^9/L ) and aspartate aminotransferase ( \geq 70 \text{ U/L} ) and lactate dehydrogenase ( \geq 600 \text{ U/L} )</td>
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<tr>
<td>Fetal growth restriction and pregnancy induced hypertension\textsuperscript{13,14}</td>
<td>estimated fetal weight (&lt; p10 ) and diastolic blood pressure ( \geq 90 \text{ mm Hg} )</td>
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and in the mid-axillary line at the level of the xyphoid process. At each measurement the distance between the recording electrodes was determined 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 1st derivative. Cardiac output (CO) was calculated as the product of SV and heart rate (HR). The systemic vascular resistance (SVR) was determined as the product of mean arterial pressure (MAP; mm Hg) and 80 divided by CO (L/min). Heart function parameters were calculated off-line with a software package that allows filtering to eliminate breathing artefacts, coherent averaging and manual selection of appropriate tracings.

**Study procedures**

Two investigators performed the measurements at the obstetrical ward and at the outpatient clinics. In the hypertension group the measurements were performed at time of inclusion in the initial study or within 12 hours after inclusion (t0), the morning following on the first measurement (t1) and once every day thereafter. Measurements were performed at about the same time in the morning, till the patient had delivered. When, at the first measurement, patients had already received plasma volume expansion, this measurement was expressed as t1. The mean values of the measurements performed at t1 and thereafter is expressed as t2. All patients were managed with bed rest.

In the control group measurements were performed on occasion of a check-up from 24 weeks gestation onwards. The average number of measurements per patient was 9; from 24 until 30 weeks a measurement every 3 weeks, from 30 until 36 weeks every two weeks, after 36 weeks weekly. For the present study only the mean values of the measurements between 24 and 32 weeks gestation were used to compare with the mean values in the hypertension groups.

Measurements were carried out in a semirecumbent position. Instructions were given not to move or talk during the recording. Blood pressure was measured before start of impedance performance (standard sphygmomanometer, Korotkoff 5 for diastolic blood pressure). Medications used were written down in the patient record form.

**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 ECG signal, which was also measured with the thoracic electrical bioimpedance technique. First, we compared
hemodynamic parameters at t0, and t1 between patients in the hypertension group with and without PVE. Second, changes between the measurements at t0 and t1 were compared between patients in the hypertension group with and without PVE. Third, the mean values of measurements performed at t1 and thereafter (=t2) in the hypertension groups and the mean values of measurements of patients in the control group were compared. Statistical calculations were performed with SPSS 12.0.2 (SPSS Inc. Chicago, Illinois, USA). Statistical analysis was performed with standard non-parametric Mann-Whitney U tests. Values were expressed by mean and standard deviation. Differences were considered statistically significant if P < .05.

Results

In total, 54 women were analyzed; 35 patients were enrolled in the hypertension group, of whom 19 were allocated to a management strategy without PVE and 16 to a management strategy with PVE, and 19 women were analyzed in the control group. Seven out of 16 patients in the hypertension with PVE group had their first bioimpedance measurement before PVE was started. Median gestational age at inclusion was 213 (178-233) days in the hypertension without PVE group versus 207 (181-235) days in the hypertension with PVE group (Table II). Baseline characteristics were comparable between hypertension groups, except for the use of antihypertensive medication, which was significantly more frequent in the hypertension without PVE group (P = .03). At the first bioimpedance measurement 4 patients were treated with intravenously administered magnesium sulphate and 19 patients used mono- or combination antihypertensive medication: α-methyldopa (n=16), labetalol (n=5), nifedipine (n=3), ketanserine (n=4). During admission 13 patients were treated with magnesium sulphate intravenously. A median of 5 measurements (range 1-20) was performed per patient, equally distributed between hypertension group with and without PVE. In 7 patients (5 from the hypertension without PVE group and 2 from the hypertension with PVE group) only one measurement was performed. At the two different test moments (t0 and t1) no differences were found in CO, SV, HR, and SVR between patients managed with and patients managed without PVE (Table III). A marginal decreased SVR in the hypertension with PVE group was observed at t1 compared to t0 (+303.68 dyne x sec/cm$^5$ in the hypertension without PVE group versus -469.91 dyne x sec/cm$^5$ in the hypertension with PVE group; P = .053). The 7 patients in the hypertension with PVE group who had not received PVE at t0 showed a non-significant decrease in SVR at t1 (2149.40 dyne x sec/cm$^5$ at t0 versus 1726.49 dyne x sec/cm$^5$ at t1; P = .06). The mean values of measurements after t1 (=t2) compared to t0 showed no differences between the hypertension without PVE group and hypertension with PVE group for all maternal cardiovascular parameters.
Comparison of these parameters between the hypertension without PVE group and hypertension with PVE group and the controls showed a significant difference in HR ($P < .001$), CO ($P = .008$) and SVR ($P < .001$), while SV did not differ ($P = .78$; Figure 1).
Discussion

This study reports the hemodynamic effects of plasma volume expansion on maternal hemodynamics in the management of severe hypertensive disorders of pregnancy as measured with the thoracic electrical bioimpedance technique. The positive effects of PVE as there are an increase in cardiac output and a reduced systemic vascular resistance, which has been reported earlier, could not be confirmed.\textsuperscript{19-21} A trend only could be demonstrated in reduction of systemic vascular resistance before and after PVE in the hypertension with PVE group in which patients served as their own controls. Another, non-invasive, study on hemodynamic parameters in pregnancies complicated by hypertensive disorders could not find any effect by PVE as well.\textsuperscript{22} The significantly higher infused volume in the PVE group is probably counteracted by strong homeostatic

\textbf{Figure 1.} Box plot of mean values of measurements for heart rate (A), stroke volume (B), cardiac output (C) and systemic vascular resistance (D) in the hypertension without PVE group, the hypertension with PVE group and control group.
mechanisms,\textsuperscript{23} causing increased diuresis and capillary permeability with leakage of fluids in the interstitial space.\textsuperscript{21,24} This regulatory mechanism probably also keeps cardiac output stable over time as was measured in non-complicated pregnancies.\textsuperscript{11}

Within the non-invasive techniques, the bioimpedance technique has been validated for uncomplicated pregnancies,\textsuperscript{9} and group and individual hemodynamic trends have been described.\textsuperscript{11} Till now, only two studies tried to validate the bioimpedance technique in pregnancies complicated by hypertension with contradictory results, but in both studies only one measurement was performed during pregnancy.\textsuperscript{10,25} The latter study observed lower values of CO by the bioimpedance technique compared to the thermodilution technique.\textsuperscript{25} In our study measurements of CO were also lower than in earlier reports.\textsuperscript{3,5} In those reports measurement of CO was performed with the thermodilution technique, the golden standard technique till now. No literature on hemodynamic effects of plasma volume expansion as measured with thoracic electrical bioimpedance is available to compare with.

Some limitations of the study should be mentioned. In the first place only 7 patients in the hypertension with PVE group had their first measurement without PVE. The observed effect on SVR could have been stronger in a larger population. Secondly, antihypertensive medication was frequently used. The effect of antihypertensives on heart rate is well known, but also other hemodynamic parameters could be influenced.\textsuperscript{26,27} Magnesium sulphate infusion has been shown to increase CO estimates in preeclampsia.\textsuperscript{28} Although in our population finally 13 patients were treated with intravenously administered magnesium sulphate, no differences were found in CO. The use of antihypertensive medication in combination with magnesium sulphate could have counteracted the effect. Thirdly, patients were enrolled at different gestational ages. A reasonable median of 5 measurements per patient was performed. As nearly all measurements per patient were performed within one week no effect of gestational age had to be expected.

Our study demonstrated the differences of the hemodynamic parameters between women with early-onset hypertensive disorders of pregnancy and normal pregnancy by means of repeated measurements during the third trimester of pregnancy. They concerned a lower heart rate and cardiac output, and a higher systemic vascular resistance. Another longitudinal study on hemodynamic parameters in hypertensive pregnancies measured by the bioimpedance technique presented similar findings.\textsuperscript{29} These differences were found in the singleton bioimpedance measurements at term and 48 h postpartum and disappeared at 2 and 6 months postpartum. Their study confirms that the bioimpedance technique is useful in the observation of longitudinally collected hemodynamic changes over time at longer intervals in women with preeclampsia. Our
study demonstrates that the technique is lacking to show short-term variations. Since severe hypertensive disorders of pregnancy can cause major maternal complications, a reliable assessment of hemodynamic parameters is essential. In these critically ill patients, cardiovascular parameters have to be evaluated at least once a day and management of hypertension and subsequent disorders has to be adjusted when necessary. Therefore, we conclude that in severe preeclampsia, where short-term variations influence management strategies, thoracic electrical bioimpedance can only be used in a research setting.


