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Reference (Published version):
Tomsin, Kathleen; Oben, Jolien; Staelens, Anneleen; Mesens, Tinne; Molenberghs, Geert; Peeters, Louis & Gyselaers, Wilfried(2013) Cardiovascular hemodynamics throughout normal pregnancy and postpartum as measured by impedance cardiography. In: ACTA OBSTETRICIA ET GYNECOLOGICA SCANDINAVICA,

DOI: 10.1016/j.ijpharm.2016.07.035
Handle: http://hdl.handle.net/1942/22791

Cardiovascular hemodynamics throughout normal pregnancy and postpartum as measured by impedance cardiography

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Running title: Impedance cardiography in pregnancy

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Conflicts of interest statement

The authors report no conflict of interest.

Abstract

Objective To evaluate the feasibility of non-invasive assessment of maternal cardiac and arterial characteristics throughout uncomplicated pregnancy and postpartum.

Design A longitudinal evaluation throughout gestation, at seven weeks postpartum and at one year postpartum.

Setting Antenatal outpatient clinic of Ziekenhuis Oost-Limburg (Genk, Belgium).

Sample 16 women with uncomplicated pregnancy.

Methods Impedance cardiography measurements were performed in supine, standing, and sitting position using a standard protocol with known reproducibility. SAS procedure MIXED for linear mixed models was used, and fitted to the data for each parameter separately: Data were binned in four-weekly intervals. Differences between gestational and postpartum measurements were evaluated by One-Sample Wilcoxon Signed Rank Tests. Data are presented as mean (standard error of mean).

Main outcome measures Gestational and postnatal evolution of blood pressure, stroke volume, cardiac output, cardiac cycle time intervals, aortic flow characteristics, total peripheral vascular resistance, and thoracic fluid content.

Results In all positions, stroke volume and cardiac output changed significantly throughout gestation (n=16; $p \leq 0.0001$), and supine values differed from standing ($p \leq 0.008$) and sitting positions ($p \leq 0.048$). As compared to early postpartum, all cardiovascular parameters remained unchanged after one year postpartum (n=12; $p \geq 0.074$), except for standing diastolic blood pressure which decreased with 5±2 mmHg ($p=0.037$).

Conclusions Gestational evolutions of left ventricular output were similar to reported changes in literature, and were influenced by maternal position. Our study illustrates that impedance cardiography has the potential to become a useful tool in perinatal medicine to assess maternal hemodynamics.

Key words

Cardiovascular Hemodynamics; Hypertension in Pregnancy; Imaging in Obs & Gyn; Impedance Cardiography; Non-Invasive; Postpartum; Prospective Observational Study

Abbreviations

BMI = body mass index
SEM = standard error of mean

Key message

Impedance cardiography allows for the non-invasive assessment of maternal cardiac and arterial characteristics. These parameters change significantly throughout gestation and postpartum, in which left ventricular output parameters are influenced by maternal position.

Introduction

Normal pregnancy is characterized by a decrease in total peripheral resistance and increased plasma volume (1). The use of non-invasive alternatives for the conventional methods to study these hemodynamics is becoming increasingly important (2, 3) to understand the cardiovascular maladaptation in pregnancy disorders such as preeclampsia (4, 5). One of these popular non-invasive techniques, i.e. impedance cardiography, correlates well with the standard thermodilution technique for cardiac output determination (3). Moreover, we have recently shown that impedance cardiography is safe and reproducible in pregnancy (6).

In this prospective study, we aim to describe the hemodynamic changes observed using impedance cardiography throughout normal pregnancy to illustrate its usefulness in the study of maternal hemodynamics.

Methods

Approval of the local ethical committee was obtained before study onset (MEC ZOL reference: 09/050). We established a longitudinal observational study in pregnant women presenting at the antenatal outpatient clinic of Ziekenhuis Oost-Limburg (Genk, Belgium) in early gestation (November 2009 - March 2010). Singleton pregnancies of women without history or symptoms of medical or cardiovascular diseases were included. All women were included at six to eight weeks of gestation based on ultrasound dates and were evaluated monthly until term. The normal course and outcome of pregnancy was verified postpartum. Measurements were repeated at six to eight weeks postpartum and one year postpartum. Postpartum exclusion criteria were new-onset of pregnancy or symptoms of medical or cardiovascular diseases.

For all women, maternal age at inclusion (years), pregestational and postpartum body mass index (BMI), nulliparity (yes or no), gestational age at delivery (weeks), and birthweight (g and percentiles) were registered.

After informed consent, all women underwent an impedance cardiography examination according to the protocol detailed previously (6, 7) using the Non-Invasive Continuous Cardiac Output Monitor™ (Software version 2.0, SonoSite, Medis Medizinische Messtechnik GmbH, Ilmenau, Germany). The impedance cardiogram (dZ/dt) is the first mathematical derivative of the thoracic impedance (Z) change over time for an alternating current with high frequency (60-100 kHz) and low amplitude (1 mA) transmitted through the thorax by a four electrode arrangement which eliminates skin resistance. After ten minutes of adaptation to the supine position, all measurements were registered in three positions: supine, sitting, and standing. Hence, the effect of aortacaval compression can be visualized.

Based on both impedance cardiogram and electrocardiogram signals (Figure 1), all cardiovascular characteristics were assessed by applying third generation algorithms incorporating known electrophysiological and clinical principles (3), and were classified into six groups as follows.

Pressures: Systolic and diastolic blood pressure (mmHg) are measured by the automated oscillometric module of the Non-Invasive Continuous Cardiac Output Monitor™-device, enabling the calculation of pulse pressure and mean arterial pressure.

Left ventricular output: Heart rate (beats/min) was calculated from the heart period duration (ms), measured as the RR-interval of the electrocardiogram-signal. Stroke volume (mL) was calculated using the Sramek-Bernstein formula, which incorporates the electrically participating chest tissue estimated from patient's characteristics (8). Cardiac output (L/min) represents the amount of blood pumped by the heart per minute, calculated as heart rate × stroke volume.

Cardiac cycle time intervals: Pre-ejection period (ms) is the period of isovolumetric ventricular contraction defined as the time interval between the electrocardiogram's Q-wave (start of ventricular depolarization) and the impedance cardiogram's B-point (opening of the aortic valve), i.e. the time needed for the ventricle to exceed the aortic pressure and start ejection (electrical systole, Figure 1). Left ventricular ejection time (ms) represents the duration of ejection (mechanical systole) (9) and is the time interval between the B- and X-point (opening and closing of the aortic valve, respectively) of the impedance cardiogram (Figure 1). Together, pre-ejection period and left ventricular ejection time represent the electromechanical systole. Diastolic time (ms) (10) is calculated as heart period duration − electromechanical systole. Both left ventricular ejection time and diastolic time are expressed as a percentage of heart period duration, i.e. left ventricular ejection time index and diastolic time index (11). Systolic time ratio is calculated as the ratio of the electrical and the mechanical systole (pre-ejection time/left ventricular ejection time).

Aortic flow: Characteristics of aortic flow were derived from the normalized Z waveform, i.e. impedance cardiogram (dZ/dt) corrected for an individual's base impedance (Z_0).

The velocity index is the equivalent of the amplitude or maximum velocity of the systolic wave (C-point), which is calculated as $1000\times((dZ/\ dt_{max})/Z_0)$ in 1/1 000/s. The acceleration index is calculated as $100\times((d^2Z/dt^2_{max})/Z_0)$ in $1/100/s^2$, which represents the equivalent of the maximum acceleration of blood flow in the aorta (d^2Z/dt^2, second mathematical derivative of the change in Z over time). The Heather index represents the amplitude of the systolic impedance cardiogram wave which is corrected for the time needed by the ventricle to reach

maximum ejection (electrocardiogram's R-wave to impedance cardiogram's C-wave; T_{RC}). This is calculated as $(dZ/dt_{max})/T_{RC}$ in Ohm/s^2. The distensibility of the aorta is estimated by total arterial compliance (mL/mmHg) (12). This is calculated as stroke volume × pulse pressure.

Total peripheral vascular resistance: Total peripheral vascular resistance in mmHg/mL/min was estimated by dividing the mean arterial pressure by cardiac output.

Thoracic fluid: The base impedance (Z_0 in Ohm) represents the overall impedance (Z) measured across the thorax, which is influenced by the amount of conducting fluid in the thorax. This fluid level is expressed as thoracic fluid content (1/kOhm).

An orthostatic index (13, 14) was calculated as a percentage of change when moving from supine to standing position: $(value_{standing}/value_{supine}) \times 100 - 100$.

In order to establish reference curves, a linear mixed model was fitted to the data for each parameter separately (15). As such, a random subject effect was included. To avoid imposing parametric structures on the curve, an unstructured profile was considered. To this end, the data were binned in four-weekly intervals between eight weeks of gestation and term. For each gestational age interval, the median value was calculated and plotted graphically. For this, SAS procedure MIXED (SAS Inc., software version 9.2, Chicago, IL, USA) was used.

Differences between gestational and postpartum measurements were evaluated by One-Sample Wilcoxon Signed Rank Tests. All data are represented as means±standard error of mean (SEM) or numerical values (%).

Results

In 16 women with uncomplicated pregnancy, nine consecutive impedance cardiography examinations were performed at 8±0, 12±0, 16±0, 20±0, 24±0, 28±0, 32±0, 36±0, and 38±0 weeks of gestation. Four women missed the last impedance cardiography examination because they delivered between 37 and 38 weeks of gestation. Postpartum measurements were performed at 7±0 weeks and at 53±0 weeks postpartum. Four women were excluded at one year postpartum for new-onset medical disease (n=1), pregnancy (n=2), and drop-out (n=1). Demographic characteristics at inclusion and pregnancy outcome are listed in Table 1. Women's BMI was 1±0 kg/m^2 lower one year postpartum (n=12) compared with their early postpartum value (p=0.040).

Gestational evolution and postpartum values of impedance cardiography measurements are shown in Figure 2 and Table 2. All parameters changed significantly throughout pregnancy in all three positions ($p\leq$0.0001).

In third trimester uncomplicated pregnancy, stroke volume and cardiac output (Figure 2) tended to fall in supine position compared with standing ($p\leq$0.008) or sitting positions ($p\leq$0.048). Gestational evolution of heart rate differed between supine and standing positions (p=0.023) as heart rate in supine position tended to rise towards term. Next to this, pre-ejection period, left ventricular ejection time index, systolic time ratio and total peripheral vascular resistance also showed a different gestational evolution between the supine and standing positions ($p\leq$0.0499). Throughout uncomplicated pregnancy, no differences in left ventricular output characteristics were observed between standing and sitting positions ($p\geq$0.398).

When comparing one-year postpartum values (53±0 weeks) to early postpartum, no significant differences were observed ($p\geq$0.074), except for standing diastolic blood pressure which decreased with 5±2 mmHg one year postpartum (p=0.037).

When comparing early gestational measurements with postpartum values, cardiac output was higher (p=0.016) in supine position due to an increase in heart rate (p=0.011), but not in stroke volume (p=0.753) (Table 2). Next to this, early gestational systolic time ratio and pre-ejection period were significantly lower ($p\leq$0.006), whereas left ventricular ejection time

index was significantly higher (p=0.041). Moreover, velocity index, acceleration index, and Heather index were higher ($p \leq 0.004$) at early gestation when compared with postpartum values. Orthostatic indices of all parameters were comparable between early gestation and early postpartum ($p \geq 0.090$).

As compared to term pregnancy, standing systolic blood pressure and pulse pressure both decreased at early postpartum ($p \leq 0.049$). During standing position, early postpartum values for stroke volume and cardiac output were decreased compared with term gestational values ($p \leq 0.008$). Systolic time ratio was increased together with an increase in pre-ejection period ($p \leq 0.028$); left ventricular ejection time index was significantly lower during the postpartum period as compared with term pregnancy (p=0.012). Thoracic fluid content was decreased at early postpartum compared with term pregnancy (p=0.013).

Discussion

In the non-critically ill pregnant woman, the use of invasive techniques such as pulmonary artery catheterization are rarely justified as they are associated with significant intrinsic morbidity. Impedance cardiography may offer a good alternative to these conventional invasive methods, allowing for a safe assessment of the cardiac and arterial system in pregnancy (6).

Specialists in hemodynamics often criticize impedance cardiography measurements because they are obtained from mathematical calculations. On top of this, their correct physiologic nature is not always easily understood. Despite these limitations, a recent meta-analysis reported good correlation between impedance cardiography measurements and those obtained by invasive methods, specifically in non-critically ill patients (3). Moreover, it has been reported that impedance cardiography measurements are reproducible under standardized conditions in non-pregnant individuals (7), in uncomplicated pregnancy, and preeclampsia (6).

Our study illustrates that gestational and postpartum evolution of impedance cardiography measurements of cardiovascular function is similar to reported observations using other methods (1, 16, 17). Our study shows the relevance of maternal position during this examination: stroke volume, cardiac output, pre-ejection period, left ventricular ejection time index, systolic time ratio, and total peripheral vascular resistance were significantly different between supine and standing positions. These left ventricular characteristics are derived from the preload-dependent parameter “left ventricular ejection time” (9, 18). Consequently, changes in these characteristics are likely to be related to the growing pregnant uterus which interferes with venous return (19-21) in the supine position. This phenomenon possibly troubles the interpretation of cardiac output evolution near term, as is indicated by the reported presence of conflicting results of cardiac output evolution from third trimester pregnancy to term (22). On top of this, different filling states amongst the female population could also explain those inconsistent results: High variability in cardiac output and plasma volume is observed in pregnancy disorders such as preeclampsia (23, 24). This variability helped to explain the reoccurrence of preeclampsia in women with a low plasma volume (25), which is suggested to be linked to venous capacitance (26, 27).

Most hemodynamic parameters are suggested to return to preconception values within 8 to 12 weeks postpartum (28), which is also true in our study. Next to this, we found that early postpartum measurements around seven weeks postpartum did not differ from one-year postpartum, except for a subclinical difference in diastolic blood pressure (Table 2). As compared to early postpartum values, we reported a higher heart rate in early pregnancy resulting in an increase in cardiac output, together with an increase in the aortic parameters velocity index, acceleration index, and Heather index, and lower systolic time ratio and pre-ejection period values. This is in line with other observations, reporting an early augmentation of sympathetic activity (29) in reaction to the primary fall in systemic vascular tone (30).

Despite the small number of women included in this study, we conclude that our observations illustrate the feasibility of impedance cardiography in the observation and registration of cardiac and arterial adaptation mechanisms throughout human pregnancy, hereby emphasizing the importance of the position of the maternal body. This opens perspectives for impedance cardiography as a potentially useful method in the cardiovascular assessment of women with gestational complications, such as hypertension, preeclampsia, or fetal growth restriction.

Acknowledgments

The authors would like to thank all the women included in this study and their husbands for their commitment to this project throughout and beyond their entire pregnancy.

Funding statement

The authors report that this study has not received any financial funding.

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Figure legends

Figure 1. The corresponding signals of the electrocardiogram and the impedance cardiogram. The impedance cardiogram (dZ/dt) is the first mathematical derivative of the change in impedance over time (Z) for an alternating current with high frequency (60-100 kHz) and very low amplitude (1 mA) transmitted through the maternal thorax by a four electrode arrangement eliminating skin resistance. Q: start of ventricular depolarization, R: peak ventricular depolarization, B: opening of aortic valve, C: peak systolic flow (dZ/dt_{max}), X: closure of aortic valve, O: opening of mitral valve, and T_{RC}: time from R to C.

Figure 2. For each gestational age, medians of cardiac output were calculated per position and presented graphically. Full, dotted and dashed lines are used for differentiation between supine, standing, and sitting positions, respectively. Significant differences between supine and standing, between supine and sitting, and between standing and sitting positions are indicated with asterisks, circles and triangles, respectively.

Tables

Table 1. Demographic characteristics and pregnancy outcome of normal pregnant women. Data are represented as means (SEM) or numerical values (%).

	Uncomplicated pregnancies (n=16)
Demographic characteristics at inclusion	
Maternal age (years)	29±1
BMI (kg/m²)	23±1
Nulliparity (%)	n=9 (56)
Pregnancy outcome characteristics	
Birthweight (g)	3387±121
Birthweight (percentile)	54±6
Gestational age at delivery (weeks)	39±0

Table 2. Impedance cardiography measurements at early gestation (supine: n=16; standing: n=14), term (supine and standing: n=12), early postpartum (supine and standing: n=16), and late postpartum (supine and standing: n=12). Data are presented as means (SEM).

		Pregnancy		Postpartum	
		8±0 weeks	*38±0 weeks*	*7±0 weeks*	*53±0 weeks*
Pressures					
systolic blood pressure	*supine*	114±2	119±4	114±2	111±3
(mmHg)	*standing*	117±2	123±4	117±3	112±3
diastolic blood pressure	*supine*	72±2	78±2	73±1	71±2
(mmHg)	*standing*	78±2	82±3	81±2	78±2
mean arterial blood pressure	*supine*	82±2	87±3	82±2	81±2
(mmHg)	*standing*	88±2	93±3	91±2	88±2
pulse pressure	*supine*	42±1	41±3	41±2	39±2
(mmHg)	*standing*	39±2	40±2	36±2	34±1
Left ventricular output					
cardiac output	*supine*	7.0±0.4	6.5±0.4	6.4±0.4	6.5±0.4
(L/min)	*standing*	6.8±0.3	7.9±0.4	6.3±0.3	6.0±0.3
heart rate	*supine*	77±2	80±2	70±2	70±2
(beats/min)	*standing*	93±3	92±3	88±3	84±3
stroke volume	*supine*	92±5	82±5	92±5	93±6
(mL)	*standing*	73±3	87±4	72±3	72±3
Cardiac cycle time intervals					
pre-ejection period	*supine*	91±3	124±5	107±3	103±4
(ms)	*standing*	102±4	113±5	127±3	122±4
left ventricular ejection time index	*supine*	37±1	33±1	35±1	36±1
(%)	*standing*	38±1	38±1	36±1	35±1
diastolic time index	*supine*	52±1	51±2	53±1	52±2
(%)	*standing*	47±1	45±1	46±1	48±1
systolic time ratio	*supine*	0.32±0.02	0.50±0.03	0.36±0.02	0.34±0.01
	standing	0.42±0.02	0.46±0.02	0.52±0.02	0.49±0.01
Aortic flow					
velocity index	*supine*	75±3	58±4	66±4	67±4
(1/1000/s)	*standing*	65±3	67±5	62±3	62±4
acceleration index	*supine*	128±7	93±6	110±7	111±8
(1/100/s²)	*standing*	124±8	123±11	119±6	116±8
Heather index	*supine*	20.7±1.4	12.7±1.5	16.1±1.3	16.3±1.4
(Ohm/s²)	*standing*	18.1±1.2	16.3±1.6	14.7±0.8	14.7±1.0
total arterial compliance	*supine*	2.2±0.1	2.1±0.1	2.3±0.1	2.4±0.1
(mL/mmHg)	*standing*	1.9±0.1	2.2±0.1	2.1±0.1	2.2±0.1
Total peripheral vascular resistance					
total peripheral vascular resistance	*supine*	12.2±0.6	14.1±1.0	13.6±0.8	13.0±0.7
(mmHg/mL/min)	*standing*	13.4±0.8	12.2±0.9	14.8±0.6	14.9±0.8
Fluid					
thoracic fluid content	*supine*	31.6±1.4	35.7±2.4	31.3±0.9	31.7±1.0
(1/kOhm)	*standing*	28.7±0.8	31.3±1.8	27.6±0.7	27.5±0.7