Left ventricular function and systemic arterial properties in normal and preeclamptic pregnancy

Mette-Elise Estensen

National Resource Centre for Women's Health and Department of Cardiology

Oslo University Hospital, Rikshospitalet

2012

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 1475

ISBN 978-82-8264-208-8

Cover: Inger Sandved Anfinsen.
Printed in Norway: AIT Oslo AS.

Produced in co-operation with Akademika publishing.
The thesis is produced by Akademika publishing merely in connection with the thesis defence. Kindly direct all inquiries regarding the thesis to the copyright holder or the unit which grants the doctorate.

DEDICATED TO FANNY & AUGUST

Acknowledgements

The present work has been carried out at the National Resource Centre for Women's Health and Department of Cardiology, Oslo University Hospital, Rikshospitalet during the years 2008-2012.

I have been very fortunate to have two of the most experienced researchers in Norway, representing two different departments and medical fields, cardiology and obstetrics, as supervisors for this work. Prof. Svend Aakhus has been the principal supervisor for this thesis, and I am most grateful for his guidance into the world of research. Learning from his excellent skills in echocardiography and hemodynamics has been a privilege. Svend Aakhus introduced me to Prof. Patrick Segers at the IBitec, Ghent University, Belgium, and this thesis could not be possible without the inspiring and positive collaboration with him and Abigail Swillens at the IBitec. Prof. Tore Henriksen has been my co-supervisor, and I am grateful for his excellent skills in the field of obstetrics, his general knowledge, and for letting me have an open door to his department at Rikshospitalet.

I would like to thank Prof. Lars Gullestad for his always inspiring support and for being my connection to the University of Oslo. I am also grateful to Prof. Otto A. Smiseth, head of the Heart and Lung Clinic at Rikshospitalet, who encouraged me to take on the task of building a multidisciplinary team for pregnant women with heart disease. This thesis has been part of that project. As a co-author, Smiseth has contributed with important scientific suggestions and positive support. Further, I want to express my thanks to Prof. Tom Tanbo, prior head of the National Resource Centre for Women's Health. He has always been supportive, and he gave me the liberty to combine my clinical work and research. I will also thank Siri Vangen, Tanbo's successor, for her support.

Warmest thanks go to my colleague and co-author Guro Grindheim. Her work, knowledge, support and friendship have meant everything for this thesis. I am also grateful to co-author Espen Remme at Institute for Surgical Research for his inspiring and positive collaboration.

I am very grateful to the head of Department of Cardiology, Lars Aaberge. He has always encouraged and supported me. I am fortunate that I have had the possibility to combine the research fellowship with clinical practice; he taught me the importance of combining good clinical work and research. A special thanks to the staff at Echo Laboratory at the Outpatient Clinic, Department of Cardiology; Pia Bryde, Joke Andreassen and Richard Massey. Warm thanks also to Rita Skårdal who have taken all the blood samples, and to Pernille Frese for her help in including patients.

A special thanks to Eldrid Langesaether at the Department of Anaesthesiology, who has encouraged and supported me, and taught me anaesthesiological skills in pregnant women. A warm thank you goes to my colleague and friend Kristina Hermann Haugaa, who has been an ideal. She has encouraged, supported and pushed me. I am also grateful to my research fellows; Jan Otto Beitnes, Christian Eek, Lene Anette Rustad, and Kaspar Broch for discussions, technical help, and friendship. I will also thank my colleagues Aina Hognestad and Kjell Pettersen for discussions, advice, and friendship.

Further, I would like to thank my family, especially my mother Jorun for her love and support, and for always being helpful in taking care of my children. Also a warm thanks to my brother Odin and my sister Gry and their families for supporting me, and for good discussions and good times. My deepest thanks go to Theis, my husband and love, for his inspiration, patience and love, for being there in every aspect of life, and being a daily reminder of what is most important. And finally, my foremost gratitude to my two wonderful children Fanny and August, who have supported me with laughter, play, fun, discussions, travels, and a lot of love during these years – I thank you with all my heart.

List of papers

1. Estensen ME, Beitnes JO, Grindheim G, Aaberge L, Smiseth OA, Henriksen T, Aakhus S. Altered left ventricular function during normal pregnancy.

Ultrasound Obstet Gynecol. 2012 Sep 24. doi: 10.1002/uog.12296. [Epub ahead of print]

2. Estensen ME, Grindheim G, Remme EW, Swillens A, Smiseth OA, Segers P, Henriksen T, Aakhus S. Systemic arterial response and ventriculo-arterial interaction during normal pregnancy.

Am J Hypertens 2012; 25:672-7

3. Grindheim G, Estensen ME, Langesaeter E, Rosseland LA, Toska K.
Changes in blood pressure during healthy pregnancy: a longitudinal cohort study.
J Hypertens 2012; 30:342-50

4. Estensen ME, Remme EW, Grindheim G, Smiseth OA, Segers P, Henriksen T, Aakhus S. Increased arterial stiffness in preeclamptic pregnancy at term, and early and late postpartum. A combined echocardiographic and tonometric study.

Submitted.

Abbreviations

ANP	atrial natriuretic peptide
BNP	brain natriuretic peptide
BMI	body mass index
BP	blood pressure
C	total arterial compliance
CI	cardiac index
CO	cardiac output
CVD	cardiovascular disease
DBP	diastolic blood pressure
DT	deceleration time
Ea	arterial elastance
EaI	arterial elastance index
EaI/ELVI	arterio-ventricular coupling index
ECG	electrocardiogram
EF	ejection fraction
ELV	left ventricular elastance
ELVI	left ventricular elastance index
ESVI	end-systolic volume index
ESWS	left ventricular wall stress at end systole
Des	LV mean inner diameter at end-systole
FPS	frames per second
FS	fraction shortening
GS	longitudinal global strain

h_{es}	LV average wall thickness
LV	left ventricle
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
LVET	left ventricular ejection time
IVSd	intra ventricular septum in diastole
NP	normal pregnancy
Pb	pressure wave reflections backward
PE	preeclampsia/preeclamptic
Pes	end-systolic pressure
Pf	pressure wave reflections forward
Pp	postpartum
PPEP	previous preeclamptic patients
R	peripheral arterial resistance
RR	cardiac cycle length
SBP	systolic blood pressure
SV	stroke volume
SVI	stroke volume index
Z_0	characteristic impedance
VAC	ventriculo-arterial coupling
Vcfc	velocity of circumferential fiber shortening

Introduction

During pregnancy, the growing fetoplacental unit induces distinct changes in maternal physiology. The maternal cardiovascular adaptation to pregnancy normally involves changes in circulating blood volume (1), cardiac output (2) and peripheral vascular resistance (3). Healthy pregnancy is often referred to as a state of high cardiac output and low peripheral resistance. This hemodynamic state involves extensive alterations in all aspects of maternal cardiovascular function such as myocardial function and contractility, heart rate, and vascular properties. Myocardial function during pregnancy has discrepantly been described as being either normal, depressed, or enhanced (4, 5). Healthy women adapt well to these cardiovascular changes which are induced by the hormonal influence of the growing fetoplacental unit, and thereby secure adequate delivery of oxygenated blood to peripheral tissues and the fetus. Adverse cardiovascular events are rare during healthy pregnancy. However, women with pre-existing cardiovascular disease may not be able to fully accommodate to pregnancy. Furthermore, undiagnosed heart disease may be disclosed during pregnancy due to the increased cardiac demands induced during pregnancy.

Worldwide, hypertensive disorders of pregnancy represent an important clinical problem with a significant maternal and perinatal morbidity and mortality (6). Hypertensive disorders of pregnancy are classified into two categories, pre-existing or gestational, and further complicated with preeclampsia. Preeclampsia is defined as pregnancy-induced hypertension with proteinuria occurring after 20 weeks of gestation. Preeclampsia occurs in 3-10% of all pregnancies (6). In western countries, the prevalence has been reported to increase over the last 30 years (7). Accordingly, an increase in prevalence from 3.3 to 4.5% has been reported in Norway from 1968 to 2002 (8). The mechanism and pathogenesis of this entity are still not well understood. This is partly due to the fact that preeclampsia refers to a set of symptoms,

and is a heterogeneous condition. Over the last decades it has become apparent that preeclampsia is not a homogenous condition with a single cause. Preeclampsia is the final response to an interaction between maternal (pregnancy-independent) and trophoblast (placenta-dependent) factors. In each individual woman the placental and maternal factors act in concert, and contribute to various degrees of cardiovascular, uteroplacental, metabolic, immunological, and neuro-endocrine changes that occur in preeclampsia. The cardiovascular system, however, will always become affected in preeclampsia as reflected by the hypertension and capillary leakage with proteinuria and edemas associated with this condition. Endothelial dysfunction seems to play a key role in the pathogenesis of preeclampsia (Figure 1).

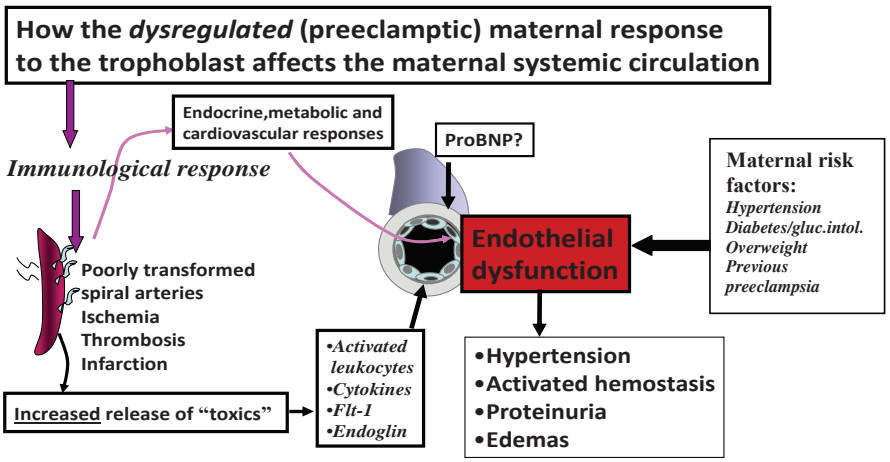

Figure 1. How the preeclamptic maternal response to the trophoblast affects the maternal systemic circulation (T. Henriksen).

As outlined above, healthy pregnancy is characterized by high cardiac output and low peripheral vascular resistance. In preeclampsia, the situation is often reversed with a hemodynamic profile more comparable to the non-pregnant state with high vascular resistance (9, 10). Other aspects of vascular properties, such as total arterial compliance and proximal aortic stiffness, have to some extent been studied in the preeclamptic population. Noninvasive investigations using pressure and flow estimates indicate that total arterial compliance is reduced, and proximal stiffness increased in preeclampsia (11, 12). Furthermore, there are some data indicating that increased sympathetic activity in these patients (13) may contribute to the typical hemodynamic state. There is extensive evidence that endothelial dysfunction plays a central role in the pathogenesis of preeclampsia that readily explains many of the cardiovascular, inflammatory, hematological, and clinical characteristics of the preeclamptic patient (14).

Currently, research in the area of hemodynamics and arterial properties in normal pregnancy and preeclampsia has several aspects. First, there is a need for detailed insight into the natural course of physiological changes during healthy pregnancy in order to define the normal ranges of hemodynamic parameters. Such knowledge is relevant for health professionals handling women in childbearing age as a theoretical background when facing pathological pregnancies or women with pre-existing medical conditions that may become influenced by pregnancy. Second, it is becoming increasingly evident that the different subgroups of preeclampsia are pathogenetically at least partly diverse (14) and need further description. Third, the significant increase in risk of cardiovascular disease later in life in previous preeclamptic women warrants data that provide pathophysiological insight that can improve health advice to women at risk (15). Given that the cardiovascular system is affected in normal pregnancy, becomes deranged in preeclampsia, and that preeclampsia is an indicator

of future cardiovascular risk, investigations of the cardiovascular system in pregnant women should be an important element in studies of women's health.

Studies of cardiovascular adaptations in the pregnant population are particularly challenging since these must be carried out without any fetomaternal risk or discomfort. Ideally, the investigations should be brief, harmless and without need for sedatives in order to avoid fetomaternal risk and alterations of normal maternal cardiovascular physiological state.

Noninvasive methods have been developed that enable a detailed assessment of systemic arterial properties and left ventricular (LV) function. By use of simultaneous echocardiography and recording of external arterial pressure waveforms, systemic vascular properties, i.e. peripheral resistance, total arterial compliance and characteristic impedance, can be estimated (16-18). Understanding of LV performance requires not only examining the properties of the LV itself, but also investigating the effects of the arterial system on the left ventricular performance. The interaction between the LV and the arterial system, i.e. the ventriculo-arterial coupling (Ea/E_{LV}), is an important determinant of cardiovascular performance and cardiac energetics, and has hitherto not been described in detail in neither normal nor pathological pregnancy.

The results of the present studies are all obtained by a comprehensive analysis of longitudinal cardiovascular data recorded by entirely non-invasive techniques and demonstrate important cardiovascular adaptations during healthy and pathological pregnancies.

Aims of thesis

The aims of the present work were:

Specific

1. To perform a clinical longitudinal study with comprehensive assessment of left ventricular function by echocardiographic measurements in normal pregnancy and postpartum (Paper 1).

2. To perform a longitudinal study with comprehensive assessment of systemic arterial properties and ventriculo-arterial coupling during normal pregnancy and postpartum (Paper 2).

3. To evaluate and compare changes in brachial arterial blood pressures during healthy pregnancy measured by two different non-invasive measurement devices (Paper 3).

4. To assess and compare systemic arterial properties and ventriculo-arterial coupling in normal pregnancy, acute preeclamptic pregnancy, and previous preeclamptic pregnancy (Paper 4).

Subjects

Three different groups of women were studied; group 1 comprised women with normal pregnancies (NP), group 2 women with acute preeclamptic pregnancies (PE), and group 3 women with previous preeclamptic pregnancies (PPEP). Written informed consent was obtained from all participants. The study was approved by the Regional Committee for Ethics in Medicine. All women received conventional medical treatment at the discretion of the responsible physician.

Group 1 Normal pregnancy (NP)

Group 1 comprised healthy women with defined normal singleton pregnancy in the first trimester. 70 women referred to the STORK project at the Obstetric Department at Rikshospitalet in the period of January 2008 to June 2008, were invited to participate in the follow up study. They were investigated at weeks 14-16 (65) (there were 5 drop-outs), weeks 22-24 (63), week 36 (61) and 6 months postpartum (63). Two women dropped out of the study because of spontaneous abortion after the first investigation, and two were lost for the 36 weeks control because of pre-term birth. Serial foetal ultrasound examinations were performed by a gynecologist confirming normal foetal anatomy and growth in all study subjects.

Group 2 Preeclamptic pregnancy (PEP)

Group 2 comprised 40 women diagnosed with preeclampsia as defined by hypertension (blood pressure > 140/90 mmHg) and proteinuria (i.e. urine protein to creatinine ratio above 30 mg/mmole creatinine or at least +1 proteinuria on urine stix on two occasions at least 24 hours apart) before delivery at any time point in pregnancy. The participants were recruited from the patients referred to the Department of Obstetrics at Rikshospitalet for evaluation and

treatment of preeclampsia in the period January 2008 to January 2009. Six months postpartum, 35 of the 40 women (i.e. 5 drop-outs) underwent a second investigation.

Group 3 Previous preeclamptic pregnancy (PPEP)

Group 3 comprised non-pregnant women who had been diagnosed with preeclampsia in previous pregnancies (delivered with preeclampsia at Rikshospitalet in the period July 2003 to June 2008). All patients referred for evaluation and treatment of preeclampsia at the Department of Obstetrics at Rikshospitalet in that period constitute a database of approximately 500 patients. From this database, we randomly selected 50 patients who were invited to participate in the study, of which 40 women agreed to participation.

I. Baseline and follow up investigations for women with normal pregnancy (NP)

Investigation:	w 14-16	w 22-24	w 36	6 mo pp
Clinical status	x	x	x	x
BP, ECG	x	x	x	x
Echocardiography	x	x	x	x
Tonometry	x	x	x	x
Blood sample	x	x	x	x

II. Baseline and follow up investigations for women with preeclamptic pregnancy (PE)

Investigation:	at term	6 mo pp
Clinical status	x	x
BP, ECG	x	x
Echocardiography	x	x
Tonometry	x	x
Blood sample	x	x

III. Investigations of women with previous preeclamptic pregnancy (PPEP)

Clinical status	x
BP, ECG	x
Echocardiography	x
Tonometry	x
Blood sample	x

In group 3 (PPEP), body mass index (BMI) and blood pressure (BP) in 1.st trimester, gestational age at diagnosis of preeclampsia, gestational age at delivery and birth weight were recorded during index pregnancy. Furthermore, peak urine protein/creatinine ratio, peak systolic and diastolic BP and antihypertensive medication at delivery were registered. Level of physical activity and family history of cardiovascular disease (CVD) were reported.

Exclusion criteria

Group 1

Hypertension (i.e. BP > 140/90 mmHg). Proteinuria (as above).

Group 1, 2 and 3

Previous myocardial infarction documented by ECG, history and/or typical cardiac enzyme pattern. Previous stroke with sequelae. Any condition which interferes with patient's possibility to comply with protocol. Significant mental disorder. Uncontrolled endocrinological and reumathological disturbances, and kidney disease.

Methods

Echocardiography

Echocardiography was performed with the subjects in a left decubitus posisition. Subjects were scanned from the parasternal and apical windows (19) by use of a digital ultrasound scanner (Vivid 7, GE Vingmed, Horten, Norway). We recorded conventional grey scale cineloops, pulsed and continuous wave Doppler recordings of blood flow velocities, and tissue-Doppler cineloops of LV. Frame rate during tissue-Doppler recordings was >100 frames per second (FPS) and during 2D-imaging >40 FPS. We used at least 3 consecutive cineloops which were obtained and stored on server for off-line analysis using dedicated software (Echopac version 7.0; GE).

The parameters left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), and ejection fraction (LVEF) were calculated by use of the Simpson's modified biplane method utilizing endocardial contours in the apical 4 and 2 chamber view (20). LV mass was calculated from parasternal M-mode registrations according to the Devereux formula, obtained by 2D of LV dimensions (average of short and long axis recording) (21).

Pulsed Doppler blood flow velocities were recorded at the mitral valve ring and tip, and in the LV outflow tract. Cardiac output (CO) was calculated from stroke volume (SV) (determined by pulse wave Doppler recordings) multiplied by heart rate (HR). The mitral peak early (E) and late (A) diastolic flow velocities were measured, and the E to A ratio and E deceleration time were calculated (22).

Pulsed Tissue Doppler recordings were obtained using a predefined 9 mm sample volume positioned at the septal and the lateral aspects of basal LV at the junction with the mitral annulus in the apical 4-chamber view (Figure 2) (23). Diastolic peak early (e') and late (a')

mitral annular tissue velocities as well as peak systolic velocity (s') are reported as the average of the septal and lateral annular values. The E/e' ratio was calculated (22). The parameters derived from Doppler and tissue-Doppler recordings were measured after 5 min rest with the woman in a left ducubitus posisition on at least 3 consecutive heart cycles and averaged.

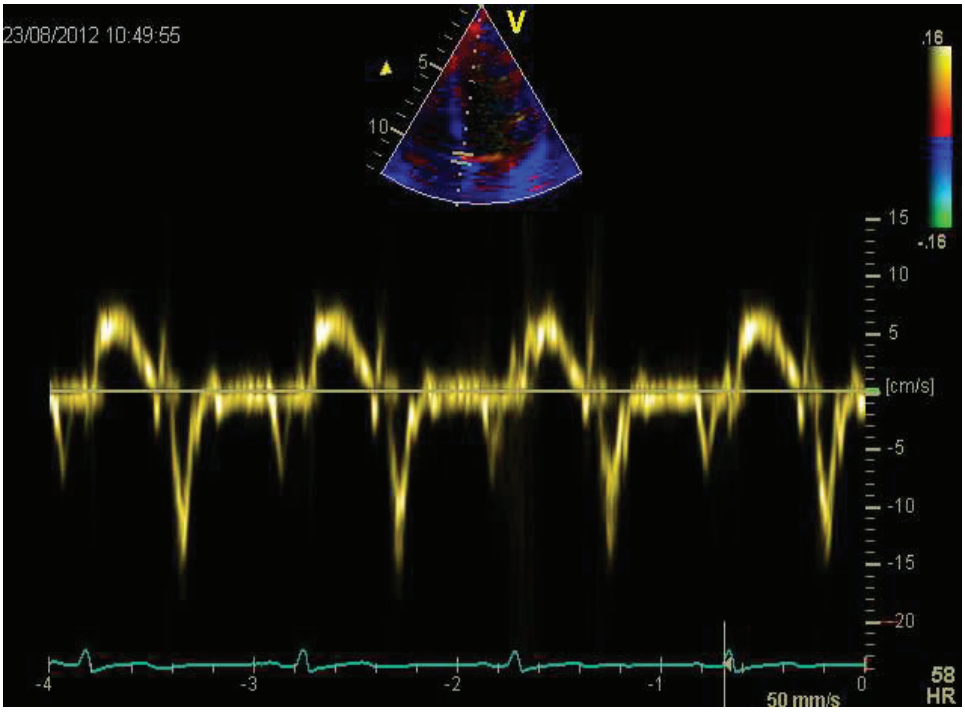

Figure 2. Pulsed Tissue Doppler recordings were obtained using a predefined 9 mm sample volume positioned at the septal and the lateral aspects of basal LV at the junction with the mitral annulus in the apical 4-chamber view.

Strain is defined as fractional change of tissue length and is expressed in a dimensionless unit conventionally as percent shortening (negative values). Strain values can be derived from tissue Doppler recordings, as well as from tracking of ultrasound speckle patterns. In this work, we used the latter approach. Briefly, speckles represent consistent ultrasound reflection patterns from tissue. Speckle presence is due to interference effects between overlapping echoes, and its occurrence is related to randomly distributed structure scatterers within a resolution cell. The software algorithm tracks the speckles from frame to frame and calculates the distance between the speckles during the heart cycle. These distance measurements provide accurate tracking of the myocardial contraction and relaxation patterns during cardiac cycle. Two-dimensional speckle tracking (2D-STE) grayscale images were acquired in apical 4 chamber, 2 chamber and long axis views. Figure 3 displays strain curves from a healthy individual. The predominant fiber orientation is longitudinal in the subendocardium and circumferential in the mid-myocardium. Longitudinal strain predominantly reflects subendocardial myofiber contraction while contraction durations by circumferential strain measure mid-myocardial contraction. We assessed peak longitudinal systolic strain in all 16 segments of the LV. Peak systolic global strain (GS) was assessed as the average of segmental strains, and used to assess global LV myocardial function (24).

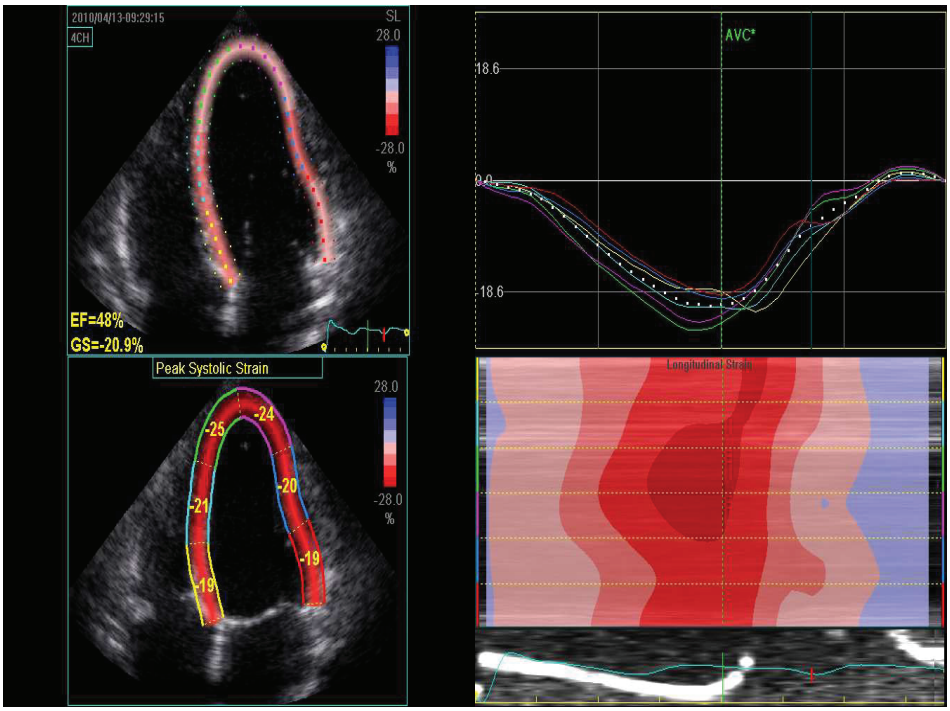

Figure 3. Speckle tracking longitudinal strain curves from 6 segments in apical 2 chamber view from a healthy pregnant individual.

All echocardiographic recordings were performed and analysed by one investigator (MEE). All echocardiographic analyses were performed offline with the observer blinded for time point.

LV contractility

In general, cardiac imaging techniques, as echocardiography, provide access to LV contractions which depend on the myocardial contractility, but is not equivalent. LV contractility is the result of the intrinsic contractile properties of the myocytes, but is also

influenced by the ventricle's loading condition and heart rate. LV contractility cannot be measured by presently available imaging techniques, but can be approached and analysed in a framework where LV contractions and afterload are incorporated (25). We used the noninvasively obtainable and preload-insensitive measure of contraction, mean velocity of LV circumferential fiber shortening normalized for heart rate (Vcfc) plotted against LV afterload measured as LV end-systolic wall stress (25) (Figure 4). Vcfc was obtained as LV fractional shortening (FS, i.e. end-diastolic minus end-systolic diameter over end-diastolic diameter) over ejection time (LVET, determined from echocardiographic registrations), and normalized for heart rate (HR) by dividing with the square root of cardiac cycle length (RR);

$Vcfc = FS\%/LVET/RR^{1/2}$.

LV meridional end systolic wall stress (ESWS or σ_{es}) (dyn), a measure of LV afterload was calculated in end-systole as

$$\sigma_{es} = P_{es} \times D_{es}/(4h_{es}\,[1+h_{es}/D_{es}])$$

where P_{es} (mmHg) is end-systolic aortic root pressure (determined from tonometric pressure estimate), D_{es} (cm) is LV mean inner diameter at end-systole, and h_{es} (cm) is LV average wall thickness (septum and posterior wall obtained from parasternal midventricular LV guided by 2D echo (average of short and long axis recordings) obtained from leading edge to leading edge at end-systole (26).

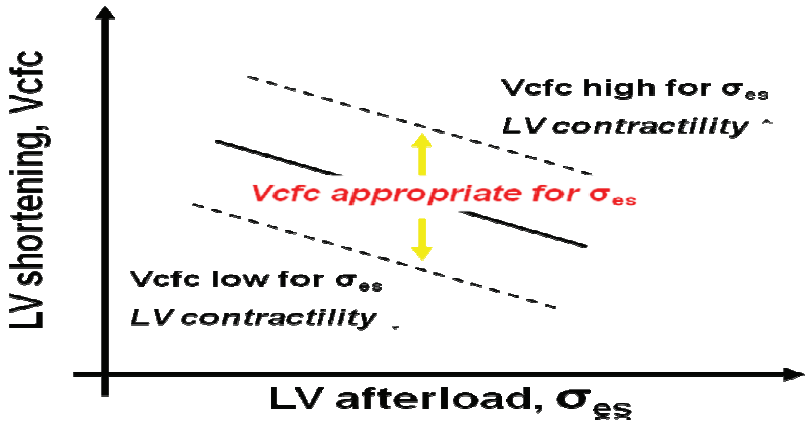

Figure 4. (25)

We used the mean velocity of LV circumferential fiber shortening normalized for heart rate (Vcfc), global strain (GS) and ejection fraction (EF) plotted against LV afterload measured as LV end-systolic wall stress (ESWS), to analyse the change in contractility during normal pregnancy.

Tonometry, external pulse trace

The right subclavian artery pulse waveform was obtained by high-fidelity external applanation tonometric device (Millar SPT-301, Millar Instruments Inc., Houston, Tx, USA) and represents the aortic root pressure waveform well (27).

The pulse transducer was manually positioned over the right subclavian artery in the medial supraclavicular region, and the pulse was traced if possible during a brief period of apnea close to end of expiration in order to reduce baseline drift during respiration. The pulse transducer was lightly positioned over the right subclavian artery with the women in the left

lateral position (Figure 5). Recordings were performed semi-simultaneously (i.e. < 5 min) with Doppler blood flow recordings with maintained subject position.

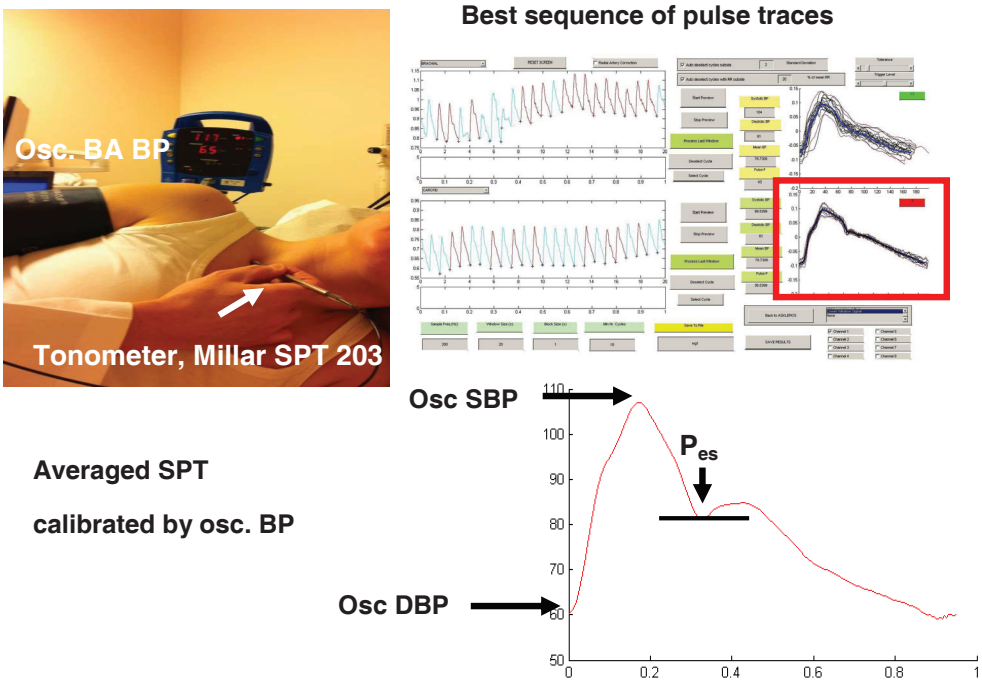

Figure 5. Technique for recording of subclavian artery pulse trace is shown in the left upper panel. The raw data recordings are shown in the right top panel. Selected cycles that are used to calculated the average pressure waveform is emphasized with thicker lines on the right top panel. The average waveform is shown in the bottom panel, calibrated by averaged systolic and diastolic blood pressure.

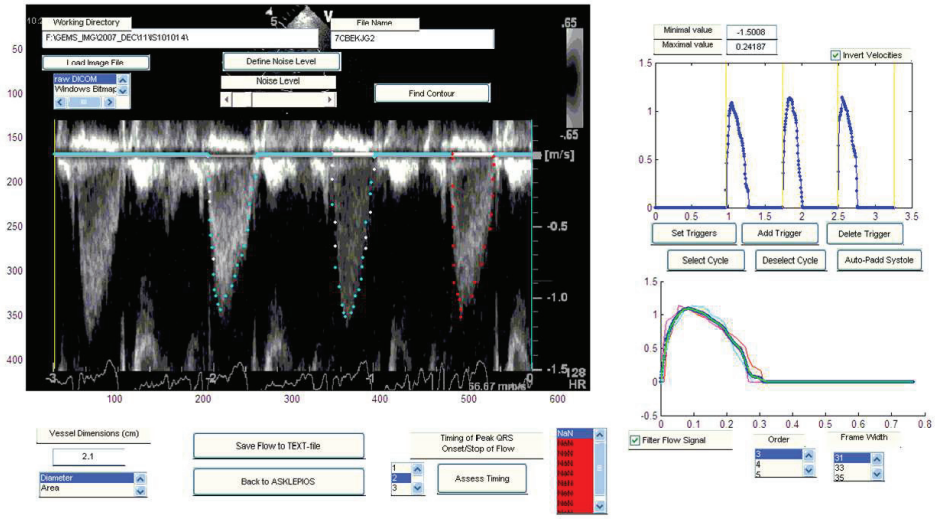

Figure 6. From the Matlab program, Doppler recordings. The raw data recordings are shown in the left panel. The operator draws points on the flow image to derive the aortic flow over three cycles. Selected cycles from Doppler registrations in LVOT that is used to calculate the average waveform is shown in the upper right panel. The average flow signal from 3 selected waveforms is shown in the lover right panel.

The tonometric recordings were performed at the end of the echocardiographic examination briefly after the Doppler recordings (i.e. < 5 min) with unchanged study subject state and position. Time consumption for tonometry was approximately 5 min. The dedicated software which we used (28) (customised in MatLab 7, MathWorks ™ Inc, Natick, Massachusetts, USA) (Figure 5, 6) enables immediate analysis of data. The tonometric signal was automatically and simultaneously transferred to a personal computer for amplification and processing (28). In order to perform analyses, at least 3 cardiac cycles with adequate tonometric pulse tracing and LVOT Doppler blood flow signals were selected (Figure 7). Feasibility for the subclavian arterial pulse trace recordings was 95%, with 5% exclusions because of suboptimal waveform quality. The subclavian arterial waveform was calibrated to its peak and nadir by brachial arterial systolic and diastolic blood pressure measurements, (taken after 10 min rest) which was obtained by automatic oscillometric technique (Dinamap ProCare 300-Monitor, Criticon, GE medical systems, USA) using a pneumatic cuff on the

right upper arm. Triple recordings were obtained, and the mean systolic and diastolic pressures were assessed as the mean of the 3 recordings.

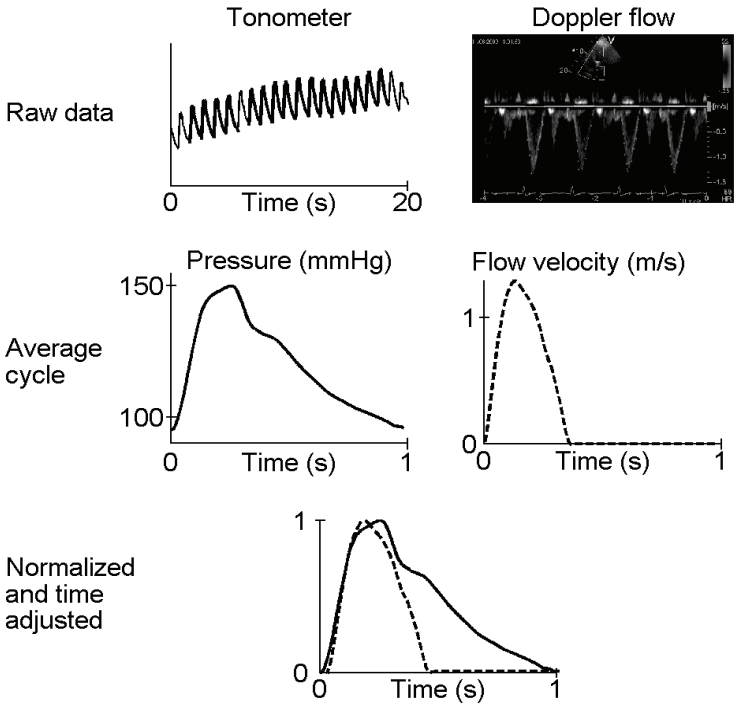

Figure 7. Illustration of the procedure to extract the average pressure and flow waveforms over one cardiac cycle. The raw data recordings are shown in the top panel. Selected cycles that are used to calculated the average pressure waveform is emphasized with thicker lines on the left. The operator draws points on the Doppler flow image to derive the aortic flow over 3 cycles as shown on the right. The average waveforms are shown in the middle panel and the bottom panel shows alignment of pressure and flow (paper IV).

Systemic arterial properties

The dedicated software we used (28) (customised in MatLab 7, MathWorks ™ Inc, Natick, Massachusetts, USA) enables immediate analyses of data on the various aspects of systemic arterial properties. The software calculated systemic arterial properties which were estimated from aortic root blood flow and pressure estimates by use of both a Fourier analysis and an estimation of parameters of a 3-element windkessel model of the systemic circulation (28, 29) (Figure 8). In this model it is assumed that peripheral vascular resistance is constant, flow out of the systemic arteries is proportional to the pressure drop, venous pressure is negligible, the pressure is equal in the entire systemic arterial tree, and arterial compliance is constant during the cardiac cycle (29).

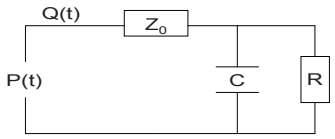

Figure 8. Diagram of the lumped parametre 3-element Windkessel model used to estimate systemic arterial properties. Measured blood flow as a function of time [Q(t)] and arterial pressure wave form as a function of time [P(t)] were inputs to the model. Z_0, characteristic impedance of the proximal aorta; C, total arterial compliance; R, total peripheral resistance.

Systemic arterial properties were characterized and described by peripheral arterial resistance (R), characteristic impedance (Z_0), total arterial compliance (C) and effective arterial elastance (Ea). Total peripheral vascular resistance, R was estimated as the ratio of mean arterial

pressure to cardiac output. Characteristic impedance, Z_0 reflects proximal aortic stiffness or resistance. This parameter was calculated both by Fourier analyses of the flow and pressure curves, as the average of amplitudes at high-frequency harmonics (3 – 10 Hz) and also as a parameter of the 3 element analogue lumped windkessel model (Figure 8). Total arterial compliance, C reflects the volume compliance of the entire systemic arterial tree, and was calculated using the pulse pressure method (PPM) and was also available as a parameter from the 3- element windkessel model (30). Ea was calculated by the ratio of ventricular end-systolic pressure (Pes) to stroke volume (SV) (determined by pulse wave Doppler recordings). In Paper 2 we also used the frequency-domain estimate of Z_0 for the wave separation analysis, and pressure wave reflections in the aorta were analyzed. The pressure wave can be separated into its forward (Pf) and backward (Pb) traveling component (i.e., the reflected wave) by use of pressure, flow and characteristic impedance data as follows: $Pf = (P+Z_0Q)/2$ and $Pb = (P-Z_0Q)/2$ (31). The reflection magnitude is given as the ratio of the amplitudes of Pb and Pf (Pb/Pf) (31).

Ventriculo-arterial coupling

In this section a method is presented to assess whether the heart operates on optimum power or efficiency, using hemodynamic principles. $E_{LV}I$ represents the left ventricular systolic elastance index and is calculated as Pes/ESVI (thus neglecting the volume intercept of the end-systolic pressure volume relationship, V0). Optimum power or efficiency, is assumed measures of ventriculo-arterial coupling (Ea/E_{LV}) which is the interaction of the LV with the arterial system. Ea/E_{LV} is a central determinant of cardiovascular performance and cardiac energetics. Ea/E_{LV} can be indexed by the ratio of effective arterial elastance (Ea; a measure of

the net arterial load exerted on the left ventricle) to LV end-systolic elastance (E_{LV}; a load-independent measure of left ventricular chamber performance). Effective arterial elastance, Ea, was calculated as end systolic pressure (Pes) divided by stroke volume (SV), and then indexed by body surface area, to yield EaI (32). Effective arterial elastance shares common units with elastance measures of left ventricular function E_{LV}, which also was indexed for body surface area (BSA) ($E_{LV}I$). Indexation of parameters measured during pregnancy is debated because of weight gain in pregnancy; in the fraction $EaI/E_{LV}I$, however, the indexation parameter m^2 will be eliminated.

The ratio between arterial and LV elastance ($EaI/E_{LV}I$) is regarded to be an index of ventriculo-arterial coupling. From the definitions of EaI and $E_{LV}I$ and the approximation that $V0 \approx 0$, it follows that $EaI/E_{LV}I = ESVI/SVI$ (33) (Figure 9).

At rest, in healthy individuals, Ea/E_{LV} is maintained within a narrow range, which allows the cardiovascular system to optimize energetic efficiency at the expense of mechanical efficacy.

In the normal physiological resting state, $EaI/E_{LV}I$ varies between 0.5 and 1.0, where values close to 0.5 indicate a maximal cardiac efficiency whereas values approaching 1.0 indicate maximal external cardiac work (34) thus providing a framework for analysis of cardiac performance and efficiency (30, 35).

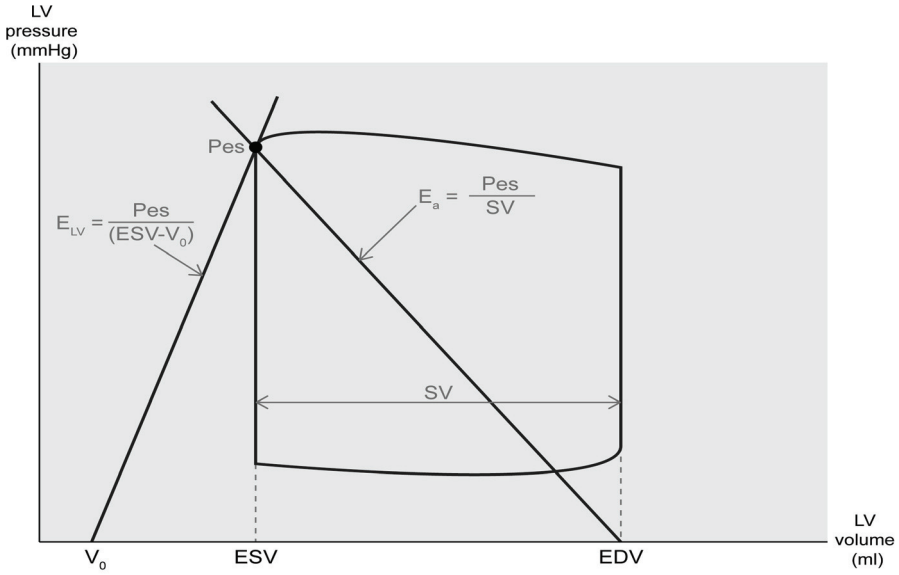

Figure 9. Schematic representation of the left ventricle pressure-volume diagram and the method used to determine the parameters of ventriculo-arterial coupling. Ea, Effective arterial elastance; EDV, end-diastolic volume; E_{LV}, left ventricular elastance; ESV, end-systolic volume; Pes, left ventricular end-systolic pressure; SV, left ventricular stroke volume; V_0, volume axis intercept of the end-systolic pressure-volume relationship. From the approximation $V_0 \cong 0$, it follows that $E_{LV} \cong Pes/ESV$ (33).

Brachial arterial blood pressure

The blood pressure was taken at every control and after 5 minutes of rest with the women in the left lateral ducubitus position. We used a pneumatic cuff on the right upper arm, and brachial arterial systolic and diastolic blood pressures were obtained in triplicate. The blood pressure was measured by oscillometric technique with Dinamap ProCare 300-Monitor (Criticon, GE medical systems, USA). Blood pressure measurements during pregnancy is debated, however the Dinamap ProCare 300 uses the same algorithm modelled on a mercury sphygmomanometry reference standard as the Dinamap® ProCare 400 which has been

validated in pregnancy and achieved the accuracy grade (A/A) according to the BHS protocol and AAMI recommendations (36).

Finometer

Finometer PRO is a noninvasive measurement device with a continuous registration of finger arterial pressure waveform. The device measures finger arterial pressure, based on the volume clamp method by Penaz co-workers (37, 38) and the physical criteria of Wesseling et al. (39). Individual level correction for systolic blood pressure was made through the return-to-flow (RTF) calibration. By application of an appropriate waveform filter that corrects the pulse wave distortion in addition to RTF calibration, the method meets the Association for the Advancement of Medical Instrumentation (AAMI) recommendations in pregnant participants (40). The recording started with the women in a sitting position on a comfortable bed. Recordings were performed with an appropriately sized finger cuff applied to the middle finger on the women's right hand and an upper arm cuff on the right arm. The height correction device was kept at heart level in order to avoid the effect of hydrostatic pressure (41). After obtaining a stable signal, the finger pressure recording was corrected against the brachial arm cuff pressure by the RTF method (42, 24). The women then lay down in a 30-degree left lateral tilt position to avoid aortic-caval compression. After falling to rest, a 120 second period of continuous blood pressure recording was obtained.

Reproducibility

Recordings from 25 randomly selected study subjects, both echocardiographic recordings and tonometric recordings were re-analyzed by an independent and echocardiographically experienced investigator (JOB), and by an independent and tonometrically experienced investigator (LAR). Intraobserver repeatability was obtained from the two measures of observer A (ME), as the mean difference with standard deviation and the intra-class correlation coefficients (ICC). Inter-observer repeatability was obtained using the same parameters from the measurements of observer A and B (JOB/LAR), respectively. For LVEDV intra- and interobserver repeatability were (mean ± SD) 1 ± 12 mL (ICC 0.81) and 1 ± 2 mL (ICC 0.89). For EF intra- and interobserver repeatability were 1.0 ± 3.0% (ICC 0.87) and 1.0 ± 3.0% (ICC 0.90). For GS intra- and interobserver repeatability were 1.3 ± 1.6% (ICC 0.81) and 0.3 ± 1.0% (ICC 0.83). For MAP intra- and interobserver repeatability were 1.0 ± 3.4 (ICC 0.97) and 1.1 ± 6.8 mmHg (ICC 0.92). For Pes, intra- and interobserver repeatability were 1.2 ± 3.9 (ICC 0.97) and 1.8 ± 7.3 (ICC 0.91).

Statistical analyses

Since we had no pregestational data, we defined the recordings at 6 months post partum as reference point, assuming that hemodynamic and vascular properties then had returned to normal (2). Continuous data are presented as mean ± standard deviation (SD). The changes in hemodynamic data during the 3 subsequent follow-up time-points during normal pregnancy and 6 months follow-up were analyzed by mixed model analysis that accounts for the positive

correlations between repeated measurements. Bonferroni post-hoc tests were applied. Correlations between variables were obtained by Pearson correlation coefficients. Unpaired t-test was used to compare wall thickness between nullipara and multipara women. Paired t-test was used to compare data between normal pregnancy at term and postpartum and one way ANOVA with appropriate post-hoc testing for multiple comparison was used to compare postpartum data between normal, preeclampsia, and previously preeclamptic pregnancy (Paper 4). All statistical analyses were performed with SPSS statistical software (SPSS 16.0 Inc. Chicago). We considered $p < 0.05$ as statistically significant.

Summary of results

Paper 1

In this study, by use of echocardiography and calibrated subclavian artery pulse trace, we found altered LV function during normal pregnancy when compared to 6 months postpartum control. The altered LV function during pregnancy (Table 1) was characterized by impaired LV EF, GS and Vcfc, i.e. LVEF decreased by 11%, GS was slightly (6%) reduced at week 36 as compared to weeks 22-24, and Vcfc was reduced by 6%. Furthermore, Vcfc was significantly decreased from 14-16 weeks to 22-24 weeks while afterload was essentially unchanged. Basal myocardial peak systolic longitudinal velocity, s', remained unchanged. LV end-systolic wall stress was reduced by 12% at 22-24 weeks as compared to 36 weeks and 6 months postpartum. Cardiac output and cardiac index (CI) increased significantly by 20% and 15% respectively, throughout pregnancy as compared to the control 6 months postpartum. Furthermore, systolic and diastolic blood pressures were reduced during pregnancy, and returned to normal values 6 months postpartum. During pregnancy, LVEDV increased by 23% returning to normal values 6 months postpartum.

There were only minor varieties in diastolic function and filling pressures during pregnancy. LV filling pressure was characterized by essentially unaltered E/e, transmitral E wave velocity decreased by 12.5% from weeks 12-14 to week 36, and was thereafter maintained reduced at 6 months postpartum. E/A ratio decreased by 17.6% from weeks 14-16 to week 36. Mitral E wave deceleration time was unchanged. e', a marker of diastolic function, was significantly reduced at 36 weeks compared to 14-16 weeks, and maintained reduced at 6 months

postpartum. Left atrial area increased by 17% during pregnancy, returning to normal values 6 months postpartum.

These findings suggest that pregnancy represents a larger load on the cardiovascular system than previously assumed.

	14-16 w	22-24 w	36 w	6 mo pp	P
EF %	**61 ± 6**	**59 ± 9**	**54 ± 8*# ¤**	**60 ± 8**	**<0.01**
GS %	**-19.0 ± 3.2**	**-19.6 ± 2.2**	**-18.1 ± 2.4¤**	**-19.2 ± 2.7**	**0.02**
Vcfc (circ/s)	**1.23 ± 0.16**	**1.14 ± 0.20***	**1.18 ± 0.21**	**1.24 ± 0.14**	**<0.01**
σ_{es} (dyn s cm^{-5})	**90.2 ± 22.6**	**87.3 ± 26.8***	**99.5 ± 23.3¤**	**99.1 ± 19.9**	**<0.01**

*Table 1. LV shortening and ES wall stress. Mean ± SD. $p < 0.05$ vs *6 mo postpartum, #14-16 w, ¤22-24 w, §36 w.*

Paper 2

In this study we assessed systemic arterial properties and interaction between the left ventricle (LV) and systemic arteries during NP by echocardiography and tonometry.

The study subjects were the same population as in Paper 1. Cardiac output increased by 20% and blood pressure decreased by 10% as compared to 6 months postpartum control. Systemic arterial properties during pregnancy showed reduced peripheral vascular resistance with a nadir at 22-24 weeks whereas proximal aortic stiffness (Z_0) and total arterial compliance (C) were not significantly changed (both were measured by windkessel model and the pulse pressure method) The arterial elastance index, EaI decreased significantly at weeks 14-16 and 22-24 as compared to 6 months postpartum by a magnitude of 21%. The LV elastance index, $E_{LV}I$, was significantly decreased at weeks 22-24 and at 36 weeks. The magnitude of decrease in $E_{LV}I$ was 29%. Early in pregnancy and postpartum, the ventriculo-arterial coupling index EaI /$E_{LV}I$, averaged 0.45 ± 0.14. In third trimester, when comparing to 6 months postpartum the index had increased significantly to 0.64 ± 0.23.

Thus, during NP there is an increase in cardiac output, and decrease in blood pressure and peripheral arterial resistance whereas central aortic properties are less altered. The increased ventriculoarterial coupling index (E_aI /$E_{LV}I$) during NP indicates a decrease in LV function not fully compensated for by vascular adaptation.

Paper 3

In Paper 3 systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were measured during pregnancy by two different measurement devices, Finometer and Dinamap, and compared. We found that SBP, DBP, and MAP reached a statistically significant trough at gestational age 22–24 weeks when using both measurement devices. When compared with the nonpregnant measurement, SBP at gestational age 22–24 weeks was 6.2 mmHg lower measured by Finometer and 7.2 mmHg lower measured by Dinamap. Furthermore DBP and MAP were 8.9 mmHg and 9.8 mmHg lower measured by Finometer. Measured by Dinamap, DBP and MAP were 4.5 mmHg and 5.4 mmHg lower at gestational age 22–24 weeks when compared with the nonpregnant state. We found that pregestational body mass index (BMI) had influence on SBP; SBP being significantly higher in women with pregestational BMI at least 25 kg/m^2 with both measurement devices. However there were no differences in SBP, DBP, or MAP depending on parity or excessive weight gain.

Thus, BP measured repeatedly by two different noninvasive devices during pregnancy and postpartum showed a statistically significant drop in mid-pregnancy, followed by a progressive increase until term.

Paper 4

In paper 4 we combined the methods from paper 1 and 2, and compared normal pregnancy (NP) with acute preeclamptic pregnancy (PE), and previously preeclamptic pregnancy (PPEP). The hemodynamics and systemic arterial properties were characterized as follows: MAP was 17% higher at term in the PE group compared with postpartum. MAP was 35% higher at term and 14% higher postpartum in PE when compared with the corresponding values in NP and 17% higher in PPEP. In the PE group, total peripheral resistance (R) was maintained unchanged from term to postpartum. In NP, R was 16% lower at term than postpartum. R was 23% higher at term and 3% higher postpartum in the PE group compared with NP.

At both term and 6 months postpartum the systemic arteries were stiffer in the PE group compared to NP. This was as reflected by elevated Z_0 (37% higher, mean of the 3-element windkessel model and the frequency domain analysis), and reduced C (12% lower, mean of the 3-element windkessel model and the pulse pressure method) and Ea (25% higher) at term. Furthermore Z_0 was 18% higher, C was 7% lower, and Ea 11% higher in PE than in NP postpartum.

Women with PPEP had higher blood pressure than NP (17%). R was not different between the groups, however were both Z_0 (39%) and Ea (14%) higher. E_aI was higher in PE patients at both term and postpartum and in PPEP as compared to NP patients. Whereas $E_{LV}I$ was lower at term in NP compared to 6 months postpartum no such difference was observed in the PE group. However the $E_{LV}I$ was almost twice as high at term in PE patients as compared to at term levels in the NP group. This leads to a higher coupling index value, $E_aI/E_{LV}I$, in NP at

term as compared to both PE patients at term and to NP postpartum. In PPEP, $E_aI/E_{LV}I$ was higher than NP at 6 months postpartum.

Thus, the altered arterial properties persisted after six months and were elevated three years postpartum in PPEP indicating that preeclampsia is associated with persistent cardiovascular disturbances.

Discussion

Pregnancy represents a unique model of morphological, hemodynamic, and functional adaptation of the heart in a physiological situation with significant transient changes in cardiac loading conditions and work requirements. A well defined characterization of maternal cardiac function during normal pregnancy is a prerequisite for identification of cardiac pathology. This is clinically highly relevant since heart disease is the leading cause of non-obstetric mortality during pregnancy. In parts of this thesis we assessed the effects of hemodynamic changes during normal pregnancy on LV function by use of echocardiography and tonometry. Moreover, it has been shown that a cardiovascular maldaptation to pregnancy impairs maternal cardiovascular health later in life. Thus pregnancy is now considered a stress test to the maternal cardiovascular system. This indicates that women planning to become pregnant should be screened for clinical and biochemical cardiovascular risk, and importantly, women presenting hypertension in pregnancy should be thoroughly investigated, treated and followed according to recommendations.

Left ventricular function during normal pregnancy

In paper 1 we found a significant increase in cardiac output, cardiac index and heart rate during normal pregnancy, which is expected and concordant with previous smaller studies (43, 44). Furthermore our data indicate that LV contraction and contractility is reduced during pregnancy. We found that LV ejection fraction was significantly reduced during pregnancy, and simultaneously we found a slight, but significant reduction in global strain in the last

trimester, compared to the measurement at gestational weeks 22-24. These findings together suggest that LV function is reduced during pregnancy. A more comprehensive analysis of contraction and contractility was obtained by incorporating LV loading conditions in the analysis. There are only a few studies on LV function which take into account the effects of loading conditions (45-49). We plotted the preload-insensitive parameter of LV contractility, Vcfc, against LV afterload measured by LV end-systolic wall stress (50), and observed that Vcfc was significantly reduced at 22-24 weeks compared to the reference measurement 6 month post partum (Figure 10). This finding suggests that not only LV contractions but LV contractility is transiently reduced during pregnancy. When plotting EF and global strain against LV afterload (Figure 11, 12) much of the same pattern appears.

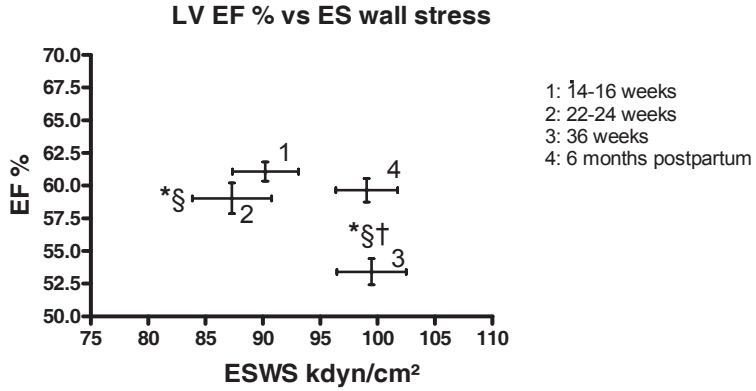

*Figure 10 . LV EF % vs. ES wall stress. Mean ± SE. p < 0.05 vs *6 mo post partum, †14-16 w, ‡22-24 w, §36 w.*

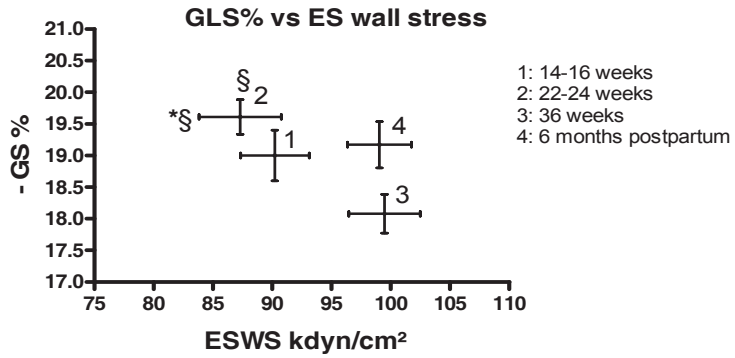

*Figure 11. Global strain vs ES wall stress. Mean ± SE. p < 0.05 vs *6 mo post partum, †14-16 w, ‡22-24 w, §36 w.*

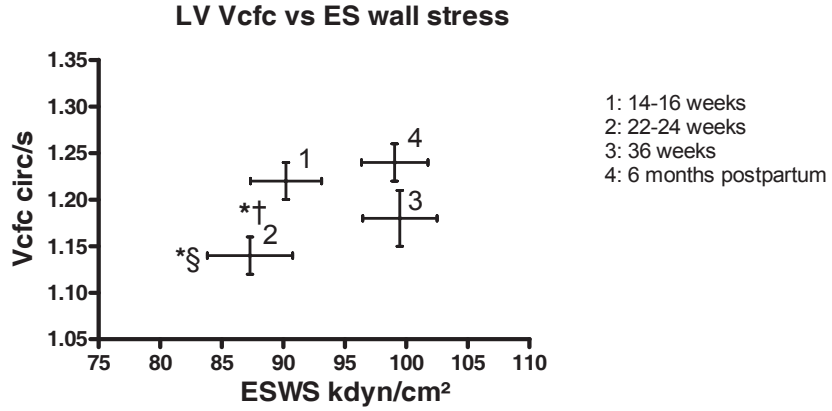

*Figure 12. LV Vcfc vs ES wall stress. Mean ± SE. p < 0.05 vs *6 mo post partum, †14-16 w, ‡22-24 w, §36 w.*

The expected LV systolic response to reduced afterload, given unchanged contractility, is increased shortening. However we found reduced Vcfc and longitudinal global strain at time point 14-16 weeks and reduced Vcfc and EF at time point 22-24 weeks, as compared to the 6 months postpartum reference. These findings suggesting that reduction in LV contractility begins in second trimester and is maintained to partum. Despite the fact that noninvasive measurements of contractility is debated, we think that the consistent leftward displacement of EF, GS and Vcfc during pregnancy (time-points 1, 2 and 3 in Figure 10-12) as compared to 6 months postpartum (time-point 4 in Figure 10-12), substantiates that LV contractility is, albeit transiently, truly reduced during pregnancy.

The finding of increased septal and posterior wall thickness during pregnancy (Paper 1) has been reported in previous smaller studies (51-53). However, the sustained increase in wall thickness that we found at 6 months postpartum has not previously been observed. Pregnancy is regarded in the literature to promote a reversible hypertrophy, and is often described as physiological hypertrophy (53). It is unknown whether LV wall thickness might occur as an adaptive response to the relative volume overload during pregnancy, or whether changes early in pregnancy decrease LV mass which then is recovered in late pregnancy and postpartum. Similar responses to increased blood volume and cardiac output over time have been observed in athletes (54).

Despite the significant changes we found in LV systolic functions during normal pregnancy, there were only minor alterations in diastolic function and filling pressures. We used tissue Doppler to characterise diastolic function during normal pregnancy, which has been reported with discrepant results in earlier and smaller studies (43, 49, 55, 56, 57). We found merely a mild, although significant, reduction of e' during pregnancy. Left atrial size increased during pregnancy, probably as a result of increased circulating blood volume. However E/e', a marker of LV filling pressure, remained unaltered during pregnancy as compared to 6 months

postpartum control. Furthermore, there was no significant change in deceleration time during pregnancy. Despite the increased demand during pregnancy, these findings indicate unaltered left ventricular filling pressure during normal pregnancy and postpartum.

As a response to the physiological demand on the mother during pregnancy, morphological changes are triggered, leading to increased LV wall thickness, mass, and chamber diameters. The reduced LV function is probably a consequence of the general physical changes in pregnancy. These findings might, assuming that pregnancy has some similarity to moderate exercise with increased cardiac output, increased peripheral perfusion (through the uterus instead of through musculature), and increased oxygen demand. Pregnancy has been described as a stress test for life. Normally the physiological demands are well tolerated. However, the implications of added physiological stress as e.g. severe obesity or preeclampsia or peripartum cardiomyopathy remains unclear, and is subject of investigation.

Systemic arterial response and ventriculo-arterial interaction during normal pregnancy

Results on systemic arterial response and ventriculo-arterial interaction during normal pregnancy have not been described in the literature. Since loading conditions are substantial during pregnancy – we also wanted to apply an analysis of ventriculo-arterial coupling or interaction. In paper 2 we present a sequential observational noninvasive follow-up study of arterial properties and the interaction of the ventricle and the arterial system during normal pregnancy and with a 6 months postpartum control. We found as expected, a significant increase in cardiac output, and decrease in blood pressure and peripheral arterial resistance. However central aortic properties are less altered. The increased ventriculo-arterial coupling index (EaI /E_{LV}I) during normal pregnancy indicates a decrease in left ventricular function not

fully compensated for by vascular adaptation. This is in concordance with our findings in Paper 1 were data support a true, although transient, reduction in LV contractility. Together, our findings in Paper 1 and 2 suggest that a normal pregnancy represents a larger load on the cardiovascular system than previously reports have assumed.

Worldwide, cardiac events in healthy pregnant women are rare, however heart disease may occasionally be disclosed during pregnancy due to the raised cardiac demands. A better knowledge of the normal systemic arterial and ventriculo-arterial response to pregnancy is needed, and these findings may serve as a basis for clinical follow-up and advisories for pregnant women.

During normal pregnancy we found that the main adaptation of systemic arterial function was a reduced peripheral resistance, whereas proximal aortic stiffness and arterial compliance were not significantly changed. In Paper 2 there was a trend towards higher arterial compliance in the first, second and third time point compared to nonpregnant state. Furthermore, there was also a trend towards lower characteristic impedance also during pregnancy. The results indicate that changes in compliance and proximal aortic stiffness are small, reflecting that large artery properties remain fairly constant in healthy women during normal pregnancy. We found arterial elastance to be significantly decreased early in pregnancy. Arterial elastance is strongly influenced by heart rate which increases during pregnancy and therefore may explain the change in arterial elastance (58). However the reflection magnitude was lower in second and third trimester compared to postpartum control. It is likely that the lower reflection coefficient is a result of vasodilatation on the arteriolar level and not of substantially altered properties in the larger arteries.

The increased demands on the heart during normal pregnancy is further described in Paper 2 by the change in the interaction between LV and the arterial system, the ventriculo-arterial coupling from a state of maximal cardiac efficiency ($E_aI/E_{LV}I$: 0.45) towards a maximal

cardiac work ($E_aI/E_{LV}I$: 0.64). When the interaction between the LV and arterial system are optimal, i.e. under normal resting conditions, the $E_aI/E_{LV}I$ ratio is usually close to unity 0.8-1.2 (59). In paper 2 we found $E_aI/E_{LV}I$, to be 0.45 both in first trimester and postpartum, reflecting an optimized cardiac efficiency. However, the coupling index, $E_aI/E_{LV}I$ increased to 0.64 in third trimester. Peripheral arterial resistance was significantly reduced throughout pregnancy when compared to the postpartum state. One would expect that this reduction in the external load of the ventricle would reduce the coupling index. The increase in coupling index during third trimester that we observed is therefore most likely due to the greater relative decrease in LV contractility than the reduction in arterial load. This reflects a shift in the ventriculo-arterial coupling from a state of maximized cardiac efficiency towards maximized cardiac external work. This is in concordance with our data on reduced LV function during normal pregnancy in Paper 1, and underscores the suggestion that pregnancy represents a larger load on the cardiovascular system than previously reports have assumed.

Changes in blood pressure during healthy pregnancy

Decreased systolic and diastolic blood pressure during pregnancy is well known changes during normal pregnancy. In Paper I and 2 we found decreased blood pressure during normal pregnancy by using Dinamap. In Paper 3 we compared two different devices, Dinamap and Finometer and measured the changes in blood pressure during normal pregnancy. The blood pressure was measured with the two different devices (the same population as in Paper 1 and 2) within 90 min repeatedly, both devices confirmed the same pattern of change during pregnancy. The main finding in Paper 3 is that pregnant women have a statistically significant drop in SBP, DBP, and MAP around 22–24 weeks of gestation, followed by a progressive

increase toward term. This is in concordance with previous reports that there is a mid-trimester drop in blood pressure during normal pregnancy. The mid trimester drop in blood pressure can be explained in two different ways. The progressive increase in blood pressure from the first measurement until term may represent a gradual restoration of BP after an initial drop very early in pregnancy. Alternatively, as concluded by others, the increase in BP is truly progressive, starting immediately after conception.

The lack of the mid-trimester drop in BP has been suggested to play a predictive role for a subsequent development of early-onset preeclampsia (< 34 weeks). This hypothesis is further supported by others (60) demonstrating a statistically significant higher SBP, DBP, and MAP at 24 weeks gestation in women who developed early-onset preeclampsia compared to both normal pregnancies and late-onset preeclampsia. Data from several recent reports have provided evidence for the predictive value of uteroplacental and maternal hemodynamics early in pregnancy with respect to subsequent development of hypertensive disorders of pregnancy (60, 61). Women presenting hypertension in pregnancy and especially women developing early-onset preeclampsia should be offered examinations aimed at detecting and correcting cardiovascular risk. The incorporation of the predictive value of a hypertensive pregnancy may help to reduce the risk of preeclampsia and cardiovascular disease in later life for these women.

Given the new insight into the relation between pregnancy induced hypertension and later cardiovascular disease, detailed knowledge on the changes occurring in normal pregnancy is essential. Hypertensive disorders of pregnancy and cardiovascular disease share many risk factors (e.g. obesity, metabolic syndrome, diabetes, premature cardiovascular disease, endothelial dysfunction, thrombophilias, inflammation and oxidative stress). In agreement with previous reports (62-64) we found that a pre-pregnant BMI higher than 25 kg/m^2 was significantly associated with a higher SBP, DBP, and MAP measured by Finometer at any

point in both pregnancy and postpartum. Using Dinamap, only SBP was significantly higher in women with a pre-pregnant BMI over 25 kg/m^2. In order to evaluate the influence of pregestational BMI on the change in BP during pregnancy, we chose BMI higher than 25 kg/m^2 as our cutoff value. This cutoff value has clinical relevance as it includes both overweight (BMI > 25 kg/m^2) and obese (BMI > 30 kg/m^2) women, which represents a group of pregnant women with higher risk of pregnancy complications and increased long term morbidity and mortality.

LV function, arterial properties and ventriculoarterial coupling; comparison between normal pregnancy, acute preeclamptic pregnancy and previously preeclamptic pregnancy

As underscored above, pregnancy is hemodynamically characterized by increased blood volume, cardiac output and heart rate, as well as a decrease in blood pressure and peripheral vascular resistance. Our previous work (Paper 1, 2 and 3) using noninvasive techniques extended these observations by describing the roles of arterial compliance, characteristic impedance and arterial elastance during normal gestation. However, preeclampsia, an entity with substantial fetal and maternal morbidity, is characterized by high blood pressure and significant less vasodilatation than that observed in normal pregnancy. In Paper 4 we showed that the systemic arteries of preeclamptic women are significantly stiffer than observed in healthy pregnant women at term, and moreover, that this phenomenon persists 6 months postpartum. The physiological response to normal pregnancy (Paper 2) is a reduction of arterial stiffness at term with lower total vascular resistance and higher compliance. Contrasting this, we found that preeclamptic women had a higher total vascular resistance and characteristic impedance, and lower compliance at term than women with healthy pregnancy.

Physiologically, central arteries are distensible and buffer the systolic output of the ventricle. As such, characteristic impedance represents the aortic impedance to pulsatile inflow from the contracting ventricle, and compliance describes the aortic capacity to store a transient increase in blood volume, i.e. the systemic arterial volume compliance. The higher characteristic impedance and lower compliance we observed in preeclamptic pregnancies at term and postpartum, indicate that central large arteries are affected in these patients. Furthermore, the results from the 3 year follow-up of previous preeclamptic women (PPEP group) substantiated evidence for a maintained increased systemic arterial stiffness and that arterial wall malfunction may persist over time in these patients. Biological tissue, including the arterial wall, has an exponential pressure-stiffness relation. The steeper slope of this relation at higher pressures effectively increases the operating stiffness. Thus, the higher blood pressure in the preeclamptic women may have contributed to the observed stiffening of their arterial parameters.

To answer this, arterial pressure levels may be therapeutically reduced in the preeclamptic groups and then compare the mechanical properties to healthy pregnancies at matched blood pressure. This is a hypothesis that is difficult to test because the pressure change must be obtained without use of vasoactive substances, and in absence of any change in neurohormonal status.

Cardiovascular diseases increase with advancing age and are associated with ventricular and arterial stiffening. The changes in characteristic impedance and compliance we observed in women with preeclampsia bears a similarity to those reported in patients as a result of aging, hypertension, and arteriosclerosis. Hence, our results provide further insight into the patophysiological basis for the increased risk of cardiovascular events in women with previous PE (65-67).

The ventriculo-arterial coupling, meaning the interaction of the heart with the systemic vasculature, is a key determinant of cardiovascular performance, and influence both magnitude and efficiency of transfer of LV stroke volume to the circulation. As given in Paper 2 the LV elastance index, $E_{LV}I$, is recognised as an important indicator of LV performance. At term, $E_{LV}I$ averaged 87% higher in women with preeclamptic pregnancies versus women with normal pregnancy. Whereas E_{LV} increases from term to the postpartum state in normal pregnancy, it decreases in preeclamptic pregnancies. Six months postpartum, LV elastance in the PE group are still 14% higher than in the normal pregnancy group. Our results suggests that cardiac performance first is substantially influenced during a preeclamptic pregnancy, and is postpartum then followed by a restoration process which is not complete at 6 months. However, patients attained a normal state 3 years postpartum as demonstrated by the comparable levels of $E_{LV}I$ in the normal pregnancy and PPEP group. We reported in Paper 2 that in healthy normal pregnancies, there is a shift towards increased cardiac work load evident by a progressive increase in ventriculo-arterial coupling towards term, followed by a restoration of work efficiency postpartum. The substantially higher E_aI in PE compared to NP is balanced by a correspondingly higher $E_{LV}I$, leaving the ratio E_a/E_{LV} unchanged from term to postpartum in PE. The resulting coupling index values are at the level where work efficiency of the heart is considered maximal (34, 35).

The alterations in circulating blood volume, blood pressure, peripheral vascular resistance, compliance, myocardial function, heart rate and the neurohormonal system, all allow the cardiovascular system to meet the increased metabolic demands of pregnancy.

This thesis shows that we non-invasively by use of an echocardiographic evaluation of left ventricle combined with tonometric external pulse trace recording can add important information on the interaction of the heart with systemic vasculature in patients susceptible for gestational cardiovascular disorders like preeclampsia, hypertension and peripartum

cardiomyopathy. Furthermore, maternal hemodynamic influence fetal growth and thereby current and future health of the newborn (68). Finally, hemodynamic characteristics during pregnancy may add to the current risk stratification tools in terms of predicting future cardiovascular disease. Insight into the mechanisms of physiological changes in normal pregnancy is essential in follow up of pregnant women with maternal structural heart disease and pregnancy.

Limitations

Preconceptional data would be the preferred reference measurements for assessing hemodynamic alterations during pregnancy, especially since we know that the major changes occurs already during the first 12 weeks of pregnancy (28). We used the 6 months postpartum control as the reference point which is generally regarded reasonable because most hemodynamic parameters return to preconception values within 8-12 weeks after delivery (29). However, some of our parameters were maintained increased at 6 months postpartum control, suggesting that normalization of postpartum hemodynamic takes longer time than presently assumed.

There are ethnic variations in cardiac function and arterial properties. In our population of women with normal pregnancy (paper 1, 2, 3 and 4), 97% were Caucasian.
Hormone and hormonal contraceptives might have influence on hemodynamic and arterial properties, unfortunately we lack information about breast feeding and use of hormonal contraceptives at 6 months control.

Since data for the PPEP was obtained in a cross-sectional study sample, comparisons between this group and the PE group must be interpreted with some caution. However, the

general patients' characteristics of the two groups were not different supporting that their status were comparable. Furthermore, we do not have access to pregestational data in any of the study groups, which proscribes any inference of cause-effect relationship between development of preeclampsia and the reported changes in arterial properties and persisting hypertension in previous preeclamptic women.

Longitudinal data during pregnancy in preeclamptic women would be preferable, in order to detect hemodynamic changes early in pregnancy that may be present before preeclampsia becomes clinically overt and which ones that occurs after clinical manifestation of the disorder.

Furthermore, studies of larger size than the present one would make it possible to study hemodynamic feature in subgroups of preeclamptic women like those with early and late onset preeclampsia, with or without foetal growth restriction and with and without pre-existing metabolic disorders like diabetes and metabolic syndrome.

Main conclusions

1. During normal pregnancy, profound alterations in LV function occur. Increases in circulating blood volume are reflected by increased CO and cardiac dimensions. LV contractility is significantly reduced, whereas filling pressures (e/e') are unchanged. These findings suggest that pregnancy represents a larger load on the cardiovascular system than previously assumed. Reference values obtained are relevant in order to identify cardiovascular dysfunction in pregnant women with heart disease.

2. During normal pregnancy there is an increase in cardiac output, and decrease in blood pressure and peripheral arterial resistance whereas central aortic properties are less altered. The increased ventriculoarterial coupling index ($E_aI/E_{LV}I$) during normal pregnancy indicates a decrease in LV function not fully compensated for by vascular adaptation.

3. Blood pressure measured repeatedly by two different noninvasive devices during pregnancy and postpartum showed a statistically significant drop in mid-pregnancy, followed by a progressive increase until term. The lack of the mid-trimester drop in blood pressure might play a predictive role for a subsequent development of early-onset preeclampsia.

4. Women with established preeclampsia are characterised by a higher resistance in the entire arterial system. The altered arterial properties persisted after six months and were also elevated three years postpartum in women with previous preeclamptic pregnancy. These changes indicate that preeclampsia induces persistent cardiovascular disturbances.

Future perspectives

Given that the cardiovascular system is affected in normal pregnancy, is deranged in preeclampsia, and that preeclampsia is an indicator of future cardiovascular risk, investigations of the cardiovascular system in pregnant women will be an important topic in studies of women's health. To follow-up this women close, has to be an important future perspective. It will not only be important to diagnose women who will develop early preeclampsia, but also to follow-up women who has suffered from previous preeclampsia. Our study shown maintained increased arterial stiffness 3 years after pregnancy, and the woman were still hypertensive. None of them were on antihypertensive medication.
Some countries now use preeclampsia as a risk factor compared to smoking, diabetes and obesity for development of CVD. This thesis supports the view that also Norway should implement preeclampsia in risk stratification for cardiovascular disease. We need further and larger study including women with previous preeclampsia to see if their arterial stiffness maintain over year.

Finally, despite advances in the prevention and management of CVD, this group of multifactorial disorders remains a leading cause of mortality worldwide. CVD is associated with multiple genetic and modifiable (environmental) risk factors (69). However, known environmental and genetic influences can only explain a small part of the variability in CVD risk. More recently the fetal environment and its role in predisposing an individual for diseases later in life has attracted increasing attention (70). For example is it well documented that poor growth conditions during fetal life is a significant risk factor for cardiovascular disease and diabetes. Fetal nutritional conditions play a major role in this in utero "programming"of later predisposition for disease. There is some evidence that maternal

hemodynamic features are associated with fetal growth (68). Besides maternal nutritional intake and metabolic status, maternal hemodynamics may take part in determining the growth conditions of the foetus probably by modifying placental blood perfusion.

References

1. Pirani BB, Campbell DM, MacGillivray I. Plasma volume in normal first pregnancy. J Obstet Gynaecol Br Commonw 1973;80:884-7.

2. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. Am J Physiol 1989;256:1060-5.

3. Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. Am J Obstet Gynecol 1993;169:1382-92.

4. Geva T, Mauer MB, Striker L, Kirshon B, Pivarnik JM. Effects of physiologic load of pregnancy on left ventricular contractility and remodelling. Am Heart J 1997;133:53-9.

5. Lang RM, Pridjian G, Feldman T, Neumann A, Lindheimer M, Borow KM. Left ventricular mechanics in preeclampsia. Am Heart J 1991;121:1768-75.

6. Roberts JM, Pearson G, Cutler J, Lindheimer M. Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy. Hypertension 2003;41:437-45.

7. Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in The United States, 1979-1986. Am J Obstet Gynecol 1990;163:460-5.

8. Dahlstrøm BL, Engh ME, Bukholm G, Øian P. Changes in the prevalence of preeclampsia in Akershus County and the rest of Norway during the past 35 years. Acta Gynecol Scand 2006;85:916-21.

9. Visser W, Wallenburg HC. Central hemodynamic observations in untreated preeclamptic patients. Hypertension 1991;17:1072-7.

10. Bosio PM, McKenna PJ, Conroy R, O'Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. Obstet Gynecol 1999;94:978-84.

11. Hibbard JU, Korcarz CE, Nendaz GG, Lindheimer MD, Lang RM, Shroff SG. The arterial system in pre-eclampsia and chronic hypertension with superimposed pre-eclampsia. BJOG 2005;112:897-903.

12. Elvan-Taspinar A, Franx A, Bots ML, Bruinse HW, Koomans HA. Central hemodynamics of hypertensive disorders in pregnancy. Am J Hypertens 2004;17:941-6.

13. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia -- a state of sympathetic overactivity. N Engl J Med 1996;335:1480-5.

14. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science 2005;308:1592-4.

15. Sattar N. Do pregnancy complications and CVD share common antecedents? Atheroscler Suppl 2004;5:3-7.

16. Aakhus S, Soerlie C, Faanes A, Hauger SO, Bjoernstad K, Hatle L, et al. Noninvasive computerized assessment of left ventricular performance and systemic hemodynamics by study of aortic root pressure and flow estimates in healthy men, and men with acute and healed myocardial infarction. Am J Cardiol 1993;72:260-7.

17. Aakhus S, Torp H, Haugland T, Hatle L. Noninvasive estimates of aortic root pressures: External subclavian arterial pulse tracing calibrated by oscillometrically determined brachial arterial pressures. Clin Physiol 1993;13:573-86.

18. Rietzschel ER, De Buyzere ML, Bekaert S, Segers P, De Bacquer D, Cooman L, et al. Rationale, design, methods and baseline characteristics of the Asklepios Study. Eur J Cardiovasc Prev Rehabil 2007;14:179-91.

19. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ;

Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.

20. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-67.

21. Roman MJ, Okin PM, Kizer JR, Lee ET, Howard BV, Devereux RB. Relations of central and brachial blood pressure to left ventricular hypertrophy and geometry: the Strong Heart Study. J Hypertens 2010;28:384-8.

22. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, Tajik AJ. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788-94.

23. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;10:165-93.

24. Gjesdal O, Hopp E, Vartdal T, Lunde K, Helle-Valle T, Aakhus S, Smith HJ, Ihlen H, Edvardsen T. Global longitudinal strain measured by two-dimensional speckle tracking echocardiography is closely related to myocardial infarct size in chronic ischaemic heart disease. Clin Sci (Lond) 2007;113:287-96.

25. Colan SD, Borow KM, Neumann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: a load-independent index of myocardial contractility. J Am Coll Cardiol 1984;4:715-24.

26. Grossmann W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975; 56: 56-64.

27. Aakhus S, Torp H, Haugland T, Hatle L. Noninvasive estimates of aortic root pressure: External subclavian arterial pulse tracing calibrated by oscillometrically determined brachial arterial pressures. Clinical Physiology 1993;13:573-586.

28. Rietzschel ER, De Buyzere ML, Beater S, Segers P, De Bacquer D, Cooman L, Van Damme P, Cassiman P, Langlois M, van Oostveldt P, Verdonck P, De Backer G, Gillebert TC. Rationale, design, methods and baseline characteristics of the Asklepios Study. Eur J Cardiovasc Prev Rehabil 2007;14:179-91.

29. Elzinga G, Westerhof N. Pressure and flow generated by the left ventricle against different impedances. Circ Res 1973;32:178-86.

30. Segers P, Rietzschel ER, De Buyzere ML, Vermeersch SJ, De Bacquer D, Van Bortel LM, De Backer G, Gillebert TC, Verdonck PR; Asklepios investigators. Noninvasive (input) impedance, pulse wave velocity, and wave reflection in healthy middle-aged men and women. Hypertension 2007;49:1248-55.

31. Murgo JP, Westerhof N, Giolma JP, Altobelli SA. Manipulation of ascending aortic pressure and flow wave reflections with the Valsalva manoeuvre: relationship to input impedance. Circulation 1981;63:122-132.

32. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Medicine 1976;17:863-71.

33. Sunagawa K, Maughan WL, Bukhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983;245:773-80.

34. Westerhof N, Stergiopulos N, Noble M I M. Snapshots of Hemodynamics, An aid for clinical research and graduate education. Power and Efficiency. Springer Science + Business media, Inc. 2005;75-80.

35. Kass DA, Grayson R. Ventriculo-arterial coupling; concepts, assumptions, and applications. Ann of Biomedl Eng 1992;20:41-62.

36. de Greef A, Ghosh D, Anthony J, Shennan A. Accuracy assessment of the Dinamap ProCare 400 in pregnancy and preeclampsia. Hypertens Pregnancy 2010; 29:198–205.

37. Penaz J. Photoelectric measurement of blood pressure, volume, and flow in the finger. Digest 10th International Conference of Medical Biological Engineering 1973; Dresden 1973. p. 104.

38. Penaz J, Voigt A, Teichmann W. Contribution to the continuous indirect blood pressure measurement. Z Gesamte Inn Med 1976;31:1030–1033.

39. Wesseling KH, de Wit B, van der Hoeven GMA, van Goudoever J, Settels JJ. Physiocal, calibrating finger vascular physiology for Finapres. Homeostasis 1995;36:67–82.

40. Hehenkamp WJ, Rang S, van Goudoever J, Bos WJ, Wolf H, van der Post JA. Comparison of Portapres with standard sphygmomanometry in pregnancy. Hypertens Pregnancy 2002;21:65–76.

41. Gizdulich P, Aschero G, Guerissi M, Wesseling KH. Effects of hydrostatic pressure of finger pressure measured with Finapres. Homeostasis 1995;36:120–129.

42. Bos WJ, van Goudoever GJ, van Montfrans GA, van den Meiracker AH, Wesseling KH. Reconstruction of brachial artery pressure from noninvasive finger pressure measurements. Circulation 1996;94:1870–1875.

43. Mesa A, Jessurun C, Hernandez A, Adam K, Brown D, Vaughn WK, Wilansky S. Left ventricular diastolic function in normal human pregnancy. Circulation 1999;2:511-7.

44. Fok WY, Chan LY, Wong JT, Yu CM, Lau TK. Left ventricular diastolic function during normal pregnancy: assessment by spectral tissue Doppler imaging. Ultrasound Obstet Gynecol 2006;28:789-93.

45. Poppas A, Shroff SG, Korcarz CE, Hibbard JU, Berger DS, Lindheimer MD, Lang RM. Serial assessment of the cardiovascular system in normal pregnancy. Role of arterial compliance and pulsatile arterial load. Circulation 1997;95:2407-15.

46. Geva T, Mauer MB, Striker L, Kirshon B, Pivarnik JM. Effects of physiologic load of pregnancy on left ventricular contractility and remodeling. Am Heart J 1997;133:53-9.

47. Simmons LA, Gillin AG, Jeremy RW. Structural and functional changes in left ventricle during normotensive and preeclamptic pregnancy. Am J Physiol Heart Circ Physiol 2002;283:1627-1633.

48. Mone SM, Sanders SP, Colan SD. Control mechanisms for physiological hypertrophy of pregnancy. Circulation 1996:15:667-72.

49. Zentener D, Du Plessis M, Brennecke S, Wong J, Grigg L, Harrap SB. Deterioratio in cardiac systolic and diastolic function late in normal human Pregnancy. Clinical Science 2009;116:599–606.

50. Colan SD, Borow KM, Neumann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: a load-independent index of myocardial contractility. J Am Coll Cardiol 1984;4:715-24.

51. Kametas NA, McAuliffe F, Hancock J, Chambers J, Nicolaides KH. Maternal left ventricular mass and diastolic function during pregnancy. Ultrasound Obstet Gynecol 2001; 18:460-6.

52. Kametas NA, McAuliffe F, Cook B, Nicolaides KH, Chambers J. Maternal left ventricular transverse and long-axis systolic function during pregnancy. Ultrasound Obstet Gynecol 2001;18:467-74.

53. Savu O, Jurcut R, Giusca S, van Mieghem T, Gussi I, Popescu BA, Ginghina C, Rademakers F, Deprest J, Voigt JU. Morphological and functional adaptation of the maternal heart during pregnancy. Circ Cardiovasc Imaging 2012;5:289-97.

54. Grossman W. Cardiac Hypertrophy: useful adaptation or pathologic process? Am J Med 1980;69:576-584

55. Bamfo JE, Kametas NA, Nicolaides KH, Chambers JB. Maternal left ventricular diastolic and systolic long-axis function during normal pregnancy. Eur J Echocardiogr 2007; 8:360-8.

56. Bamfo JE, Kametas NA, Nicolaides KH, Chambers J. Reference ranges for tissueDoppler measures of maternal systolic and diastolic left ventricular function. Ultrasound Obstet Gynecol 2007;29:414-20.

57. Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. Am J Obstet Gynecol 1994;3:849-56.

58. Segers P, Stergiopulos N, Westerhof N. Relation of effective arterial elastance to arterial system properties. Am J Physiol Heart Circ Physiol 2002;282:1041–1046.

59. Kass DA, Grayson R. Ventriculo-arterial coupling; concepts, assumptions, and applications. Ann of Biomedl Eng 1992;20:41-62.

60. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension 2008; 52:873–880.

61. De PC, Kametas N, Rencoret G, Strobl I, Nicolaides KH. Maternal cardiac output between 11 and 13 weeks of gestation in the prediction of preeclampsia and small for gestational age. Obstet Gynecol 2008;111:292–300.

62. Ochsenbein-Ko¨lble N, Roos M, Gasser T, Huch R, Huch A, Zimmermann R. Cross sectional study of automated blood pressure measurements throughout pregnancy. BJOG 2004;111:319–325.

63. Nama V, Antonios TF, Onwude J, Manyonda IT. Mid-trimester blood pressure drop in normal pregnancy: myth or reality? J Hypertens 2011;29:763–768.

64. Thompson ML, Williams MA, Miller RS. Modelling the association of blood pressure during pregnancy with gestational age and body mass index. Paediatr Perinat Epidemiol 2009;23:254–263.

65. Irgens HU, Reisæter L, Irgens LM, Lie RT. Long term mortality among mothers and fathers after pre-eclampsia: population based cohort study. BMJ 2001;323:1213-7.

66. Romundstad PR, Magnussen EB, Smith GD, Vatten LJ. Hypertension in pregnancy and later cardiovascular risk: common antecedents? Circulation 2010;122:579-84.

67. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet 2001;357:2002-6.

68. Rang S, van Montfrans GA, Wolf H. Serial hemodynamics measurements in normal pregnancy, preeclampsia, and intrauterine growth restriction. Am J Obstet Gynecol 2008;198:519.e1-519.e9.

69. Henriksen T, Haugen G, Bollerslev J, Kolset SO, Drevon CA, Iversen PO, Clausen T. Fetal nutrition and future health. Tidsskr Nor Laegeforen 2005;17:442-4.

70. Low FM, Gluckman PD, Hanson MA. Developmental plasticity and epigenetic mechanisms underpinning metabolic and cardiovascular disease. Epigenomics 2011;3:279-294.

I

II

III

IV