



KATI TIHTONEN

Maternal Haemodynamics in Hypertensive
and Normotensive Pregnancy



ACADEMIC DISSERTATION

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To my family

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals.

I Tihtonen K, Kööbi T and Uotila J (2006): Arterial stiffness in preeclamptic and chronic hypertensive pregnancies. *Eur J Obst Gyn Repro Biol* 128: 180-186.

II Tihtonen K, Kööbi T, Vuolteenaho O, Huhtala H and Uotila J: Natriuretic peptides and hemodynamics in preeclampsia. *Am J Obstet Gynecol*, in press.

III Tihtonen K, Kööbi T and Uotila J: Hemodynamic adaptation during pregnancy in chronic hypertension. Submitted.

IV Tihtonen K, Kööbi T, Yli-Hankala A and Uotila J (2005): Maternal hemodynamics during cesarean delivery assessed by whole-body impedance cardiography. *Acta Obstet Gynecol Scand* 84: 355-361.

V Tihtonen K, Kööbi T, Yli-Hankala A and Uotila J (2006): Maternal haemodynamics in pre-eclampsia compared with normal pregnancy during caesarean delivery. *Br J Obstet Gynaecol* 113: 657-663.

ABBREVIATIONS

AI augmentation index
AGA appropriate for gestational age
ANP atrial natriuretic peptide
BNP B-type natriuretic peptide
CI cardiac index
CO cardiac output
CNP C-type natriuretic peptide
CSA cross sectional area
CVP central venous pressure
DAP diastolic arterial blood pressure
ESS left ventricle end-systolic stress
HR heart rate
HRV heart rate variability
ICG_{WB} whole-body impedance cardiography
ICG_{TH} thoracic impedance cardiography
IRT isovolumetric relaxation time
IUGR intrauterine growth retardation
LCW left cardiac work
LVEF left ventricle ejection fraction
LVFS left ventricle fractional shortening
MAP mean arterial pressure
NO nitric oxide
NT-proANP N-terminal proatrial natriuretic peptide
NT-proBNP N-terminal proB-type natriuretic peptide
PACWP pulmonary capillary wedge pressure
PAP pulmonary artery pressure
PP pulse pressure
PVR pulmonary vascular resistance
PWV pulse wave velocity
RAS renin-angiotensin-aldosterone system
RR risk ratio
SAP systolic arterial blood pressure
SGA small for gestational age
SI stroke index
SI/PP stroke index/pulse pressure ratio
SV stroke volume
SVR systemic vascular resistance
SVRI systemic vascular resistance index
TVI time velocity integral
V_{CFC} mean velocity of circumferential fiber thickening

ABSTRACT

The first aim of the study was to explore haemodynamic differences, especially in vascular properties and in associations between cardiac natriuretic peptides and haemodynamics, in hypertensive disorders – pre-eclampsia and chronic hypertension – and in normotensive pregnancies. Our second aim was to elucidate differences in haemodynamics during the course of pregnancy in chronically hypertensive women and normotensive women. Our third aim was to define differences in haemodynamic reactions during Caesarean delivery in normotensive and pre-eclamptic pregnancies. Haemodynamic data were obtained by whole-body impedance cardiography.

In the third trimester, baseline haemodynamics of pre-eclampsia differed from those in chronic hypertensive and normotensive pregnancies by showing higher systolic blood pressure (SAP) and systemic vascular resistance (SVRI) and lower cardiac index (CI) and heart rate (HR). Women with chronic hypertension had higher SAP, mean arterial pressure (MAP), diastolic blood pressure (DAP) and SVRI compared with uncomplicated subjects. In parameters describing arterial stiffness, pre-eclamptic women had significantly lower arterial compliance (stroke index to pulse pressure ratio, SI/PP), higher pulse pressure (PP) and faster pulse wave velocity (PWV), but women with chronic hypertension had only higher PWV when compared with normotensive controls. In both hypertensive groups strong correlations were found between arterial stiffness and afterload (MAP and SVRI).

Circulating concentrations of the amino-terminal fragment of pro-atrial natriuretic peptide (NT-proANP) and the amino-terminal fragment of pro-b-type natriuretic peptide (NT-proBNP) were significantly higher in pre-eclamptic women compared with chronic hypertensive and normotensive women. Moreover, NT-proANP and NT-proBNP concentrations were significantly higher in chronic hypertensive pregnancies than in normotensive ones. In pre-eclamptic women NT-proANP levels showed significant correlations with SAP and SVRI, while NT-proBNP levels correlated significantly with SVRI and CI. These correlations persisted in the subgroup of non-medicated pre-eclamptic women, except in the case of NT-proBNP and CI. In women with chronic hypertension no correlations emerged between natriuretic peptide concentrations and haemodynamics, but in the subgroup of non-medicated subjects NT-proANP and arterial pressure (SAP, MAP, DAP), and NT-proBNP and SVRI correlated significantly.

In women with chronic hypertension arterial blood pressure (SAP, MAP, DAP), SVRI and PWV remained significantly higher during the course of pregnancy and after delivery compared with normotensive pregnant women. In the early second trimester, women with chronic hypertension had significantly lower SIs and NT-proANP concentrations than controls.

In pre-eclamptic parturients, preload infusion increased both SI and HR, causing a significant rise in CI, while in healthy parturients only HR rose. In both groups, spinal blockade reduced SVRI, but CI remained stable. At the moment of delivery CI increased significantly in both groups. In pre-eclamptic pregnancies no increase in SI occurred and the rise in CI was due entirely to an increase in HR, while in normal pregnancies a significant increase in both SI and HR was observed. In both study groups SVRI decreased significantly simultaneously. After the disappearance of anaesthesia, haemodynamic data in the control group were similar to those at baseline, whereas SI and CI decreased significantly in the group with pre-eclampsia. During early puerperium no significant differences in SI, HR or CI between the study groups were found, but high SVRI and MAP persisted in pre-eclamptic versus normotensive parturients.

In conclusion, the divergent haemodynamics of pre-eclampsia include vasoconstriction of peripheral arteries, but also stiffer large conduit arteries compared with normotensive and chronic hypertensive pregnancies. High afterload is associated with high NT-proANP and NT-proBNP concentrations in pre-eclampsia. This implies that high natriuretic peptide levels in pre-eclampsia reflect the strain on the heart caused by high afterload, rather than the function of the heart expressed as SI or CI. The inability of pre-eclamptic parturients to increase SI at the moment of delivery, and even decreasing SI after delivery, may suggest dysfunction of the left ventricle to adapt to volume load caused by delivery and prompts concern for the increased risk of pulmonary oedema during delivery and the early postpartum period in these parturients. The haemodynamics of chronic hypertension during pregnancy are characterised by persistent high vascular resistance and arterial stiffness. Low SI and NT-proANP values found in chronic hypertensive pregnancies during the early second trimester also suggest reduced intravascular volume increase during pregnancy.

INTRODUCTION

Hypertensive disorders are the most common complications during pregnancy, affecting 15-24% of pregnancies (James and Nelson-Piercy 2004, Kaaja et al. 2005). The disorders include pre-eclampsia, gestational hypertension, chronic hypertension and superimposed pre-eclampsia (NIH 2000). Pre-eclampsia and gestational hypertension cover 70% of hypertensive disorders of pregnancy (Sibai 2003). Pre-eclampsia affects about 5–10% of pregnancies (O'Brien et al. 2000) and the incidence of chronic hypertension in pregnancy is estimated to be 3–5% (James and Nelson-Piercy 2004).

In respect of complications, the most problematic disorder is pre-eclampsia. It has remained the major cause of maternal and perinatal morbidity and mortality (Sibai and Kupferminc 2005). Maternal complications in pre-eclampsia are related to high blood pressure, endothelial dysfunction, multi-organ failure and cardiopulmonary failure (Sibai 2003). Compared with normotensive pregnancies, chronic hypertension is also associated with an increased risk of adverse maternal and perinatal outcome, especially in the case of superimposed pre-eclampsia and severe hypertension (Sibai and Anderson 1986, McCowan et al. 1996).

Uncomplicated pregnancy requires profound maternal haemodynamic changes to adjust to increased volume load. Increased intravascular volume is needed to create uteroplacental circulation for the developing and growing fetus (Dukekot et al. 1993). Furthermore, at the end of pregnancy, during delivery and during the early puerperium, thorough haemodynamic adaptation takes place to adapt to ceased uteroplacental circulation (Robson et al. 1989b). In healthy pregnancy increased volume load and haemodynamic changes are well tolerated and the course of pregnancy, delivery and early puerperium are uneventful in most cases. Haemodynamic adaptation in pre-eclampsia diverges from that in normotensive pregnancies (Hays et al. 1985, Visser and Wallenburg 1991) and may predispose pre-eclamptic women to cardiopulmonary complications during pregnancy, at delivery and in early puerperium. Furthermore, in cases of chronic hypertension, the underlying haemodynamic aberrancy compared with normotensive subjects (Messerli et al. 1981, Beevers et al. 2001, Mayet and Hughes 2003) may change haemodynamic adaptation in the course of pregnancy in these subjects.

In normotensive pregnancy vascular relaxation in peripheral arteries and enhanced arterial compliance in conduit arteries has a crucial role in allowing increased intravascular volume without a rise in blood pressure during pregnancy (Poppas et al. 1997). In hypertensive disorders, the divergent haemodynamic adaptation includes impaired vasorelaxation; higher peripheral vascular resistance has been found in pre-eclampsia (Visser and Wallenburg 1991) and in

chronic hypertensive pregnancies (Kuzniar et al. 1982) compared with normotensive pregnancies. Since in non-pregnant subjects the distensibility of the arteries has been shown to be proportional to blood pressure (Laurent et al. 1994), it could be assumed that higher blood pressure is also associated with lower arterial compliance in hypertensive pregnancies.

The divergent haemodynamic adaptation in pre-eclampsia includes increased strain on the heart, reflected in higher left ventricular mass and signs of diastolic dysfunction in pre-eclampsia compared with normotensive pregnancies (Borghi et al. 2001). Furthermore, the concentrations of cardiac natriuretic peptides – sensitive markers of cardiac dysfunction in non-pregnant populations – have also been found to be higher in pre-eclampsia (Castro et al. 1994). However, the relationship between cardiac natriuretic peptides and deviant haemodynamics in hypertensive pregnancies has not been well established.

The aim of this study was to assess haemodynamic differences in hypertensive disorders – especially in respect of vascular properties. In addition, the association between cardiac natriuretic peptides and haemodynamics in hypertensive disorders was studied to extend knowledge of the workload of the heart and haemodynamics during pregnancy. The study was also conducted to define the differences in haemodynamic adaptation between chronic hypertensive and normotensive pregnancies during the course of pregnancy. The last aim was to clarify haemodynamic changes at delivery and in early puerperium in normotensive and pre-eclamptic pregnancies and find differences in haemodynamic reactions that could make pre-eclamptic parturients more prone to cardiopulmonary complications during and after delivery.

REVIEW OF THE LITERATURE

1. Haemodynamic adaptation in normotensive pregnancy

Normal pregnancy requires profound maternal haemodynamic changes and extracellular volume expansion to create adequate uteroplacental circulation for the developing and growing fetus (Duvekot and Peeters 1994a). This physiological adaptation in pregnancy is complex, involving the integration of a variety of regulatory organ systems that are still scarcely known (Thornburg et al. 2000).

The primary trigger for crucial adaptive alterations in pregnancy has remained obscure, but it is commonly accepted that a fall in systemic vascular tone precedes extracellular volume increase and major haemodynamic changes (Duvekot and Peeters 1994a, Carbillon et al. 2000). Furthermore, the physiological alterations in volume homeostasis and the cardiovascular system are parallel and the steepest changes take place during the first half of pregnancy (Duvekot and Peeters 1994a, Thornburg et al. 2000). Disturbances in haemodynamic adaptation or volume expansion are associated with pregnancy complications such as intrauterine growth restriction and pre-eclampsia (Carbillon et al. 2000).

1.1. Extracellular volume increase

The indicator dilution technique has been generally used to estimate plasma volume during pregnancy. A commonly used indicator is albumin labelled with Evan's Blue dye (Whittaker and Lind 1993) or radioactive compounds (Pritchard 1965, Lund and Donovan 1967). Likewise, red blood cell mass can be estimated by labelling red blood cells with radioactive indicators such as ^{51}Cr (Pritchard 1965) or iron (Caton et al. 1951).

Based on the results of a longitudinal study starting at 20 weeks of gestation, total blood volume was found to steadily increase up to 32 weeks, then until the end of pregnancy a slight rise was found and an absolute maximum was reached at 36 weeks (Thomsen et al. 1993). During pregnancy, total blood volume has been found to increase to 40% above the non-pregnant level (Caton et al. 1951, Pritchard 1965, Thomsen et al. 1993).

When total plasma and red cell volumes have been estimated separately, a similar pattern of increase has been found. Measurements starting at 6 gestational weeks showed a sharp rise in total plasma volume up to 24 gestational weeks and a progressive but smoother increase until term. The mean

rise in plasma volume during pregnancy was 1500 ml, or 50%. The red cell volume increase was less, but changes during pregnancy were comparable with those in plasma volume. The mean red cell volume rose by 400 ml, or 20% (Lund and Donovan 1967). The findings concerning the magnitude of change in plasma volume and in red blood cell volume are consistent with other studies (Chesley 1972, Whittaker and Lind 1993)

The discrepancy between the expansion of plasma and red cell volume causes physiological haemodilution during pregnancy. The advantages of gestational volume expansion and haemodilution are mainly to create uteroplacental circulation, but it is also assumed to provide protection against excessive peripartal blood loss and to prevent thromboembolic events during pregnancy (Lee 1991).

Although the exact mechanisms behind volume increase are still largely unknown, activation of the renin-angiotensin-aldosterone system (RAS) by arterial underfilling has been thought to be an important factor in modulating volume homeostasis and inducing volume expansion during pregnancy (Duvekot and Peeters 1994a, Carbillion et al. 2000). The RAS involves two important factors – angiotensin II and aldosterone. Angiotensin II increases the secretion of arginine vasopressin, the principal physiological effect of which is retention of water by the kidney, thus acting as an antidiuretic hormone. Moreover, aldosterone has an effect of sodium and fluid retention in the kidney (Ganong 1989).

Angiotensin II is one of the most potent known vasopressor (Ganong 1989). Although active angiotensin concentrations are increased in peripheral blood until 30 weeks of gestation (Skinner et al. 1972), the vasoconstrictive effect of angiotensin II on systemic and renal vessels is extremely reduced during pregnancy (Gant et al. 1973). The mechanism of attenuated vasopressor effect of RAS during pregnancy is not known (Carbillion et al. 2000). But based on animal models increased nitric oxide (NO) and prostacyclin - the endothelium-derived relaxing factors- may have a role in resisting the effect of angiotensin II during pregnancy. Furthermore angiotensin II may also stimulate NO production (Nathan et al. 1995, Magness et al. 1996).

Other factors considered to modulate volume homeostasis during pregnancy include placental production of oestrogen (Longo 1983), uteroplacental circulation acting as an arteriovenous shunt (Longo 1983, Lee 1991) and resetting of the osmoregulatory system (Duvekot et al. 1993). Red cell volume increase is thought to be induced by the increased erythropoietin levels found in pregnancy (Manasc and Jepson 1969).

1.2. Haemodynamic changes

The definitions of the main haemodynamic variables are presented in Table 1 (Ganong 1989).

Table 1.*Definitions of the main haemodynamic parameters.*

Stroke volume - SV (ml)	Quantity of blood ejected from the left ventricle with each beat
Stroke index - SI (ml/m ²)	Stroke volume / body surface area
Heart rate - HR (beats/minute)	Number heart beats per minute
Cardiac output - CO (L/min)	Stroke volume x heart rate
Cardia index - CI (L/min/m ²)	Cardiac output / body surface area
Systemic vascular resistance - SVR / Total peripheral vascular resistance - TPR (dyne x s/cm ⁵)	Impediment to blood flow in peripheral vasculature
Systemic vascular resistance index - SVRI (dyne x s/cm ⁵ /m ²)	Systemic vascular resistance / body surface area
Mean arterial pressure - MAP (mmHg)	Diastolic blood pressure + 1/3 of pulse pressure
Pulse pressure - PP (mmHg)	Systolic blood pressure - diastolic blood pressure
Pulse wave velocity - PWV (m/s)	Speed of the pulse wave created by the left ventricle ejection
Left cardiac work - LCW (kg x m)	The amount of work the left ventricle must perform to pump blood each minute
Left cardiac work index - LCWI (kg x m/m ²)	Left cardiac work / body surface area

1.2.1. Heart rate and stroke volume

Heart rate has been found to increase steadily through pregnancy towards the third trimester (Mabie et al. 1994, Van Oppen et al. 1996, Clapp and Capeless 1997) or remain stable after the second trimester (Ayala et al. 1997). The highest heart rates observed during pregnancy have been 16%–35% higher than non-pregnant values (Mabie et al. 1994, Van Oppen et al. 1996, Clapp and Capeless 1997). An increase in heart rate has been observed as early as at five weeks of gestation when compared to non-pregnant values (Duvekot et al. 1993).

Increased heart rate during early pregnancy is thought to be a compensatory attempt to maintain cardiac output in a state of relative hypovolaemia resulting from initial vasorelaxation. Later in pregnancy a higher heart rate compared with the non-pregnant level is assumed to be necessary to circulate the extra volume (Duvekot et al. 1993).

An initial rise in heart rate is followed by an increase in stroke volume. It has been found to increase during the first trimester, reach a plateau in mid-pregnancy and decrease towards the end of pregnancy (Atkins et al. 1981, Duvekot et al. 1993, Van Oppen et al. 1996). Compared with pre-pregnancy values, stroke volume has been found to be significantly increased by 8 weeks (Clapp and Capeless 1997) and 12 weeks of gestation (Atkins et al. 1981). The highest values observed during the second trimester have been 11–13% greater and during the third trimester they are 6–7% lower than non-pregnant values (Duvekot et al. 1993, Van Oppen et al. 1996). In contrast, stroke volume has also been found to remain stable (Clapp and Capeless 1997, Poppas et al. 1997) or to increase further (Mabie at al. 1994) during the third trimester.

An enhancement of stroke volume is due to the higher venous return to the heart caused by expanding blood volume during pregnancy (Duvekot et al. 1993, Duvekot and Peeters 1994b). According to the Frank-Starling law the more the ventricle is filled with blood during diastole, the greater the volume of ejected blood will be during the systolic contraction (Ganong 1989). Besides of the increased preload of the heart, stroke volume increase during the first trimester is thought to be augmented by the decrease in afterload due to pregnancy-induced vasorelaxation (Duvekot et al. 1993, Duvekot and Peeters 1994b).

1.2.2. Cardiac output

Changes in heart rate and stroke volume lead to an increase in cardiac output during pregnancy (Duvekot and Peeters 1993, Clapp and Capeless 1997). Higher cardiac output values compared with non-pregnant values have been measured as early as at 5 weeks of gestation owing to an elevated heart rate compared to non-pregnant values (Duvekot et al. 1993). Significantly increased cardiac output values compared with non-pregnant values have been found by 8 weeks (Clapp and Capeless 1997) and 12 weeks of gestation (Atkins et al. 1981). Most of the rise in cardiac output appears to occur during the first half of pregnancy – 60 to 90% of the total increase in cardiac output during the pregnancy (Mabie et al. 1994, Clapp and Capeless 1997, Poppas et al. 1997).

The results of longitudinal studies indicate increased cardiac output during the first half of pregnancy, but discrepancies exist about the changes during the second half of pregnancy. After an original steep rise in cardiac output in the first trimester, it has been found to continue rising and to reach a plateau by 18 to 26 weeks of gestation, being up to 40 % higher than in the non-pregnant state. Towards the third trimester cardiac output has been found to decrease (Duvekot et al. 1993, Van Oppen et al. 1996). Cardiac output has also been found to increase slightly towards the term after the second half of pregnancy (Mabie et al. 1994, Clapp and Capeless 1997), but also to remain stable (Poppas et al. 1997). The highest values of cardiac output during pregnancy have been found to be 32–52% higher than in non-pregnant subjects (Duvekot et al. 1993, Mabie et al. 1994, Clapp and Capeless 1997, Poppas et al. 1997).

1.2.3. Peripheral vascular resistance

Systemic vascular resistance has been found to decrease below non-pregnant reference values even by 5 week's gestation, when the non-pregnant reference values were obtained from the study subjects three months after delivery (Duvekot et al. 1993). Lower systemic vascular resistance during the first trimester has been confirmed in other studies, but in these studies the first measurements were obtained later, at 8 to 10 gestational weeks (Easterling et al. 1990a, Duvekot et al. 1993, Mabie et al. 1994, Van Oppen et al. 1996, Clapp and Capeless 1997).

In longitudinal studies the nadir of systemic vascular resistance has been found during the second trimester of pregnancy, with the lowest values obtained

have varied from 16 to 26 weeks of gestation (Duvekot et al. 1993, Mabie et al. 1994, Van Oppen et al. 1996, Clapp and Capeless 1997). In most of the studies the steepest change in systemic vascular resistance has also occurred during the first half of pregnancy (Easterling et al. 1990a, Mabie et al. 1994, Clapp and Capeless 1997), being > 85% of the total decrease occurring during the pregnancy (Clapp and Capeless 1997). During the third trimester the trend in systemic vascular resistance has varied. It has been found to remain stable (Clapp and Capeless 1997) or to increase (Duvekot et al. 1993, Van Oppen et al. 1996). On the other hand, in studies by Duvekot and associates (1993) and Van Oppen and associates (1996) the steepest change in systemic vascular resistance took place during the third trimester.

In the studies mentioned above, systemic vascular resistance was calculated from the equation: $MAP \times 80$ divided by CO. Cardiac output estimations were obtained by the Doppler (Easterling et al. 1990a, Duvekot et al. 1993, Mabie et al. 1994), or by the M-mode method (Clapp and Capeless 1997) or by means of thoracic electrical bioimpedance (Van Oppen et al. 1996).

1.2.4. Arterial stiffness

In addition to vasorelaxation of peripheral arteries, changes in larger conduit arteries are also found. In a longitudinal study by Poppas and associates (1997) arterial compliance was found to increase approximately 30% during the first trimester of pregnancy compared to the values of non-pregnant subjects. Thereafter it remained increased during the second and third trimester. Global arterial compliance was calculated from non-invasive measurements of subclavian pulse tracing and aortic Doppler velocities. Increased arterial compliance is thought to be an adaptive mechanism of the vasculature to accommodate increased volume load during pregnancy (Poppas et al. 1997).

1.2.5. Blood pressure

In most longitudinal studies steady decreases in systolic blood pressure, mean arterial pressure and diastolic blood pressure occur until a nadir is reached during the second trimester – ranging from 16 to 21 week's gestation – followed by an increase in blood pressure at term (Easterling et al. 1990a, Van Oppen et al. 1996, Ayala et al. 1997, Clapp and Capeless 1997). At the end of pregnancy blood pressure has been found to return to the level found in early pregnancy (Van Oppen et al. 1996, Ayala et al. 1997) or to the pre-pregnancy level (Clapp and Capeless 1997). Pulse pressure has been found to remain rather stable during pregnancy (Thadhani et al. 2001).

In contrast, systolic blood pressure, mean arterial pressure and diastolic blood pressure have also been found to remain relatively stable throughout pregnancy (Mabie et al. 1994, Poppas et al. 1997). Or a significant increase in mean arterial pressure occurring in the third trimester with otherwise stable MAP during the course of pregnancy has also been found (Duvekot et al. 1993).

Compared with non-pregnant values, MAP has been found to be significantly lower during the first and second trimester (Mabie et al. 1994, Clapp and Capeless 1997), or the second trimester (Van Oppen et al. 1996). In the third trimester, from 27–34 gestational weeks onwards, MAP has been found to be comparable to that in non-pregnant subjects (Mabie et al. 1994, Van Oppen et al. 1996, Clapp and Capeless 1997).

In these studies, blood pressures were measured with a cuff sphygmomanometer (Duvekot et al. 1993, Mabie et al. 1994, Van Oppen et al. 1996) or by means of an automated ambulatory blood pressure device (Ayala et al. 1997, Clapp and Capeless 1997). The haemodynamic changes found in different longitudinal studies are presented in Table 2.

1.2.6. Autonomic cardiovascular control

Autonomic function can be assessed non-invasively by means of cardiovascular reflex tests, such as heart rate variability (HRV) (Ekholm and Erkkola 1996, Rang et al. 2002).

Heart rate variability can be estimated by spectral analysis of an array of R-R intervals derived from electrocardiographic data (Rang et al. 2002). The spectrum of variation of heart rate is divided into low frequency and high frequency. Vagal activity is the major contributor to the high frequency component and low frequency is considered to reflect both sympathetic and vagal activity (Ekholm and Erkkola 1996, Rang et al. 2002). Furthermore, in cardiology, decreased HRV is considered to reflect increased sympathetic and decreased parasympathetic modulation of the heart (Stein et al. 1999). Besides the autonomic nervous system, these parameters are also affected by respiratory rate and change in posture (Ekholm and Erkkola 1996, Rang et al. 2002).

In one study, mean HRV and high frequency variability were found to be significantly lower in the third trimester of pregnancy compared with the mean values observed in the sixth week of pregnancy, but no significant changes in low frequency oscillations existed (Lucini et al. 1999). In another study, compared with non-pregnant women, both high and low frequency variability of the heart rate were significantly lower in pregnant women (Ekholm et al. 1997). Even if changes in respiratory rate and blood volume during pregnancy may affect reflexes in HRV, these findings suggest that pregnancy may decrease vagal control of the heart (Lucini et al. 1999). In contrast, HRV (low and high frequency) has also been found to remain stable during pregnancy (Rang et al. 2004).

Table 2. *Longitudinal studies on haemodynamic changes during normotensive pregnancy.*

Reference	Haemodynamic parameters	Preconception	First trimester	Second trimester	Third trimester	Postpartum	Method for CO estimation	Posture	Number of subjects
Easterling et al. 1990	CO (L/min)		10-13	22-25	38	6 weeks	Doppler echocardiography	left lateral	89
	TPR (dynexs/cm ⁵)		6.2	7.2	7.3	5.6			
	MAP (mmHg)		1060	880	960	1220			
Mabie et al. 1994	SI (ml/m ²)		8-11	20-23	36-39	12 weeks	Doppler echocardiography	left lateral	18
	HR (beats/min)		49	55	55	49			
	CI (L/min/m ²)		80	82	88	69			
	TPR (dynexs/cm ⁵)		4.0	4.5	4.8	3.3			
	MAP (mmHg)		1008	917	829	1277			
Duvekot et al. 1993	SV (ml)		5-8	25	35	3 months	Doppler echocardiography	left lateral	10
	HR (beats/min)		75	72	68	73			
	CO (L/min)		79	87	85	66			
	TPR (dynexs/cm ⁵)		5.73	6.53	5.78	4.78			
	MAP (mmHg)		1193	1066	1257	1570			
Van Oppen et al. 1996	SV (ml)		10-18	18-26	32-42	12 weeks	thoracic electrical bioimpedance	sitting	50
	HR /beats/min)		85	85	70	75			
	CO (L/min)		87	90	92	80			
	SVR (dynexs/cm ⁵)		7.26	7.60	6.37	5.91			
	MAP (mmHg)		966	901	1118	1175			

Tabel 2. *Continued.*

Reference	Haemodynamic parameters	Preconception	First trimester	Second trimester	Third trimester	Postpartum	Method for CO estimation	Posture	Number of subjects
Clapp and Capeless 1997	SV (ml)	82	8	24	38	12 weeks	M-mode echocardiography	lateral	30
	HR (beats/minute)	57	92	97	96	94			
	CO (L/min)	4.69	64	69	72	60			
	TPR (dynexs/cm ⁵)	1428	5.9	6.72	6.91	5.65			
	MAP (mmHg)	84	1080	928	946	1175			
Poppas et al. 1997	SV (ml)		12	20	31	8 weeks	Doppler echocardiography	left lateral	14
	HR (beats/min)		95	99	99	87			
	CO (L/min)		70	77	80	66			
	TPR (dynexs/cm ⁵)		6.8	7.6	7.9	6			
	MAP (mmHg)		885	766	743	1040			
Mesa et al. 1999	SV (ml)		10	24	34	1.7 months	Doppler echocardiography	left lateral	37
	HR (heart rate)		62	68	71	68			
	CO (L/min)		74	83	87	68			
	SVR (dynexs/cm ⁵)		4.6	5.6	6	4.6			
	MAP (mmHg)		1485	1201	1143	1446			
			83	81	82	84			

Values are means obtained from the mentioned references. CO, cardiac output; TPR, total peripheral resistance; MAP, mean arterial pressure; SI, stroke index; HR, heart rate; CI, cardiac index, SVR; systemic vascular resistance.

1.2.7. Possible causes of discrepancies between studies

The discrepancies between studies in haemodynamic data during pregnancy can partly be explained by the different methods used. In previous studies, haemodynamic data has been obtained by Doppler echocardiography (Easterling et al. 1990a, Duvekot et al. 1993, Mabie et al. 1994, Poppas et al. 1997), M-mode echocardiography (Clapp and Capeless 1997) and thoracic impedance cardiography (Van Oppen et al. 1996). The possible inaccuracies associated with these methods are discussed later in the section “Methods used to measure haemodynamic parameters during pregnancy”.

The posture of a subject when haemodynamic parameters are measured could also explain disagreements between studies. An enlarging uterus has an impact on maternal haemodynamics during the course of pregnancy and this is further modified by the posture of the subject. In a supine posture a gravid uterus causes aortocaval compression, leading to lower cardiac output. This phenomenon is seen as soon as at 20–24 weeks of gestation and it is enhanced in late pregnancy (Metcalf et al. 1981). A sitting posture has a similar effect: lower cardiac output throughout pregnancy compared with the left lateral position (Metcalf et al. 1981). An explanation for low cardiac output in sitting or standing postures could be pooling of blood in dependent vessels, leading to reduced venous return (Sala et al. 1995, Van Oppen et al. 1996). However, haemodynamic measurements in longitudinal studies have been obtained mostly in a semi-left-lateral position (Easterling et al. 1990a, Duvekot et al. 1993, Mabie et al. 1994, Clapp and Capeless 1997, Poppas et al. 1997), although a sitting position has also been used (Van Oppen et al. 1996).

Other confounding factors could be heterogeneity of the study population and variation of the haemodynamics between study subjects. When haemodynamic data from nulliparous and parous women have been compared, significantly greater changes in stroke volume, cardiac output and systemic vascular resistance in parous versus nulliparous women have been observed (Clapp and Capeless 1997). All the studies referred to above have included both parous and nulliparous women (Duvekot et al. 1993, Mabie et al. 1994, Van Oppen et al. 1996, Ayala et al. 1997, Clapp and Capeless 1997, Poppas et al. 1997), except for one including only nulliparous subjects (Easterling et al. 1990a).

Some inaccuracies in haemodynamic differences between pregnant and non-pregnant women may also arise if the reference data on non-pregnant women is obtained during the post-partum period. In a study by Capeless and Clapp (1997), stroke volume remained elevated and systemic vascular resistance decreased compared with pre-conceptual values at six and twelve weeks after delivery, suggesting that the haemodynamic changes caused by pregnancy might still persist during this period. Use of non-pregnant reference values obtained at or before twelve weeks after delivery (Easterling et al. 1990a, Mabie et al. 1994, Van Oppen et al. 1996) may result in underestimation of haemodynamic changes during pregnancy.

1.3. Functional and structural changes of the heart

1.3.1. Changes in left ventricle structure

The maternal heart has shown adaptive changes as a reaction to physiological volume overload during pregnancy. In longitudinal studies, left ventricular posterior wall thickness in diastole and left ventricular mass increase during pregnancy as estimated by the ultrasonographic echocardiography M-mode technique (Duvekot et al. 1993, Mabie et al. 1994, Poppas et al. 1997, Mesa et al. 1999, Schannwell et al. 2002). Left ventricular hypertrophy becomes apparent during the second trimester and is most marked at the end of pregnancy (Duvekot et al. 1993, Mabie et al. 1994). Maximal left ventricular mass during pregnancy has been found to be 12–30% higher than in the non-pregnant state (Duvekot et al. 1993, Mabie et al. 1994, Poppas et al. 1997). Increases in blood volume and cardiac output in pregnancy are considered to cause this left ventricle hypertrophy (Mesa et al. 1999).

1.3.2. Diastolic function of the heart

The increment in left ventricular mass found in pregnancy might lead to decreased ventricular compliance and restrict the diastolic function of the heart (Moran et al. 2002). Left ventricular diastolic function can be assessed at the isovolumetric relaxation phase and filling phase of the left ventricle at the mitral valve by Doppler echocardiography. In cases of diastolic dysfunction, isovolumetric relaxation time (the time from aortic closure to mitral valve opening) is increased (Yamamoto et al. 1996a). During ventricular diastole, mitral inflow has two peaks: early inflow, called the E-wave and atrial contraction, called the A-wave. Diastolic impairment is associated with a low E/A ratio (Ommen and Nishimura 2003). Besides the factors affecting left ventricular compliance and relaxation, these parameters are also affected by the contractility of the left ventricle, preload and afterload (Mabie et al. 1994).

In longitudinal studies the E wave/A wave ratio has been found to decrease with advancing gestational age (Mesa et al. 1999, Kametas et al. 2001), but no change in isovolumetric relaxation time (IVRT) has been found (Mesa et al. 1999). Compared with non-pregnant women the E wave/A wave peak velocity ratio has been found to be significantly reduced in pregnant women during the third trimester (Borghi et al. 2000, Moran et al. 2002).

1.3.3. Systolic function of the heart

Systolic function of the left ventricle can be assessed from the left ventricular ejection fraction (LVEF) or left ventricular fractional shortening (LVFS) by ultrasonographic echocardiography. Besides of the contractile performance,

these parameters are also influenced by heart rate, preload and afterload (Duvekot and Peeters 1994a).

In most of the longitudinal studies no significant changes in LVEF or LVFS have been found during the course of pregnancy (Mabie et al. 1994, Poppas et al. 1997, Mesa et al. 1999). In contrast, LVEF and LVFS have also been found to decrease significantly during the third trimester, compared with first trimester values (Schannwell et al. 2002).

In a cross-sectional study no significant differences in LVEF or LVFS were found between pregnant women in the third trimester and non-pregnant subjects (Borghini et al. 2000). However, LVFS has also been found to be significantly higher during the course of pregnancy compared with non-pregnant reference values (Mabie et al. 1994).

1.4. Peripartum haemodynamic changes

1.4.1. Caesarean delivery under regional anaesthesia

Caesarean delivery includes procedures that challenge maternal haemodynamics and might predispose the parturient to harmful cardiovascular complications. Spinal anaesthesia induces the risk of maternal hypotension, which could be worsened by the supine posture and vena cava compression by the uterus (Rout and Rocke 1999, Morgan et al. 2001). This complication is tried to avoid by preloading, vasopressor infusion and left lateral uterine displacement during the surgical procedure (Jackson et al. 1999, Morgan et al. 2001). Maternal hypotension after spinal blockade also jeopardizes placental circulation and may result in neonatal acidaemia (Jackson et al. 1999, Morgan et al. 2001). Delivery itself loads the vasculature by diminishing blood flow to the uterus, relief of the pelvic veins, and vena cava inferior compression by the contracting uterus (Niswonger and Langmade 1970, Rout and Rocke 1999).

1.4.1.1. Effects of spinal anaesthesia

Spinal anaesthesia-induced hypotension (a decrease in systolic pressure to 80% of the baseline value or systolic pressure <90–100 mmHg) occurs approximately 5–12 minutes after the blockade (Riley et al. 1995, Park et al. 1996). After fluid preloading and left lateral positioning of the parturient, hypotension has coincided with a decrease in systemic vascular incidence and stable cardiac output (Park et al. 1996), but also with a decrease in stroke volume and cardiac output, but stable total peripheral resistance (Robson et al. 1992).

The fetal umbilical artery Doppler pulsatility index has been found to increase after spinal blockade and to have negative correlation with maternal cardiac output, but not with maternal blood pressure. This might suggest that peripheral vasodilation after spinal blockade may direct the blood flow away from the placental circulation (Robson et al. 1992). Furthermore, the pulsatility index of the uterine artery has been found to have an increasing tendency after

spinal blockade, but this finding was transient and was not statistically significant (Karinen et al. 1995). Despite these changes, the conditions of newborns, as assessed by Apgar score and umbilical artery pH, were good (Robson et al. 1992, Karinen et al. 1995).

1.4.1.2. Prevention and treatment of spinal anaesthesia-induced hypotension

Volume expansion before spinal anaesthesia is aimed at preserving cardiac output despite vasodilation of the peripheral vasculature. Preload infusion has been shown to reduce the incidence of hypotension significantly after spinal blockade (Rout and Rocke 1999, Morgan et al. 2001). However, opposite findings also exist (Jackson et al. 1999).

Infusions used for preloading are crystalloids and colloids. Both types of preload infusion have been shown to increase blood volume, as measured by indocyanine green pulse spectrophotometry (Ueyama et al. 1999), and cardiac output as estimated by Doppler echocardiography (Robson et al. 1992) or the dye dilution technique (Ueyama et al. 1999).

Compared with colloids, crystalloids have been more inconsistent in preventing hypotension. Incidences of hypotension have been 62%–75% in groups receiving Ringer's solution and 17%–38% in groups receiving hydroxyethylstarch solution as a preload (Karinen et al. 1995, Ueyama et al. 1999). Furthermore, only 28% of the Ringer's solution but 100% of the hydroxyethylstarch solution remained in the vascular space 30 minutes after administration (Ueyama et al. 1999). Hypotension has also been shown to be more severe, and more doses of ephedrine have been required to treat it in a crystalloid group than in a colloid group (Siddik et al. 2000). Neither type of preload infusion has been found to have an effect on placental circulation as estimated by uterine artery pulsatility index (Karinen et al. 1995).

Ephedrine is a vasopressor used to correct post-spinal anaesthesia hypotension. Administration of ephedrine in hypotensive parturients resulted in increased ejection fraction, stroke volume and cardiac output. This finding suggested that preload to the heart was enhanced by the vasoconstricting effect of ephedrine when hypovolemia has been corrected (Ramanathan et al. 1986).

1.4.1.3. Delivery

In the earliest studies concerning haemodynamics during Caesarean section under spinal anaesthesia, delivery of the newborn and the placenta was associated with a 41–55% increase in cardiac output compared with the pre-anaesthetic level (Ueland et al. 1968, Niswonger and Langmade 1970). The increment of cardiac output was found to be the result of increases in stroke volume and heart rate (Niswonger and Langmade 1970) or only an increase in stroke volume (Ueland et al. 1968). Meanwhile, arterial blood pressure remained relatively stable (Ueland et al. 1968, Niswonger and Langmade 1970). In contrast, in a later study, delivery coincided with stable cardiac index, but a significant decrease in systemic vascular resistance together with decreased mean arterial pressure compared with the baseline values (Park et al. 1996).

When studies under epidural anaesthesia are also included, delivery has been associated with increased cardiac output, varying from 8% to 37% compared

with baseline values (Ueland et al. 1972, James et al. 1989, Robson et al. 1989a). In these studies the enhancement of cardiac output was due to a rise in heart rate (Ueland et al. 1972) or a rise in stroke volume (James et al. 1989, Robson et al. 1989a). The increase in cardiac output after delivery coincided with a simultaneous decrease in systemic vascular resistance varying from 6% to 25%, and arterial pressure remained stable (Ueland et al. 1972, James et al. 1989, Robson et al. 1989a).

The observed postpartum changes could be partly explained by the physiological events at the moment of delivery. The contracting uterus expelling approximately 500 ml blood into the systemic circulation could induce volume load in the vasculature (Ueland et al. 1968). The relief of supine vena cava occlusion also augments cardiac output by removing the pooling of blood in the lower extremities (Ueland et al. 1968, Milson et al. 1985). In most studies a simultaneous decrease in peripheral vascular resistance has compensated for the increase in cardiac output, allowing stable blood pressure (Ueland et al. 1972, James et al. 1989, Robson et al. 1989a).

1.4.1.4. Early postpartum period

There is a lack of data on the haemodynamic changes during the very early postpartum period after Caesarean section under spinal anaesthesia. At the time of closure of the abdominal wall, cardiac output has been found to decrease, while remaining at a higher level compared with baseline before anaesthesia induction. The decrease in cardiac output was due to lowering of the heart rate, while stroke volume persisted at the level found immediately after delivery. Mean arterial pressure decreased and vascular resistance dropped to a level below baseline values (Niswonger and Langmade 1970).

After Caesarean delivery under epidural anaesthesia, cardiac output and stroke volume remained elevated at 30 and 60 minutes after delivery and thereafter values were similar to preoperative ones up to 24 hours after delivery. No significant changes in mean arterial pressure took place between delivery and the first post-partum day (James et al. 1989). Cardiac output and stroke volume have also been found to decrease to less than preoperative values as soon as one hour after delivery and to decrease further during the first post-partum day. Furthermore, total peripheral vascular resistance had increased by one hour after delivery compared with the values at delivery and before operation and it remained at a higher level during the first post-partum day. Systolic blood pressure remained stable during this period, but diastolic pressure was significantly lower at 24 hours after delivery than preoperatively (Robson et al. 1989a).

Based on the above studies, cardiac output and stroke volume have been found to remain increased after delivery, but discrepancies exist about the time period when the haemodynamic parameters return to their baseline values. Studies concerning delivery during Caesarean section are presented in Table 3.

Table 3. *Studies on delivery during Caesarean section under regional anaesthesia in normotensive parturients.*

Reference	Haemodynamic parameter	Before operation	After anaesthesia induction	Before delivery	Immediately after delivery	After delivery	Mode of anaesthesia	Method for CO estimation	Position	Subjects
Ueland et al. 1968	SV (ml) HR (beats/minute) CO (L/min) arterial pressure (mmHg)	62 90 5.4 124/72	35 109 3.6 66/38	63 96 5.5 96/58	106 85 8.4 118/65	abdomen open	spinal	dye dilution	supine	12
Niswonger and Langmade 1970	SV (ml) HR (beats /min) CO (L/min) TPR (dynesxs/cm5) MAP (mmHg)	77 82 6.29 1490 110	75 97 6.95 1067 85		98 91 8.81 958 88	incision closure	spinal (8) epidural (1)	dye dilution		9
Ueland et al. 1972	SV (ml) HR (beats/minute) CO (L/min) TPR (dynesxs/cm5) blood pressure (mmHg)	69 85 5.88 1255 116/72	62 92 5.52 1243 101/65	81 81 6.57 1026 102/67	81 91 7.34 925 106/68	10 minutes 1 hour	epidural	dye dilution	supine	13
James et al. 1989	CO (L/min)	6.63	7.88	start of operation	at the end of operation	15 min 1 hour	epidural	Doppler	left lateral	11
Robson et al. 1989a	SV (ml) HR (beats/minute) CO (L/min) TPR (dynesxs/cm5) blood pressure (mmHg)	84 85 7.14 937 113/68		84 84 7.08 920 107/65	95 81 7.69 879 113/67	1 hour	epidural	Doppler	left lateral	15

Values are means obtained from the mentioned studies. SV, stroke volume; HR, heart rate; CO, cardiac output; TPR, total peripheral resistance.

1.4.2. Vaginal delivery

1.4.2.1. First stage

Cardiac output and mean arterial pressure have been found to increase during the course of delivery. The mean increment of cardiac output was 13% and that of arterial pressure 11% at > 8 cm cervical dilation compared with pre-labour values in parturients receiving pethidine and nitrous oxide for analgesia in a left semi-lateral position. This increase in cardiac output was a result of an increase in stroke volume. Contractions further increased cardiac output due to increases in both heart rate and stroke volume. The increment in cardiac output during contractions became progressively greater as labour proceeded. During the end of the first stage the increase was approximately 34% compared with values observed between contractions. Contractions also increased mean arterial pressure by 12% (Robson et al. 1987a).

The mode of anaesthesia may modify the haemodynamics. The increment of cardiac output during the course of the first stage was due to a rise in stroke volume in parturients receiving local anaesthesia – paracervical and pudendal block. Meanwhile, in parturients receiving epidural anaesthesia, heart rate increased. A contraction in the supine position further increased cardiac output by approximately 15–20% and the rise was due to an increase in stroke volume regardless of the type of anaesthesia (Ueland and Hansen 1969a).

The posture of the parturient during delivery also affects haemodynamics (Ueland and Hansen 1969b). Cardiac output and stroke volume have been found to increase by 22% and 27%, respectively, with a change in position from supine to side, measured between contractions. A contraction in a supine position caused rises in cardiac output (25%), stroke volume (33%) and pulse pressure (26%). In the lateral position the increments in haemodynamic parameters caused by contractions were less: cardiac output 8%, stroke volume 8% and pulse pressure 6%. The parturients did not receive any sedation prior to the evaluations (Ueland and Hansen 1969b).

1.4.2.2. Second stage

During the second stage of labour cardiac output has been found to increase by 49% compared with pre-labour values in parturients receiving local anaesthesia and by 24% in parturients receiving epidural anaesthesia. The increment in cardiac output was the result of a rise in stroke volume in both groups. Furthermore, in both groups contractions further increased cardiac output owing to an increase in heart rate in the local anaesthesia group and stroke volume in the epidural anaesthesia group. Measurements were obtained in the supine position. In the epidural anaesthesia group systolic and diastolic blood pressure remained stable throughout delivery, while in the local anaesthesia group both arterial blood pressures were found to increase significantly during the second stage of labour compared with the early stage (Ueland and Hansen 1969a).

The haemodynamics of the second stage of labour are assumed to be modified by the Valsalva effect, causing rapid changes in arterial and venous

pressure (Ueland and Hansen 1969a). Bearing down drives blood from the lungs to the heart and raises the blood pressure. As breath holding is continued, blood pressure begins to fall as a result of increased intrathoracic pressure compressing the veins and decreasing the venous return and cardiac output. At the moment of release of the held breath cardiac output is restored and blood pressure suddenly increases (Ueland and Hansen 1969a, Ganong 1989).

1.4.2.3. Delivery

In parturients receiving epidural or spinal anaesthesia, cardiac output has been found to increase by 20%–59% immediately after delivery compared with pre-anaesthesia baseline values. The rise in cardiac output has been found to result in an increase in stroke volume. Furthermore, total peripheral resistance has been found to decrease by 27% and mean arterial pressure to remain relatively stable (Ueland and Hansen 1969a, Niswonger and Langmade 1970). Cardiac output has been found to be decreased by 6% 60 minutes after vaginal delivery (Ueland and Hansen 1969a). Studies concerning haemodynamics during vaginal delivery are presented in Table 4.

Table 4. *Studies on haemodynamical changes during vaginal delivery in normotensive parturients.*

Reference	Haemodynamic parameter	Stage of labour					Mode of anaesthesia	Method for CO estimation	Subjects	Position
		First stage	Second stage	Delivery	Postpartum					
Ueland and Hansen 1969a		early	late			10 minutes				
	SV (ml)	69	79	83	102	98	paracervical and pudendal block	dye dilution technique	10	supine
	HR (beats/minute)	83	82	93	94	79				
	CO (L/min)	5.5	6.4	7.7	9.3	7.7				
	SV (ml)	67	70	72	91	101	epidural	dye dilution technique	13	
	HR (beats/minute)	89	96	92	91	80				
	CO (L/min)	5.8	6.3	6.4	8.3	8.2				
Niswonger and Langmade 1970		after anaesthesia								
	SV (ml)	79			99	106	spinal (n=8)	dye dilution technique	11	not mentioned
	HR (beats/minute)	79			79	73	epidural (n=2)			
	CO (L/min)	6.2			7.3	7.6				
	TPR (dynesxs/cm5)	1642			1182	1203				
	MAP (mmHg)	109			100	108				
Robson et al. 1987a		early	late			1 hour				
	SV (ml)	94	96			98	pethidine nitrous oxide	Doppler	15	left lateral
	HR (beats/minute)	80	83			76				
	CO (L/min)	7.5	7.9			7.4				
	MAP (mmHg)	86	91			92				

Values are means obtained from the mentioned references. Measurements have been obtained between contractions. SV, stroke volume; HR, heart rate; CO, cardiac output; TPR, total peripheral resistance; MAP, mean arterial pressure.

1.5. Haemodynamics during puerperium

1.5.1. First postpartum days

Delivery has also been found to cause significant haemodynamic changes in early puerperium. As early as during the first and second postpartum days cardiac output as well as stroke volume have been found to be decreased to under the values observed at the end of pregnancy. During these days heart rate, systolic blood pressure and total peripheral vascular resistance remained at levels comparable to those in the third trimester, but diastolic blood pressure was significantly lower. A further decrease in cardiac output was observed by the sixth postpartum day owing to reduced heart rate. Total peripheral vascular resistance was increased significantly and blood pressure remained stable after six postpartum days. Haemodynamic measurements were obtained by Doppler echocardiography and the mode of delivery was Caesarean section (Robson et al. 1989a). After vaginal delivery cardiac output has been found to remain at pre-labour values for up to 48 hours, while stroke volume increased and heart rate decreased significantly (Robson et al. 1987c).

The finding of declining cardiac output during the first few days postpartum is consistent with the finding of blood volume changes during the puerperium. In a study by Ueland and associates (1968) maternal blood volume changes during the early puerperium were estimated by means of a dilution technique using radioactive iodinated albumin. The mean blood loss after Caesarean delivery was 1000 ml. The mean decrease in blood volume was 16% during the first three days postpartum compared with pre-labour values and a further decrease was observed on the fifth postpartum day.

On the other hand, Pouta and associates (1996a) found left atrial dimensions to be increased during the first to third postpartum days compared with values during the third trimester of pregnancy. They used left atrial dimensions estimated by M-mode echocardiography as an indirect measurement of preloading. This finding suggests increased preloading of the heart during the first few postpartum days. Increased preloading could be a result of mobilisation of excessive body fluids accumulated during pregnancy. Their study included both vaginal deliveries and Caesarean sections.

Excessive bleeding may modify haemodynamics after delivery. Parturients experiencing blood loss greater than 500 ml after delivery have been found to have lower stroke volume but higher heart rate compared with controls during the first 48 hours after delivery. Because of the raised heart rate, no net effect on cardiac output was found (Robson et al. 1989b).

1.5.2. Later postpartum period

Later in the puerperium the accelerated maternal circulatory function during pregnancy further normalizes. Robson and associates (1987b) reported that by two weeks after delivery cardiac output had decreased by 29% and stroke volume by 10% compared with values during the third trimester. These values continued to decline until 24 weeks after delivery (end of the follow-up period), by 19% and 34% respectively. Heart rate had decreased by 21% two weeks after delivery and remained stable thereafter. The same pattern of recovery was observed in left atrial dimensions – a significant decrease by two weeks after delivery and stable thereafter. The left ventricle end-diastolic volume had decreased rapidly by two weeks postpartum, but the decline continued up to 24 weeks.

In systolic and diastolic blood pressure no significant differences were found over the first 12 weeks after delivery, but blood pressure was increased by 24 weeks after delivery compared with values at the end of pregnancy. Furthermore, left ventricular mass had decreased significantly by 12 weeks after delivery and it continued to decrease up to 24 weeks (Robson et al. 1987b).

In contrast, in another study, haemodynamic changes have also been found to be relatively stable after six weeks postpartum. Cardiac index had fallen under the level found during the third trimester by six weeks after delivery and it remained stable thereafter, by twelve weeks postpartum (end of follow-up period). The findings were similar considering stroke index, heart rate, left ventricular mass and left ventricular fractional shortening. Total peripheral resistance had increased by six weeks after delivery and it remained at that level at twelve weeks postpartum. No significant changes in mean arterial pressure were found during the third trimester and up to twelve weeks postpartum (Mabie et al. 1994).

These findings suggest relatively rapid recovery from increased circulating blood volume and preload during the first weeks after delivery, but slower haemodynamic changes may still take place 24 weeks after delivery (Robson et al. 1987b). It has also been suggested that haemodynamics after pregnancy might not return to pre-pregnancy levels. Haemodynamic parameters including stroke volume, cardiac output and left ventricular end-diastolic volume have remained significantly higher, and vascular resistance has remained significantly lower after twelve weeks and also one year after delivery compared with values observed in the same subjects before the pregnancy (Capeless and Clapp 1991, Clapp and Capeless 1997).

2. Haemodynamics in pre-eclampsia

2.1. *Definition of hypertensive pregnancy*

The prevailing limits for hypertension in pregnancy are systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg. The most common definitions concerning hypertension in pregnancy are 1) gestational hypertension, 2) pre-eclampsia, 3) chronic hypertension and 4) superimposed pre-eclampsia (NIH).

In gestational hypertension blood pressure rises after 20 week's gestation in a previously normotensive woman. Pre-eclampsia is defined as hypertension with exceptional new onset proteinuria (> 0.3 g per 24 hours or urine protein concentration > 0.1 g/L) existing after 20 week's gestation in a previously normotensive woman. Chronic hypertension includes increased blood pressure before 20 week's gestation or medicated hypertension. Superimposed pre-eclampsia is defined by a sudden increase in blood pressure or new onset proteinuria or development of HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count) in a woman with chronic hypertension (NIH).

2.2. *Blood volume*

Compared with normotensive pregnancies pre-eclamptic women have been found to have significantly lower total blood volume – 17% less than in uncomplicated pregnancy (Silver et al. 1998). The average plasma volume has been found to be 9–21% lower in pre-eclamptic compared with normotensive pregnancies (Chesley 1972, Silver et al. 1998) and 30–40% lower in cases with severe pre-eclampsia (Chesley 1972). However, no significant difference in red blood cell volume has been found (Silver et al. 1998). Furthermore, women destined to become pre-eclamptic have been found to have lower plasma volume (versus women with normotensive pregnancies) before the clinical state of pre-eclampsia (Hays et al. 1985). The difference in plasma volume is due to endothelial dysfunction (Silver et al. 1998) and lower oncotic pressure in pre-eclampsia (Oian et al. 1986).

2.3. *Haemodynamic changes*

2.3.1. *Cardiac output and peripheral vascular resistance*

2.3.1.1. Longitudinal studies

Discrepancies between studies as regards differences in cardiac output and peripheral vascular resistance in normotensive and pre-eclamptic pregnancies exist. Cardiac index has been found to be consistently higher in a group of women with pre-eclampsia compared with women with normotensive pregnancies in a longitudinal study starting at 10 week's gestation and

continuing till six weeks postpartum. The high cardiac index was the result of a higher heart rate in pre-eclampsia and this difference persisted during the period of symptomatic disease. Meanwhile no significant differences were found in stroke volume or total peripheral resistance between the groups during their pregnancies. The pre-eclamptic group included nine and the normotensive group eighty-nine nulliparous women (Easterling et al. 1990a).

In another longitudinal study 400 primigravidas were haemodynamically monitored from 10 week's pregnancy till 36 week's pregnancy. Twenty-four women in the study group eventually developed pre-eclampsia. Compared with normotensive pregnant women pre-eclamptic parturients had significantly higher cardiac outputs, but no differences in total peripheral vascular resistance were found before clinical diagnosis of pre-eclampsia. High cardiac output as early as at 10–14 week's gestation was significantly associated with subsequent pre-eclampsia. This association became further strengthened during the pregnancy, peaking at an RR ratio of 6.7 (95% CI 3.5–12.8) at 28–32 week's gestation. Subsequent hyperdynamic haemodynamic crossover from high cardiac output with normal peripheral vascular resistance to low cardiac output with high peripheral vascular resistance coincided with clinical diagnosis of pre-eclampsia. Values for heart rate and stroke volume were not reported (Bosio et al. 1999).

2.3.1.2. Cross-sectional studies

Compared with longitudinal studies more haemodynamic data exist in regard to cross-sectional studies. In non-medicated pre-eclamptic women with varying degrees of severity of pre-eclampsia, cardiac output has been found to be significantly lower and systemic vascular resistance higher than in normotensive pregnancies (Kuzniar et al. 1982, Groenendijk et al. 1984, Borghi et al. 2000, San-Frutos et al. 2005). Furthermore, cardiac output correlated inversely with mean blood pressure in pre-eclampsia (Kuzniar et al. 1982). In these studies both stroke volume and heart rate have been found to be lower in pre-eclampsia compared with values in healthy controls (Kuzniar et al. 1982, San-Frutos et al. 2005), but higher (Groenendijk et al. 1984) or comparable (Borghi et al. 2000) heart rates have also been found.

Also a hyperdynamic model of hemodynamics in preeclampsia has been found. In a study of thirty-one pre-eclamptic women, over half (52%) had high cardiac output and low cardiac output was found in 32%. Pre-eclamptic women who had low cardiac output all had high vascular resistance, but pre-eclamptic women with high cardiac output had normal to low systemic vascular resistance. All the study women were considered to have severe pre-eclampsia (Yang et al. 1996).

2.3.1.3. The effects of medical treatment

The use of medical treatment may change haemodynamics in pre-eclampsia. Cardiac index has been found to be significantly lower and systemic vascular resistance higher in untreated pre-eclamptic patients compared with pre-eclamptic parturients treated with various types of medication (dihydralazine, magnesium or diazepam) and intravenous fluids. In addition, variability of the haemodynamic parameters was found to be less in untreated pre-eclamptic

women compared with treated subjects (Visser and Wallenburg 1991). The findings were similar in pre-eclamptic parturients treated with magnesium sulphate, intravenous fluid administration and some patients receiving hydralazine. Cardiac output was found to be normal to high and systemic vascular resistance normal to high in medicated pre-eclamptic women when compared with normotensive pregnant women in other studies. In a subgroup of eight women with pulmonary oedema cardiac index was found to range from upper normal to high, with normal systemic vascular resistance (Mabie et al. 1989).

The effects of medical treatments – plasma volume expansion and antihypertensive medication – have also been studied separately. Untreated pre-eclamptic parturients were found to have uniformly low cardiac index and high systemic vascular resistance. Intravenous hydration increased cardiac index to the level found in normotensive women and decreased systemic vascular resistance without changes in blood pressure. But vasodilation with dihydralazine resulted in a further lowering in systemic vascular resistance and also a fall in blood pressure accompanied by an increase in cardiac index (Groenendijk et al. 1984, Belfort et al. 1989). Administration of dihydralazine alone caused an increase in heart rate and cardiac index and a decrease in systemic vascular resistance and blood pressure (Belfort et al. 1989)

Magnesium sulphate (bolus and infusion) has been found to cause a rapid and significant fall in systemic vascular resistance and a significant rise in cardiac index. The rise in CI was due to a rise in both heart rate and stroke index. Mean arterial pressure decreased for a short period after bolus administration, but remained relatively stable afterwards (Scardo et al. 1995).

When compared with normotensive pregnant women, pre-eclamptic women under antihypertensive medication (clonidine or hydralazine) have been found to have significantly higher mean arterial pressure and systemic vascular resistance and lower cardiac index and heart rate (Simmons et al. 2002).

These findings emphasize the effect of treatment of pre-eclampsia in modifying maternal haemodynamics and may partly explain the divergent haemodynamic findings in pre-eclampsia.

2.3.2. Arterial stiffness

Disturbances in arterial compliance might also be involved in the aberrant haemodynamic adaptation in pre-eclampsia. Improved macrovascular compliance – femoral arterial and venous compliance – has been paralleled by a fall in peripheral vascular resistance in healthy parous women, but not in previously pre-eclamptic parturients during the first trimester of pregnancy. Arterial compliance was assessed by means of a non-invasive radiofrequency technique and venous compliance was assessed by means of measurement of intravenous volume and pressure changes (Spaanderman et al. 2000). Furthermore, pulse pressure has been found to be higher during the whole of pregnancy in pre-eclamptic versus normotensive parturients. An elevated pulse pressure in nulliparas during the first trimester was also associated with an increased risk of pre-eclampsia (Thadhani et al. 2001).

In a cross-sectional study carotid-femoral pulse wave velocity obtained by applanation tonometry was significantly higher in pre-eclamptic versus normotensive parturients (Elvan-Taspinar et al. 2004). In addition, in a study by Rönback and associates (2005) pre-eclamptic women had a significantly higher heart rate-adjusted aortic augmentation index versus normotensive pregnant women. This finding reflects increased systemic arterial stiffness in pre-eclampsia. Applanation tonometry on the radial artery was used to obtain the aortic augmentation index.

2.3.3. Blood pressure

The blood pressure pattern has been shown to be different in pregnancies remaining normotensive versus those destined to develop pre-eclampsia. In normotensive pregnancies blood pressure steadily decreases from the beginning of the pregnancy till 21 week's gestation, followed by a rise up to the end of the pregnancy. This pattern was not seen in women who later developed pre-eclampsia or gestational hypertension: blood pressure remained stable until 22 week's gestation and linearly increased in the second half of the pregnancy (Ayala et al. 1997).

Furthermore, in another study, blood pressure was found to be significantly higher as early as in first trimester 24-hour measurements in future pre-eclamptic parturients ($n = 23$) versus normotensive parturients ($n = 124$) and this difference was preserved during the second trimester, even if values in hypertensive parturients remained normotensive ($< 140/90$ mmHg) (Hermida et al. 200). Consistently higher blood pressure throughout pregnancies complicated by pre-eclampsia, compared with normotensive pregnancies, has also been found in other studies (Easterling et al. 1990a, Thadhani et al. 2001). Cross-sectional studies concerning haemodynamics in pre-eclampsia versus normotensive pregnancies are presented in Table 5.

2.3.4. Autonomic cardiovascular control

In cross-sectional studies women with pre-eclampsia have had higher peripheral sympathetic output compared with normotensive pregnant women. Sympathetic vasoconstrictor activity measured by means of intraneural microelectrodes in the blood vessels of skeletal muscle has been found to be approximately three times higher in pre-eclampsia and in pregnancy-induced hypertension compared with that in normotensive women (Schobel et al. 1996, Greenwood et al. 1998). Furthermore, women destined to become pre-eclamptic presented increased peripheral resting sympathetic activity as early as during the first trimester of pregnancy compared with normotensive pregnant women (Rang et al. 2004).

Pre-eclamptic pregnancies have also been characterized by a significantly reduced high frequency peak, compared with healthy pregnancies, indicating decreased vagal control of the heart in pre-eclampsia (Eneroth-Grimfors et al. 1994, Yang et al. 2000).

Similar to heart rate variability, spectral analysis can be used to assess variation in systolic blood pressure. Low frequency is associated with sympathetic regulation, medium frequency is related to both sympathetic and parasympathetic control and high frequency is vagally mediated (Ekholm et al. 1997, Rang et al. 2002). Women with pre-eclampsia have been found to have significantly increased medium frequency and high frequency of systolic blood pressure, suggesting that both parasympathetic and sympathetic control of blood pressure may be increased in pre-eclampsia (Ekholm et al. 1997).

2.4. Functional and structural changes of the heart

Left ventricular mass has been found to be 17–21% greater in pre-eclampsia compared with normotensive pregnancies (Borghgi et al. 2000, Simmons et al. 2002). Increased left ventricular mass is thought to maintain left ventricular performance despite the high afterload in pre-eclampsia, but it could also disturb the function of the left ventricle. In non-medicated pre-eclamptic women E wave/A wave peak velocities have been found to be significantly decreased compared with that in normotensive pregnancies, but no significant differences were found between the groups in IVRT (Borghgi et al. 2000). Isovolumetric relaxation time was also comparable in normotensive subjects and pre-eclamptic patients on antihypertensive medication (clonidine or hydralazine). Medicated pre-eclamptic women had greater E and A wave velocities, reflecting changes in passive filling of the ventricle and a more important role of atrial systole in more hypertrophied ventricle (Simmons et al. 2002).

In systolic left ventricular performance no significant difference has been found in LVFS or LVEF between pre-eclamptic and normotensive pregnancies (Borghgi et al. 2000, Simmons et al. 2002). The inverse relationship between ventricular end-systolic stress (ESS) and mean velocity of circumferential fibre thickening (V_{CFC}) has been considered as a load-independent measure of contractility (Colan et al. 1984). No significant difference in the ESS/ V_{CFC} relationship between normotensive and pre-eclamptic pregnancies has been found. These findings imply that left ventricular contractility is preserved in pre-eclampsia (Simmons et al. 2002)

Table 5. *Haemodynamics in pre-eclamptic women compared with those with normotensive pregnancies.*

Reference	Method	Subjects	Gestational age	Medical treatment	Haemodynamic parameters	Pre-eclampsia	Normotensive pregnancy	p-value	
Kuzniar et al. 1982	M-mode echocardiography	PE 19	36 (30-40)	non-medicated	SV (ml)	89±16	101±14	<0.02	
					HR (beats/min)	68±9	75±10	<0.05	
		CO (L/min)	5.9±1.0		7.5±1.3	<0.001			
		SVR(dynexs/cm5)	1727±408		877±197	<0.001			
		MAP (mmHg)	125±11		83±11	<0.001			
Groenendijk et al. 1984	thermodilution	PE 10	32 (27-37)	non-medicated	HR (beats/min)	100 (90-130)	84 (70-90)		
					CI (L/min/m2)	2.8 (2.0-3.3)	4.5 (4.0-5.0)		
		healthy 4	32 (28-34)		SVR (dynexs/cm5)	1943 (1480-2580)	1021		
					MAP (mmHg)	121 (113-136)	95 (93-106)		
		PE 10			plasma volume expansion and dihydralazine	HR (beats/min)	82 (70-100)	84 (70-90)	
						CI (L/min/m2)	4.4 (3.9-5.0)	4.5 (4.0-5.0)	
						SVR (dynexs/m5)	947 (782-1028)	1021	
						MAP (mmHg)	102 (97-116)	95 (93-106)	
Easterling et al. 1987	Doppler echocardiography	PE 36		magnesium sulfate (n=9) non-medicated (n=27)	SV (ml)	91± 26	82 ± 26		
					HR (beats/min)	83 ± 14	83 ± 11		
		healthy 18			CO (L/min)	7.4± 2.0	6.6 ± 1.8		
					SVR (dynexs/m5)	1324 ± 388	996 ± 294		
					MAP (mmHg)	113± 8	77± 10		

Visser and Wallenburg 1991	thermodilution	PE 87	30 (25-34)	non-medicated	SI (ml/m ²)	46 (25-75)	51 (38-61)	NS	
		healthy 10	29 (28-30)		HR (beats/min)	74 (51-110)	82 (68-93)	<0.05	
					CI (L/min/m ²)	3.3 (2.0-5.3)	4.2 (3.5-4.6)	<0.001	
					SVRI (dynexs/cm ⁵ /m ²)	3003 (1771-5225)	1560 (1430-2019)	<0.001	
					MAP (mmHg)	125 (92-156)	83 (81-99)	<0.001	
			PE 47	29 (25-34)	dihydralazine, magnesium sulfate, diazepam and intravenous fluids	SI (ml/m ²)	52 (32-82)	51 (38-61)	NS
			healthy 10			HR (beats/min)	85 (62-135)	82 (68-93)	NS
						CI (L/min/m ²)	4.3 (2.4-7.6)	4.2 (3.5-4.6)	NS
						SVRI (dynexs/cm ⁵ /m ²)	2212 (1057-3688)	1560 (1430-2019)	<0.005
						MAP (mmHg)	120 (80-154)	83 (81-99)	<0.001
Scardo et al. 1995	thoracic electrical bioimpedance	PE 15	32	non-medicated	CI (L/min/m ²)	3.6 (2.5-6.2)	4.6 (2.5-6.6)	<0.05	
		healthy 11	31		SVRI (dynexs/cm ⁵ /m ²)	2465 (990-3750)	1377 (960-1610)	<0.05	
					MAP (mmHg)	112	84	<0.05	
Borghi et al. 2000	Doppler echocardiography	PE 40	28 ±6	non-medicated	HR (beats/min)	87± 13	85±11	NS	
		healthy 35	31 ±4		CO (L/min)	6.5±1.0	7.9±1.0	<0.05	
					TPR (dynexs/cm ⁵)	1320±278	779±203	<0.005	
					MAP (mmHg)	107±8	77±9	<0.001	
Simmons et al. 2002	Doppler echocardiography	PE 15	35 (31-39)	clonidine (n=12) hydralazine (n=6)	HR (beats/min)	71±14	85±10	<0.005	
		healthy 44	32 (27-37)		CI (L/min/m ²)	4.1±1.1	4.2±0.9	<0.005	
					SVR (dynexs/cm ⁵)	1129±318	852±190	<0.005	
					MAP (mmHg)	101±14	76±6	<0.005	
San-Frutos et al. 2005	thoracic electrical bioimpedance	PE 15	36 (32-40)	non-medicated	SV (ml)	60±20	80±20	0.05	
		healthy 18	40 (38-41)		HR (beats/min)	66±9	84±8	0.002	
					CO (L/min)	4.1±1.3	7.1±1.5	0.003	
					SVR (dynexs/cm ⁵)	2270±841	828±225	0.0004	
					MAP (mmHg)	116	72	<0.001	

Values are means and ± standard deviations or (range) obtained from the mentioned references. NS, not significant; SV, stroke volume; SI, stroke index; HR, heart rate; CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index; MAP, mean arterial pressure.

2.5. *Peripartum haemodynamic changes during delivery*

2.5.1. *Caesarean section under regional anaesthesia*

Caesarean section increases the risk of cardiopulmonary morbidity associated with pre-eclampsia (Terrone et al. 2000), and pre-eclampsia has been found to be a significant risk factor for postoperative cardiac failure (Roopnarinesingh et al. 1996). The state of hypovolaemia and vasospasm often associated with pre-eclampsia is thought to place the patient at an unusually high cardiopulmonary risk during Caesarean section (Hood and Curry 1999).

Infusion with Ringer's solution before Caesarean section has been found to result in an increment in central venous pressure, with stable arterial pressure in pre-eclamptic parturients (Karinen et al. 1996, Pouta et al. 1996b). Preload infusion has also been found to increase atrial natriuretic peptide concentrations in pre-eclamptic parturients and the increase was more pronounced compared with that in normotensive parturients (Pouta et al. 1996b).

Previously, epidural anaesthesia was preferred to regional anaesthesia in pre-eclamptic parturients owing to a reputation for cardiovascular instability in spinal anaesthesia. This was based upon the high incidence of hypotension in normotensive parturients associated with rapid onset of sympathetic blockade (Rout 2001). Despite the fear of excessive hypotension, the incidence of clinically significant hypotension after spinal anaesthesia induction has been found to be less in severely pre-eclamptic parturients compared with normotensive parturients (17% vs. 53%, $p = 0.006$). Hypotension was also less severe and less ephedrine was required to treat it in pre-eclamptic versus normal parturients (Aya et al. 2003). Furthermore, when pre-eclamptic parturients receiving spinal or epidural anaesthesia were compared, no significant differences were found in arterial pressure, intraoperative ephedrine use or neonatal Apgar scores between the groups in a retrospective cohort study (Hood and Curry 1999).

After induction of spinal anaesthesia, arterial pressure and central venous pressure have been found to decrease significantly in pre-eclamptic parturients. Central venous pressure decreased towards the baseline level after spinal blockade, but remained stable afterwards. Furthermore, uterine circulation was not affected by spinal anaesthesia or preloading in pre-eclampsia: the mean pulsatility index of the uterine artery remained stable after these procedures (Karinen et al. 1996).

In a study in which the haemodynamic effects of epidural anaesthesia were evaluated, mean arterial pressure was found to decrease significantly, while the cardiac index and central venous pressure remained stable. Systemic vascular resistance decreased, but it was statistically insignificant. The study involved parturients undergoing Caesarean section and those with vaginal delivery (Newsome et al. 1986).

2.5.2. Delivery and early postpartum period

There are few studies in which the effect of delivery on the haemodynamics of pre-eclampsia have been considered. Newsome and associates (1986) did not find any significant changes in cardiac output or systemic vascular resistance in pre-eclamptic parturients after vaginal delivery or delivery after Caesarean section under epidural anaesthesia. Furthermore, the haemodynamics remained stable for two hours after delivery. Haemodynamic results associated with the different modes of delivery were not reported separately. In contrast, in a study by Graham and Goldstein (1980), cardiac output had increased by 28% fifteen minutes after delivery of the placenta. This study also involved a combination of parturients with vaginal delivery under epidural anaesthesia and those with delivery by Caesarean section. Cardiac output had returned towards the baseline level by thirty to forty-five minutes after delivery of the placenta. Furthermore, in a study by Phelan and Yurth (1982), cardiac output was increased by 10% thirty minutes after delivery, compared with baseline values, and it remained elevated for two hours after delivery. Simultaneously, a 40% decrease in systemic vascular resistance was observed and it remained decreased for two hours after delivery. This study included parturients with spontaneous delivery and those who underwent Caesarean section.

In the studies mentioned above, haemodynamic measurements were obtained by means of the thermodilution technique. Furthermore, all participants in the studies had severe pre-eclampsia and were treated by means of magnesium sulphate infusion and hydralazine, when necessary (Graham and Goldstein 1980, Phelan and Yurth 1982, Newsome et al. 1986).

2.6. Haemodynamics during puerperium

Data on haemodynamic changes during puerperium after pre-eclamptic pregnancy are scarce. In one study, parturients with severe pre-eclampsia had unchanged cardiac output, stroke volume, heart rate, total peripheral resistance and mean arterial pressures one to two hours after vaginal delivery. The values obtained after delivery were compared with reference values obtained during early labour. All parturients received a constant infusion of magnesium sulphate. Cardiac output measurements were obtained by the thermodilution technique (Benedetti et al. 1980).

Findings were similar when haemodynamic data of pre-eclamptic patients obtained one day after delivery were compared with values before delivery: no significant changes were observed in cardiac output, heart rate, stroke volume, mean arterial pressure or total systemic resistance. However, when compared with healthy parturients, cardiac output was lower and total systemic resistance and mean arterial pressure were higher in pre-eclampsia. At one month postpartum, differences in haemodynamics between healthy and pre-eclamptic parturients had disappeared. The method used for haemodynamic assessment was M-mode echocardiography (Lang et al. 1991).

In a study by Easterling and associates (1990a) the haemodynamics of pre-eclampsia were found to include high cardiac output with normal total peripheral resistance. Six weeks after delivery the difference in cardiac output persisted, while no difference in mean arterial pressure was found, owing to significantly lower total peripheral vascular resistance in previously pre-eclamptic women compared with normotensive women. The haemodynamic data were obtained by Doppler echocardiography.

When considering the mobilisation of increased extracellular volume after pregnancy, no significant changes were observed in left atrial dimension at one to three days postpartum compared with the dimensions during the third trimester of pregnancy in pre-eclampsia. Meanwhile, in normotensive pregnancies, left atrial dimension increased significantly after delivery, suggesting that excessive body fluids accumulated during pregnancy increase venous return and enhance preload to the heart (Pouta et al. 1996a).

3. Haemodynamics in chronic hypertensive pregnancy

Much less attention has been paid to haemodynamic adaptation during the course of pregnancy in women with chronic hypertension.

Plasma volume has been shown to increase steadily until the third trimester of pregnancy in women with chronic hypertension. In one study, the mean plasma volume increase during pregnancy was 52%, in the third trimester. The study included ten women with chronic hypertension and previous diuretic medication had been discontinued during the first trimester (Sibai et al. 1984). Furthermore, in women with chronic hypertension delivering newborns of appropriate for gestational age no differences in plasma volumes at 20–25 and 26–29 week's gestation were found when compared with normotensive pregnant women (Sibai et al. 1982). On the contrary blood volume of chronic hypertensive women has also been found significantly lower compared to normotensive women, when measurements were obtained from 24 week's gestation (Arias 1975). In a study by Gallery and associates (1979), plasma volume in women with chronic hypertension was inversely related to blood pressure and directly correlated with fetal growth.

In women with mild to moderate chronic hypertension without antihypertensive medication, systolic and diastolic pressures were significantly higher than in normotensive pregnancies throughout the pregnancy. However, the trend of blood pressure paralleled the trend found in the normotensive control group (Benedetto et al. 1996).

During the third trimester no differences have been found in stroke index, cardiac index, heart rate, left ventricle end-diastolic or end-systolic volumes between normotensive and chronic hypertensive pregnancies, but systemic vascular resistance and arterial blood pressure were significantly higher in hypertensive parturients. Haemodynamic data were obtained by M-mode echocardiography (Kuzniar et al. 1982).

Rapid ejection time – an indicator of vascular compliance – has been found to be high and to correlate with mean arterial pressure in women with chronic hypertension during the third trimester of pregnancy. This finding suggests low arterial compliance in these parturients. The study did not include reference data from normotensive pregnancies (Fukushima 1999).

4. Methods used to measure haemodynamic parameters during pregnancy

In previous studies both invasive and non-invasive methods have been used to estimate haemodynamic parameters during pregnancy, both in normal and in complicated pregnancies. The earliest studies on cardiovascular function were carried out by means of dye dilution techniques. Since then improvement of the techniques has led to the replacement of earlier methods and the most used techniques have been combined two-dimensional and Doppler or M-mode echocardiography, impedance cardiography and Swan-Ganz pulmonary artery thermodilution catheter monitoring (Duvekot and Peeters 1994b).

4.1. *Dye dilution technique*

The dye dilution technique was first described by Hamilton and associates (1932). In this technique a known amount of indicator dye – indocyanine green or Evan's blue – is injected into an arm vein and serial samples of arterial blood are taken. Cardiac output is equal to the amount of indicator injected divided by its average concentration in arterial blood after a single circulation through the heart (Ganong 1989).

This technique has two main disadvantages. Calibration of the densitometer used to measure indicator change is time consuming and the half-life of the dye used limits the frequency of measurements that can be carried out (Tibby and Murdoch 2002). Haemodynamic studies involving use of this technique during pregnancy were mostly carried out in the 1970's and were concentrated on haemodynamic changes at delivery (Ueland and Hansen 1969, Niswonger and Langmade 1970, Ueland et al. 1972).

4.2. *Pulmonary artery catheter and thermodilution*

Swan and associates introduced the pulmonary artery catheter into clinical medicine in 1970. Direct haemodynamic data that can be obtained by use of the pulmonary artery catheter are central venous pressure (CVP), pulmonary artery pressure (PAP) and pulmonary artery capillary wedge pressure (PACWP). Stroke volume (SV) and cardiac output (CO) are derived by way of the thermodilution technique. The principal of the thermodilution technique is similar to that described above in dye dilution, with temperature being the

indicator. Furthermore, it is possible to calculate mean arterial pressure (MAP), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) and left ventricular stroke work (LVSW) from the data obtained from the catheter (Fox et al. 1996).

Most of the studies (as well as clinical practice) involving use of the pulmonary artery catheter include parturients with pre-eclampsia. Some of these studies have elucidated the haemodynamic profile in severe pre-eclampsia (Groenendijk et al. 1984, Mabie et al. 1989, Visser and Wallenburg 1991), and some investigators have examined the effects of therapy such as fluid replacement and antihypertensive medication (Groenendijk et al. 1984, Belfort et al. 1989, Visser and Wallenburg 1991) on the haemodynamics of pre-eclampsia. The haemodynamic changes during Caesarean section under epidural anaesthesia (Graham and Goldstein 1980, Newsome et al. 1986) and under general anaesthesia (Rafferty and Berkowitz 1980) have also been studied. A few studies have also covered vaginal delivery (Phelan and Yurth 1982, Newsome et al. 1986). However, several small studies have also included normotensive pregnancies during the third trimester (Groenendijk et al. 1984, Visser and Wallenburg 1991).

The disadvantage of thermodilution is the invasive nature of catheterisation, which predisposes the subject to serious complications such as pneumothorax, venous thrombosis, cellulitis, infections and arrhythmia. The rate of complications has varied from 1.3% to 2.8% in obstetric patients. Some reports of maternal deaths also exist (Young and Johanson 2001). The risk of complication naturally limits the clinical and study use of pulmonary artery catheterisation. In clinical use catheterisation is recommended for critically ill pre-eclamptic parturients in cases of refractory oliguria or pulmonary oedema (Fox et al. 1996, Young and Johanson 2001). At present most haemodynamic studies are carried out by means of non-invasive methods.

4.3. Echocardiography

Echocardiographic estimation of cardiovascular pump function can be carried out by M-mode or Doppler ultrasonographic methods.

4.3.1. M-mode echocardiography

M-mode and two-dimensional echocardiography was introduced to clinical practice in the 1960's and 1970's. It allows visualization of ventricular wall thickness and motion, in addition to exclusion of valvular abnormality. It can be used to estimate the dimensions and volumes of the ventricular cavities and walls: left ventricular end-systolic dimension and volume, left ventricular end-diastolic dimension and volume. Furthermore, ejection fraction, left ventricular fractional shortening, left ventricular mass and stroke volume can be derived. Stroke volume in this method is calculated from the difference in left ventricular volumes between diastole and systole of the cardiac cycle (Duvekot and Peeters 1994b, Young and Johanson 2001, Brown 2002).

M-mode echocardiography includes some potential inaccuracies and limitations. The resolution of two-dimensional echocardiography ranges from 0.3 to 1.5 mm. In a comparison of echocardiography-derived stroke volume with thermodilution, a 10% change in stroke volume corresponded only to a 0.7 mm change in ventricular radius (Brown 2002). Furthermore, the shape of the left ventricle in this method is assumed to be ellipsoid. However, this normal shape of the ventricle is disturbed in pregnancy and the geometric assumptions have not been validated in pregnant women, which may cause inaccuracy in stroke volume measurements, especially in late pregnancy (Robson et al. 1987c, Robson 2000).

4.3.2. Doppler echocardiography

Doppler ultrasonography has been used to investigate maternal haemodynamics since the early 1980's. The stroke volume equation in this method is based on the product of the cross-sectional area (CSA) of the outflow tract obtained in two-dimensional ultrasonography and the time velocity integral (TVI) obtained by pulse wave Doppler ultrasonography (Robson 2000). The TVI represents the area under the Doppler flow velocity curve (Dukekot and Peeters 1994b). Besides stroke volume and cardiac output estimations, this method is used to evaluate diastolic function of the left ventricle: E (early diastolic) wave and A (late diastolic) wave peak velocities, ratio of the E wave to A wave peak velocities and the isovolumetric relaxation time (IVRT). The IVRT is the time interval between closure of the semilunar valve and opening of the atrioventricular valve. These values are obtained from transmitral Doppler flow velocities (Mesa et al. 1999, Robson 2000). Doppler echocardiography can be carried out trans-thoracically or trans-oesophageally.

Aortic Doppler echocardiography has been validated by means of thermodilution using a pulmonary artery catheter in pre-eclamptic parturients. In measurements of cardiac output these methods correlated well ($r = 0.91-0.95$) (Easterling et al. 1987, Easterling et al. 1990b). However, in a study by Penny and associates (2000), oesophageal Doppler monitoring underestimated cardiac output by approximately 40% compared with values obtained by the thermodilution method. Validation by thermodilution has been carried out only in critically ill obstetric patients or in pre-eclamptic parturients requiring a pulmonary artery catheter (Easterling et al. 1987, Easterling et al. 1990b, Belfort et al. 1994, Penny et al. 2000).

Doppler echocardiographic methods have some disadvantages. Continuous measurements are possible by trans-oesophageal echocardiography, but hazards such as lip injuries, pharyngeal or laryngeal bleeding, arrhythmia or respiratory distress are possible (Andel et al. 1997). Furthermore, sedation may be required to ease the tolerability of the procedure (Turner 2003). The use of trans-thoracic echocardiography for continuous haemodynamic measurements is limited because holding of the transducer is not feasible for long periods. Doppler echocardiography is also an operator-dependent method. Inter-observer variability has been reported to be approximately 10%. Doppler echocardiography requires a learning curve to achieve adequate aortic velocity

signals. Positioning of the probe between the Doppler beam and blood flow is of great importance when measuring velocity and volume, and during prolonged monitoring repositioning of the probe is mandatory if displacement occurs (Berton and Cholley 2002, Cholley and Singer 2003).

4.3.3. Studies during pregnancy

As a result of the increasing use of echocardiography (M-mode and Doppler), data from prospective serial haemodynamic measurements during uncomplicated and complicated pregnancies has become available (Duvekot et al. 1993, Clapp and Capeless 1997, Poppas et al. 1997, Bosio et al. 1999, Valensise et al. 2000). These methods have also extended our knowledge about left ventricular structure and function during hypertensive and normotensive pregnancies (Lang et al. 1991, Mesa et al. 1999, Borghi et al. 2000, Simmons et al. 2002, Novelli et al. 2003). In addition, several investigators have explored the association between maternal haemodynamics and fetal growth (Nisell et al. 1988, Duvekot et al. 1995, Tsyvian et al. 2002, Vasapollo et al. 2002). Serial measurements during Caesarean section, vaginal delivery and puerperium have also been carried out by echocardiographic methods (Robson et al. 1987a, Robson et al. 1987b, James et al. 1989, Robson et al. 1989)

4.4. Impedance cardiography

In 1966 Kubicek and associates (1966) introduced a new non-invasive method of measuring cardiac output – impedance cardiography. The method is based on measurement of changes in electrical impedance in the vasculature during the cardiac cycle. A constant alternating current is applied to the body with current electrodes. Another pair of electrodes placed between the current electrodes measures the voltage generated. Hence, it possible to calculate impedance according to Ohm's law, $R = U:I$, where I is current, U is voltage and R is resistance. According to Kirchow's law, electric current passes through the conductors with lowest impedance. In the body the lowest electrical resistivities are found in blood and plasma, thus the pulsatile changes during the cardiac cycle in these tissues are reflected in the measured impedance. Impedance changes during systole and diastole are partly dependent on volume changes in the vasculature, which enables the calculation of stroke volume (Kööbi et al. 1997a, Nieminen 2000).

4.4.1. Thoracic impedance cardiography

The first impedance method used was thoracic impedance cardiography (ICG_{TH}). In this method electrodes are placed at the neck and another on the thoracic cage at the level of the xiphoid process. Using ICG_{TH}, the results of longitudinal studies of haemodynamic changes during uncomplicated pregnancies (Atkins et al. 1981, Van Oppen et al. 1996) and studies on haemodynamics during

Caesarean section in healthy parturients (Secher et al. 1979, Milsom et al. 1983, Ramanathan et al. 1986, Ouzounian et al. 1996) are available to date.

Data on cardiac output estimation by ICG_{TH} compared with other methods are scarce. In pre-eclamptic patients the measurement of cardiac output by ICG_{TH} was compared with M-mode echocardiography and good agreement was found (Scardo et al. 2000). The coefficient of correlation was 0.77 when cardiac output estimations obtained from ICG_{TH} and the thermodilution method in healthy parturients in the third trimester were compared (Secher et al. 1979). No significant differences in stroke volumes evaluated by ICG_{TH} and the dye dilution technique in healthy parturients before Caesarean section were found, but during the procedure values estimated by ICG_{TH} were significantly lower compared with the dye dilution technique (Milsom et al. 1983).

However, the ICG_{TH} method involves some inaccuracies. Apart from the original assumption, thoracic impedance cardiography measurements reflect impedance changes in all organs and peripheral tissues in the thoracic region. It is assumed that less than 20% of the current applied reaches the aorta and other large vascular organs, where the heart-related pulsation and flow characteristics are considered to be in close relationship to the stroke volume (Kauppinen et al. 1998). Since arterial flow to peripheral thoracic tissues may correlate poorly to stroke volume, it may produce errors in SV estimation obtained by ICG_{TH}. Furthermore, ICG_{TH} is not capable of taking into account changes in the distribution of blood flow between the extremities and the thoracic cage. For example, when blood supply is reduced in the extremities and the same volume is redistributed to the thorax, ICG_{TH} will result erroneous increase in SV, since it does not measure extremities. For that reason, errors in SV and CO are expected in subjects with peripheral vasoconstriction or vasodilation (Kööbi 1997a).

4.4.2. Whole-body impedance cardiography

Whole-body impedance cardiography (ICG_{WB}) was developed by Tishchenko in the 1970s. It is an alternative to ICG_{TH} as an impedance method. These methods differ from each other in placement of the electrodes, the frequency of the alternating current and the stroke volume equation. In ICG_{WB} a pair of electrically connected electrodes is applied to the wrists and another pair is placed on the ankles instead of the electrodes applied around the thoracic cage, as in the case of ICG_{TH}. The standard electrode configuration is shown in Figure 1. In this electrode configuration the recorded heart synchronous changes in impedance reflect the weighted sum of the pulsatile plethysmograms of almost the whole vascular system, in contrast to ICG_{TH}, which measures only the thoracic region. As there are no other good conducting tissues parallel to the vicinity of the electrodes, it is assumed that most of the current applied passes through the main arterial trees, where the stroke volume-related pulsation occurs (Kööbi et al. 1997a).

Stroke volume (SV) equation in ICG_{WB} is: $SV = k \times H^2 \times \frac{\Delta Z / Z_c \times C}{Z_0 \times D}$

In the equation H is height (cm), ΔZ the amplitude of heart synchronous impedance variation (Ω), Z_c the calibration factor (0.1Ω), Z_0 baseline impedance of the body (Ω), C duration of the cardiac cycle, and D the duration from the largest deflection of the heart synchronous impedance variation to the onset of the next cycle. The coefficient k ($\Omega \times \text{cm}$) is derived from blood resistivity, the relationship between the distance of the voltage electrodes and body height, it also includes the patient's body mass index and haematocrit (Kööbi et al. 1997a).

Previously this method did not receive widespread attention because of the lack of a computerized measuring device, but recently a microprocessor-based ICG_{WB} method has been introduced and validated- CircMon™ B202 (JR Medical Ltd, Tallinn, Estonia). The accuracy and repeatability of the cardiac output measurement by this method has been compared against invasive methods- thermodilution and the Fick method- in non-pregnant population. The ICG_{WB} method has shown a close agreement with thermodilution, the mean CO difference (bias) between the methods being 0.00 L/min. And the repeatability value (RV) was considerably better: RV 0.46 L/min for ICG_{WB} and 1.05 L/min for thermodilution. The bias between the Fick method and ICG_{WB} was 0.32 L/min (Kööbi et al. 1997b).

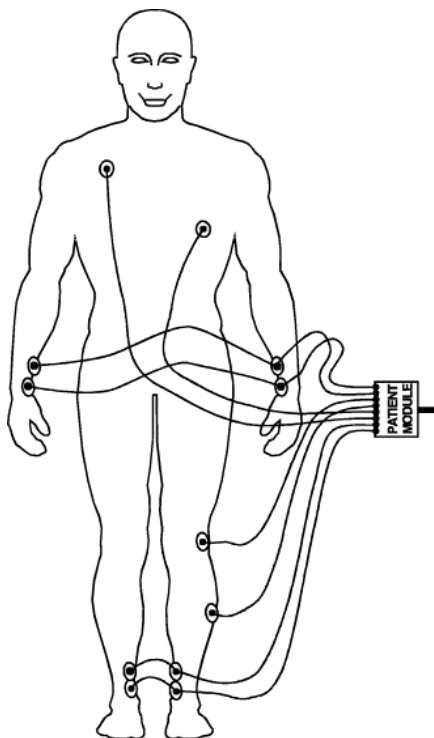


Figure 1. Placement of electrodes in whole-body impedance cardiography. Reprinted from Kööbi T et al. (2003): Simultaneous non-invasive assessment of arterial stiffness and haemodynamics- a validation study. *Clin Physiol & Func Im* 23: 31-36, with permission from Blackwell Publishing.

5. Cardiac natriuretic peptides

5.1. Synthesis, storage and metabolism

Cardiac natriuretic peptides consist of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). The third member of the natriuretic peptides is C-type natriuretic peptide, which is found in endothelial cells, kidney cells and the central nervous system in humans (Stoupakis and Klapholz 2003).

The main cardiac site of synthesis of ANP is atrial myocytes of the heart, but it is also released from the cardiac ventricle. In healthy subjects the secretion of ANP by ventricles is considerably less than that of atria, but in the case of congestive heart failure, ventricular hypertrophy or dilated cardiomyopathy, the expression of ventricular ANP is extensively increased (Ruskoaho 1992, Yasue et al. 1994). The central nervous system, lung, adrenal gland, kidney and vascular tissue are also known to express ANP, but the levels are less than 1% compared with the heart origin of ANP (Ruskoaho 1992). The principal storage form of ANP in the myocytes is propeptide (proANP). When proANP is released to the circulation it is cleaved into biologically active C-terminal ANP and inert N-terminal ANP (NT-proANP) in equimolar amounts. However, the concentration of NT-proANP in the circulation is 10–20 times higher compared with that of C-terminal ANP, because NT-proANP is more stable and has a longer half-life in the circulation (Vesely 1995).

In contrast to ANP, BNP is mainly synthesized and secreted from the cardiac ventricles and much less from the atrial myocytes (Yasue et al. 1994). As in the case of ANP, the expression of BNP is remarkably elevated in patients with congestive heart disease and in these cases ventricular secretion is enhanced and further exceeds the secretion from the atria (Ogawa et al. 1995). BNP was first identified in porcine brain (Sudoh et al. 1988) and later it was found to be secreted into the circulation from the porcine heart (Saito et al. 1989). In humans BNP is more abundant in cardiac myocytes than in the central nervous system (Ruskoaho 1992). Similarly to ANP, the principal storage form of BNP is propeptide (proBNP). Furthermore, proBNP is cleaved into physiologically active C-terminal proBNP and inert N-terminal proBNP (NT-proBNP). NT-proBNP is also more stable than C-terminal BNP, thus making the measurement of NT-proBNP more reliable (Hunt et al. 1997).

Natriuretic peptides are metabolised by enzymatic degradation (neutral endopeptidase) and by receptor-mediated endocytosis (natriuretic peptide receptor-C). Neutral endopeptidase is found in vascular endothelium and in proximal renal tubules of the kidney (Seymour et al. 1995). Natriuretic peptide receptor-C is distributed in vascular endothelium, vascular smooth muscle, the adrenals, kidney and heart (Nussenzveig et al. 1990).

In contrast to ANP and BNP, CNP does not act as a cardiac hormone, but as a neuropeptide or an endothelium-derived autocrine regulator. It is mainly distributed throughout the vascular walls in human brain and is considered to mediate vasorelaxation and probably to inhibit the growth of vascular smooth muscle cells and endothelial cells in the central nervous system (Ogawa et al. 1995).

5.2. Physiology of cardiac natriuretic peptides

The most important stimulus for ANP release is mechanical stretch of the atria caused by increased volume or pressure load (Ruskoaho 1992). Release of ANP after atrial stretch is fast and enhanced plasma concentrations of ANP are found within minutes after acute stretch of the heart (Laine et al. 1996). Besides stretch of the atria, several hormones and vasoactive peptides stimulate secretion of ANP. Noradrenaline, angiotensin II, vasopressin and endothelin-1 are potent ANP secretagogues (Ruskoaho 1992). Tachycardia (Tikkanen et al. 1985), hypoxia (Ruskoaho 1992) and hyperosmolality (Arjamaa and Vuolteenaho 1985) also enhance the release of ANP, while nitric oxide may have an inhibitory effect (Leskinen et al. 1995).

Much less is known about the regulatory mechanisms of BNP compared with those of ANP. However, myocyte stretch and pressure have been shown to stimulate BNP from the atria (Mäntymaa et al. 1993) and ventricles (Kinnunen et al. 1993). Secretion of BNP starts more slowly compared with that of ANP. After acute stretch of the heart increased BNP concentrations are found after a few hours (Laine et al. 1998).

The physiological function of both cardiac natriuretic peptides – ANP and BNP – is to relieve the workload of the heart by causing vasorelaxation, increasing natriuresis and diuresis and enhancing capillary permeability. They also inhibit the renin-angiotensin-aldosterone-system (RAS) (Tikkanen et al. 1985, Holmes et al. 1993, Ogawa et al. 1995).

5.3. Clinical implications of cardiac natriuretic peptides in the non-pregnant population

In chronic congestive heart failure, the increased workload and also activation of neurohumoral factors (RAS and sympathetic nervous system) increases the concentrations of ANP and BNP. Increased levels of cardiac peptides are also found in left ventricle hypertrophy, tachycardia, atrial fibrillation and ventricle extrasystole (Tikkanen et al. 1985).

In a clinical setting high ANP and BNP concentrations are associated with left ventricular systolic and diastolic dysfunction and left ventricular hypertrophy (Yamamoto et al. 1996b). The ability to identify left ventricular dysfunction has been found to be different as regards the various natriuretic peptides. In symptomatic patients BNP has proved to have higher sensitivity and specificity for left ventricular systolic dysfunction, left ventricular diastolic dysfunction and left ventricular hypertrophy compared with ANP or NT-proANP (Yamamoto 1996b, Cowie 1997). The most novel cardiac peptide for diagnostic purposes is NT-proBNP. High NT-proBNP concentrations have been found to correlate inversely with left ventricular ejection fraction and values have been found to rise with increasing cardiac decompensation. The increase of NT-proBNP concentrations in cardiac dysfunction exceeded those of BNP and overall, NT-proBNP concentrations have been found to be 4-fold higher than BNP concentrations. This suggests that NT-proBNP could be an even more sensitive marker of early cardiac impairment than BNP (Hunt et al. 1997).

5.4. Cardiac natriuretic peptides in normotensive pregnancy

5.4.1. Atrial natriuretic peptide

Whether circulating ANP concentrations are increased in normal pregnancy has been a subject of controversy. Based on a meta-analysis including 28 studies, ANP levels were slightly increased during the first and second trimesters when compared with those in non-pregnant subjects. During the third trimester the level was 41% higher and significantly increased compared with non-pregnant values. However, in these studies ANP concentrations remained in the physiological range during pregnancy. The maximum values were reached during early puerperium (< one week after delivery), being 148% greater than non-pregnant levels, but after 6 weeks no difference was found (Castro et al. 1994).

When considering the changes in ANP concentrations during the course of pregnancy, the highest levels have been found during the third trimester and a further steep increase has appeared immediately after delivery and in early puerperium (Castro et al. 1994, Yoshimura et al. 1994). In contrast, the highest values have also been found during the first trimester of pregnancy when ANP concentrations were assayed in each trimester and six to thirteen weeks postpartum (Sala et al. 1995).

Normal pregnancy is a state of physiological volume expansion and ANP has been considered to have an important role in controlling volume homeostasis during pregnancy. The stimulus for enhanced ANP concentrations during pregnancy could be atrial stretch caused by volume load. This view is supported by the finding of positive significant correlation between changes in ANP concentrations and changes in SI during pregnancy (Sala et al. 1995). Other possibilities could be decreased metabolic clearance, extra-atrial ANP production or agonist-induced ANP release (e.g., catecholamines, endothelin) during pregnancy. However, neither catecholamines nor endothelin are increased in normal pregnancies and no evidence for placental ANP production exists (Castro et al. 1994). Again, metabolic clearance of ANP has been found to be increased by 16 weeks of gestation and to remain elevated thereafter (Irons et al. 1996).

Dramatically increased ANP levels after delivery may be explained by multiple factors enhancing intravascular volume load during the postpartum period: disappearance of the uteroplacental shunt, relief of pelvic vein and inferior vena cava compression, and extravascular volume moving into intravascular space (Castro et al. 1994). The association of increased left atrial dimensions with increased ANP concentrations during the first few days postpartum days compared with third trimester values supports this view (Pouta et al. 1996a).

5.4.2. B-type natriuretic peptide

Far fewer studies have concentrated on B-type natriuretic peptide. Plasma levels of BNP have proved to be higher at term than in the first trimester, and

furthermore, levels increased immediately after delivery and were still enhanced three days postpartum (Yoshimura et al. 1994). Compared to non-pregnant values no significant differences during the course of pregnancy have been found (Itoh et al. 1993). On the contrary, during the third trimester BNP concentrations have also been found to be significantly higher than in non-pregnant controls (Borgi et al. 2000).

5.5. Cardiac natriuretic peptides in hypertensive pregnancy

5.5.1. Atrial natriuretic peptide

Women with gestational hypertension have been found to have 52% higher ANP concentrations compared with women with normotensive pregnancies, and women with pre-eclampsia have been found to have ANP values 130% higher in a meta-analysis. No significant differences were found between pregnancies with chronic hypertension and normotensive pregnancies (Castro et al. 1994). In contrast, in several studies no differences in ANP concentrations between pre-eclampsia, pregnancy-induced hypertension and normotensive pregnancies have been found (Frenkel et al. 1995, Marlettini et al. 1991).

Intravascular volume has been shown to be decreased in pre-eclampsia compared with normal pregnancies (Fievet et al. 1988), and right atrial pressure has been found to be low in untreated pre-eclamptic parturients (Visser et al. 1987). Data about the degree of left atrial stretch in pre-eclampsia is conflicting. Atrial dimensions have been found to be significantly increased (Pouta et al. 1996a) or comparable (Borghini et al. 2000) in normotensive and pre-eclamptic pregnancies. It is therefore assumed that high ANP levels in pre-eclampsia do not reflect the underlying volume status (Castro et al. 1994).

5.5.2. B-type natriuretic peptide

The concentrations of B-type natriuretic peptide and NT-proBNP in pre-eclampsia have been found to be significantly higher when compared with those in normotensive pregnancies (Itoh et al. 1993, Furuhashi et al. 1994, Okuno et al. 1999, Borghi et al. 2000, Fleming et al. 2001, Kale et al. 2005). In severe pregnancy-induced hypertension BNP values were higher than in the mild form of the disease (Itoh et al. 1993). Furthermore, multigravidas had higher levels of NT-proBNP than primigravidas in normal pregnancies and in hypertensive pregnancies (Fleming et al. 2001). During delivery and in the early puerperium no significant differences were found in BNP values between pre-eclamptic and normotensive subjects (Furuhashi et al. 1994, Okuno et al. 1999). A different diurnal pattern of BNP concentration between pre-eclamptic and normotensive pregnancies has been found. BNP concentrations were found to be higher during night-time compared to the values obtained during day-time in normotensive pregnancies. This diurnal variation of BNP was not found in pre-eclampsia-concentrations were high during the whole study period (Kaaja et al. 1999).

AIMS OF THE STUDY

During the course of pregnancy profound haemodynamic changes are needed to adapt to increased intravascular volume load to create uteroplacental circulation. At the moment of delivery and in early puerperium thorough haemodynamic changes are needed to adapt to ceased uteroplacental circulation. Hypertensive pregnancies – pre-eclampsia and chronic hypertension – are associated with divergent haemodynamic adaptation in pregnancy. The first hypothesis to be tested in this study was that the deviant haemodynamics of pre-eclampsia and chronic hypertensive pregnancies involve not only deficient vasorelaxation of peripheral arteries, but also stiffer larger conduit arteries. Furthermore, aberrant haemodynamics in hypertensive pregnancies place a strain on the heart and increase the circulating concentrations of biochemical markers of cardiac dysfunction. In non-pregnant subjects the haemodynamics of chronic hypertension differ from normotensive ones and the second hypothesis was that the underlying haemodynamic disorder in chronic hypertension changes haemodynamic adaptation during pregnancy. The third hypothesis to be tested was that the haemodynamics of pre-eclampsia result in aberrant haemodynamic reactions compared with those in normotensive pregnancies during delivery and in early puerperium.

The specific aims of the studies were:

1. To assess haemodynamics in pre-eclampsia and chronic hypertensive pregnancies in respect of arterial stiffness in conduit arteries (I).
2. To establish the association between natriuretic peptides and maternal haemodynamics in pre-eclampsia and chronic hypertensive pregnancies (II).
3. To assess haemodynamic changes during pregnancy and early puerperium in women with chronic hypertension compared with women with normotensive pregnancies (III).
4. To investigate maternal haemodynamics during Caesarean delivery - focusing especially on delivery - and early puerperium in uncomplicated pregnancies (IV).
5. To evaluate maternal haemodynamics during Caesarean delivery and early puerperium in pre-eclamptic parturients (IV).

SUBJECTS AND METHODS

1. Subjects and study designs

The subjects were recruited to the study protocols from the Department of Obstetrics and Gynaecology, Tampere University Hospital, Finland and from the antenatal clinic of the City of Tampere, Finland. Table 6 describes the study population, aims of the studies, main haemodynamic parameters and biochemical markers used and trimester of pregnancy at the time of study measurements. All studies were prospective. Studies I, II and V were cross-sectional, study III longitudinal and cross-sectional and study IV was descriptive.

The inclusion criteria for normotensive women with uncomplicated pregnancies were: no previous diseases, blood pressure under 140/90 mmHg and negative stix-test for proteinuria during the course of pregnancy. Pre-eclamptic patients were not known to have pre-existing hypertension, renal disease, heart disease or diabetes. Pre-eclampsia was diagnosed if two blood pressure measurements were greater than 140/90 mmHg and if consistent proteinuria of more than 300 mg/day existed after 20 week's gestation. Pre-eclampsia was considered severe if arterial pressure remained \geq 160/110 mmHg and proteinuria exceeded 5 g/day. Women were classified as having chronic hypertension if arterial pressure was \geq 140/90 mmHg pre-conception, in the first half of pregnancy or if the patient received antihypertensive medication during these periods. Women with chronic hypertension complicated by other medical conditions were excluded. If hypertension was exacerbated or new onset proteinuria existed, the subject was classified as having superimposed pre-eclampsia. The diagnostic criteria of maternal hypertensive disorders followed National Institutes of Health guidelines (NIH 2000).

Studies I, II, III and V partly involved the same subjects. The group of healthy parturients and women with chronic hypertension were the same in studies I, II and III. NT-proBNP values were missing from four women in the healthy group and from three in the chronic hypertension group, reducing the number of subjects in study II. Pre-eclamptic women were the same in studies I and II, one missing NT-proBNP concentration reducing the group of pre-eclampsics in study II. Furthermore, patients with pre-eclampsia in study V were also included in studies I and II.

In study I 30%, in study II 21% and in study V 60% of the pre-eclamptic subjects had severe pre-eclampsia. The antihypertensive medication used was labetalol and the peroral doses varied between 200–600 mg daily. In study V one parturient was given a labetalol infusion (0.35 mg/minute). In study I 25%, in study II 21% and in study V 40% of the pre-eclamptic women received antihypertensive medication.

In women with chronic hypertension peroral labetalol (200–400 mg daily) was used as antihypertensive medication. In study I 44% and in study II 40% of the women with chronic hypertension had labetalol. Furthermore, in study III 11% of the women with chronic hypertension were medicated during the second trimester of pregnancy and 44% in the third trimester and during early puerperium. In study III two of the women with chronic hypertension had superimposed pre-eclampsia and were excluded from the final study group. In studies I and II none of the women with chronic hypertension had superimposed pre-eclampsia.

Gestational age was confirmed by ultrasonographic examination prior to 20 weeks of gestation in all cases. The characteristics of the study population are shown in Tables 7 and 8

Table 6. *Characteristics of the studies, aims, main variables and study populations in the original publications.*

	Aims of the study	Main variables	Study population	Trimester of pregnancy at study measurements
Study I	assess arterial stiffness in large, conduit arteries in preeclamptic, chronic hypertensive and healthy pregnancy	SI/PP, PWV, PP, SAP, MAP, DAP, SVRI, SI, HR, CI	pre-eclamptic pregnancies (n=20) chronic hypertensive pregnancies (n=18) normotensive pregnancies (n=29) non-pregnant healthy women (n=29)	third trimester
Study II	establish the association between natriuretic peptides and maternal haemodynamics in pre-eclamptic, chronic hypertensive and normotensive pregnancy	NT-proANP, NT-proBNP, SI, HR, CI, SAP, MAP, DAP, SVRI, LCWI	pre-eclamptic pregnancies (n=19) chronic hypertensive pregnancies (n=15) normotensive pregnancies (n=26)	third trimester
Study III	determine haemodynamic changes during the pregnancy and early puerperium in chronic hypertensive and in normotensive pregnancy	SI, HR, CI, SAP, MAP, DAP, PP, SI/PP, PWV, SVRI, LCWI, NT-proANP	chronic hypertensive pregnancies (n=20) normotensive pregnancies (n=30)	early second trimester late second trimester third trimester early puerperium
Study IV	investigate haemodynamic changes during Caesarean delivery and in early puerperium in normotensive pregnancy	SI,HR, CI, SVRI, MAP	normotensive pregnant women (n=10) pregnant women with cardiac disease (n=2)	third trimester early puerperium
Study V	evaluate haemodynamic changes in pre-eclamptic compared to normotensive pregnancy during Caesarean delivery and in early puerperium	SI, HR, CI, SVRI, MAP	pre-eclamptic women (n=10) normotensive pregnant women (n=10)	third trimester early puerperium

SI/PP, stroke index to pulse pressure ratio; PWV, pulse wave velocity; PP, pulse pressure; SAP, systolic blood pressure; MAP, mean arterial pressure; DAP, diastolic blood pressure; SVRI, systemic vascular resistance index, SI, stroke index; HR, hear rate; CI, cardiac index; NT-proANP, amino-terminal of pro-atrial natriuretic peptide; NT-proBNP, amino-terminal of b-type natriuretic peptide; LCWI, left cardiac work index.

Table 7.*Characteristics of the study population at trial entry in studies I & II.*

	Study I				ANOVA p-value	Study II			Kruskal-Wallis p-value
	Healthy pregnancy n=29	Pre-eclampsia n=20	Chronic hypertension n=18	Non-pregnant n=29		Healthy pregnancy n=26	Pre-eclampsia n=19	Chronic hypertension n=15	
age (years)	27 (20-33)	32 (19-43)	32 (23-40)	27 (20-33)	<0.001	27(20-30)	33 (19-43)	33(23-40)	0.003
percentage of primiparous	100	85	72		* 0.006	100	89	87	0.2*
body mass index (kg/m ²)	27 (22-33)	28 (21-32)	30 (24-37)	24 (18-35)	<0.001	27 (23-33)	28 (25- 32)	30 (26-36)	0.07
gestational age at study entry (weeks)	35 (33-37)	33 (27-39)	35 (33-37)		0.03	35 (33-36)	33 (27-39)	34 (32-36)	0.009
gestational age at delivery (weeks)	40 (35-42)	34 (28-39)	38 (35-41)		<0.001	40 (35-42)	33 (28-39)	38 (35-41)	0.001
systolic blood pressure (mmHg)	120 (100-132)	160 (140-180)	138 (105-170)	117 (100-132)	<0.001	120 (96-134)	155 (140-180)	138 (101-170)	<0.001
diastolic blood pressure (mmHg)	76 (58-88)	100 (90-112)	94 (72-120)	69 (50-86)	<0.001	76(58-88)	100 (90-112)	94 (80-120)	<0.001
daily proteinuria (g/day)						< 0.3	4.0 (0.4-9.4)	< 0.3	<0.001

In study I values are expressed as mean (range).

In study II values are expressed as median (range).

* Fisher's Exact Test

Reprinted and modified from Tihtonen et al. (2006): Arterial stiffness in preeclamptic and chronic hypertensive pregnancies. Eur J Obstet Gynecol Repro Biol 128: 180-186 and

Tihtonen et al.: Natriuretic peptides and hemodynamics in preeclampsia. Am J Obstet Gynecol, in press, with permission from Elsevier.

Table 8.*Characteristics of the study population at trial entry in studies III & IV.*

	Study III		p-value	Study IV-V		
	Healthy n=29	Chronic hypertension n=18		Pre-eclampsia n=10	Healthy n=10	p-value
age (years)	27 (20-33)	32 (23-41)	<0.001	34 (24-43)	30 (24-38)	0.1
percentage of primiparous	100	72	*0.003	80	50	*0.4
body mass index (kg/m ²)	24.3 (19.1-31.9)	27.0 (21.8-50.7)	0.02	26 (22-30)	30 (25-41)	0.049
gestational age at first measurements (weeks)	14 (13-15)	14 (13-15)				
gestational age at second measurements (weeks)	25 (22-26)	24 (22-26)				
gestational age at third measurements (weeks)	35 (33-37)	35 (33-37)				
gestational age at delivery (weeks)	40 (35-42)	38 (35-41)	0.2	34 (28-38)	40 (39-41)	<0.0001
systolic blood pressure (mmHg)	119 (100-135)	140 (105-170)	<0.001	166 (137-204)	127 (101-171)	0.001
diastolic blood pressure (mmHg)	76 (58-88)	95 (80-120)	<0.001	105 (90-122)	66 (61-72)	<0.0001
daily proteinuria (g/day)				6.3 (1.52-11.35)	<0.3	<0.0001

Values are expressed as mean(range).

* Fisher's Exact Test

Reprinted and modified from Tihtonen et al. Hemodynamic adaptation during pregnancy in chronic hypertension, submitted.

Tihtonen et al. (2006): Maternal haemodynamics in pre-eclampsia compared with normal pregnancy during caesarean delivery.

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2. Haemodynamic monitoring

A non-invasive cardiovascular monitoring device (CircMon B202; JR Medical Ltd., Tallinn, Estonia) was used for the measurement of haemodynamic parameters in studies I, II, III, IV and V. Cardiac pump function parameters obtained were stroke volume, heart rate, cardiac output, systemic vascular resistance, left cardiac work and pulse wave velocity. This cardiovascular monitoring device applies whole-body impedance cardiography to measure cardiac output. The parameters obtained were indexed to body surface area to minimize the effect of body size on these parameters (i.e. CI, cardiac output index; SI, stroke volume index; SVRI, systemic vascular resistance index; LCWI, left cardiac work index). Body surface area (BSA) was calculated from the following formula: $BSA (m^2) = 0.007184 \times \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425}$. Furthermore, the following equations were used for calculating SVRI and LCWI: $SVRI = 80 \times (\text{MAP-CVP})/CI$ and $LCWI = 0.0144 \times (\text{MAP-PACWP}) \times CI$. As a non-invasive method the CircMon B202 uses average normal values of CVP (3 mmHg) and PACWP (6 mmHg) for calculation (Mabie et al. 1989, Visser and Wallenburg 1991). Arterial stiffness was evaluated by pulse pressure (PP), and pulse wave velocity (PWV) and arterial compliance estimated by the ratio of SI to PP (SI/PP) (Safar et al. 1998). The ICG_{WB} derived SI was averaged over a period of 30 s as well as PP obtained from Finapres-blood pressure monitor. PWV was measured between the base of the aorta and the popliteal artery. The measurement is based on synchronous recording of electrocardiogram, whole-body impedance cardiogram and impedance plethysmogram of the popliteal artery (Kööbi et al. 2003).

The standard electrode placement used in the studies is presented in the Review of the literature (Figure 1) and an example of haemodynamic recording during Caesarean section in Figure 2.

Since heart-related impedance changes of whole body impedance cardiography depend on the amount of red blood cells in the vessels (Kööbi et al. 1997a), blood samples for haematocrit were obtained before the measurements to adjust impedance-derived parameters to individual haematocrit.

In studies I and II the haemodynamic recordings were obtained during the third trimester of pregnancy. After fifteen minutes of rest the participants were placed in a left lateral position to displace the gravid uterus from the aorta and inferior vena cava and to allow the legs to be at the level of the heart. Recording in this position was maintained continuously for fifteen minutes. The values obtained for the analyses were averages over 30 seconds from beat-to-beat measurements during the most stable recording. In study I haemodynamic measurements were repeated in normotensive women six months after delivery to obtain the non-pregnant reference group. Haemodynamic recording was carried out as previously. In study III haemodynamic data were obtained longitudinally during the early (13–15 weeks' gestation) and late (22–26 weeks' gestation) second trimester, third trimester (33–37 weeks' gestation) and on the

second to fifth postpartum days. The study protocol was similar to that mentioned above in studies I and II.

In studies IV and V the haemodynamic recordings were obtained during Caesarean section. The first measurement was before fluid preloading and after preloading the recording was continuous until the parturient could bend and extend her ankles i.e. after disappearance of anaesthesia. The haemodynamic measurements at baseline and during Caesarean section were obtained in a left lateral position. After disappearance of the anaesthesia the parturients were in a supine position to avoid the possible painful effect of the surgical wound in a semilateral position. The measurements were repeated on the second to fifth postpartum days, in a supine position. The whole-body impedance cardiography derived SI, HR, CI and SVRI were analysed as average values for 30 seconds at the following time points: baseline, after preloading, at the point of lowest measured blood pressure after spinal blockade, immediately after delivery of newborn and placenta, at skin closure, after anaesthesia had disappeared and once on the second to fifth postpartum day.

In studies I, II and III blood pressure was measured continuously beat-to-beat by means of the non-invasive Finapres 2300, Ohmeda (Englewood, CO, USA) from the finger. An experienced nurse always controlled arterial pressure with a brachial cuff according to the conventional auscultatory Riva-Rocci method. The level of the finger with the Finapres blood pressure device was changed so that systolic blood pressure corresponded with the Riva-Rocci method at the beginning of the measurements. Korotkoff phase I and IV were used to record systolic and diastolic blood pressure.

In studies IV and V blood pressure was measured from the arm by means of an automated non-invasive arterial pressure device (Hewlett-Packard M1960A, Boeblingen, Germany) during Caesarean section. Blood pressure was obtained every five minutes and after the induction of spinal anaesthesia, every two minutes. Blood pressure measured by the automated device was verified by the conventional manual Riva-Rocci method in each subject at the beginning of the study. In postpartum measurements the conventional Riva-Rocci method was used.

Mean arterial pressure was calculated as diastolic blood pressure plus $\frac{1}{3}$ of pulse pressure. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure.

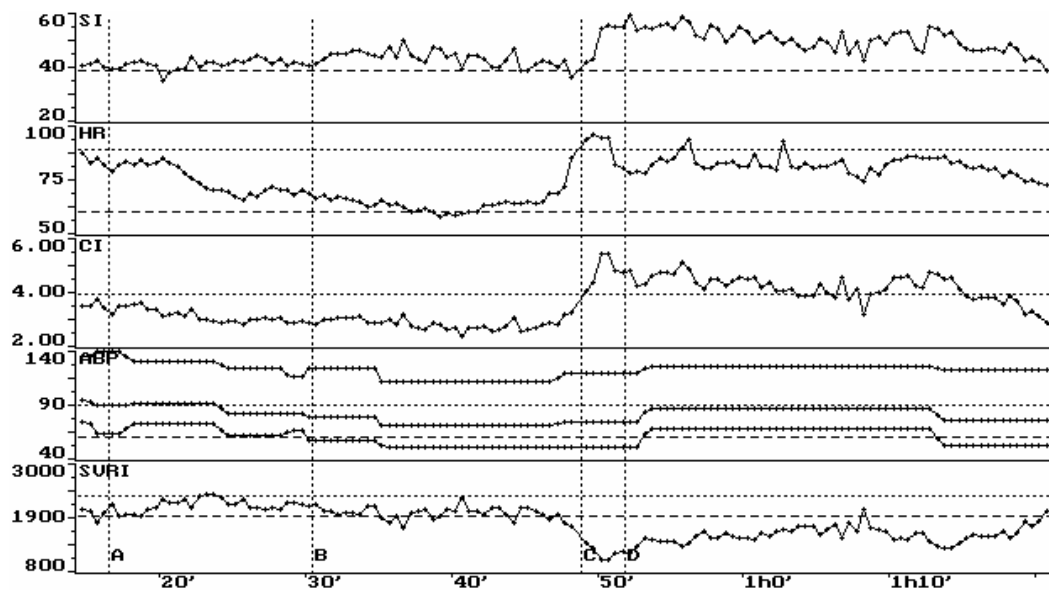


Figure 2. An example of the haemodynamic recording in a healthy parturient during Caesarean section. SI, stroke index; HR, heart rate; CI, cardiac index; ABP, arterial blood pressure; SVRI, systemic vascular resistance index. A = after preloading, B = operation starts, C = delivery of the newborn, D = removal of the placenta. Reprinted from Tihonen et al. (2005): *Maternal hemodynamics during cesarean delivery assessed by whole-body impedance cardiography. Acta Obstet Gynecol Scand 84: 355-361*, with permission from Taylor and Francis.

3. Analysis of cardiac natriuretic peptides

The plasma levels of NT-proANP and NT-proBNP in study II were determined by means of radioimmunoassays utilizing antisera directed to NT-proANP₄₆₋₇₉ and NT-proBNP₁₀₋₂₉ (Ala-Kopsala et al. 2004). Recombinant full-length NT-proANP₁₋₉₈ and NT-proBNP₁₋₇₆ were used as calibrators and tracers in the respective assays. The sensitivity of the NT-proANP assay was 60 pmol/L and that of the NT-proBNP assay 40 pmol/L. In five normotensive women the NT-proBNP concentration was under the detection limit; in results the values were considered to be 40 pmol/L, which was the lowest detected value. In study III, NT-proANP concentrations were measured by means of a commercially available IRMA method using two monoclonal antibodies (codes 7801 and 7901, Medix Biochemica, Kauniainen, Finland). The detection limit of the method was 50 pmol/L. None of the measured values were under the detection limit. An NT-proANP concentration ≤ 255 pmol/L and a NT-proBNP concentration ≤ 86 pmol/L were considered normal values (Ala-Kopsala et al. 2004). The blood samples were obtained during day-time.

4. Fluid administration and regional anaesthesia during Caesarean section

The subjects in studies IV and V received hydroxyethyl starch (6%), 10 ml/kg over 15–30 minutes, as preloading infusion. Thereafter hydroxyethyl starch (6%) was infused at 10 ml/kg/h during the operation. After the operation bleeding was estimated and volume depletion replaced by Ringer infusion or erythrocytes, if considered necessary. Furthermore, spinal anaesthesia was induced after preload fluid infusion. It was performed using a 25- or 27-gauge spinal needle at the L2-L3 or L3-L4 intervertebral space with the subject in the right lateral position. The women received a mean of 2.5 ml (range 2.4–2.7 ml) of 0.5% hyperbaric bupivacaine. Thereafter they were repositioned supine in a slight left-lateral position. The surgical procedure was initiated when the level of sensory block was deemed adequate.

Maternal hypotension was defined as a decrease in systolic arterial pressure to 80% of baseline or a systolic pressure of less than 100 mmHg. Hypotension was treated by intravenous ephedrine infusion: ephedrine (50 mg in 100 ml 0.9% NaCl) was given until normotension was restored; typically 40 mg of ephedrine was needed.

5. Statistical analysis

In study I, outcome parameters were analysed using one-way analysis of variance (ANOVA) to detect significant changes in the entire study group. In the presence of significant values, Bonferroni's *post hoc* test for multiple comparisons was used. Differences between normotensive pregnancies and non-pregnant women were reanalyzed with paired samples *t*-test. Comparisons between medicated and non-medicated subjects were made with the independent samples *t*-test. Pearson's correlation coefficient was used to estimate associations between different haemodynamic parameters. The difference in the percentages of primiparous women between the groups was compared by Fisher's exact test. Outcome parameters are expressed as mean and range or standard deviation.

In study II the differences between three study groups were compared by means of the Kruskal–Wallis test. If statistical significance was shown, the *post hoc* Mann–Whitney *U*-test was used in further analysis. The difference in the percentages of primiparous women between the groups was compared by means of Fisher's exact test. Comparisons between medicated and non-medicated subjects were made with the Mann–Whitney *U*-test. Spearman's correlation coefficient (r_s) was calculated to estimate associations between haemodynamic parameters and natriuretic peptides and other laboratory parameters. Data are presented as median and range, when necessary.

In study III repeated measures analysis of variance (RANOVA) was used to analyse outcome parameters. Paired samples *t*-tests were used to detect changes within the study groups between subsequent points and independent samples *t*-

tests to detect significant differences between the study groups. Outcome parameters are presented as mean and range or standard error of the mean.

In studies IV and V outcome parameters were analysed using repeated measures analysis of variance (RANOVA) to detect significant changes in haemodynamic parameters in the entire group and coherence of the haemodynamic parameters between the groups over time. Differences between the groups at each time point were examined *post hoc* using independent samples *t*-tests. Paired samples *t*-tests were used to detect changes within the groups. In study V differences in haemodynamic parameters between successive measurement points were expressed as percentage changes to describe reactions to interventions. Data are presented as mean and range, standard error of the mean, or standard deviation.

In all studies differences were considered statistically significant if $p \leq 0.05$. Statistical analysis was performed using SPSS for Windows software (version 11.0, SPSS Inc., Chicago, IL) on a standard PC.

6. Ethical considerations

The Ethics Committee of Tampere University Hospital approved the study protocols. All women participating gave their informed written consent before entering the study protocol.

RESULTS

1. Haemodynamics and concentrations of natriuretic peptides in normotensive pregnancy

During the course of pregnancy, the most significant haemodynamic changes appeared between the late second (22–26 week's gestation) and third trimester (33–37 week's gestation): SI, CI, SI/PP and LCWI decreased and SVRI, PWV and PP increased. After delivery SAP, PP, SVRI and PWV further increased and SI/PP decreased (III). The results are presented in Figures 3 -5.

In the third trimester of pregnancy normotensive pregnancies had lower PWV and PP compared to non-pregnant controls after reanalysis. In normotensive pregnancies a significant linear correlation was found between SI/PP and SVRI ($r = -0.42$, $p = 0.03$), the finding was similar in the case of non-pregnant controls ($r = -0.54$, $p = 0.008$). Furthermore in healthy pregnancies PWV and SI/PP correlated significantly ($r = -0.60$, $p = 0.001$). In either group no other significant correlations between PP or PWV and other haemodynamic parameters were found- apart from expected correlations between PP and SAP as well as PP and SI/PP (I).

The mean concentrations of NT-proANP during the early (290 ± 23 pmol/L) and late (256 ± 22 pmol/L) second trimester were high and above the concentrations considered pathological (≥ 255 pmol/L) in the non-pregnant population. Towards the third trimester of pregnancy NT-proANP levels (219 ± 14 pmol/L) decreased significantly ($p = 0.001$) compared with values in the late second trimester. After delivery NT-proANP concentrations increased significantly (<0.001) and were exceptionally high (441 ± 3 pmol/L) (III).

Among healthy pregnancies 23% had high NT-proANP concentrations (> 255 pmol/L) and 31% had high NT-proBNP concentrations (> 86 pmol/L) in the third trimester. NT-proANP had no significant correlations between the measured haemodynamic parameters. The median NT-proBNP concentration in the third trimester was 59 pmol/L (40-130) pmol/L. Significant correlations between NT-proBNP and DAP ($r_s = 0.40$, $p = 0.04$) as well as between NT-proBNP and MAP ($r_s = 0.44$, $p = 0.02$) were found. (II).

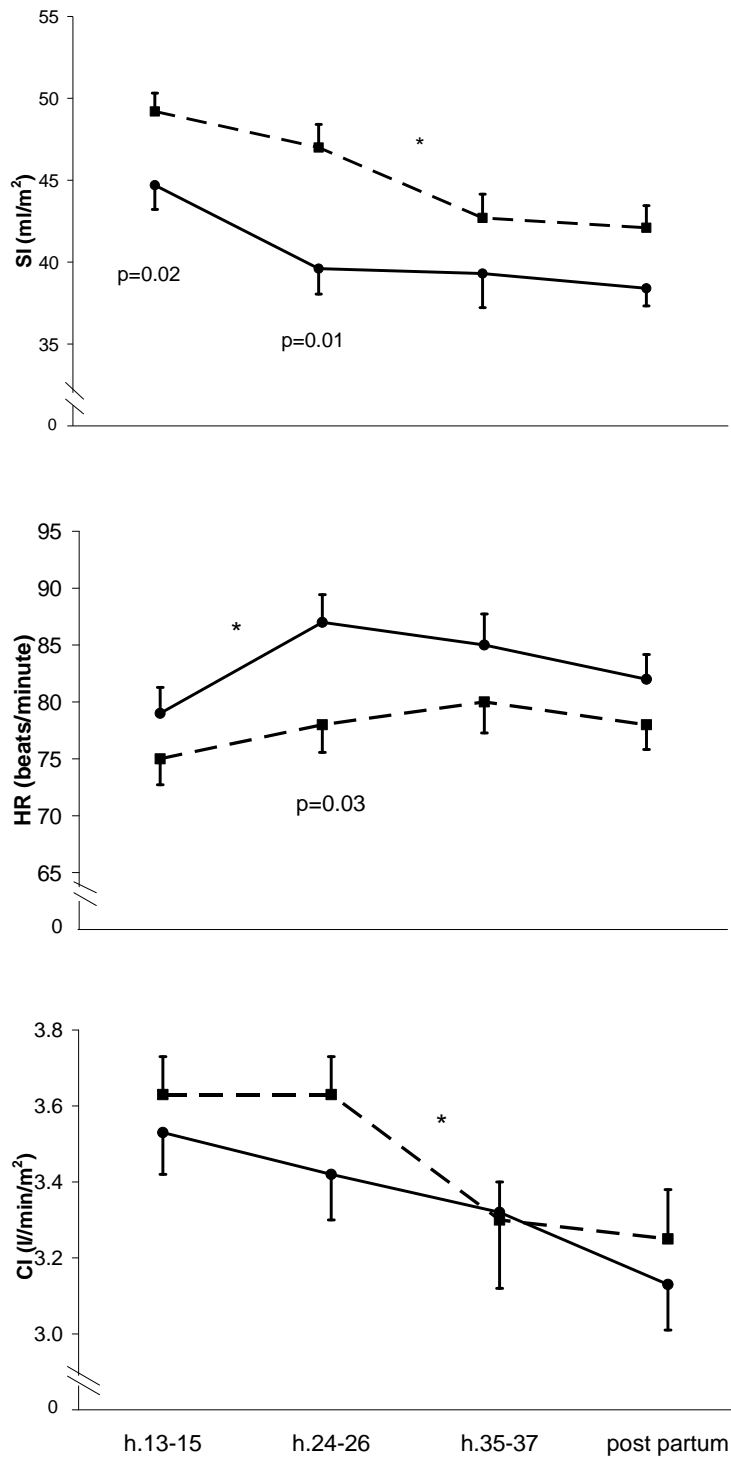


Figure 3. Changes in SI, HR and CI during pregnancy and after delivery in chronic hypertensive (●) and normotensive (■) pregnancies. Values are expressed as mean and standard error of the mean. Values of p refer to significant differences between study groups and * refers to a significant difference ($p \leq 0.05$) between subsequent measurements within a study group.

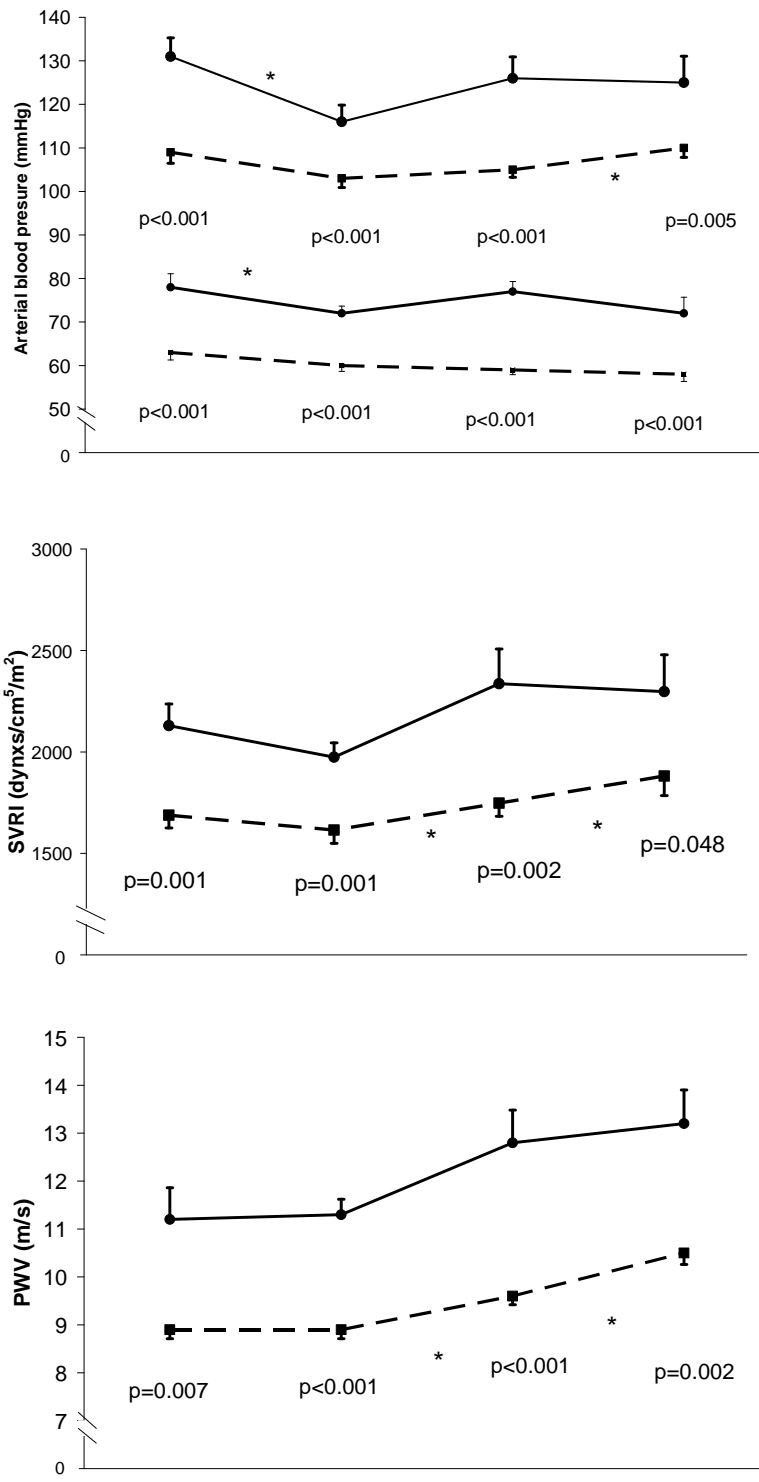


Figure 4. Changes in arterial blood pressure (SAP, DAP), SVRI and PWV during pregnancy and after delivery in chronic hypertensive (●) and normotensive (■) pregnancies. Values are expressed as mean and standard error of the mean. Values of p refer to significant differences between study groups and * refers to a significant difference ($p \leq 0.05$) between subsequent measurements within a study group.

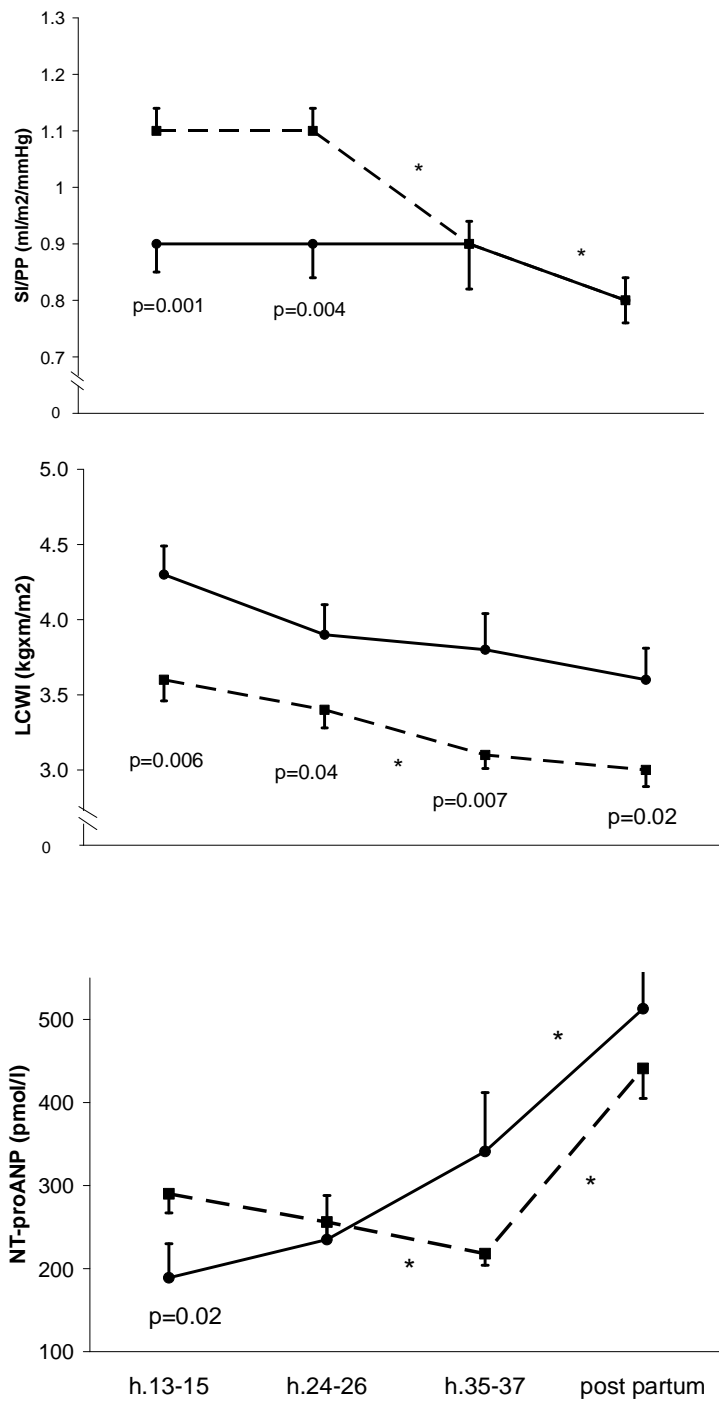


Figure 5. Changes in SI/PP, LCWI and concentrations of NT-proANP during pregnancy and after delivery in chronic hypertensive (●) and normotensive (■) pregnancies. Values are expressed as mean and standard error of the mean. Values of *p* refer to significant differences between study groups and * refers to a significant difference ($p \leq 0.05$) between subsequent measurements within a study group.

2. Haemodynamics of pre-eclampsia in the third trimester

2.1. Haemodynamic differences in pre-eclampsia compared with normotensive and chronic hypertensive pregnancies (I, II)

Pre-eclamptic pregnancies differed from normotensive pregnancies in showing higher SVRI ($p < 0.0001$), SAP ($p < 0.0001$), MAP ($p < 0.0001$) and DAP ($p < 0.0001$) and lower CI ($p = 0.001$) and HR ($p = 0.02$) (I, II). Compared with women with chronic hypertensive pregnancies pre-eclamptic women had lower HR ($p = 0.002$) and CI ($p = 0.02$) and higher SVRI ($p = 0.001$) and SAP ($p = 0.002$) (I, II), Table 9.

2.2. Arterial stiffness in the third trimester (I)

Arterial stiffness was significantly increased in pre-eclamptic versus normotensive pregnancies, as expressed by lower SI/PP ($p < 0.0001$) and higher PP ($p < 0.0001$) and PWV ($p < 0.0001$) in pre-eclampsia. Furthermore, SVRI in pre-eclamptic women was significantly higher ($p < 0.0001$) than in normotensive pregnant women. Findings were similar considering differences between pre-eclamptic and non-pregnant women: lower SI/PP ($p < 0.0001$), higher PP ($p = 0.001$), PWV ($p < 0.0001$) and SVRI ($p < 0.0001$). Compared with chronic hypertensive pregnancies SI/PP ($p < 0.0001$) was lower and PP ($p < 0.0001$) and SVRI ($p = 0.001$) higher in pre-eclampsia, Table 9.

Strong linear correlations were found between arterial stiffness and afterload (MAP and SVRI). Since mean arterial pressure is defined by diastolic arterial pressure and pulse pressure, correlations between PP, SI/PP and MAP were expected (Table 10). Linear correlation between pulse wave velocity and mean arterial pressure is illustrated in Figure 6.

Table 9. *Haemodynamic data in the study groups (I).*

	Healthy parturients n=29	Pre-eclampsia n=20	p	Chronic hypertension n=18	p	Non-pregnant n=29	p
SI/PP (ml/m ² xmmHg)	0.94 (0.19)	0.59 (0.14)	<0.0001	0.85 (0.30)	1.0	0.93 (0.20)	0.9
PWV (m/s)	9.6 (1.0)	13.8 (3.9)	<0.0001	12.8 (2.7)	<0.0001	9.0 (0.8)	0.003
PP (mmHg)	46 (7)	66 (15)	<0.0001	49 (14)	1.0	53 (10)	< 0.001
SAP (mmHg)	105 (11)	147 (25)	<0.0001	126 (20)	<0.001	111 (13)	0.2
MAP (mmHg)	74 (8)	101 (16)	<0.0001	94 (12)	<0.0001	76 (9)	0.3
DAP (mmHg)	59 (7)	79 (13)	<0.0001	77 (9)	<0.0001	58 (8)	<0.001
SVRI (dynxs/cm ⁵ /m ²)	1748 (385)	3049 (527)	<0.0001	2336 (698)	<0.001	1811 (422)	0.4
SI (ml/m ²)	43 (7)	39 (6)	0.4	39 (8)	0.5	49 (8)	0.04
HR (beats/minute)	80 (12)	69 (11)	0.02	85 (11)	0.7	69 (14)	0.03
CI (L/min/m ²)	3.3 (0.5)	2.6 (0.4)	<0.0001	3.3 (0.8)	1.0	3.4 (0.7)	0.9

Values are expressed as means (SD), p-values refer to differences between healthy parturients and the study group.

SI/PP, arterial compliance; PWV, pulse wave velocity; PP, pulse pressure; SAP, systolic blood pressure;

MAP, mean aretrial pressure; DAP, diastolic blood pressure; SVRI, systemic vascular resistance index; SI, stroke index;

HR, heart rate; CI, cardiac index.

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Table 10.*Linear correlation between arterial stiffness and haemodynamic data in hypertensive pregnancies.*

	Pre-eclampsia n=20						Chronic hypertension n=18					
	SI/PP		PP		PWV		SI/PP		PP		PWV	
	correlation	p	correlation	p	correlation	p	correlation	p	correlation	p	correlation	p
SAP (mmHg)	-0.65	0.002	0.91	<0.0001	0.59	0.006	-0.75	0.0001	0.90	<0.0001	0.61	0.007
MAP (mmHg)	-0.54	0.02	0.77	<0.0001	0.54	0.01	-0.68	0.002	0.74	<0.0001	0.58	0.01
DAP (mmHg)	-0.40	0.08	0.59	0.006	0.46	0.04	-0.53	0.02	0.47	0.048	0.47	0.05
SVRI (dynxs/cm5/m2)	-0.57	0.009	0.54	0.01	0.53	0.02	-0.84	<0.0001	0.70	0.001	0.57	0.01
SI (ml/m ²)	0.49	0.03	0.11	0.6	-0.33	0.2	0.78	<0.0001	-0.25	0.3	-0.44	0.07
HR (beats/minute)	-0.40	0.08	0.09	0.7	0.29	0.2	0.10	0.7	-0.25	0.3	0.11	0.7
CI (L/min/m ²)	0.06	0.08	0.2	0.4	-0.03	0.9	0.7	<0.0001	-0.3	0.2	-0.3	0.2

SAP, systolic blood pressure; MAP, mean arterial blood pressure; DAP, diastolic blood pressure; SVRI, systemic vascular resistance index;

SI, stroke index; HR, heart rate; CI, cardiac index; SI/PP, arterial compliance; PP, pulse pressure; PWV; pulse wave velocity.

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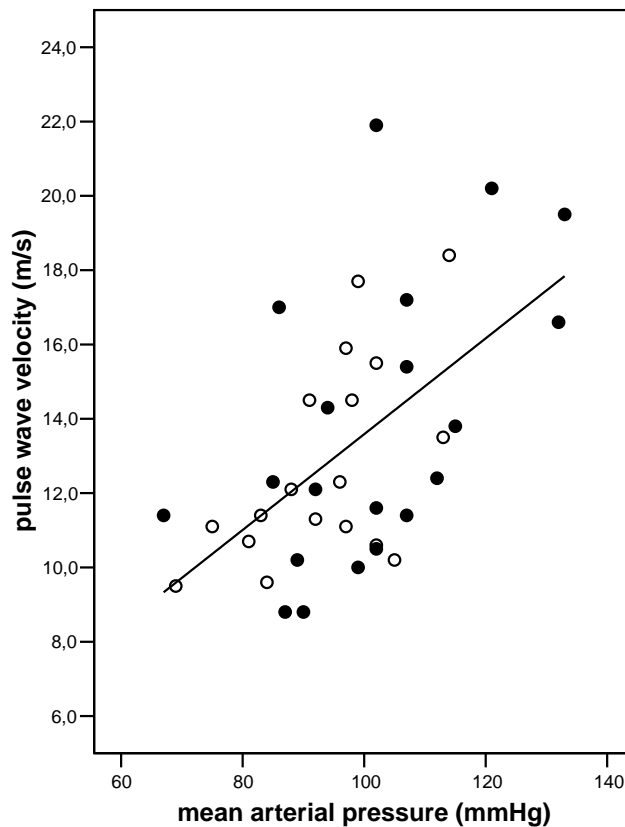


Figure 6. Linear correlation between pulse wave velocity and mean arterial pressure in (●) pre-eclamptic parturients and (○) parturients with chronic hypertension. There was a significant correlation between these parameters ($r = 0.33$, $p < 0.0001$). Reprinted from Tihtonen et al. (2006): Arterial stiffness in preeclamptic and chronic hypertensive pregnancies. *Eur J Obstet Gynecol Repro Biol* 128 (180-186), with permission from Elsevier.

2.3. Natriuretic peptides and haemodynamics in the third trimester (II)

The median concentrations of NT-proANP [888 pmol/L (240- 2054 pmol/L)] and NT-proBNP [190 pmol/L (87-1945 pmol/L)] were significantly higher in pre-eclamptic women than in women with chronic hypertensive ($p = 0.002$, $p = 0.017$, respectively) and normotensive pregnancies ($p < 0.001$, $p < 0.001$, respectively). Among pre-eclamptic women 95% had high NT-proANP concentrations (< 255 pmol/L) and 100% had high NT-proBNP concentrations (> 86 pmol/L).

In pre-eclamptic women NT-proANP concentrations correlated significantly with SAP ($r_s = 0.55$, $p = 0.02$) and SVRI ($r_s = 0.60$, $p = 0.009$). Furthermore, NT-proBNP concentrations and CI ($r_s = 0.48$, $p = 0.04$) and NT-proBNP and SVRI ($r_s = 0.53$, $p = 0.03$) showed significant correlations. When medicated women were excluded from the study group, NT-proANP and SAP ($r_s = 0.65$, $p = 0.008$), NT-proANP and MAP ($r_s = 0.59$, $p = 0.02$), NT-proANP and SVRI ($r_s = 0.81$, $p < 0.001$) and NT-proBNP and SVRI ($r_s = 0.68$, $p = 0.005$) had significant correlations. The scatter plot of NT-proANP and SAP in the complete study groups and in the non-medicated subgroups of hypertensive women are illustrated in Figure 7.

2.4. The effects of antihypertensive medication on haemodynamics and natriuretic peptides (I, II)

In pre-eclamptic pregnancies five out of twenty (I) and four out of eighteen (II) women received antihypertensive medication. The antihypertensive medication used was a peroral regimen of labetalol (200–600 mg/day). Two parturients (I, II) receiving labetalol had severe pre-eclampsia.

There were no significant differences in SI, HR, CI, arterial blood pressure or SVRI between the medicated and non-medicated pre-eclamptic women in either study (I, II). Furthermore, differences in haemodynamic parameters between normotensive pregnant women and pre-eclamptic women excluding medicated hypertensive women were calculated separately. The haemodynamic differences found between the study groups were comparable to the original results, which also included medicated hypertensive pregnancies (I, II).

Median NT-proANP concentrations were significantly higher in medicated pre-eclamptic patients [1477 pmol/L (785-2054 pmol/L)] compared with non-medicated patients [803 pmol/L (240-1647 pmol/L)]. The result considering NT-proBNP was similar 607 pmol/L (167-1945 pmol/L) vs. 167 pmol/L (87-454 pmol/L), respectively (II).

2.5. The effect of clinical severity of pre-eclampsia on haemodynamics (I, II)

Severe pre-eclampsia affected six (I, II) and mild-moderate pre-eclampsia fourteen (I) and thirteen (II) subjects. No significant differences in haemodynamic parameters were observed between these groups (I, II). Furthermore, no differences were noted in arterial stiffness between patients with severe disease or moderate to mild disease (I). No significant differences in concentrations of cardiac natriuretic peptides (NT-proANP, NT-proBNP) between these groups were found (II).

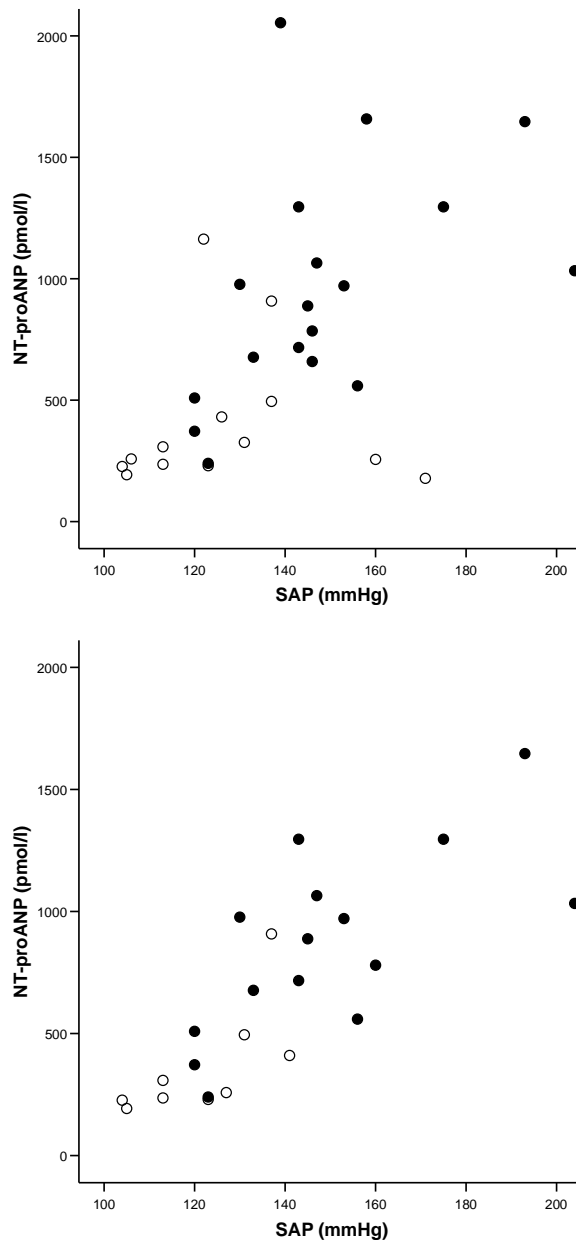


Figure 7. Scatter plot of NT-proANP concentrations and systolic blood pressure (SAP) in hypertensive pregnancies (● pre-eclampsia, ○ chronic hypertension). Above: in the whole preeclamptic group the correlation was significant ($r_s = 0.55$, $p = 0.02$), while in chronic hypertension no correlation was found ($r_s = 0.07$, $p = 0.8$).

Below: In non-medicated pregnant women with hypertension correlations between NT-proANP and SAP were significant in both groups ($r_s = 0.65$, $p = 0.008$ in pre-eclamptic women, $r_s = 0.84$, $p = 0.005$ in women with chronic hypertension). Reprinted from Tihtonen et al.: Natriuretic peptides and hemodynamics in preeclampsia. *Am J Obstet Gynecol*, in press, with permission from Elsevier.

2.6. Correlations of laboratory tests with haemodynamics and cardiac natriuretic peptides (I, II)

In pre-eclamptic pregnancies daily proteinuria and PP showed a positive correlation ($r = 0.56$, $p = 0.02$), but correlations between other laboratory test results (haemoglobin count, platelet count, uric acid, alanine transaminase and d-dimer of fibrin) and arterial stiffness or blood pressure were not found (I). Circulating concentrations of natriuretic peptides did not have any significant correlations with laboratory test data (platelet count, uric acid, daily proteinuria, alanine transaminase, lactic dehydrogenase and d-dimer of fibrin) in cases of pre-eclampsia (II).

2.7. Birth weight and haemodynamics in hypertensive pregnancies

Eight infants in the pre-eclampsia group and two in the chronic hypertension group were small for gestational age (SGA; birth weight under the fifth percentile), while all newborns of normotensive women were appropriate for gestational age (AGA). Heart rate ($p = 0.006$) and CI ($p = 0.04$) were significantly lower in hypertensive women giving birth to SGA versus AGA infants but no differences were found in parameters describing arterial stiffness (SI/PP, PP, PWV) (I).

3. Haemodynamics in chronic hypertensive pregnancy

3.1. Changes in haemodynamics and concentrations of NT-proANP during pregnancy and early puerperium (III)

The most significant changes in subjects with chronic hypertension occurred between the early second trimester (13–15 week's gestation) and late second trimester (22–26 week's gestation): SAP, MAP, DAP and PP decreased and HR increased significantly. During the third trimester the haemodynamic parameters remained stable compared with values in the late second trimester. Furthermore, after delivery haemodynamic parameters were comparable to the values in the third trimester, except for higher PP.

The mean NT-proANP concentrations during the early (189 ± 41 pmol/L) and late (235 ± 53 pmol/L) second trimester remained within the limits considered physiological in the non-pregnant population, but a high mean concentration (314 ± 71 pmol/L) was found in the third trimester of pregnancy. After delivery NT-proANP levels (513 ± 79 pmol/L) were increased significantly compared with the values found in the third trimester. The results are presented in Figures 3 - 5.

3.2. Haemodynamic and NT-proANP differences between chronic hypertensive pregnancy and normotensive pregnancy (III)

In chronic hypertensive pregnancies SAP, MAP, DAP, PP, PWV, SVRI and LCWI remained at significantly higher levels compared with those in normotensive pregnancies during the whole pregnancy and early puerperium. Furthermore, SI, HR, SI/PP and concentrations of NT-proANP were significantly different between the groups over time. During the second trimester SI and SI/PP were significantly lower in women with chronic hypertension. Furthermore, the mean NT-proANP concentration during the early second trimester was significantly lower in chronic hypertensive pregnancies versus controls. The interaction between time and study groups was significant in respect of SAP ($p = 0.007$), MAP ($p = 0.02$), DAP ($p = 0.04$), SVRI ($p = 0.03$), SI/PP ($p = 0.04$) and PP ($p = 0.004$). Instead no significant differences in CI between the groups were found. The differences in haemodynamic parameters and NT-proANP concentrations between the study groups, and *post hoc* p -values are illustrated in Figures 3 - 5.

3.3. Arterial stiffness in the third trimester (I)

Pregnant women with chronic hypertension were found to have higher PWV and SVRI when compared with normotensive controls, and compared with non-pregnant women PWV ($p < 0.0001$) and SVRI ($p < 0.0001$) were higher. Compared with pre-eclamptic pregnancies, SI/PP, PP and SVRI were lower in cases of chronic hypertension (Table 9).

In chronic hypertensive pregnancies strong correlations were found between arterial stiffness and afterload (MAP and SVRI). Since mean arterial pressure is defined by diastolic arterial pressure and pulse pressure, correlations between PP, SI/PP and MAP were expected (Table 10).

3.4. Natriuretic peptides and haemodynamics in the third trimester (II)

Median NT-proANP [283 pmol/L (178-1163 pmol/L)] and NT-proBNP [98 pmol/L (52-184 pmol/L)] concentrations were found to be significantly higher than in normotensive pregnancies, but significantly lower than in pre-eclamptic women. In the chronic hypertension group 69% had high (> 255 pmol/L) NT-proANP and 70% had high (> 86 pmol/L) NT-proBNP concentrations (II).

No significant correlations between natriuretic peptides and haemodynamic parameters were found. However, when medicated women were excluded from the study group, NT-proANP and SAP ($r_s = 0.84$, $p = 0.005$) and MAP ($r_s = 0.83$, $p = 0.005$), and NT-proBNP and DAP ($r_s = 0.70$, $p = 0.04$) and SVRI ($r_s = 0.79$, $p = 0.04$) correlated significantly (II). A scatter plot of NT-proANP and

SAP in the complete study group and in the non-medicated subgroups of hypertensive women is illustrated in Figure 7.

3.5. The effect of antihypertensive medication on haemodynamics and natriuretic peptides during pregnancy (I,II,III)

In the chronic hypertension group eight out of eighteen (I) and six out of fifteen (II) women received peroral labetalol (200–400 mg/day). In a longitudinal study two women received peroral labetalol at 200–400 mg daily when entering the study. During the third trimester and postpartum an additional six women received labetalol, the dosage being similar to that mentioned above (III).

Considering the haemodynamic parameters during the third trimester, only SI was significantly lower in the medicated women versus non-medicated women with chronic hypertension (II). Furthermore, differences in haemodynamic parameters between normotensive pregnancies and chronic hypertensive pregnancies excluding the medicated women were calculated separately. Differences found between the study groups were comparable to the original results when the medicated hypertensive patients were also included (I).

The median concentration of NT-proANP in the third trimester was higher in medicated [379 pmol/L (178-1163 pmol/L)] than in non-medicated [246 pmol/L (193-908 pmol/L)] subjects, but the difference was not statistically significant. The median concentrations of NT-proBNP were comparable between the subgroups [100 pmol/L (67-184 pmol/L) vs. 94 pmol/L (52-141 pmol/L), respectively] (II).

In a longitudinal study no differences in haemodynamic parameters and NT-proANP concentrations between non-medicated and medicated women during the course of pregnancy were found (III).

4. Maternal haemodynamics during Caesarean delivery in normotensive and pre-eclamptic pregnancy

4.1. Baseline haemodynamics (IV,V)

Mean MAP (114 ± 6 vs. 86 ± 4 mmHg, $p = 0.001$) and SVRI (3709 ± 321 vs. 2221 ± 179 dynxs/cm⁵/m², $p = 0.001$) were significantly higher, and SI (35 ± 2 vs. 42 ± 1 ml/m², $p = 0.005$) and CI (2.5 ± 0.1 vs. 3.2 ± 0.3 L/min/m², $p = 0.045$) significantly lower in pre-eclamptic parturients than in women with uncomplicated pregnancies in the baseline measurements. No difference in heart rate between pre-eclamptic (73 ± 4 beats/min) and normotensive women (74 ± 4 beats/min) existed.

4.2. Preloading (IV,V)

Preloading infusion with 6% hydroxyethyl starch (10 ml/kg over 15-30 minutes) in both study groups resulted in different haemodynamic changes. In pre-eclamptic pregnancies preloading was associated with an elevation in SI (40 ± 2 ml/m², $p = 0.045$), HR (81 ± 3 beats/min, $p = 0.03$) and CI (3.2 ± 0.2 L/min/m², $p = 0.004$), whereas in normal pregnancies only HR (89 ± 5 beats/min, $p < 0.0001$) increased significantly when compared with the baseline values. The difference in SI reaction after preload infusion almost reached statistical significance ($p = 0.056$), while changes in other parameters were similar in the respective groups. Data on haemodynamic changes during Caesarean delivery are presented in Table 11 and in Figure 8.

4.3. Spinal blockade (IV,V)

Mean arterial pressure decreased significantly in pre-eclamptic parturients (102 ± 5 mmHg, $p = 0.003$) and in healthy parturients (74 ± 7 mmHg, $p = 0.004$) after spinal blockade compared with the values after preloading. The reduction in MAP was due to reduced SVRI (2459 ± 215 vs. 1629 ± 183 dyn \times s/cm⁵/m², respectively) in both groups, while CI and SI remained stable. Compared with the baseline measurements the reduction in SVRI was significant in pre-eclamptic women ($p = 0.008$) as well as in healthy parturients ($p = 0.005$).

In normal pregnancies 80% and in pre-eclamptic patients 30% became hypotensive after spinal blockade. In both groups ephedrine increased MAP (14% in healthy parturients and 9% in pre-eclamptic parturients) and SVRI (14% and 16% respectively). Typically, 40 mg of ephedrine was needed before normotension was restored, in both study groups.

4.4. Delivery (IV,V)

Immediately after delivery the mean CI (3.8 ± 0.3 L/min/m²) was 22% higher compared with the value after spinal blockade (52% higher compared with baseline values) in pre-eclamptic patients and 34% (4.7 ± 0.2 L/min/m²) higher (47% higher compared with baseline) in the control group. In pre-eclamptic pregnancies no increase in SI occurred and the rise in CI was due entirely to an increase in HR (95 ± 5 beats/min), while in normal pregnancies a significant increase in both SI (50 ± 2 ml/m², $p = 0.01$) and HR (94 ± 4 beats/min, $p = 0.002$) compared with baseline values was observed. The difference in percentage change in SI between the groups was significant ($p = 0.02$). Among the pre-eclamptic parturients, only one woman showed an increase in SI. This patient had severe pre-eclampsia complicated by HELLP syndrome. Her SI increased 12% at the time of delivery, remaining lower, however, than the mean SI in the control group.

The simultaneous decrease in SVRI ($2010 \pm 189 \text{ dyn} \times \text{s/cm}^5 / \text{m}^2$) was 17% compared with the value after spinal blockade and the mean MAP ($94 \pm 7 \text{ mmHg}$) decreased, reaching the lowest value during the surgical procedure in pre-eclamptic parturients. In the control group, SVRI ($1362 \text{ dyn} \pm 77 \times \text{s/cm}^5 / \text{m}^2$) decreased 6%, while the mean MAP ($82 \pm 4 \text{ mmHg}$) remained stable ($p = 0.03$ for the percentage change difference in MAP between the groups). Bleeding was moderate and similar in both groups: in the pre-eclampsia group, 415 ml and in the group of normotensive women, 550 ml. Only one parturient in the group of normotensive women required blood transfusion after Caesarean section.

The changes in haemodynamic parameters were instant at the moment of delivery of the newborn. In normotensive pregnancies haemodynamic changes were maintained for an average of ten minutes (except in one parturient, for 30 minutes) after delivery until the values returned to the level before the delivery. In pre-eclamptic parturients the finding was similar: haemodynamic changes persisted for a mean of ten minutes after delivery before pre-delivery values were reached.

4.5. Disappearance of anaesthesia (IV, V)

At the disappearance of anaesthesia, haemodynamic values were restored to baseline levels in uncomplicated pregnancies. In pre-eclamptic women, however, SVRI and MAP values returned to baseline, but profound decreases in CI ($2.2 \pm 0.1 \text{ L/min/m}^2$, $p = 0.006$), SI ($32 \pm 2 \text{ ml/m}^2$, $p = 0.02$) and HR ($68 \pm 2 \text{ beats/min}$, $p = 0.003$) compared with the values after delivery were recorded. During this period the mean values of SI, CI and HR reached their nadirs in the whole study period. The changes in SI and CI differed between the groups ($p = 0.04$ and $p = 0.03$ respectively).

4.6. The effects of medication on haemodynamics during Caesarean delivery (V)

Four pre-eclamptic parturients received antihypertensive medication during Caesarean delivery – three patients received an peroral regimen of labetalol (200–600 mg/day) and one was given a labetalol infusion (0.35 mg/minute; labetalol 500 mg in 500 ml 0.9% NaCl). Three of the medicated parturients had severe disease. There were no differences in age, gestational age or body mass index between patients with or without antihypertensive medication. Furthermore, the values of the haemodynamic parameters at baseline and during the surgical procedure between the medicated and non-medicated pre-eclamptic parturients were comparable.

Spinal blockade-induced hypotension was treated with intravenous ephedrine in both study groups. The haemodynamic changes after delivery were alike in parturients treated and not treated with ephedrine in both study groups.

4.7. Early puerperium (IV,V)

During the early puerperium (second to fifth postpartum days) there were no significant differences in SI (38 ± 3 vs. 41 ± 2 ml/m²), HR (83 ± 2 vs. 77 ± 4 beats/min) or CI (3.1 ± 0.2 vs. 3.2 ± 0.2 L/min/m²) between the pre-eclamptic and uncomplicated pregnancies. In contrast, SVRI (2629 ± 304 vs. 1817 ± 125 dyn \times s/cm⁵ / m², $p = 0.03$) and MAP (98 ± 4 vs. 74 ± 5 mmHg, $p = 0.002$) still remained significantly higher in pre-eclamptic women compared with normotensive parturients. However, during the early puerperium in pre-eclamptic parturients SVRI ($p = 0.03$) and MAP ($p = 0.001$) were significantly lower compared with the values at baseline.

Table 11. Percentual changes in haemodynamic parameters between successive periods of analysis during Caesarean section.

	Healthy parturients	Pre-eclamptic parturients	p
Fluid preloading	mean (SD)	mean (SD)	
SI (ml/m ²)	-3.0 (17.3)	+10.8 (12.3)	0.056
HR (beats/minute)	+21.2 (12.3)	+11.7 (13.2)	NS
CI (L/min/m ²)	+18.5 (36.3)	+23.4 (18.4)	NS
SVRI (dynxs/cm ⁵ /m ²)	-1.9 (26.9)	-11.1 (21.4)	NS
MAP (mm/Hg)	+9.9 (9.9)	+6.2 (11.4)	NS
Spinal blockade			
SI (ml/m ²)	+2.7 (5.2)	+0.7 (7.9)	NS
HR (beats/minute)	-2.9 (18.5)	-2.6 (10.8)	NS
CI (L/min/m ²)	+3.8 (25.7)	+4.3 (19.9)	NS
SVRI (dynxs/cm ⁵ /m ²)	-19.3 (40.0)	-8.0 (32.9)	NS
MAP (mm/Hg)	-21.4 (22.9)	-9.2 (7.8)	NS
Delivery of the fetus and the placenta			
SI (ml/m ²)	+16.1 (14.1)	-0.2 (12.6)	0.02
HR (beats/minute)	+13.9 (25.7)	+19.9 (31.4)	NS
CI (L/min/m ²)	+34.2 (36.1)	+21.6 (38.2)	NS
SVRI (dynxs/cm ⁵ /m ²)	-5.7 (38.9)	-16.5 (27.8)	NS
MAP (mm/Hg)	+15.4 (22.0)	-7.4 (16.8)	0.03
Disappearance of anesthesia			
SI (ml/m ²)	-2.5 (13.1)	-19.0 (16.5)	0.04
HR (beats/minute)	-11.7 (12.7)	-18.6 (8.2)	NS
CI (L/min/m ²)	-14.7 (14.4)	-33.3 (17.3)	0.03
SVRI (dynxs/cm ⁵ /m ²)	+49.0 (52.0)	+83.8 (64.1)	NS
MAP (mm/Hg)	+20.4 (24.3)	+14.1 (26.1)	NS

Values are expressed as mean per cent(SD).

p-values refer to the difference between the groups, values less than 0.1 are given.

SI, stroke index; HR, heart rate; CI; cardiac index; SVRI, systemic vascular resistance index;

MAP, mean areterial pressure.

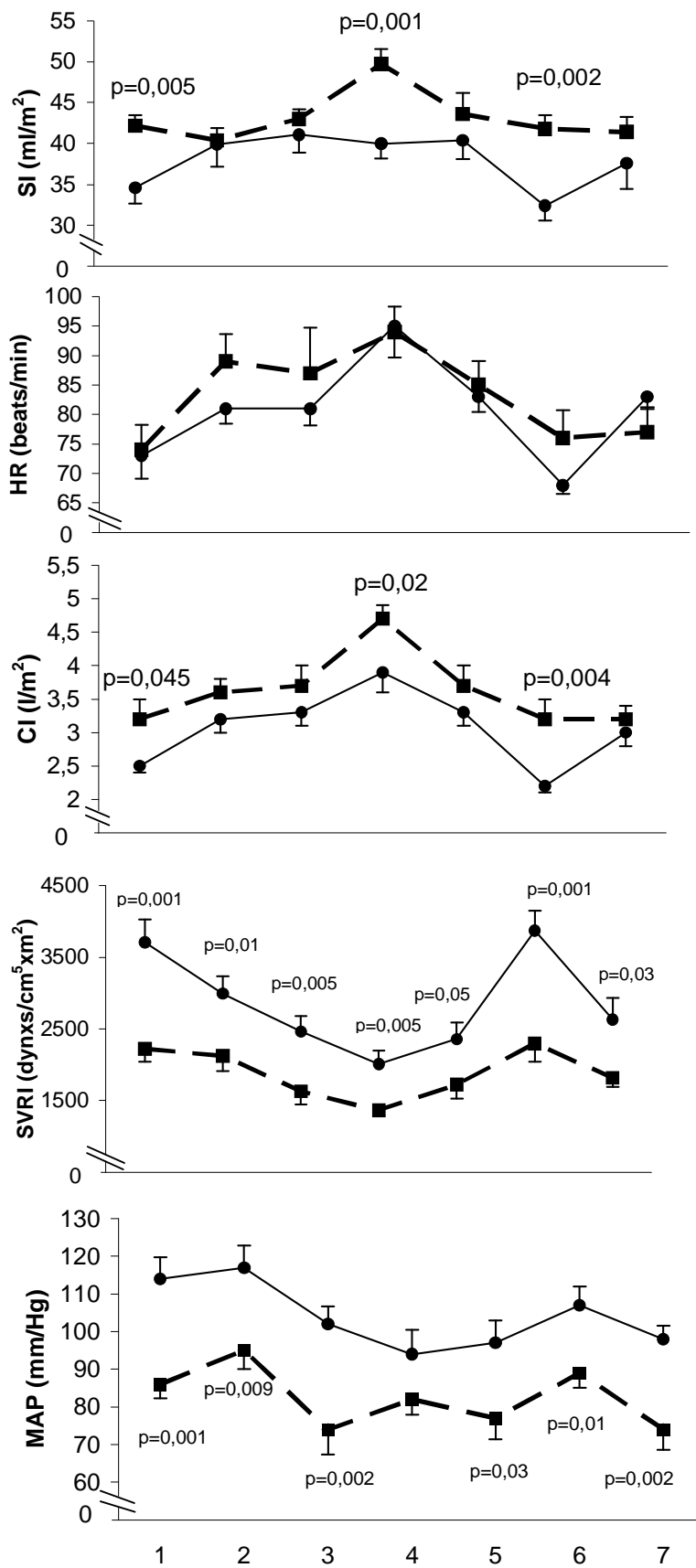


Figure 8. Trends in haemodynamic variables during Caesarean section in healthy (■) and pre-eclamptic (●) parturients. Values are expressed as mean and SE of the mean. 1 = baseline, 2 = after preloading, 3 = after spinal blockade, 4 = delivery, 5 = skin closure, 6 = disappearance of the anaesthesia, 7 = postpartum day. Reprinted from Tihtonen et al. (2006): Maternal hemodynamics in pre-eclampsia compared with normal pregnancy during cesarean delivery. *Br J Obstet Gynaecol* 113: 657-663, with permission from Blackwell.

DISCUSSION

1. Methodology

We used a non-invasive and continuous cardiovascular monitoring device (CircMon B202; JR Medical Ltd., Tallinn, Estonia) connected to an arterial blood pressure device (Finapres 2300; Ohmeda, Englewood, CO, USA) to measure haemodynamic parameters in our studies. The advantage of this method is that the function of the cardiovascular system (SI, HR, CI, LCWI) and vascular properties (SVRI, PWV, SI/PP, arterial blood pressure) can be measured simultaneously beat-to-beat non-invasively, and direct relations between the parameters are obtained.

From an ethical point of view, it would not have been grounded to use invasive methods. The invasive methods, such as thermodilution, have been considered to be reliable in the assessment of cardiovascular function, but because of the risk of serious complications their use is restricted mostly to critically ill patients (Fox et al. 1996).

The widely used technique of ultrasonographic echocardiography would have been an alternative non-invasive method. Validation of the ultrasonographic technique in pregnant populations has been carried out between the aortic Doppler method and thermodilution in critically ill parturients. Correlations between the methods have been good (> 0.9) (Lee et al. 1988), but the Doppler method has been found to underestimate cardiac output consistently, by 35% (Penny et al. 2000). Cardiac output measurements made by M-mode echocardiography may include inaccuracies during pregnancy. Cardiac output estimation is based on measurements of left ventricular dimensions and in cardiac output calculations the shape of the left ventricle is assumed to be ellipsoid. However, this geometric assumption has not been validated in pregnant women and the normal shape of the ventricle is changed during pregnancy (Robson 2000). Furthermore, both of these techniques are highly operator-dependent. Accurate velocity measurements require exact alignment between the Doppler beam and blood flow and knowledge of the angle at which the blood flow is insonated (Berton and Cholley 2002). M-mode echocardiography is also dependent on the accuracy of measurement of the radius of the ventricle; a 10% change in stroke volume corresponds to only a 0.7 mm change in ventricular radius (Brown 2002).

Advantages of whole-body impedance cardiography include operator independence, continuous beat-to-beat measurements of various haemodynamic parameters, non-invasiveness, ease of application and no stress on the patient. The benefit of continuous recording of various haemodynamic parameters simultaneously was evident in the measurements during Caesarean delivery. In

previous studies haemodynamic data have been obtained periodically at different time intervals before and after delivery. The techniques used have been the dye dilution technique (Ueland et al. 1972) and Doppler ultrasonography (James et al. 1989, Robson et al. 1989). In these studies the length and timing of changes in cardiac output after delivery have varied (Ueland et al. 1972, James et al. 1989, Robson et al. 1989). Because of the methodology used in our studies, we were able to document sudden changes in haemodynamic parameters simultaneously and follow the trends in haemodynamic adaptation at the moment of delivery - all more precisely than previously.

The disadvantage of ICG_{WB} is that it has not been validated against other non-invasive or invasive techniques in pregnant populations. State-of-the-art evaluation of non-invasive cardiac output measurement methods presupposes simultaneous comparisons with two validated invasive methods. This is needed because there is no sufficiently accurate invasive gold standard for cardiac output measurement available (Kööbi et al. 1997b). Only in a three-method setup and using the Bland-Altman approach (Bland and Altman 1986) can we reliably conclude whether the accuracy and precision of a non-invasive method is lower or at least at the same level as in contemporary invasive methods. Use of invasive methods for evaluation of the patient groups in the current study would have been almost impossible, for ethical reasons. Evaluation by means of other non-invasive methods (e.g. Doppler ultrasonography) would have been questionable because these methods have significantly more sources of inaccuracy and imprecision than ICG_{WB}, even in the non-pregnant population (Kööbi et al. 1999).

Can pregnancy change the accuracy of whole-body impedance cardiography measurement? One of the most significant factors related to pregnancy is an increase of extracellular water volume, resulting in a decrease of baseline impedance. However, baseline impedance changes are not of marked significance in the stroke volume equation of ICG_{WB} (Kööbi et al. 1999). Another factor that could theoretically influence the measurements is impedance changes related to fetal cardiac activity. On the basis of our experience this is not the case, because fetal cardiac activity is not seen in recorded signals. Therefore, its influence on measurement results could be at most negligible. We can conclude that there are no major factors influencing significantly the accuracy and precision of ICG_{WB} in the pregnant population.

In non-pregnant subjects ICG_{WB} has shown good agreement with thermodilution (no bias in CO, SV or SI, limits of agreement in CO -1.37–1.37 L/min) and the direct Fick method (bias -0.32 L/min, limits of agreement -2.24–1.60 L/min) in the measurement of cardiac output (Kööbi et al. 1997a, Kööbi et al. 1997b). The repeatability value of consecutive single measurements in ICG_{WB} proved to be considerably better than in thermodilution (0.57 L/min vs. 1.10 L/min) (Kööbi et al. 1997b).

2. Haemodynamic findings in pre-eclampsia

2.1. Baseline haemodynamics

The baseline haemodynamics of pre-eclampsia have remained a controversial issue. In our cross-sectional studies (I, II), pre-eclamptic women in a resting left lateral position were characterised by having high arterial blood pressure and SVRI and low CI. This finding is consistent with those in most previous studies (Groenendijk et al. 1984, Visser and Wallenburg 1991, Bosio et al. 1999, Borghi et al. 2000). In contrast, hyperdynamic haemodynamics – low vascular resistance with inappropriately high cardiac output – have also been observed in pre-eclampsia (Easterling et al. 1990, Yang et al. 1996).

Low CI in our studies was a consequence of lower HR, but no significant difference in SI compared with normotensive pregnancies existed (I, II) – except in the subgroup of pre-eclamptic patients undergoing elective Caesarean delivery due to preceding pre-eclampsia (V). In previous haemodynamic studies stroke index has been found to be similar to that in normotensive controls (Visser and Wallenburg 1991). On the other hand, HR has varied, being lower (Visser and Wallenburg 1991), higher (Groenendijk et al. 1984) or comparable (Borghi et al. 2000) to that in normotensive pregnancies.

One reason for the lower heart rate found in pre-eclampsia in our study could be vagal stimulation of the heart. The lower compliance of the left ventricle with increased end-diastolic volume (Borghi et al. 2000) could increase left ventricular filling pressure concomitantly with increased pressure in the atria. Higher pressure in the atria and ventricle could stimulate the baroreceptors of the atria and left ventricle, exciting vagal innervation of the heart and producing a lower heart rate. Reduced heart rate could also be an essential mechanism to limit the cardiac index and prevent a further rise in blood pressure. However, attenuation of parasympathetic control of the heart rate has been observed in pre-eclampsia in previous studies (Eneroth-Grimfors et al. 1994, Yang et al. 2000).

In a subgroup of pre-eclamptic parturients undergoing Caesarean section as a result of worsening preeclampsia, SI was found to be lower than that in uncomplicated pregnancies. There are several factors that might affect stroke volume in pre-eclamptic pregnancy. Stroke volume is dependent on preload of the heart and systolic function of the left ventricle. Components of venous return, i.e. intravascular volume and ventricular compliance, are the determinants of preload. In pre-eclampsia intravascular volume has been found to be lower than in normotensive pregnancies (Chesley 1972). In our study, pre-eclamptic women with low SI had preceding pre-eclampsia. The patients with severe pre-eclampsia had massive proteinuria (mean 8.1 g/day), which could lower plasma colloid oncotic pressure and lead to a decrease in intravascular volume. Furthermore, restricted SI was corrected by volume preloading, and SI and CI reached levels found in normotensive pregnancies. This finding suggests lower intravascular volume in these parturients.

The other factor affecting preload of the heart is ventricular compliance. In a study by Borghi and associates (2000), higher left ventricular mass and a lower ratio of E wave to A wave peak velocities were found in pre-eclampsia. In

contrast, left ventricular end-diastolic volume was significantly increased in pre-eclampsia versus normotensive pregnancies. This finding did not support reduced preload despite lower ventricular compliance in pre-eclampsia. Furthermore, systolic function of the heart has been found to be comparable to that in normotensive pregnancies (Borghi et al. 2000).

The difference in SI between pre-eclamptic and normotensive women in our study implies that the course of pre-eclampsia can modify the haemodynamics. Proceeding and worsening pre-eclampsia could partly be a result of hypoperfusion of the organs related to the depletion of intravascular volume, together with low stroke volume and cardiac output.

In our study antihypertensive medication did not have significant effect on the baseline haemodynamics of pre-eclampsia, which is probably due to limited number of study subjects.

2.2. Arterial stiffness

Besides increased peripheral vasoconstriction, we found larger conduit arteries to be stiffer in pre-eclamptic women than in women with normotensive pregnancies or pregnant women with chronic hypertension.

Blood pressure includes a steady component (mean arterial pressure) and a pulsatile component (pulse pressure). Mean arterial pressure is defined as the product of total peripheral resistance and cardiac output (Ganong 1987). In our study SVRI was significantly higher and CI lower in pre-eclampsia compared with normotensive pregnancies, which implies an effect of exceptional peripheral vasoconstriction on high MAP in pre-eclampsia.

The pulsatile component of blood pressure – pulse pressure – is mainly determined by left ventricular ejection and the geometric and viscoelastic properties of large conduit arteries. Haemodynamically larger conduit arteries transform the pulsatile flow generated by the contracting left ventricle into a steady flow at the peripheral arteries (London and Guerin 1999a, London and Guerin 1999b). In non-pregnant hypertensive populations, pulse pressure and other parameters reflecting arterial stiffness in the larger arteries have been the subjects of extensive attention, because they have been shown to predict cardiovascular risk independently (Amar et al. 2001). Generally, in our studies no differences were found in SI between the pre-eclamptic and normotensive pregnancies, suggesting the influence of divergent viscoelastic properties of the arteries on high PP in pre-eclampsia.

In non-pregnant subjects with chronic hypertension, it is unclear whether arterial stiffness is the result of changes in the properties of the arterial wall, prevailing high blood pressure, or both (London and Guerin 1999b). However, in normotensive and hypertensive subjects, the distensibility of the arteries has been shown to be proportional to blood pressure (Laurent et al. 1994). We found significant correlations between arterial stiffness and afterload in pre-eclampsia: SI/PP and SVRI, PP and SVRI, PWV and SVRI. Findings in pregnant women with chronic hypertension were similar, but in healthy pregnant women only SI/PP correlated with SVRI. Our finding supports the view of high arterial

stiffness being a physiological reaction to high arterial blood pressure in pre-eclampsia. This finding is similar to that found in a study by Elvan-Taspinar and associates (2004). Pre-eclamptic subjects were found to have higher PWV and augmentation index (AI) than pregnant women with normotension, chronic hypertension or pregnancy-induced hypertension. Furthermore, PWV showed significant correlation with MAP in each study group, but the correlation in pre-eclampsia was especially strong ($r = 0.81$). On the other hand, in a study by Rönnback and associates (2005) pre-eclamptic women had significantly higher heart rate-adjusted augmentation indices and they were independently associated with pre-eclampsia and heart rate (augmentation index is known to be influenced by heart rate), but not with mean arterial pressure.

Despite the high arterial blood pressure and correlations between arterial stiffness and afterload in pregnant women with chronic hypertension in our study, arterial stiffness was not as evident in these patients as in pre-eclampsia – only PWV was increased compared with that in normotensive subjects. The difference in arterial stiffness between pre-eclamptic women and women with chronic hypertension might imply differences in the properties of the arterial wall. The endothelium has an active role in contributing to arterial elasticity in healthy humans. Nitric oxide (NO), an endothelium-derived vasodilator, has been shown to preserve arterial elasticity in healthy humans (Kinlay et al. 2001). Endothelial dysfunction is a fundamental part of the pathophysiology of pre-eclampsia. Compared with those in normal pregnancies, NO levels have been found to be lower in pre-eclamptic parturients (Seligman et al. 1994, Schiff et al. 1992), suggesting impaired vascular smooth muscle relaxation, enhancing arterial stiffness.

The finding of increased arterial stiffness extends our knowledge about possible haemodynamic adverse effects in pre-eclampsia. The pulse pressure wave created by left ventricle ejection is known to be reflected back at branches and discontinuities of arteries and to summate with the forward pulse pressure wave (London and Guerin 1999b). As an artery stiffens, pulse wave velocity increases and the pulse wave returns during systole instead of diastole. The earlier return of pulse wave velocity increases the end-systolic stress on the left ventricle, amplifies systolic pressure and may even impair coronary perfusion by way of decreased diastolic pressure (Watanabe et al. 1993). Besides the high afterload associated with raised peripheral vascular resistance, arterial stiffness may further increase the load on the heart and contribute to the functional and structural changes found in the left ventricle of pre-eclamptic women (Borghetti et al. 2000, Simmons et al. 2002).

2.3. Cardiac natriuretic peptides and haemodynamics

In our study pre-eclamptic parturients had distinctly higher circulating concentrations of natriuretic peptides – NT-proANP and NT-proBNP – compared with chronically hypertensive and healthy parturients and the median

values were above the levels considered to be pathological in the non-pregnant population. This finding is consistent with the results of previous studies (Otsuki et al. 1987, Fievet et al. 1988, Mikkelsen et al. 1991, Itoh et al. 1993, Pouta et al. 1996b, Pouta et al. 1997).

2.3.1. *NT-proANP*

In our evaluation, NT-proANP concentrations and afterload (SVRI and SAP) had significant correlations in pre-eclamptic subjects, but no correlations were found between NT-proANP levels and CI or SI. No significant correlations between haemodynamic data and NT-proANP were found in the normotensive pregnant women or those with chronic hypertension.

The physiological stimulus for NT-proANP secretion is atrial stretch by way of mechanical or pressure load. However, evidence of atrial stretch in pre-eclampsia is conflicting: atrial dimensions in pre-eclamptic parturients have been found to be greater than (Pouta et al. 1996) or similar to (Borghgi et al. 2000) those in healthy pregnancies. Furthermore right atrial pressure has found to be low in pre-eclamptic women (Visser et al. 1987). High NT-proANP concentrations may reflect the workload sensed by the heart in pre-eclampsia. ANP is predominantly released from the myocytes of the atria, but after long-lasting workload it is also secreted from the myocytes of the ventricles—especially in the case of ventricular hypertrophy (Lee et al. 1988, Yasue et al. 1994). An increased ventricular proportion of ANP could be a reason for increased NT-proANP levels found in pre-eclampsia. This is consistent with a previous finding of correlation between ANP and left ventricular mass (Borghgi et al. 2000), and also with our finding of NT-proANP correlation with increased afterload in pre-eclampsia.

In addition to the haemodynamic associations with NT-proANP, other factors could contribute to the high concentrations of NT-proANP in pre-eclampsia. Despite massive proteinuria and high uric acid levels, no significant correlations were found between NT-proANP levels and plasma uric acid concentrations or the level of daily proteinuria in pre-eclamptic women, excluding reduced metabolic clearance as a reason for high concentrations of natriuretic peptides. Furthermore, no difference has been observed in ANP metabolic clearance in patients with pre-eclampsia when it was compared during pregnancy and four months after delivery (Irons et al. 1997). Abnormal secretion of endothelial factors such as endothelin-1 and nitric oxide may play a role. Endothelin-1 is a potent stimulant of atrial natriuretic peptide release and endothelin-1 concentrations have been found to be high in pre-eclampsia (Paarlberg et al. 1998). Nitric oxide has been shown to be an inhibitory factor of ANP release (Leskinen et al. 1995). Compared with women having normal pregnancies, NO levels have been found to be lower in pre-eclamptic parturients (Seligman et al. 1994). Furthermore, negative inotropic agents such as β -blockers are known to have stimulative activity on ANP (Laine et al. 1998). Our study included patients treated with labetalol. Concentrations of NT-proANP were significantly higher in medicated pre-eclamptic subjects compared with non-medicated ones. The

association between natriuretic peptides and afterload was even stronger in the subgroup of non-medicated pre-eclamptic women. These findings suggest that labetalol may have an impact on the concentrations of natriuretic peptides and modulate the haemodynamic association of natriuretic peptides in hypertensive pregnancies.

2.3.2. *NT-proBNP*

NT-proBNP is regarded as a sensitive marker discerning early cardiac dysfunction and has been found to correlate with the ejection fraction in non-pregnant subjects with cardiac impairment (Hunt et al. 1997). In our study, despite high NT-proBNP concentrations, pre-eclamptic women were able to maintain stroke indices as high as those in healthy pregnancies. A significant inverse correlation between NT-proBNP concentrations and CI was found in the whole pre-eclampsia group, but the correlation was not significant in the subgroup of non-medicated pre-eclamptic women. This finding suggests that antihypertensive medication may modify the association between CI and NT-proBNP in pre-eclampsia. On the other hand, a significant correlation between SVRI and NT-proBNP concentrations was found in the whole pre-eclamptic study group and this correlation was even stronger in the subgroup of non-medicated pre-eclamptic women. As in the case of NT-proANP, high NT-proBNP concentrations found in pre-eclampsia might also indicate the strain of afterload on the heart. This view is consistent with a previous finding of an association between increased left ventricular mass and high BNP concentrations in pre-eclampsia (Borghi et al. 2000).

2.3.3. *Severity of pre-eclampsia*

The circulating concentrations of natriuretic peptides did not reflect the clinical severity of pre-eclampsia: no differences in natriuretic peptide concentrations were found between cases of severe pre-eclampsia and those with mild to moderate disease. The insignificant differences in natriuretic peptide levels could be due to small sample sizes of the subgroups, but it also implies that pre-eclampsia might strain the heart by way of increased workload even in mild forms of the disease.

In contrast, in a study by Pouta and associates (1997) NT-proANP concentrations were significantly higher in severe pre-eclampsia than in the milder form of the disease. Furthermore, they found significantly higher NT-proANP values at entry into the study in the subgroup of pre-eclamptic women who later developed severe pre-eclampsia.

3. Haemodynamic findings in pregnant women with chronic hypertension and in normotensive pregnancy

3.1. Haemodynamic adaptation and concentrations of NT-proANP during the course of pregnancy

In non-pregnant populations the impairment of haemodynamics in chronic hypertension is commonly characterized by increased peripheral vascular resistance associated with normal to low cardiac output (Beevers et al. 2001, Mayet and Hughes 2003). However, especially in mild essential hypertension, in young subjects or in early-stage hypertension, peripheral vascular resistance has been found to be normal and cardiac output increased (Messerli et al. 1981, Messerli et al. 1982, Nichols et al. 1986). During pregnancy, high peripheral vascular resistance or high cardiac output could disturb haemodynamic adaptation and result in elevated blood pressure.

We found higher arterial pressure in pregnant women with chronic hypertension to be caused by consistently elevated peripheral vascular resistance during the whole of pregnancy. No differences in CI were observed in comparison with normotensive pregnancies. Findings of higher SVRI and indifferent CI in pregnant women with chronic hypertension compared with normotensive ones agree with previous findings in a cross-sectional study (Kuzniar et al. 1982). Furthermore, in our study, higher PWV in pregnant women with chronic hypertension during the whole study period was observed, reflecting stiffer larger arteries in hypertensive subjects. These findings suggest that the vasculature of chronic hypertension might be partly resistant to the prime trigger of vascular relaxation that exists in normal pregnancies, or the capacity to relax is limited.

No significant differences in haemodynamic parameters were found between medicated and non-medicated hypertensive women. This finding is likely due to a small number of subjects in the subgroups.

3.1.1. Second trimester

Hypertensive pregnancies were associated with significantly lower SI during the early and late second trimester. A reason for decreased SI could be lower preloading of the heart resulting from the reduced increase in intravascular volume in chronic hypertension. This view is further supported by significantly lower NT-proANP concentrations in women with chronic hypertension compared with normotensive subjects during the early second trimester. Since the known physiological stimulus for ANP secretion is atrial stretch by way of mechanical load (Ruskoaho 1992), it could be assumed that in parturients with chronic hypertension the volume load was apparently less and NT-proANP levels remained in the physiological range, excepting the high values found in

normotensive pregnancies during the early second trimester. In an earlier study no significant difference in plasma volume was found between pregnant women with chronic hypertension and those with normotensive pregnancies, but the measurements were carried out from 20 week's gestation and did not cover early pregnancy (Sibai et al. 1982). On the contrary blood volume of chronic hypertensive women has also found to be significantly lower compared to normotensive pregnancies. In this study measurements were obtained from 24 week's gestation (Arias 1975). However, in our study lower SI was compensated for by higher HR in cases of chronic hypertension, and no differences were found in CI between the groups.

Reduced intravascular volume expansion may involve disadvantages during pregnancy. In a previous study, normotensive pregnancies complicated by intrauterine fetal growth restriction (IUGR) involved lower stroke volume and cardiac output compared with pregnancies with appropriate-for-gestational age (AGA) fetuses. Lower stroke volume was due to smaller left ventricle end-diastolic volume and left atrial maximal dimensions, suggesting reduced plasma volume in pregnancies with IUGR (Vasapollo et al. 2002). In pregnancy-induced hypertension, the finding was similar considering lower stroke volume and cardiac output in women with small-for-gestational age (SGA) fetuses compared with women with AGA fetuses (Nisell et al. 1988). However, in our study only two newborns were SGA in the chronic hypertension group, while all newborns were AGA in normotensive women.

3.1.2. Third trimester

Compared with the second trimester, significant reductions in CI, SI and SI/PP and increases in SVRI, PWV and PP occurred in the last trimester in normotensive pregnancies. Changes in CI, SI and SVRI during the last trimester are consistent with those reported in earlier studies (Duvekot et al. 1993, Van Oppen et al. 1993), although controversies exist (Mabie et al. 1994). Reduced venous return due to the gravid uterus compressing the veins, larger amounts of blood stored in capacitance veins or a greater proportion of fluid escaping from the intravascular to the extravascular space have been thought to be reasons for decreasing SI at the end of pregnancy. We also found NT-proANP concentrations to be significantly lower than in the late second trimester, which is consistent with the assumption of decreased preload on the heart. Besides of the diminishing vasorelaxation in the peripheral vasculature, larger arteries were observed to stiffen towards the end of pregnancy. Interestingly, a similar phenomenon was not seen in parturients with chronic hypertension: CI, SI and SVRI remained stable. Since the position of the parturients and gestational ages were similar in the study groups, a decrease in SI would also have been expected in hypertensive subjects. In non-pregnant subjects with chronic hypertension there is a central shift in blood volume caused by reduced venous compliance (Mayet et al. 2003). Persistently reduced venous compliance and a more central shift of blood volume could be one reason for stable SI and CI at the end of the pregnancy in hypertensive subjects.

The mean NT-proANP concentration increased above the level considered pathological in non-pregnant subjects during the third trimester in parturients with chronic hypertension, while SI remained stable. This might suggest that there are other factors besides preloading resulting in high NT-proANP concentrations in chronic hypertension. ANP could reflect workload of the heart (Yasue et al. 1994). In our study LCWI remained higher during the whole study period in hypertensive women. However, LCWI tended to decrease throughout pregnancy and the highest values were observed earlier in the second trimester, when NT-proANP concentrations were low in women with chronic hypertension. On the other hand, the highest NT-proANP values were observed after delivery, when the lowest LCWI values were measured. Antihypertensive medication may play a role. During the third trimester eight women in our study received labetalol. Beta-blockers are known to induce ANP secretion (Laine et al. 1998). The mean NT-proANP concentration was higher in medicated subjects (437 pmol/L vs. 340 pmol/L), but the difference was not significant. The insignificant difference could be due to limited number of subjects in study. This finding might however imply that medication elevates NT-proANP concentrations and may mask the association between afterload and natriuretic peptides, as in pre-eclampsia.

3.2. Haemodynamic adaptation during puerperium

After delivery, measurements were carried out on the second to fifth postpartum day, which limited our view of postpartum adaptation to a relatively short period. In normotensive women signs of disappearance of vasorelaxation (higher SVRI, SAP, PWV and lower SI/PP compared with values in the third trimester) were observed during the first postpartum days, but SI, HR and CI remained at the level measured during the third trimester of pregnancy. In women with chronic hypertension, haemodynamics remained relatively stable after delivery. Compared with the third trimester only PP increased. This finding further emphasizes the limited effect of pregnancy on vascular tone in chronic hypertension compared with normotensive pregnancies.

Concentrations of NT-proANP were exceptionally high in both groups during the postpartum period. High NT-proANP values probably indicated the activity of fluid movement from the extravascular compartment to the intravascular space, and an increased intravascular volume might require high NT-proANP values to cope with it. However, this volume shift was not reflected in changes of SI or CI in either group.

4. Haemodynamic adaptation at delivery and in early puerperium in pre-eclamptic and normotensive pregnancy

4.1. Haemodynamic changes at delivery in normotensive pregnancy

At the moment of delivery, uteroplacental circulation suddenly diminishes. Thorough haemodynamic adaptation has been reported to occur at delivery in normotensive pregnancies. Our finding of 47% higher CI, 39% lower SVRI and stable MAP in healthy pregnancies after delivery of the placenta, compared with baseline values, is consistent with the results of previous studies (Ueland et al. 1972, James et al. 1989, Robson et al. 1989). Even cardiac output has also been found to be stable at the moment of delivery (Park et al. 1996). We could also demonstrate that the increase in CI was due to significant increases in both HR and SI. These findings suggest that there is a sudden volume load in the vasculature at the moment of delivery as the blood from the contracting uterus and pooled blood in the lower extremities is expelled into the vasculature. This volume load results in an increase in cardiac index and a lower systemic vascular resistance index simultaneously.

In the studies mentioned above haemodynamic measurements have been obtained periodically at different time intervals before and after delivery according to the techniques used (Ueland et al. 1972, James et al. 1989, Robson et al. 1989). The timing of high cardiac output after delivery has varied from ten to ninety minutes (Ueland et al. 1972, Robson et al. 1989, James et al. 1989). Since we used a continuous method to measure haemodynamic parameters, we were able to document the fact that haemodynamic changes at the moment of delivery are sudden – appearing instantly at the moment of delivery of the newborn and lasting on average for ten minutes, before returning to the levels observed just before delivery. After Caesarean section, at the moment of skin closure SI, HR and CI still remained at higher levels and SVRI at a lower level compared with baseline values. These changes could be partly due to still continuing adaptation towards volume load at delivery, but they are also affected by persisting regional anaesthesia and fluid preloading. The baseline haemodynamic values were obtained after disappearance of anaesthesia. Excessive bleeding, and the quality and quantity of intravenous fluid preloading can modify the recovery from Caesarean delivery and partly explain the variability of cardiac output changes after delivery in different studies. In our study, bleeding was moderate (average 415 ml) and the fluid preloading protocol before and during the surgical procedure was standardized.

4.2. *Haemodynamic changes at delivery in pre-eclampsia*

In previous studies haemodynamic changes after delivery in pre-eclamptic parturients have varied, but information is scarce. Cardiac output has been found to increase by 11% measured 30 minutes after delivery compared with baseline values. Furthermore, delivery has been associated with decreased mean arterial pressure and systemic vascular resistance, but stable stroke index (Phelan and Yurth 1982). In contrast, cardiac output has also been found to remain stable and mean arterial pressure to decrease significantly with a tendency of systemic vascular resistance to be lower at the moment of delivery (Newsome et al. 1986). Both of these studies included parturients delivering vaginally.

In our study profound haemodynamic changes took place at the moment of delivery – 52% higher CI and 46% reduced SVRI compared with the baseline values observed before preloading, and the reaction was comparable to that in normotensive parturients. The increased CI was due only to higher heart rate, and SI remained stable. This reaction was significantly different from that in normotensive parturients, in which both HR and SI increased significantly.

Stable SI at the moment of delivery may indicate poorer preload of the heart compared with healthy parturients. Because of the hypovolaemia and poorly perfused placenta during pregnancy in pre-eclampsia, there could be less pooling of blood volume in the uterus and lower extremities and the volume load caused by delivery might be less than in uncomplicated pregnancies. Another reason for the lacking increase in SI could be restricted cardiac adaptation to sudden volume load. The heart in pre-eclampsia has shown mild diastolic impairment as a result of increased afterload (Borghi et al. 2000). A state of diastolic dysfunction could also explain the unchanged SI measurements after delivery. In our study, low SI found in baseline measurements in pre-eclampsia was corrected by preload infusion and afterwards SI in pre-eclampsia was maintained at the level in normotensive pregnancies until the moment of delivery. Presumably, the heart might be able to compensate for sudden volume load only by increasing HR, not by adjusting SI, despite decreased afterload – mean arterial pressure and systemic vascular resistance – after delivery. The observed haemodynamic pattern of failed increase in SI after delivery accompanied by volume load from the diminishing uterine circulation underlines the risk of relative heart failure, exposing the patient to the risk of pulmonary oedema after delivery in pre-eclampsia.

At the moment of delivery in healthy pregnancies, diminished systemic vascular resistance was consistent with increased CI, and MAP remained stable. In contrast, in pre-eclamptic women mean arterial pressure fell and it reached a nadir during Caesarean delivery. This sudden opening of the peripheral circulation, concomitant with inadequate cardiac output, may lead to underfilling of the vasculature and compromise oxygenation of the tissues.

After the surgical procedure haemodynamic reactions also differed significantly between the normotensive and pre-eclamptic parturients. After disappearance of anaesthesia SVRI reverted to the baseline level, but CI and MAP remained significantly decreased in pre-eclampsia, while in normotensive pregnancies these values were at the same level as in baseline measurements. The decrease in CI was due to significant decreases in SI and HR. This finding

reflects a persisting risk of pulmonary oedema and more labile haemodynamics of pre-eclampsia after delivery compared with normotensive pregnancy.

4.3. Haemodynamic changes in early puerperium

During the second to fifth postpartum day pre-eclamptic parturients had re-established CI as well as SI at the same level as in normal pregnancies, although vasospastic features of the disease persisted, reflected in higher SVRI and MAP compared with normotensive subjects. However, mean MAP and SVRI values had decreased below the baseline level in pre-eclampsia. The lowered afterload might be one factor allowing the heart to recover from the adaptive state of pre-eclampsia, inducing CI and SI to increase. Withdrawal of excessive fluid from the extravascular space into the intravascular space (Pouta et al. 1996a) may also augment SI and CI in pre-eclamptic parturients.

5. Clinical implications

Our studies mostly concentrated on the physiological differences between pre-eclamptic pregnancies, normotensive pregnancies and those with chronic hypertension in respect of the haemodynamics. However, our results also disclosed some clinical implications.

We found significantly different haemodynamic reactions at the moment of delivery and after delivery until the disappearance of anaesthesia between pre-eclamptic and normotensive pregnancies. The most significant differences were inability to increase SI at the moment of delivery and even decreasing SI and CI after delivery in pre-eclampsia. Unchanged SI at delivery may be a contributing factor to the risk of pulmonary oedema, together with other risk factors such as low plasma colloid osmotic pressure, increased capillary permeability and hypertension in pre-eclampsia (Rout 2001).

Immediately after delivery until the disappearance of anaesthesia SI further declined, and because of the lack of increased heart rate CI also decreased in pre-eclamptic women, suggesting a critical period in haemodynamic recovery after delivery. The amount of bleeding in our study groups was moderate and similar among the groups. However, in pre-eclamptic parturients even this moderate bleeding might cause relative hypovolaemia because of the pre-existing hypovolaemia during pregnancy, resulting in lower SI and CI compared with those in normotensive parturients during this period. Excessive bleeding might further affect haemodynamic adaptation and this underlines the importance of volume optimization in pre-eclamptic parturients after delivery. Our findings emphasize the need for careful post-partum follow up in pre-eclamptic patients.

They also underline caution in the use of antihypertensive medication that might limit cardiac function in pre-eclamptic parturients during the post-partum period.

In both of the hypertensive groups – pre-eclampsia and chronic hypertension – the cause of elevated blood pressure was increased peripheral resistance, while no increased CI compared with that in normotensive pregnancies was found. Our haemodynamic findings favour antihypertensive medication targeted at lowering peripheral vascular resistance rather than restricting cardiac output, when antihypertensive medication is needed during the course of pregnancy.

Cardiac natriuretic peptide concentrations have been used to aid in the diagnosis of heart failure in non-pregnant populations (Cowie et al. 1997, Shapiro et al. 2003). The sensitivity and specificity of high NT-proANP concentrations in indicating low ejection fraction and left ventricular hypertrophy have been 0.67–0.73 and 0.63–0.79 respectively (Yamamoto et al. 1996b). In addition, NT-proBNP concentrations have been shown to have an inverse correlation with left ventricular ejection fraction (Hunt et al. 1997). In our study NT-proANP concentrations in pre-eclamptic pregnancies correlated with afterload, but not with the function of the heart estimated by SI and CI. As regards NT-proBNP, only the highest values correlated with low CI in pre-eclampsia, but the number of subjects was limited. It appears that in clinical practise high circulating concentrations of cardiac natriuretic peptides reflect the workload of the heart, but cannot be used to assess the function of the heart.

CONCLUSIONS

1. Aberrant haemodynamic adaptation in pre-eclampsia includes increased arterial stiffness of the larger arteries and high resistance in small peripheral arteries and arterioles evaluated by whole-body impedance cardiography. Exceptionally high arterial stiffness could be related to high blood pressure and it could be further enhanced by the endothelial dysfunction found in pre-eclampsia, since despite high blood pressure in women with chronic hypertension, the increase of arterial stiffness in pre-eclampsia exceeded that in chronic hypertension.

2. Circulating concentrations of natriuretic peptides (NT-proANP and NT-proBNP) are significantly higher in pre-eclamptic subjects compared with pregnant normotensive women or pregnant women with chronic hypertension. In non-medicated pre-eclamptic women, NT-proANP and NT-proBNP concentrations are associated with high afterload but not with stroke index or cardiac index. This suggests that high natriuretic peptide concentrations reflect the strain on the heart caused by high afterload and pressure in pre-eclampsia.

3. Haemodynamics among women with chronic hypertension during pregnancy and after delivery are characterized by significantly increased peripheral vascular resistance and arterial stiffness compared with normotensive pregnant women. Lower SI and lower NT-proANP concentrations found in pregnant women with chronic hypertension compared with controls in the early second trimester might be associated with reduced intravascular volume expansion in pregnant women with chronic hypertension.

4. The moment of delivery is associated with a significant increase in cardiac output and a decrease in systemic vascular resistance in normotensive pregnancies. Intact physiological compensation mechanisms are required to adapt to the sudden volume load at the moment of delivery.

5. At the moment of delivery pre-eclamptic parturients were unable to increase stroke volume, thus differing from healthy parturients. The unchanged SI at the moment of delivery and even diminishing SI after delivery could be the result of lower volume preload after delivery or dysfunction of the left ventricle in pre-eclampsia in adapting to sudden volume load at the moment of delivery. The inability to adapt to increased volume after delivery could expose pre-eclamptic parturients to the risk of cardiovascular complications, such as pulmonary oedema.

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A handwritten signature in black ink, appearing to read "K. Tirkkonen". The signature is written in a cursive style with a large initial 'K' and a long, sweeping underline.

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ORIGINAL COMMUNICATIONS

NATRIURETIC PEPTIDES AND HEMODYNAMICS IN PREECLAMPSIA

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High NT-proANP and NT-proBNP concentrations in preeclamptic women reflect the strain on the heart caused by high afterload.

NATRIURETIC PEPTIDES AND HEMODYNAMICS IN PREECLAMPSIA

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preeclampsia; natriuretic peptides; NT-proANP; NT-proBNP; hemodynamics

Abstract

Objective To evaluate the relationship between natriuretic peptides (NT-proANP and NT-proBNP) and hemodynamic parameters in preeclampsia.

Study Design A cross-sectional study of nineteen preeclamptic, fifteen chronic hypertensive and twenty-six normotensive women in the third trimester of pregnancy. Stroke index (SI), heart rate (HR), cardiac index (CI), systemic vascular resistance index (SVRI) and left cardiac work index (LCWI) were derived by whole-body impedance cardiography. Systolic blood pressure (SAP), diastolic blood pressure (DAP) and mean arterial pressure (MAP) were measured. The plasma levels of NT-proANP and NT-proBNP were determined with radioimmunoassays.

Results NT-proANP and NT-proBNP concentrations were significantly higher in preeclamptic women compared to chronic hypertensive and normotensive pregnancies. Preeclamptic women had lower CI and HR and higher SAP, MAP and SVRI than the control groups. In preeclampsia NT-proANP correlated significantly with SAP and SVRI, meanwhile NT-proBNP correlated significantly with SVRI and CI. These correlations persisted in the subgroup of non-medicated preeclamptic women, except in the case of NT-proBNP and CI.

Conclusion High NT-proANP and NT-proBNP concentrations in preeclampsia reflect the strain on the heart caused by high afterload, rather than the function of the heart expressed as SI or CI.

Introduction

Natriuretic peptides are polypeptide hormones produced by the heart. Excretions of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are increased by cardiac overload. The physiological function of natriuretic peptides is to relieve the workload of the heart by increasing natriuresis and diuresis, enhancing capillary permeability and relaxing the peripheral vasculature.¹

The principal storage form of ANP- proANP- is cleaved into active ANP and an inert amino-terminal fragment of pro-ANP (NT-proANP), similar to the case of BNP. N-terminal fragments are secreted in equimolar amounts with ANP and BNP, but are more stable and have a longer half-life, being thus more suitable for diagnostic requirements.¹ For clinical purposes natriuretic peptides and their N-terminal fragments have been regarded as markers of abnormal left ventricle diastolic or systolic function and structure- especially in chronic heart failure in a nonpregnant population.^{2,3}

In preeclamptic parturients, the concentrations of ANP, NT-proANP, BNP and NT-proBNP have proved to be higher compared to normal pregnancies,⁴⁻⁹ although some controversy exists.^{10,11}

Increased ANP concentrations in preeclampsia have been associated with decreased plasma volume, decreased plasma aldosterone concentration and decreased renin activity compared to normotensive pregnancies.⁴ Enhanced natriuresis after ANP infusion has been demonstrated in preeclamptic parturients.¹² Besides these physiological functions, high ANP and BNP concentrations have been associated with left ventricular changes such as increased left ventricle mass and increased left ventricle end-diastolic and end-systolic volumes in preeclampsia.¹³

The hemodynamic adaptation in preeclampsia differs from normal pregnancies by exceptional vasoconstriction.¹⁴⁻¹⁶ An increased afterload may result in changes in the function and structure of the left ventricle in preeclamptic women.^{13,17} Since high natriuretic peptides are regarded as a sign

of restricted left ventricle function, our hypothesis was that NT-proANP and NT-proBNP concentrations could reflect the impaired maternal hemodynamics of preeclampsia, and the aim was to further elucidate the association between natriuretic peptides and hemodynamics in preeclampsia. Reference data were obtained from healthy women with uncomplicated pregnancies and pregnant women with chronic hypertension.

Material and methods

The study cohort comprised nineteen women with preeclampsia, twenty-six healthy women with uncomplicated pregnancies and fifteen pregnant women with chronic hypertension in the third trimester. The study was carried out at Tampere University Hospital. The procedure was explained to each subject and written consent was obtained. The Ethics Committee of Tampere University Hospital approved the study.

Preeclamptic patients had no pre-existing hypertension, renal disease, heart disease or diabetes.

Preeclampsia was diagnosed if two measured blood pressures were greater than 140/90 mmHg and if consistent proteinuria of more than 300 mg/day existed. The following laboratory tests were carried out on preeclamptic women on admission: blood cell count including platelet count, uric acid, alanine transaminase, d-dimer of fibrin and collection for daily proteinuria. Preeclampsia was considered severe if arterial pressure remained $\geq 160/110$ mmHg and proteinuria exceeded 5 g/day. Six of the preeclamptic women met the criteria for severe disease. Four patients received an antihypertensive peroral regimen of labetalol 200-600 mg daily during the study period; two of the four had severe preeclampsia. Inclusion criteria for healthy pregnancies were: no previous diseases, blood pressure under 140/90 mmHg and negative stix-test for proteinuria. Women were classified as having chronic hypertension if arterial pressure was $\geq 140/90$ mmHg preconceptionally, in the first half of pregnancy, or the patient received antihypertensive medication during these periods. At the time of inclusion in the study, six women received antihypertensive medication: peroral labetalol 200-400 mg daily. None of the chronic hypertensive subjects had superimposed preeclampsia. Demographic data are presented in Table I.

The circulation monitoring device CircMonTM B202 (JR Medical Ltd, Tallinn, Estonia) was used for the estimation of heart rate (HR), stroke volume, cardiac output, systemic vascular resistance

and left cardiac work. The measurement of beat-to-beat stroke volume in this device is based on whole-body impedance cardiography, a detailed description of this method being available in other publications.^{18, 19} As heart-related impedance changes depend on the magnitude of the blood cell concentration in the vessels,²⁰ blood samples for hematocrit were obtained before the measurements to adjust impedance-derived hemodynamic parameters to individual hematocrit. Hemodynamic parameters obtained were indexed to body surface area to avoid the effect of body size on them (i.e. CI, cardiac index; SI, stroke index; SVRI, systemic vascular resistance index; LCWI, left cardiac work index). LCWI was derived by the following formula $LCWI = 0.0144 \times [MAP - PACWP] \times CI$. SVRI was derived from the equation $SVRI = 80 \times [MAP - CVP] / CI$. As a non-invasive method the CircMonTMB202 uses constant average normal values of CVP (3 mmHg) and PACWP (6 mmHg) for these calculations. PACW and CVP have been found to be within normal range in healthy pregnant volunteers and in preeclampsia.^{14, 21}

Systolic blood pressure (SAP) and diastolic blood pressure (DAP) were measured continuously beat-to-beat by non-invasive Finapres-blood pressure monitor Ohmeda 2300 (Englewood, CO, USA) at the finger level. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus $\frac{1}{3}$ of pulse pressure.

Participants were examined after fifteen minutes of rest in left lateral position to avoid the effect of the gravid uterus on the circulation. Recording in this position was maintained continuously for fifteen minutes. The values obtained for the analyses were averages over 30 seconds during the most stable recording.

The plasma levels of NT-proANP and NT-proBNP were determined with radioimmunoassays utilizing antisere directed to NT-proANP₄₆₋₇₉ and NT-proBNP₁₀₋₂₉, as described in detail elsewhere.²² The sensitivities of the assays were 60 pmol/l and 40 pmol/l plasma, respectively. In five normotensive women the NT-proBNP concentration was under detection limit; in results the values were considered to be 40 pmol/l, which was the lowest detected value. An NT-proANP concentration ≤ 255 pmol/l and NT-proBNP ≤ 86 pmol/l were considered normal values.²²

The differences between three groups were compared by Kruskal-Wallis test. If statistical significance was shown, the post hoc Mann-Whitney U-test was used in further analysis. The difference in the percentage of primiparous between the groups was compared by Fisher's exact test. Comparisons between two groups were made with Mann-Whitney U-test. Spearman's correlation coefficient (r_s) was calculated to estimate associations between hemodynamic parameters and natriuretic peptides and other laboratory parameters. Differences were considered statistically significant if $p \leq 0.05$. Data are presented as median and range, when necessary. Statistical analysis was performed using SPSS for Windows (version 11.0, SPSS Inc, Chicago, IL) on a standard PC.

Results

Concentrations of NT-proANP and NT-proBNP were significantly higher in preeclamptic women compared to chronic hypertensive and healthy subjects. In chronic hypertensive women NT-proANP and NT-proBNP were significantly higher than in normotensive pregnancies. Finding is illustrated in Figure 1. Among healthy pregnancies 23% had high NT-proANP concentration (≥ 255 pmol/l) and 31% had high NT-proBNP concentration (≥ 86 pmol/l). Meanwhile, in women with chronic hypertension 69% and 70% and in preeclamptic women 95% and 100% had high NT-proANP and high NT-proBNP concentrations, respectively. A strong positive correlation between NT-proANP and NT-proBNP ($r_s=0.75$, $p<0.001$) in the whole study population was found.

Preeclamptic women had significantly lower CI and HR and higher SAP, MAP and SVRI compared to the two other groups. Chronic hypertensive women differed from the healthy ones in higher SAP, MAP, DAP and SVRI. SI was alike between the study groups. Results on natriuretic peptides and hemodynamic parameters are set out in Table II. The differences in hemodynamic parameters and natriuretic peptides between the study groups were similar when women with antihypertensive medication were excluded from the groups of preeclampsia and chronic hypertension. The hemodynamic parameters were comparable between medicated and non-medicated women in the groups of preeclampsia and chronic hypertension. Only SI was significantly lower in medicated compared to non-medicated chronic hypertensive women. NT-proANP and NT-proBNP concentrations were significantly higher in medicated than in non-medicated preeclamptic women. Data shown in Table III.

In preeclamptic women NT-proANP correlated significantly with SAP ($r_s= 0.55$, $p=0.02$) and SVRI ($r_s= 0.60$, $p=0.009$). Furthermore, NT-proBNP and CI ($r_s=0.48$, $p=0.04$) and NT-proBNP and SVRI

($r_s=0.53$, $p=0.03$) had significant correlations. Natriuretic peptides showed no significant correlations with the laboratory test findings (hematocrit, platelet count, uric acid, alanine transaminase, d-dimer of fibrin and daily proteinuria) in preeclampsia. In women with chronic hypertension no significant correlations emerged between natriuretic peptides and hemodynamics. In healthy pregnancies only NT-proBNP and DAP ($r_s=0.40$, $p=0.04$) as well as NT-proBNP and MAP ($r_s=0.44$, $p=0.02$) had significant correlations.

Correlations between hemodynamics and natriuretic peptides were calculated in the subgroups of non-medicated women in hypertensive pregnancies. Significant correlations between NT-proANP and SAP ($r_s=0.65$, $p=0.008$), NT-proANP and MAP ($r_s=0.59$, $p=0.02$), NT-proANP and SVRI ($r_s=0.81$, $p<0.001$) and NT-proBNP and SVRI ($r_s=0.68$, $p=0.005$) were found in the preeclampsia group. In chronic hypertension correlations were noted between NT-proANP and SAP ($r_s=0.84$, $p=0.005$), NT-proANP and MAP ($r_s=0.83$, $p=0.005$), NT-proANP and DAP ($r_s=0.70$, $p=0.04$) and NT-proBNP and SVRI ($r_s=0.79$, $p=0.04$). Scatter plot of NT-proaANP and SAP in the whole study groups and in the non-medicated subgroups of hypertensive women are illustrated in Figure 2.

Preeclamptic pregnancies were divided into severe and mild to moderate preeclampsia groups. Severe preeclampsia comprised six and preeclampsia thirteen subjects. No significant differences were found between the groups in concentrations of natriuretic peptides or hemodynamic parameters.

Two parturient with the highest NT-proBNP concentrations in the preeclampsia group had severe preeclampsia medicated with labetalol. The hemodynamic parameters in these women were comparable with those in the rest of the preeclamptic women. In the group of chronic hypertension one of the two subjects with the highest NT-proANP was receiving labetalol medication. In both of

these women CI was lower (2.9-2.8 l/min/m²) and one (not medicated) had higher SVRI (2725 dyn x s/cm⁵/m²) when compared to the rest of the chronically hypertensive subjects.

Comment

In our study preeclamptic pregnancies had significantly higher natriuretic peptide -NT-proANP and NT-proBNP- concentrations compared to chronic hypertensive and normotensive pregnancies and the median values were above the level considered to be pathological in a non-pregnant population.

High NT-proANP levels are associated with left ventricular hypertrophy and diastolic or systolic dysfunction in non-pregnant populations with suspected cardiac disease.³ In preeclamptic women the heart has shown adaptive changes towards high afterload, for example increased left ventricle mass and signs of left ventricle dysfunction.^{13,17} High ANP concentrations have been associated with high left ventricle mass and increased end-diastolic and end-systolic volumes in preeclampsia.¹³ In our study, the hemodynamics in preeclamptic pregnancies were characterized by significantly lower CI and higher SVRI, SAP and MAP compared to the other study groups. However, the low cardiac index was due mainly to lower HR with no significant difference in SI between the study groups. We found no correlation between SI or CI and NT-proANP in preeclamptic pregnancies. On the other hand, there was a significant correlation between NT-proANP and afterload (SVRI and SAP) in preeclampsia and the correlations were even stronger in the subgroup of non-medicated women. These findings suggest that high NT-proANP levels in preeclamptic pregnancies reflect rather the strain on the heart caused by high afterload than a functional impairment of the heart as estimated by SI or CI. Under prolonged workload of the heart- especially in the presence of left ventricular hypertrophy- also ventricular besides atrial myocytes are known to secrete ANP.²³ The increased proportion of ventricular origin of ANP due to high afterload could be one reason for enhanced concentrations of NT-proANP in preeclampsia. In our study LCWI was higher in preeclamptic pregnancies compared to healthy, even if the difference was not statistically significant.

The most novel natriuretic peptide in clinical use is NT-proBNP, since the assay for it has only recently been introduced. NT-proBNP is regarded as a sensitive marker discerning early cardiac dysfunction and has been found to correlate with the ejection fraction in non-pregnant subjects with cardiac impairment.²⁴ In our study NT-proBNP concentrations were significantly higher in preeclamptic women. Despite high NT-proBNP concentrations, preeclamptic women were able to maintain stroke indices as high as those in the healthy pregnancies in our material. The significant inverse correlation between NT-proBNP and CI was found in the whole preeclampsia group, but the correlation was not significant in the subgroup of non-medicated preeclamptic women. This finding suggests that the antihypertensive medication may modify the association between CI and NT-proBNP in preeclampsia. On the other hand the significant correlation between SVRI and NT-proBNP was found in the whole study group of preeclampsia and this correlation was even stronger in the subgroup of non-medicated preeclamptic women. As in the case of NT-proANP, high NT-proBNP concentrations found in preeclampsia might also indicate the strain of the afterload to the heart. This view is also in consistency with the previous finding of the association between increased left ventricular mass and high BNP concentrations in preeclampsia.¹³

In only a few previous studies natriuretic peptide concentrations in parturients with chronic hypertension have been measured: ANP has been found to be similar^{11, 25, 26} compared to normotensive pregnancies. We found higher NT-proANP and NT-proBNP concentrations in chronic hypertensive women compared with normotensive ones. And over half of the pregnant chronic hypertensive women had natriuretic peptide concentrations above the value considered pathological in a non-pregnant population. In our study, afterload (higher SVRI and arterial blood pressure) was also significantly increased and workload (higher LCWI) increased in chronic hypertensive parturients compared to normotensive pregnancies. And in the subgroup of non-medicated chronic hypertensive subjects correlations between afterload and natriuretic peptides

were found as in the case of preeclampsia. This suggests that higher natriuretic peptide concentrations in chronic hypertensive pregnancies are also associated with higher afterload compared to healthy pregnancies. The level of arterial blood pressure, SVRI and natriuretic peptides in chronic hypertensive women remained significantly lower compared to preeclamptic pregnancies. This might imply that the left ventricle tolerated the level of afterload in chronic hypertension better than in preeclampsia. Another possibility is that other factors besides the cardiac strain caused by high afterload contribute to high natriuretic concentrations in preeclampsia.

A possible explanation for the high natriuretic peptide concentrations in preeclampsia could be reduced metabolic clearance of the N-terminal proatriuretic peptides due to renal impairment. Despite massive proteinuria and high uric acid levels, no significant correlations were found between the natriuretic peptide (NT-proANP and NT-proBNP) levels and plasma uric acid concentrations or the level of proteinuria in preeclamptic women in our study. Endothelial factors such as endothelin-1 and nitric oxide may play a role. Endothelin-1 is a potent stimulant for atrial natriuretic release and the endothelin-1 concentration has been found to be high in preeclampsia.²⁷ Nitric oxide (NO) has shown inhibitory effects on ANP release.²⁸ Compared to normal pregnancies NO levels have been found to be lower in preeclamptic parturients.²⁹ Also negative inotropic pharmacies such as β -blockers are known to exert a stimulatory effect on ANP. Some preeclamptic as well as chronic hypertensive women here were treated with labetalol, which is a combined α - and β -blocker. In our study medicated preeclamptic women had significantly higher NT-proANP and NT-proBNP values compared to non-medicated ones. Moreover, the associations between the natriuretic peptides and afterload were stronger when medicated women were excluded from the study group of preeclampsia. In the case of chronic hypertension associations between natriuretic peptides and afterload was found only in the subgroup of non-medicated subjects. These findings

suggest that labetalol may have had an impact on the concentrations of natriuretic peptides and modulated the hemodynamic association of natriuretic peptides in hypertensive pregnancies.

The concentrations of natriuretic peptides here could not reveal the clinical severity of preeclampsia: no differences in natriuretic peptide concentrations were found between severe and mild to moderate preeclampsia. The insignificant differences in natriuretic peptide concentrations could be due to small sample size of the subgroups. But it also implies that preeclampsia might strain the heart by increased workload even in milder forms of the disease.

The concentrations of the natriuretic peptides -NT-proANP and NT-proBNP- in normotensive pregnancies were within normal range and significantly lower than in preeclamptic women. This finding is in concert with those in previous studies.^{30,31} In normal pregnancy, the heart is challenged by increased blood volume and there is evidence of functional and structural adaptation of the heart also during normal pregnancy.³²⁻³⁴ Increased ANP concentrations have been found to parallel increased heart rate, cardiac output and stroke volume and decreased total peripheral vascular resistance during a healthy pregnancy.³⁵ Hence natriuretic peptides have been considered to play an important role in homeostasis during pregnancy. In our study the hemodynamics in normal pregnancies differed significantly from the preeclamptic pregnancies by higher CI, HR and lower SVRI and arterial pressure. The normal range of natriuretic peptide concentrations may suggest that homeostasis is achieved by normal natriuretic peptide secretion and that the hemodynamic changes during normal pregnancy do not strain the heart.

In conclusion, we found natriuretic peptides (NT-proANP and NT-proBNP) to be significantly higher in preeclamptic compared to normotensive or chronic hypertensive pregnancies. NT-proANP and NT-proBNP concentrations were associated with high afterload found in preeclampsia which

suggests that high natriuretic peptide concentrations reflect the strain on the heart caused by high afterload in preeclampsia.

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Table I.	Demographic data			
	Preeclampsia n=19	Healthy pregnancy n=26	Chronic hypertension n=15	Kruskal-Wallis p-value
age (years)	33 (19-43)	27 (20-33)	33 (23-40)	0.003
body mass index (kg/m ²)	27.7 (24.7- 32.0)	27.4 (22.6-33.4)	30.3 (26.2- 36.2)	0.07
percentage of primiparous	89	100	87	0.2*
gestational age at admission (weeks)	33 (27-39)	35 (33-36)	34 (32-36)	0.009
gestational age at delivery (weeks)	33 (28-39)	40 (35-42)	38 (35-41)	0.001
systolic blood pressure on admission (mmHg)	155 (140-180)	120 (96-134)	138 (101-170)	<0.001
diastolic blood pressure on admission (mmHg)	100 (90-112)	76 (58-88)	94 (80-120)	<0.001
proteinuria (g/day)	3.9 (0.4-9.4)	< 0.3	< 0.3	<0.001
uric acid (mmol/l)	0.3 (0.3-0.5)			
platelet count (x 10 ⁹ /l)	238 (134-332)			
alanine transaminase (U/l)	12 (6-86)			
d-dimer of fibrin (mg/l)	0.2 (0.2-0.4)			

Values are expressed as median(range), except in the case of percentage of primiparous.

*Fisher's Exact Test

Natriuretic peptides, hematocrit values and hemodynamic data in the study groups.

Table II.	Preeclampsia n=19	Healthy pregnancy n=26	Chronic hypertension n=15	Kruskal-Wallis p-value
Hct (%)	35 (28-42)	35 (30-43)	36 (32-38)	0.5
NT-proANP(pmol/l)	888 (240-2054)	202 (85-389)*	283 (178-1163) †‡	<0.001
NT-proBNP(pmol/l)	190 (87-1945)	59 (40-130)*	98 (52-184) †‡	<0.001
SI (ml/m ²)	39 (30-51)	40 (31-72)	39 (25-62)	0.2
HR (beats/min)	71 (55-89)	78 (57-106)*	84 (59-105) †	0.005
CI (l/min/m ²)	2.7 (2.1-3.3)	3.4 (2.5-4.5)*	3.0 (1.9-5.3) †	<0.001
SAP (mmHg)	146 (120-204)	103 (90-124) *	123 (93-171) †‡	<0.001
MAP (mmHg)	102 (85-133)	73 (64-89) *	90 (69-114) †‡	<0.001
DAP (mmHg)	78 (63-101)	59 (49-74) *	77 (57-90) ‡	<0.001
SVRI (dynxs/cm ⁵ /m ²)	2874 (2321-4411)	1679 (1168-2810) *	2084 (1178-4044) †‡	0.001
LCWI (kgxm/m2)	3.4 (2.6-4.8)	2.9 (2.3-3.9)	3.5 (2.1-6.3)	0.06

Values are expressed as median (range).

Hct, hematocrit; NT-proANP, N-terminal fragment of ANP; NT-proBNP, N-terminal fragment of BNP;

SI, stroke index; HR, heart rate; CI, cardiac index; SAP, systolic blood pressure;

MAP, mean arterial pressure; DAP, diastolic blood pressure; SVRI, systemic vascular resistance index, LCWI, left cardiac work index.

* p< 0.05 (Mann-Whitney U-test, compared with preeclampsia).

† p< 0.05 (Mann-Whitney U-test, compared with preeclampsia).

‡ p<0.05 (Mann-Whitney U-test, compared with healthy pregnancy).

Table III. Natriuretic peptides and hemodynamics in hypertensive medicated and non-medicated pregnancies.

	Preeclampsia		Chronic hypertension	
	non-medicated n=15	medicated n=4	non-medicated n=9	medicated n=6
Hct (%)	35 (28-42)	35 (31-38) 1477 (785-	34 (31-37)	37 (32-38)
NT-proANP (pmol/l)	803 (240-1647)	2054)†	246 (193-908)	379 (178-1163)
NT-proBNP (pmol/l)	167 (87-454)	607 (167-1945)†	94 (52-141)	100 (67-184)
SI (ml/m ²)	40 (32-46)	32 (30-51)	41(33-62)	33 (25-44)†
HR (beats/minute)	67 (55-87)	75 (66-89)	78 (57-97)	87 (76-105)
CI (l/min/m ²)	2.7 (2.3-3.0)	2.6 (2.1-3.3)	3.1 (1.9-5.3)	2.8 (2.2-4.1)
SAP (mmHg)	144 (120-204)	152 (139-175)	113 (99-160)	129 (106-171)
MAP (mmHg)	102 (85-133)	103 (94-121)	87 (69-113)	97 (83-114)
DAP (mmHg)	78 (63-101)	79 (71-94)	69 (57-90)	81 (72-85)
SVRI (dynxs/cm ⁵ /m ²)	2874 (2405-3841)	2965 (2321-4411)	1954 (1178-3462)	2444 (1810-4044)
LCWI (kgxm/m ²)	3.3 (2.6-4.8)	3.4 (3.3-4.2)	4.0 (2.1-6.3)	3.3 (2.8-5.1)

Values are expressed as median (range).

p-values refer to differences between non-medicated and medicated subjects.

NT-proANP, N-terminal fragment of ANP; NT-proBNP, N-terminal fragment of BNP; SI, stroke index; HR, heart rate; CI, cardiac index; SAP, systolic blood pressure MAP, mean arterial pressure; DAP, diastolic blood pressure; SVRI, systemic vascular resistance index; LCWI, left cardiac work index.

† <0.05 (Mann-Whitney U-test, compared with non-medicated subjects).

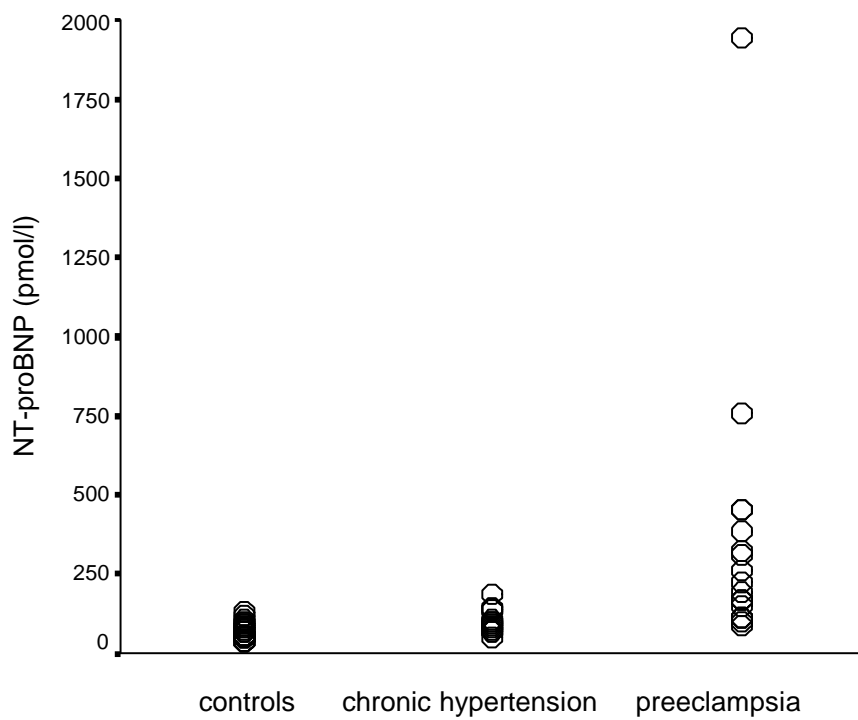
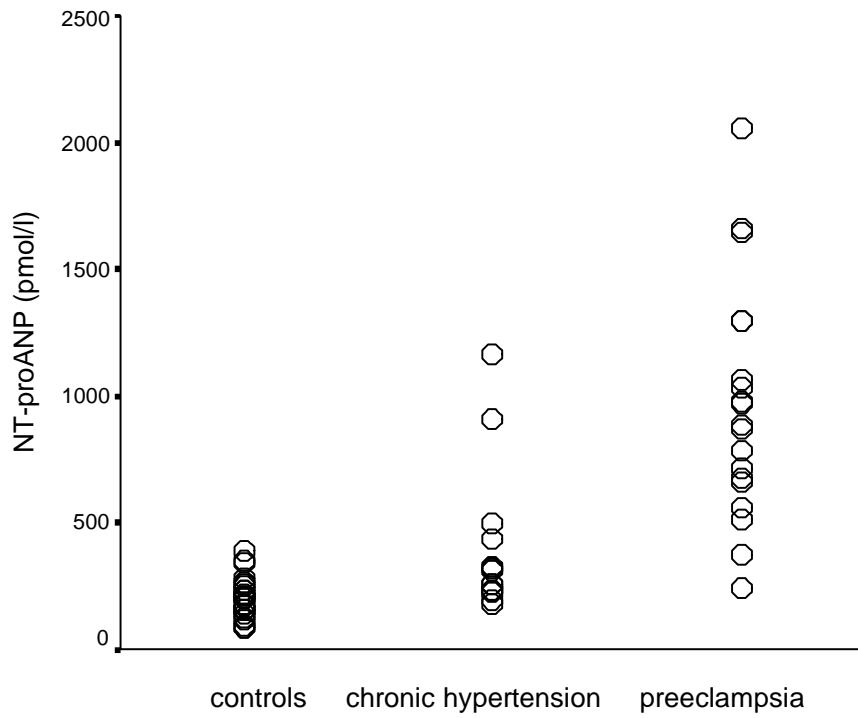


Figure 1. NT-proANP and NT-proBNP concentrations in the different study groups. Concentrations of natriuretic peptides in preeclamptic pregnancies were significantly higher compared to chronic hypertensive or uncomplicated pregnancies. In chronic hypertensive women NT-proANP and NT-proBNP were significantly higher than in normotensive women.

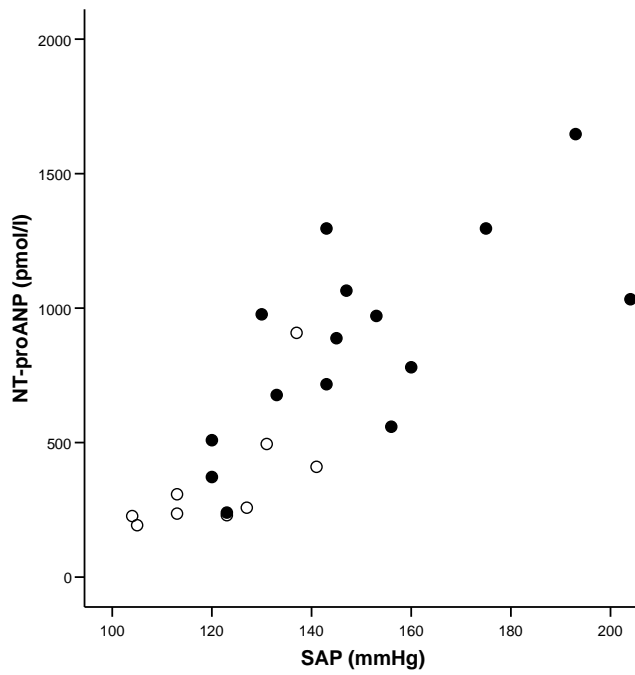
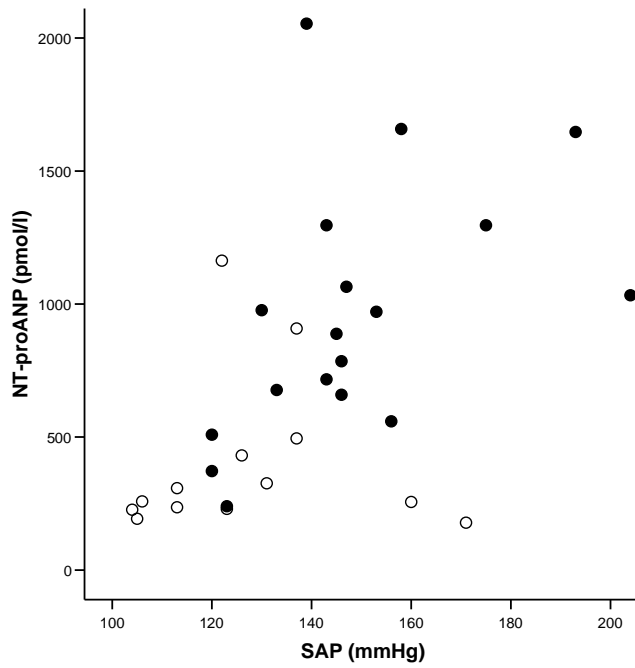


Figure 2. Scatter plot of NT-proANP concentrations and systolic blood pressure values (SAP) in hypertensive pregnancies (● preeclampsia ○ chronic hypertension). Above: In the whole preeclamptic group the correlation was significant ($r_s=0.55$, $p=0.02$), while in the whole group of chronic hypertensive women no correlation was found ($r_s=0.07$, $p=0.8$).

Below: In the hypertensive subgroup of non-medicated correlations between NT-proANP and SAP were significant in both groups ($r_s=0.65$, $p=0.008$ in preeclamptic women, $r_s=0.84$, $p=0.005$ in chronic hypertensive women).

Maternal hemodynamics during cesarean delivery assessed by whole-body impedance cardiography

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Background. This descriptive study was designed to evaluate maternal hemodynamics and cardiovascular responses to delivery during cesarean section (CS) under spinal anesthesia. We also assessed the feasibility of a noninvasive and continuous method of measuring cardiac output, namely whole-body impedance cardiography (ICG_{WB}), during elective CS. Because of the techniques used in previous studies, only fractionated data on maternal hemodynamics during CS are available to date.

Methods. We studied 10 healthy women with normal pregnancies and two pregnant women with heart disease undergoing elective CS. Mean arterial pressure (MAP), heart rate (HR), stroke index (SI), cardiac index (CI) and systemic vascular resistance index (SVRI) were recorded continuously during CS, during the period of dissipation of anesthesia and on the second to fifth postpartum day. Analysis of variance for repeated measurements (ANOVA) and the paired sample *t*-test were used in statistical analysis.

Results. The hemodynamic parameters could be registered continuously during the whole procedure. At the point of delivery, a 47% increase in CI and a 39% decrease in SVRI were recorded, while MAP remained stable. These changes occurred within 2 min of delivery of the newborn and persisted on average for 10 min.

Conclusion. Sudden and significant hemodynamic changes take place at the moment of delivery. Intact physiological cardiovascular compensation mechanisms are needed to adapt to these challenges. Whole-body impedance cardiography may offer a useful non-invasive tool to monitor hemodynamics during cesarean section.

Key words: cesarean section; hemodynamics; whole-body impedance cardiography; pregnancy; delivery

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Cesarean section (CS) is a common surgical procedure, but relatively little is known about concomitant maternal hemodynamics. Former

studies have concentrated mostly on the effects of fluid preloading to prevent hypotension induced by regional anesthesia (1,2). Events at and beyond delivery are documented to a lesser extent. The period of delivery is brief and significant changes in cardiac output (CO) after delivery have been reported using intermittent measurements at varying time intervals (3–6). Measurements of CO during CS have previously been assessed by thermodilution (7), dye dilution (5,6), Doppler ultrasound (4) and thoracic

Abbreviations:

ABP: arterial blood pressure; CS: cesarean section; TEB: thoracic electrical bioimpedance; ICG_{WB}: whole-body impedance cardiography; MAP: mean arterial pressure; CI: cardiac index; CO: cardiac output; SI: stroke index; HR: heart rate; SVRI: systemic vascular resistance index; SEM: standard error of the mean; SD: standard deviation; TPR: total peripheral vascular resistance.

electrical bioimpedance (TEB) (3,8). Because of the techniques used, only fractionated data on maternal hemodynamics during CS are available to date.

Whole-body impedance cardiography (ICG_{WB}) is a noninvasive, operator-independent and continuous method of measuring cardiovascular events. It has been reported previously to be a reliable method (9), providing beat-to-beat values of stroke volume. We hypothesized that ICG_{WB} could provide contributory hemodynamic data during cesarean delivery. The aim of this study was therefore to apply ICG_{WB} to test the feasibility of this method and extend the evaluation of maternal cardiovascular responses throughout CS.

Materials and methods

We studied 10 healthy women with normal pregnancy undergoing elective cesarean delivery under spinal anesthesia. Five parturients were nulliparous and five were parous. The mean gestational age at delivery was 40 weeks (range 39–41 weeks). All cesarean sections were elective including diagnoses such as breech presentation, previous cesarean sections and narrow pelvis. The mean age was 30 years (range 24–38 years) and the mean body mass index at the time of enrollment was 30.4 kg/m² (range 23–41 kg/m²). The mean hematocrit before preloading was 36% (range 33–40%). Two further parturients with heart disease were recorded separately. One had stenosis of the aortic valve and the other operated tetralogy of Fallot. Both of them underwent preoperative cardiologic examination and cardiac conditions were found to be stable.

The study was conducted at Tampere University Hospital. The procedure was explained to each subject and written consent was obtained. The local Ethics Committee approved the study.

CircMon B202 (JR Medical Ltd, Tallinn, Estonia) was used in estimation of heart rate, stroke volume, cardiac output and systemic vascular resistance. Parameters obtained were indexed to body surface area. In ICG_{WB}, stroke volume estimation is based on resistance changes in the vasculature of the whole body during the cardiac cycle (10).

Blood pressure was measured automatically by a non-invasive arterial pressure measuring device (Hewlett-Packard M1960A, Boeblingen, Germany) every 5 min and after the induction of anesthesia every 2 min.

As heart-related impedance changes depend on the amount of blood cell concentration in the vessels (10), blood samples for hematocrit were obtained before the operation, after preloading and in the postpartum period to adjust impedance-derived hemodynamic parameters to individual hematocrit. The baseline hemodynamic values were recorded prior to preloading in the left-lateral position. An intravenous catheter was then inserted into a peripheral vein and hydroxyethyl starch (6%) 10 mL/kg infused over 15–30 min. Thereafter, hydroxyethyl starch (6%) was infused 10 mL/kg/h during the operation. Once preloading was completed, the impedance cardiography recording was continuous throughout the operation in the slightly left-lateral position. The recording was completed after the operation when the spinal blockade had disappeared and the patient was able to bend and extend her ankles. Measurements were

repeated on the second to fifth postpartum day in the left-lateral position.

Spinal anesthesia was induced after preload infusion using a 25- or 27-gauge spinal needle at the L2–L3 or L3–L4 intervertebral space with the patient in the right lateral position. The patients received a mean 2.5 mL (range 2.4–2.7 mL) of 0.5% hyperbaric bupivacaine. Thereafter, the patients were repositioned supine with a slightly left-lateral position. Hypotension was defined as a decrease in mean arterial pressure to less than 80% of baseline or a systolic pressure of less than 100 mmHg. Hypotension was treated by ephedrine infusion (ephedrine 50 mg in 100 mL 0.9% NaCl) and the mean dosage was 0.53 mg/kg.

The surgical procedure was initiated when the level of sensory block was satisfactory for the operation.

After the operation blood loss was estimated and circulation volume, if necessary, replaced by Ringer-infusion and erythrocytes.

The hemodynamic parameters were analyzed as average values for 30 s in the following periods: baseline, after preload, after spinal anesthesia induction at the point of the lowest measured blood pressure (mean 7 min after spinal blockade), before surgery, immediately after delivery of the newborn and placenta, after skin closure, after the disappearance of spinal blockade and on the second to fifth postpartum day.

Statistical analysis was performed using SPSS for Windows (version 11.0). Outcome parameters were analyzed using analysis of variance for repeated measurements (ANOVA) to detect significant changes in parameters over time. To estimate changes in hemodynamic parameters compared to the baseline values or the preceding period, a paired sample *t*-test was used. Differences were considered significant at *p* < 0.05. All data are presented as mean, range or standard error of the mean, when necessary.

Results

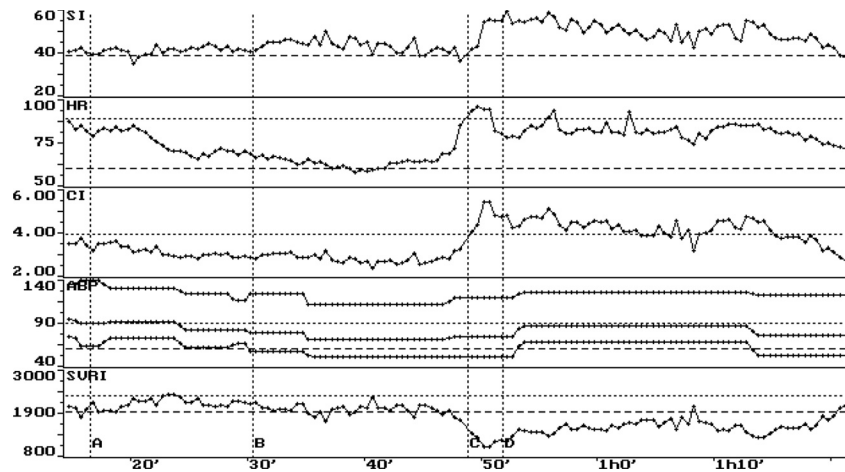
The hemodynamic parameters were in all cases successfully measured and hemodynamic changes could be followed continuously during the whole surgical procedure. Examples of the trends in hemodynamic parameters are shown in Figs 1 and 2.

The main results concerning mean arterial pressure (MAP), cardiac index (CI), stroke index (SI), heart rate (HR) and systemic vascular resistance index (SVRI) analysis are shown in Table I and Fig. 3. The ANOVA proved significant changes in all hemodynamic parameters over time.

Preloading increased MAP and HR, but SI and CI were not affected. Hematocrit was lowered after preloading in average 7%.

Spinal anesthesia lowered SVRI. MAP was significantly lower than after preloading (70.2 ± 6.1 mmHg, *p* < 0.0001), but CI and SI remained stable. Ephedrine was given to eight of the 10 parturients as treatment for hypotension. In hypotonic parturients mean MAP was 65.6 ± 6.9 mmHg. After ephedrine infusion MAP (81.8 ± 5.0 mmHg) reverted back to baseline level and SVRI (1939 ± 166 dyn s/cm⁵/m²) increased significantly in hypotonic patients.

Fig. 1. An example of the hemodynamic recording in a healthy parturient during cesarean section. Sudden increases in heart rate, stroke index and cardiac index were observed at the moment of the delivery. A, after preloading; B, operation starts; C, delivery of the newborn; D, removal of the placenta. SI, stroke index; HR, heart rate; CI, cardiac index; ABP, arterial blood pressure; SVRI, systemic vascular resistance index.



Hemodynamically, the most striking changes were noted immediately after the delivery of the newborn. CI increased 47% compared to baseline and 34% compared to values prior to delivery, due to significant increases in both HR and SI. However, MAP was maintained stable because of a significant (39%) decrease in SVRI. These changes were maintained on average for 10 min (except in one patient for 30 min) after delivery, before the values returned to the level before delivery.

Two patients did not receive ephedrine before the delivery, but the hemodynamic changes after delivery were similar to hypotonic patients: a 54% increase in CI and a 41% decrease in SVRI compared to the baseline values.

After the disappearance of the spinal blockade the hemodynamic parameters were similar to the baseline values.

During the first postpartum days, MAP was lower compared to baseline, CI maintained the same level and SVRI showed a tendency to decrease.

The baseline hemodynamic values in the patient with operated tetralogy of Fallot were

similar to healthy ones: CI 3.2 L/min/m², MAP 84 mmHg and SVRI 2018 dyns/cm⁵/m². The baseline values in the patient with aortic valve stenosis were 4.5 L/min/m², 86 mmHg and 1483 dyns/cm⁵/m², respectively. In comparison to the healthy pregnant parturients, the patient with aortic valve stenosis could not raise either cardiac or stroke index after delivery and consequently she had pulmonary edema documented by chest radiograph. She was admitted to the intensive care unit after delivery for 2 days, but made a complete recovery. Changes in hemodynamic variables in this patient during CS are shown in Fig. 2. By contrast, the course of CS was similar to that in healthy parturients in the patient with operated tetralogy of Fallot.

Discussion

Whole-body impedance cardiography was successfully used in monitoring hemodynamics in pregnant healthy parturients during CS. It offered the occasion to follow cardiovascular responses during the operation continuously.

Fig. 2. The hemodynamic recording of the patient with aortic stenosis during cesarean section. During the operation low stroke index and high heart rate were noted. At the moment of delivery no marked rise in cardiac index was achieved and the patient was found to have pulmonary edema during the operation. A, after preloading; B, operation starts; C, delivery of the newborn; D, removal of the placenta. SI, stroke index; HR, heart rate; CI, cardiac index; ABP, arterial blood pressure; SVRI, systemic vascular resistance index.

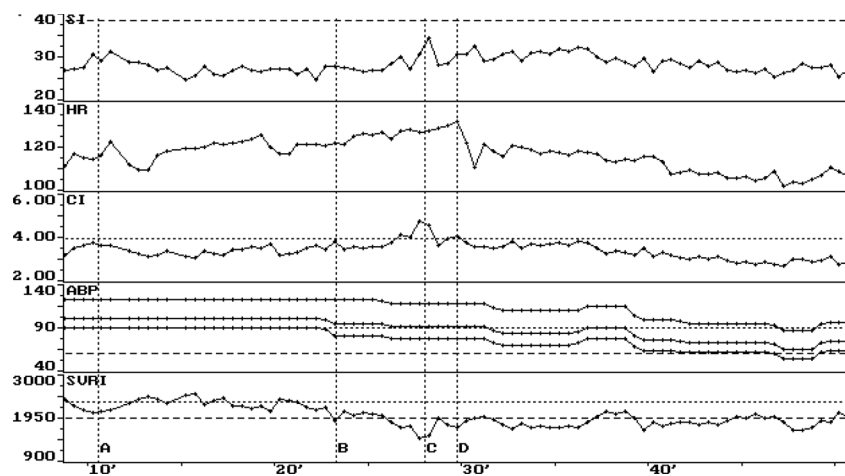


Table I. Summary of maternal hemodynamics during cesarean delivery

	Baseline	After preload	After spinal blockade	Before surgery	After delivery	After operation	Disappearance of anesthesia	Postpartum
		<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>
SI (ml/m ²)	42.2 (1.3)	40.4 (1.5)	43.0 (1.3)	42.0 (1.3)	49.7 (1.8)	43.6 (2.6)	41.8 (1.7)	41.4 (1.9)
HR (beats/min)	74 (4)	89 (5)	88 (8)	90 (6)	94 (4)	85 (4)	76 (5)	77 (4)
CI (l/min/m ²)	3.2 (0.3)	3.6 (0.2)	4.1 (0.5)	3.5 (0.2)	4.7 (0.2)	3.7 (0.3)	3.2 (0.3)	3.2 (0.2)
SVRI (dyn s/cm ⁵ /m ²)	2221 (179)	2123 (209)	1531 (173)	1883 (126)	1362 (76)	1724 (209)	2195 (255)	1817 (125)
MAP (mmHg)	86.2 (3.8)	94.7 (5.0)	70.2 (6.0)	82.7 (3.6)	81.7 (4.0)	77.4 (6.2)	89.2 (4.0)	74.1 (5.3)

Values are expressed as mean (SEM)

p-values refer to the difference between the measured point and baseline

SI, stroke index; HR, heart rate; CI, cardiac index; SVRI, systemic vascular resistance index; MAP, mean arterial pressure

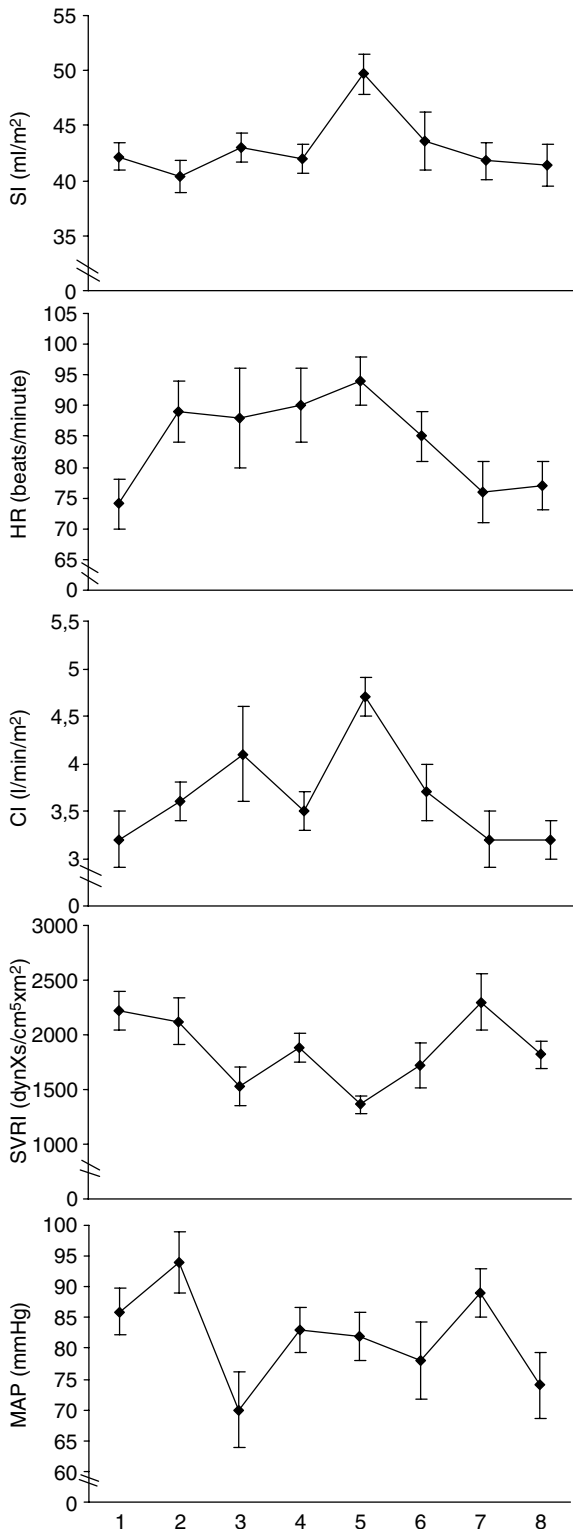


Fig. 3. Trends in hemodynamic variables during cesarean section in healthy parturients. Values are expressed as mean and standard errors of the mean. 1, baseline on left-lateral position; 2, after preloading with hydroxyethyl starch (6%); 3, after spinal blockade at the point of the lowest measured arterial blood pressure; 4, before surgery; 5, delivery of the newborn; 6, after skin closure; 7, disappearance of anesthesia; 8, on the second to fifth postpartum day. SI, stroke index; HR, heart rate; CI, cardiac index; SVRI, systemic vascular resistance index; MAP, mean arterial pressure.

From the practical point of view, ICG_{WB} was easy to apply, it was well tolerated by the patients, and measurements were technically adequate during the whole surgical procedure. Our study demonstrated the continuity of hemodynamic changes during CS performed under spinal anesthesia, showing the magnitude and duration of the increase in cardiac index associated with the delivery of a newborn.

Previously used methods for cardiac output estimates may bring certain disadvantages with regard to their use during CS. Thermodilution or dye dilution techniques require catheterization of the pulmonary artery. The procedure may involve serious complications, which limits the routine use of these techniques (11). Transthoracic Doppler echocardiography is operator-dependent and time-consuming and cannot be used for continuous measurements. The reliability of stroke volume and cardiac output determinations by TEB has been questioned (12). The mean stroke volumes determined by TEB have been significantly lower than those determined by the dye dilution technique in patients undergoing CS (13) and comparisons of TEB to thermodilution have revealed poor agreement (14). This can be explained by the assumption that most of the thoracic bioimpedance signals originate from smaller vessels and peripheral tissues of the thorax rather than from the aorta and large vascular trees. Impedance changes in these smaller vessels may have a poor correlation to stroke volume (12). Because of the changes in vascular tone in peripheral tissues outside the thorax during pregnancy and under regional anesthesia, TEB may miss fundamental information on hemodynamics in these cases. In ICG_{WB} , the four-limb electrode configuration represents the heart-related impedance signal from nearly the whole body, including the circulation in the abdomen and lower extremities (15). Consequently, ICG_{WB} may be assumed to be more reliable in measuring cardiac output during parturition and regional anesthesia. These limitations of TEB may become significant in serious disturbances of circulation. However, in healthy parturients in the present study, CI and SI determined by ICG_{WB} were similar to those determined by TEB in an earlier study by Milsom et al., both in absolute values and in trends (3).

ICG_{WB} has not yet been validated by other invasive or noninvasive techniques in pregnant patients. However, earlier studies with patients undergoing coronary artery bypass ICG_{WB} have shown a good agreement with thermodilution and direct oxygen Fick methods in the measurement of cardiac output (9,10). Repeatability

values were not calculated in this study, but in a previous study ICG_{WB} had a considerably better repeatability value than the thermodilution method (10).

Our results confirmed those of the most previous studies on hemodynamics during CS. Regional anesthesia reduced SVRI and caused hypotension (5,8,16). Colloid infusion as preload has been shown to be more effective than crystalloids in reducing the incidence of hypotension and increasing cardiac output (17,18). In our study, preloading with hydroxyethyl starch (6%) increased mean arterial pressure but did not fully compensate the reduction in systemic vascular resistance induced by regional anesthesia: 80% of patients received ephedrine as treatment for hypotension. Ephedrine has been shown to increase blood pressure by increasing cardiac output (19). In the present study the impact of ephedrine was an increase in SVRI, not in CI.

Hemodynamic changes associated with preloading and spinal anesthesia have been widely discussed, but surprisingly, little attention has been paid to the period of delivery. In our study, the most striking hemodynamic changes were recorded immediately after the delivery of the newborn and the placenta. A significant rise in CI and a decrease in SVRI were recorded within 2 min after delivery of newborn and placenta, reflecting a sudden volume load in the vascular space. The previous studies based on single measurements after delivery have shown an increase in CI of the same magnitude (3,6,20), but we demonstrated the timing and the duration of these changes in CS more precisely.

Various alterations immediately after the delivery may explain these hemodynamic changes. Prolonged compression of intraabdominal arteries (mostly intestinal) during the pregnancy may result in decreased arterial tone in this region, which starts to recover after delivery. Extra blood from the contracting uterus is expelled to the systemic circulation. Contracting uterus facilitates vena cava compression and compression on pelvic veins to allow better venous return to the heart. Despite active bleeding associated with delivery, the blood volume pooled in the uterus, placenta, abdomen and lower extremities during pregnancy momentarily overcomes the blood loss. Sudden hemodynamic compensation mechanisms such as a significant decrease in SVRI are needed to control the volume overload in this rapidly changing situation.

It is difficult, however, to exclude the impact of spinal anesthesia and ephedrine on hemodynamic changes at the moment of delivery. However,

when compared to hemodynamic changes after delivery under general or epidural anesthesia and after vaginal delivery the changes are similar. Under general anesthesia CO increased by 23–28% (3, 4) and total peripheral vascular resistance (TPR) decreased by 16% (3); under epidural anesthesia the values were 31% and 35%, respectively (3). After vaginal delivery CO increased 20% and TPR decreased 27% (5).

The sudden hemodynamic changes associated with delivery during CS may be hazardous to a parturient with impaired physiological adaptation. Our descriptive study included one patient with aortic stenosis. As the ability of this patient to raise cardiac output was restricted by her heart disease, she could not tolerate the volume load after delivery, and consequently she developed pulmonary edema. Patients with acquired or congenital heart diseases, especially left heart obstruction, cardiomyopathies or deteriorated vascular regulation (e.g. some forms of hypertension) might benefit from continuous monitoring of hemodynamics during CS.

In conclusion, we evaluated hemodynamic changes during cesarean section using whole-body impedance cardiography continuously in healthy women with uncomplicated pregnancy. The cardiac index increases rapidly in association with delivery, loading the heart and circulation, and necessitates intact physiological compensation systems. Whole-body impedance cardiography is a promising tool to monitor hemodynamics during cesarean section and might be useful in the future. Additional research is required to validate this method with other methods of measuring cardiac output during pregnancy.

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Maternal haemodynamics in pre-eclampsia compared with normal pregnancy during caesarean delivery

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Objective To determine how pre-eclampsia modifies maternal haemodynamics during caesarean delivery.

Design Prospective study.

Setting Tampere University Hospital, Finland.

Population Ten pre-eclamptic parturients and ten healthy parturients with uncomplicated pregnancies scheduled for elective caesarean section under spinal anaesthesia.

Methods Haemodynamic parameters were assessed by whole-body impedance cardiography noninvasively.

Main outcome measures Stroke index (SI), heart rate (HR), cardiac index (CI), systemic vascular resistance index (SVRI) and mean arterial pressure (MAP) were recorded before operation, continuously during caesarean section, during the period of dissipation of anaesthesia and on the second to fifth postpartum day.

Results Baseline haemodynamics in women with pre-eclampsia differed significantly from healthy women in higher SVRI and

MAP and lower SI and CI. In women with pre-eclampsia, preload infusion increased both SI and HR, causing a significant rise in CI, while in healthy parturients, only HR rose. In both the groups, spinal blockade reduced SVRI but CI remained stable. At the moment of delivery, CI increased in both groups. In uncomplicated pregnancies, both SI and HR increased, but in women with pre-eclampsia, SI was not altered and the rise in CI was due to an increase in HR only. After the reversal of anaesthesia, haemodynamics in the control group returned to baseline values, whereas in women with pre-eclampsia, SI and CI fell to levels that were significantly lower than the levels observed before surgery.

Conclusions In women with pre-eclampsia, inability to increase SI at the moment of delivery may suggest dysfunction of the left ventricle to adapt to volume load caused by delivery and prompts concern for the increased risk of pulmonary oedema.

Keywords Caesarean delivery, haemodynamics, pre-eclampsia, spinal anaesthesia, whole-body impedance cardiography.

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Introduction

Pre-eclamptic parturients have an increased risk for caesarean section by reason of the high incidence of intrauterine growth restriction, fetal distress and prematurity.¹ Unfortunately, caesarean section increases the risk of cardiopulmonary morbidity associated with pre-eclampsia.² Pre-eclampsia has also been shown to be a significant risk factor for postoperative cardiac failure.³ Divergent haemodynamic adaptation during the pregnancy may render pre-eclamptic parturients prone to cardiopulmonary complications during caesarean section.

Caesarean delivery involves interventions potentially harmful for haemodynamics. Sympathetic blockade induced by regional anaesthesia disposes to hypotension^{4–6} and exposes the fetus to the risk of hypoxaemia especially in cases of intrauterine growth restriction. The effects of hypotension may be intensified by the low cardiac output often found in women with pre-eclampsia.^{7,8} Also, the moment of delivery constitutes a challenge. We and others have shown that in healthy parturients, delivery by caesarean section is associated with a significant rise in cardiac output,^{9–13} suggesting a rapidly increased volume load in the vasculature. Cardiac output is

also known to rise in women with pre-eclampsia at the moment of delivery under general¹⁴ and epidural anaesthesia,¹⁵ but how pre-eclampsia modifies haemodynamic adaptation to delivery in respect of factors apart from cardiac output is not known.

Since the maternal haemodynamics in pre-eclampsia differ from those in uncomplicated pregnancy,^{7,8,16,17} we hypothesised that cardiovascular reactions during the course of caesarean section will also differ between pre-eclamptic and healthy parturients. The objective of this study was to define haemodynamic changes during caesarean section in pre-eclamptic parturients. Reference data were obtained from ten healthy pregnant women with uncomplicated pregnancy undergoing elective caesarean delivery, published separately in an earlier paper.¹³

Methods

The study was carried out at Tampere University Hospital. The procedure was explained to each subject and a written consent was obtained. The local Ethics Committee approved the study.

Ten women with pre-eclampsia undergoing elective caesarean delivery were studied. Parturients with pre-existing hypertension, renal disease or heart disease were excluded. Pre-eclampsia was diagnosed if blood pressure exceeded 140/90 mmHg and if proteinuria of more than 300 mg/day persisted.

Of the ten women with pre-eclampsia, six met the criteria of severe disease, with an arterial pressure constantly greater than 160/110 mmHg and proteinuria exceeding 5.0 g/day. Three women received an antihypertensive peroral regimen of labetalol 200–600 mg/day and one was given a labetalol infusion of 0.35 mg/minute (labetalol 500 mg in 500 ml of 0.9% NaCl). No other medication was used.

The control group comprised ten healthy parturients with normal pregnancy undergoing elective caesarean section. The description of these women is given in an earlier

publication.¹³ The main characteristics of the women are shown in Table 1.

Since gestational age at delivery differed between healthy controls and pre-eclamptic parturients, the baseline haemodynamics of an additional ten healthy primiparous women were recorded at gestational week 34 (the mean gestational age for pre-eclamptic parturients). These ten women had an uncomplicated pregnancy and were matched by age and body mass index (BMI) with those of healthy parturients. The baseline haemodynamic measurements were not different between the healthy parturients at 34 weeks of gestation and the control group of the study. Thus, the difference in gestational age between the study groups was not considered to influence the results.

CircMon B202 (JR Medical Ltd, Tallinn, Estonia) was used for the noninvasive estimation of heart rate (HR), stroke volume, cardiac output and systemic vascular resistance. This cardiovascular monitoring device applies whole-body impedance cardiography to measure cardiac output. Impedance cardiography is based on the measurement of changes in electrical impedance in the vasculature during the cardiac cycle. Current and voltage electrodes were applied to the wrists and to the ankles. Impedance changes during systole and diastole were used to calculate stroke volume. A more detailed description of this method is available in other publications.^{18,19}

Stroke volume (quantity of blood ejected from the left ventricle with each beat), cardiac output (stroke volume × HR) and systemic vascular resistance (impediment to blood flow in peripheral vasculature) were indexed to body surface area to minimise the effect of the body size on these parameters (i.e. cardiac index [CI], stroke index [SI] and systemic vascular resistance index [SVRI]).

Blood pressure was measured by an automated noninvasive arterial pressure device (Hewlett-Packard M1960A, Boehringer, Germany) for every 5 minutes and after the induction of spinal anaesthesia every 2 minutes. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one-third of pulse pressure.

Table 1. Subject details

Subject details	Pre-eclamptic parturients, <i>n</i> = 10	Healthy parturients, <i>n</i> = 10	<i>P</i>
Age (years)	34 (24–43)	30 (24–38)	NS
Percentage of primiparous	80	50	NS
Gestational age at delivery (weeks)	34 (28–38)	40 (39–41)	<0.0001
BMI (kg/m ²)	26 (22–30)	30 (25–41)	0.049
Systolic blood pressure (mmHg)	166 (137–204)	127 (101–171)	0.001
Diastolic blood pressure (mmHg)	105 (90–122)	66 (61–72)	<0.0001
Daily proteinuria (g/day)	6.3 (1.52–11.35)	<0.3	<0.0001
Haematocrit (%)	35 (31–39)	36 (33–40)	NS

NS, not significant. Values are expressed as mean (range).

The baseline haemodynamic values were recorded prior to preload infusion in left lateral position. An intravenous catheter was then inserted into a peripheral vein. Women in both groups received hydroxyethyl starch (6%) 10 ml/kg over 15–30 minutes as preloading infusion. Thereafter, hydroxyethyl starch (6%) 10 ml/kg/hour was infused during the operation.

Once preloading was completed, whole-body impedance cardiography recording was continued throughout the operation. The recording was completed after the operation, when anaesthetic effect of spinal blockade had disappeared and the woman was able to bend and extend her ankles.

Spinal anaesthesia was induced after fluid infusion. It was performed using a 25- or 27-gauge spinal needle at the L2–L3 or L3–L4 intervertebral space, with the woman in the right lateral position. The women received a mean 2.5 ml (range 2.4–2.7 ml) of 0.5% hyperbaric bupivacaine. Thereafter, they were repositioned supine with slight left lateral position. The surgical procedure was initiated when the level of sensory block was deemed adequate.

Maternal hypotension was defined as a decrease in systolic arterial pressure to 80% of baseline or a systolic pressure of less than 100 mmHg. Hypotension was treated by intravenous ephedrine infusion: ephedrine 50 mg in 100 ml of 0.9% NaCl was given until normotension was restored; typically 40 mg of ephedrine was needed. After the operation, bleeding was estimated and volume depletion replaced by Ringer infusion or erythrocytes, if considered necessary.

The whole-body impedance cardiography derived SI, HR, CI and SVRI were analysed as average values for 30 seconds at the following time points: baseline, after preloading, at the point of lowest measured blood pressure after spinal blockade, immediately after delivery of newborn and placenta, at skin closure, after the anaesthesia had disappeared and on the second to fifth postpartum day.

Statistical analysis was performed using SPSS for Windows (version 11.0; SPSS Inc., Chicago, IL, USA) on a standard PC. Outcome parameters were analysed using repeated measurements analysis of variance (RANOVA) to detect significant changes in the entire group and coherence between the groups over time. Differences between the groups at each time point were examined *post hoc* using independent samples *t* test. A paired samples *t* test was used to detect changes within the groups. Differences in haemodynamic parameters between successive measurement points were expressed as percent changes to describe reactions to interventions. Differences were considered statistically significant if $P \leq 0.05$. All data are presented as mean and SD, SE of the mean or range, when appropriate.

Results

The main results concerning SI, HR, CI, SVRI and MAP at baseline, during caesarean section, after the disappearance of

anaesthesia and in the early postpartum period are shown in Figure 1.

The women in the control group and those with pre-eclampsia differed significantly from each other in baseline measurements. The mean MAP and SVRI were significantly higher and, in contrast, SI and CI significantly lower in women with pre-eclampsia than in normal pregnancies. Based on RANOVA, SVRI ($P = 0.002$) and MAP ($P = 0.012$) remained at a significantly higher level, and SI ($P = 0.069$) and CI ($P = 0.063$) showed a tendency to remain lower in pre-eclamptic parturients compared with healthy parturients during the whole surgical procedure. The coherence between the groups during caesarean section was significantly different in respect of SI ($P = 0.01$) and SVRI ($P = 0.002$).

The haemodynamic reactions to fluid preloading, spinal anaesthesia, delivery and disappearance of anaesthesia, expressed as percent changes of haemodynamic parameters between the successive points of analysis are compared between the groups as shown in Table 2.

Preload administration was associated with an elevation in SI, HR and CI in women with pre-eclampsia, whereas in normal pregnancies, only HR increased. The difference in SI reaction after preload infusion almost reached statistical significance ($P = 0.056$), while changes in other parameters were similar in the respective groups.

Spinal blockade caused similar changes in both groups: SVRI and MAP were reduced, while CI and SI were preserved stable. Eighty percent of women in the normal pregnancies and 30% of women with pre-eclampsia became hypotensive. In both groups, ephedrine increased MAP (14% in healthy parturients and 9% in pre-eclamptic parturients) and SVRI (14 and 16%, respectively). Furthermore, haemodynamic changes after delivery were alike between parturients treated and not treated with ephedrine in both study groups.

Immediately after delivery, the mean CI was 22% higher compared with the value after spinal blockade (52% higher compared with the baseline values) in women with pre-eclampsia and 34% higher (47% higher compared with baseline) in women in the control group. However, in pre-eclamptic pregnancies, no increase in SI occurred and the rise in CI was due entirely to an increase in HR, while in normal pregnancies, a significant increase in both SI and HR was observed. The difference in the percent change in SI between the groups was significant ($P = 0.02$). Among pre-eclamptic parturients, SI was increased in only one woman. This woman had severe pre-eclampsia complicated by HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome. Her SI increased to 12% at the moment of delivery, however, remaining lower than the mean SI in the women in control group.

The simultaneous decrease in SVRI was 17% compared with the value after spinal blockade, and the mean MAP decreased, reaching the lowest value during the surgical procedure

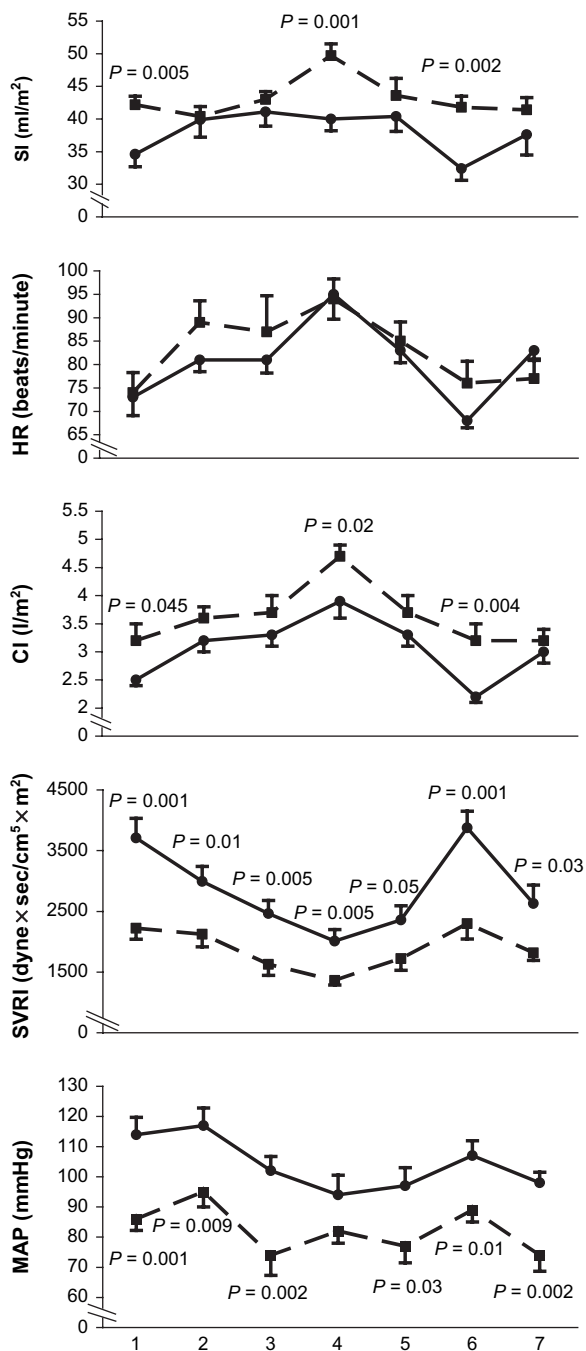


Figure 1. Trends of haemodynamic variables during caesarean section in healthy (■) and pre-eclamptic (●) parturients. Values are expressed as mean and SE of the mean. 1 = baseline in left lateral position, 2 = after preloading with 6% hydroxyethyl starch, 3 = after spinal blockade (at the point of the lowest measured arterial blood pressure), 4 = before surgery, 5 = immediately after delivery of the newborn and the placenta, 6 = skin closure and 7 = disappearance of anaesthesia.

in pre-eclamptic parturients. In the control group, SVRI decreased 6%, while the mean MAP remained stable ($P = 0.03$ for the percent change difference in MAP between the groups). Bleeding was moderate (550 ml or less) and similar in both groups.

With reversal of anaesthesia, the haemodynamic values were restored to baseline level in normal parturients. In women with pre-eclampsia, SVRI and MAP returned to baseline, but profound decreases in CI, SI and HR were recorded. During this period, the values reached the nadir of the whole study period. The changes in SI and CI differed between the groups ($P = 0.04$ and $P = 0.03$, respectively).

During the postpartum days, there were no significant differences in SI, HR or CI between the groups, but SVRI and MAP still remained significantly higher in women with pre-eclampsia than in normal parturients.

Three of four pre-eclamptic parturients receiving labetalol medication had severe disease. There were no differences in age, gestational age or BMI between women with and without antihypertensive medication. Furthermore, the values of the haemodynamic parameters at baseline and during the surgical procedure between the medicated and the nonmedicated parturients were comparable. In the baseline measurements, only MAP was higher in parturients with severe pre-eclampsia compared with the rest of the pre-eclamptic parturients. Otherwise, the haemodynamic parameters were similar during caesarean section.

Discussion

The haemodynamics of pre-eclampsia have remained a controversial issue. Cardiac output has been found to be high with high systemic vascular resistance,¹⁶ high with low to normal vascular resistance¹⁷ and low with high systemic vascular resistance.^{7,8} Besides the varying baseline haemodynamics of pre-eclampsia, they may be further modified by treatment^{7,8} or pre-existent disease such as diabetes and renal or cardiovascular disorders. The progress of pre-eclampsia also influences the haemodynamics.²⁰ In our study, there were profound differences between the study groups in the baseline measurements, suggesting a state of low cardiac output with high vascular resistance in pre-eclampsia. CIs were uniformly low, the range in CI in women with pre-eclampsia was narrow and the highest CI did not reach the mean value of CI in normal pregnancies. As the indication for caesarean delivery was in all cases worsening pre-eclampsia, this might suggest that at least, the end stage of pre-eclampsia would be associated with low CI.

In our data, the low CI seen in pre-eclamptic parturients was due to low SI. Women with severe pre-eclampsia had massive proteinuria (mean 8.1 g/day), which presumably caused depletion in intravascular volume, reflected in low SI. Besides assumed hypovolemia, the low SI could be further

Table 2. Percentual changes in haemodynamic parameters between successive periods of analysis

	Healthy parturients		Pre-eclamptic parturients		P
	Mean	SD	Mean	SD	
Fluid preloading					
SI (ml/m ²)	-3.0	17.3	+10.8	12.3	0.056
HR (beats/minute)	+21.2	12.3	+11.7	13.2	NS
CI (l/minute/m ²)	+18.5	36.3	+23.4	18.4	NS
SVRI (dyne × sec/cm ⁵ × m ²)	-1.9	26.9	-11.1	21.4	NS
MAP (mmHg)	+9.9	9.9	+6.2	11.4	NS
Spinal blockade					
SI (ml/m ²)	+2.7	5.2	+0.7	7.9	NS
HR (beats/minute)	-2.9	18.5	-2.6	10.8	NS
CI (l/minute/m ²)	+3.8	25.7	+4.3	19.9	NS
SVRI (dyne × sec/cm ⁵ × m ²)	-19.3	40.0	-8.0	32.9	NS
MAP (mmHg)	-21.4	22.9	-9.2	7.8	NS
Delivery of the fetus and the placenta					
SI (ml/m ²)	+16.1	14.1	-0.2	12.6	0.02
HR (beats/minute)	+13.9	25.7	+19.9	31.4	NS
CI (l/minute/m ²)	+34.2	36.1	+21.6	38.2	NS
SVRI (dyne × sec/cm ⁵ × m ²)	-5.7	38.9	-16.5	27.8	NS
MAP (mmHg)	+15.4	22.0	-7.4	16.8	0.03
Disappearance of anaesthesia					
SI (ml/m ²)	-2.5	13.1	-19.0	16.5	0.04
HR (beats/minute)	-11.7	12.7	-18.6	8.2	NS
CI (l/minute/m ²)	-14.7	14.4	-33.3	17.3	0.03
SVRI (dyne × sec/cm ⁵ × m ²)	+49.0	52.0	+83.8	64.1	NS
MAP (mmHg)	+20.4	24.3	+14.1	26.1	NS

NS, not significant.

Values are expressed as mean percent and SD. P values refer to the difference between the groups and values less than 0.1 are given.

explained by possible depressed left ventricular performance attributable to the high blood pressure in pre-eclampsia. Borghi *et al.*²¹ have shown adaptive changes as a reaction to high afterload in the left ventricular structure and function in pre-eclampsia—higher left ventricular mass, higher left ventricular end-systolic and end-diastolic volumes and lower ejection fraction compared with normal pregnancies.

In pre-eclamptic parturients, preload infusion augmented SI and CI to the level of healthy parturients, while in uncomplicated pregnancies, only HR increased. It might be assumed that in normal pregnancies, intravascular volume and the preload of the heart were already sufficient and only higher HR was required to circulate the extra volume infused. In contrast, the more pronounced rise in SI in pre-eclamptic parturients might reflect an existing hypovolemia and inadequate preload, which was corrected by fluid administration. This finding was similar to that previously reported. Circulatory volume has been demonstrated to increase during crystalloid fluid preloading measured indirectly by an increase in central venous pressure^{22,23} and an increase in cardiac output estimated by Doppler ultrasound²⁴ in women with pre-eclampsia.

After preload infusion, SVRI showed a tendency to decrease in pre-eclamptic parturients. Therefore, despite the vasoconstriction in pre-eclampsia, the vasculature was able to dilate as a reaction to volume load. MAP remained stable, suggesting that the reduction in SVRI was sufficient to compensate the increase in CI, preventing blood pressure from rising.

At the moment of delivery, a significant increase in SI and CI in normal pregnancies conveys the view of momentarily increased preload of the heart, as the blood from the contracting uterus and pooling in the lower extremities is expelled into the vasculature.¹³ The unchanged SI observed in women with pre-eclampsia during delivery was an unexpected reaction significantly different from the women in the control group. It may indicate poorer preload of the heart compared with normal parturients. By reason of the hypovolemia and poorly perfused placenta during pregnancy, there is less pooling blood volume in the uterus and lower extremities and the volume load caused by delivery might be less than in uncomplicated pregnancies. Heavy bleeding during the operation might also reduce the volume load, but there was no difference in the amount of bleeding between the groups. A third explanation for the lacking increase in SI in pre-eclamptic

parturients could be restricted cardiac adaptation to sudden volume load. Adaptive changes in the heart may lead to poorer left ventricular performance in pre-eclampsia.^{21,25} A state of diastolic dysfunction could explain the unchanged SI measurements after delivery in our women with pre-eclampsia. Presumably, the heart might be able to compensate sudden volume load only by increasing HR and not by adjusting SI, despite decreased MAP after delivery.

At the moment of delivery, there was also a marked decrease in SVRI in both groups, but in pre-eclamptic parturients, the simultaneous increase in CI was not enough to compensate the reduction in SVRI and, consequently, MAP decreased, while in healthy parturients, it remained stable. This sudden opening of the peripheral circulation concomitant with inadequate cardiac output may lead to underfilling of the vasculature and compromise the oxygenation of tissues. However, the low blood pressure was later corrected by increasing SVRI.

In our study, although there was no clinical case of pulmonary oedema, the observed haemodynamic pattern of failed increase in SI after delivery accompanied by volume load, high HR and lowering CI underlines the risk of relative heart failure and pulmonary oedema after delivery in pre-eclampsia. Low SI and CI, and so the risk of pulmonary oedema, persisted and even worsened during the study period, until the anaesthesia had disappeared. Our haemodynamic findings are in keeping with the clinical fact that the risk of postpartum pulmonary oedema is high during the first postpartum day in pre-eclampsia.

During the later postpartum period, the CI as well as SI in the women with pre-eclampsia had been re-established at the same level as in normal pregnancies, indicating rapid recovery of the heart, but vasospastic features of the disease persisted during the second to fifth postpartum day. However, the mean MAP and SVRI in pre-eclamptic parturients were below the baseline during the postpartum period. The lowered afterload might be one factor allowing the heart to recover from the adaptive state of pre-eclampsia and it could also induce CI to increase. Withdrawal of the excessive fluid compartment from the extravascular space during early puerperium²⁶ may also enhance SI and CI in pre-eclamptic parturients.

In conclusion, we found pre-eclampsia to be a state of low cardiac output and high systemic vascular resistance. Volume preload administration attenuated the vasospastic and hypovolemic features of the condition, re-establishing CI at the level of normal parturients and reducing SVRI. At the moment of delivery, pre-eclamptic parturients were not able to increase SI, thus differing from healthy parturients. The unchanged and even diminishing SI could be due to lower volume preload after delivery or due to diastolic dysfunction of the left ventricle in pre-eclampsia to adapt to sudden volume load at the moment of delivery, exposing the parturient to the risk of pulmonary oedema. During the early

puerperium, CI in women with pre-eclampsia recovered to the level of healthy parturients, but vasospastic features still persisted.

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