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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de biomedische wetenschappen

Masterproef

Intrarectal pressure measurements and postpartum hemodynamic changes in hypertensive gestations

Promotor :
Prof. dr. Lena DE RYCK

Promotor :
Prof. Dr. WILFRIED GYSELAERS

Ann Heymans

Scriptie ingediend tot het behalen van de graad van master in de biomedische wetenschappen

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List of abbreviations

2dPP	Two days postpartum
6wPP	Six weeks postpartum
ACI	Acceleration index
ACS	Abdominal Compartment syndrome
BCM	Body cell mass
BIA	Bio-electrical impedance analysis
BMI	Body Mass Index
BW	Birth weight
CiMON	Continuous intragastric pressure monitoring
CO	Cardiac output
CTG	Cardiotocography
DBP	Diastolic blood pressure
EAP	External applied pressure
ECG	Electrocardiography
ECM	Extracellular mass
ECW	Extracellular water
EH	Essential hypertension
EPE	Early preeclampsia
FFM	Fat free mass
FFMH	Fat free mass hydrated
FM	Fat mass
FMLV	Foley manometer low volume
GH	Gestational hypertension
HELLP	Hemolysis elevated liver enzymes and low platelets
HI	Heather index
HR	Heart rate
HVI	Hepatic vein velocity index
IAH	Intra-abdominal hypertension
IAP	Intra-abdominal pressure
ICG	Impedance cardiography
ICU	Intensive care unit
ICW	Intracellular water
IQR	Interquartile range
IUGR	Intra-uterine growth restriction
IRP	Intrarectal pressure
IVP	Intravesical pressure
LK-RIVI	Left kidney renal interlobar venous impedance index
LK-VPTT	Left kidney venous pulse transit time
LK-UtAA-APTT	Left uterine arcuate artery arterial pulse transit time
LK-UtAA-RI	Left uterine arcuate artery resistance index
LK-UtAA-PI	Left uterine arcuate artery pulsatility index
LPE	Late preeclampsia
MAP	Mean arterial pressure
MnV	Minimum velocity
MxV	Maximum velocity
NICCOMO	Non-Invasive Continuous Cardiac Output Monitor

PCC	Pearson correlation coefficient
PE	Preeclampsia
PI	Pulsatility index
PVR	Peripheral vascular resistance
RI	Resistance index
RK-RIVI	Right kidney renal interlobar venous impedance index
RK-VPTT	Right kidney venous pulse transit time
R-UtAA-APTT	Right uterine arcuate artery arterial pulse transit time
R-UtAA-RI	Right uterine arcuate artery resistance index
R-UtAA-PI	Right uterine arcuate artery pulsatility index
RIVI	Renal interlobar venous impedance index
RM MANOVA	Repeated measures multivariate analysis of variance
SBP	Systolic blood pressure
SPCC	Spearman correlation coefficient
SV	Stroke volume
UP	Uncomplicated pregnancies
VI	Velocity index
TAC	Total arterial compliance
TBW	Total body water
TFC	Thoracic fluid content
VPTT	Venous pulse transit time

Samenvatting

A Postnatale cardiovasculaire aanpassingen in hypertensieve zwangerschappen

Inleiding: In pre-eclampsie (PE) kunnen er aberrante aanpassingen optreden in het cardiovasculaire stelsel. Deze kunnen het risico op de ontwikkeling van cardiovasculaire ziekten op latere leeftijd, verhogen. Het doel van onze studie is hemodynamische parameters in de onmiddellijke postnatale periode te observeren en de verschillen tussen hypertensieve en ongecompliceerde zwangerschappen te bestuderen.

Materiaal & methoden: Dit is een observationele studie, waarbij het cardiovasculaire stelsel met behulp van impedantie cardiografie, gecombineerde elektrocardiogram - Doppler ultrasonografie en bio-elektrische impedantie werd bestudeerd. Dit werd antenataal, twee dagen postnataal en zes weken na de bevalling in ongecompliceerde (UP) (n=26), gestationele hypertensieve (GH) (n=3) en preeclamptische zwangerschappen (PET) (n=9) uitgevoerd.

Resultaten: Antenataal is er een significante verhoging in de parameters van de lichaamsvloeistoffen (totaal lichaamswater, extracellulair water (ECW) en overmaat ECW) in PET ten opzichte van UP. Deze verschillen zijn zes weken na de bevalling verdwenen. Antenataal en twee dagen postnataal, is er een verhoogde bloeddruk (systolische en diastolische) in GH en PET ten opzichte van UP. Deze drukverschillen vervagen zes weken na de bevalling. Antenataal is er een verlaagde veneuze compliantie in PET. Zes weken postnataal, is de veneuze compliantie verhoogd in vrouwen met PE vergeleken met UP.

Discussie & conclusie: Antenataal is er een verhoogde lichaamsvloeistof aanwezig in hypertensieve zwangerschappen, deze verdwijnt zes weken na de bevalling. Een centrale arteriële verstoring werd ook opgemerkt in PET en normaliseert ook zes weken postnataal. Een veneuze verstoring is antenataal geobserveerd en is zes weken na de bevalling nog aanwezig. Verder onderzoek zal moeten uitwijzen of deze veranderingen aanwezig blijven en het risico tot de ontwikkeling van cardiovasculaire ziekten, verhogen.

B Intrarectale drukmetingen

Inleiding: De symptomen van PE kunnen ontstaan door een verhoogde intra-abdominale druk (IAP). Het waarnemen van IAP in de zwangerschap heeft vele uitdagingen. Één daarvan is het ontwikkelen van een ideale meettechniek. Het doel van deze studie is de validatie van de rectale intra-abdominale drukmeting door deze te vergelijken met de intravesicale druk.

Materiaal & methoden: Vijftien geventileerde en verdoofde volwassen patiënten werden geïncludeerd op de intensieve zorg in Antwerpen. Intra-abdominale drukken werd indirect gemeten via het rectum en de blaas.

Resultaten: Zeven patiënten werden geëxcludeerd (46.67%) door schommelende IAP waarden of door IAP waarden buiten fysiologisch bereik. Er werd een lage correlatie aangetoond tussen de intravesicale en intrarectale druk (R<.370). Ook een lage bruikbaarheid (Pearson correlatie coefficiënt <.527) van de intrarectale metingen werd aangetoond. Bland-Altman plots tonen een bias van 5.6 mmHg.

Discussie & conclusie: Onze data tonen aan dat de IAP gemeten door de rectale katheter niet vervangen kan worden door de blaasmeting, door een slechte bruikbaarheid en herhaalbaarheid.

Abstract

A Postpartum hemodynamic changes in hypertensive gestations

Introduction: Hemodynamic maladaptations may endure postpartum in the arterial and venous system of women with a history of preeclampsia (PE), causing persistent cardiovascular impairment. The goal of this study is to evaluate the changes of cardiovascular parameters in the immediate postpartum period and investigate differences between hypertensive and uncomplicated pregnancies.

Materials & methods: In this observational study, the cardiovascular system was measured using combined electrocardiography – Doppler ultrasonography, with bio-electrical impedance analysis and impedance cardiography. These hemodynamic parameters were measured antepartum, two days postpartum and six weeks postpartum in uncomplicated pregnancies (UP) (n = 26), gestational hypertensive pregnancies (GH) (n = 3) and preeclamptic pregnancies (PE) (n = 9).

Results: Several body composition parameters were antepartum significantly increased in hypertensive pregnancies (total body water, extracellular water (ECW) and excess ECW) compared to normotensive gestations, but diminished six weeks postpartum. The pressure parameters of the hemodynamic assessment were antepartum and two days postpartum significantly increased. These pressure differences have fainted between UP and PE, six weeks postpartum. Antepartum, a low venous compliance is found in women with PE. Six weeks postpartum, the venous compliance is higher in women with PE compared to UP.

Discussion & conclusions: Antepartum, there is a presence of an abnormal fluid distribution in hypertensive women, which diminishes at six weeks postpartum. The results of the hemodynamic parameters demonstrate that antepartum, there is an arterial and venous hemodynamic dysfunction. Six weeks postpartum, the arterial hemodynamic dysfunction has normalized, however alterations in the venous system endure. Future studies are needed to evaluate whether these alterations remain in a longer postpartum period.

B Intrarectal pressure measurements

Introduction: The pathophysiology of PE might be associated with a maladaptation of the cardiovascular system due to an elevated intra-abdominal pressure (IAP). Measuring IAP in pregnancy faces different challenges of which developing an ideal measuring technique is probably the toughest. Therefore, the goal is to validate the rectal intra-abdominal pressure measurement technique by comparing this with the intrabladder.

Materials & methods: Fifteen patients sedated and ventilated adult patients admitted on the ICU (Antwerp, Belgium) were included. Intra-abdominal pressure was measured indirectly intermittently through the rectum and the bladder.

Results: Seven patients (46.67%) were excluded, because of their IAP fluctuations or values out of physiological range. A low correlation between intravesical pressure and intrarectal pressure was demonstrated (R>.370) and a low feasibility (Pearson correlation coefficient <.527) was found for intrarectal measurements. Bland-Altman plots showed a bias of 5.6 mmHg and limits of agreements of 15 mmHg.

Discussion & conclusions: Our data show that the IAP measured by the rectal catheter cannot replace the IAP monitoring by the FMLV, due to a poor feasibility and repeatability of this technique.

Originally, the goal of my thesis was to evaluate the longitudinal course of intra-abdominal pressure (IAP) values during pregnancy in normotensive and hypertensive pregnancies. However, a pilot study was previously conducted in which the IAP was measured in a supine, recumbent and hands and knees position in 29 pregnant term women. These preliminary data showed IAP values out of physiological range. Therefore, the intrarectal pressure measurement technique had to be validated first. Since this validation study would be performed at ZNA Antwerp and ethical approval had to be obtained, an additional project was added to my internship and became the primarily subject of this thesis.

A Postpartum hemodynamic changes in hypertensive gestations

1 Introduction

During pregnancy the body of the mother will undergo important anatomical and physiological adaptations. Anatomical changes will occur mostly in the third trimester: the abdomen will dramatically enlarge due to an increasingly growing foetus. Physiological changes including changes of the cardiovascular, renal, haematological, metabolic and respiratory systems are needed to provide a suiting environment for the foetus and will develop throughout the course pregnancy. Errors or inaccuracies in this complex system of adaptation are a risk for developing gestational complications, which might cause detrimental repercussions for mother and child, with a maternal mortality of respectively 0.23% and 0.016% in developing and developed countries (1). Postpartum haemorrhage and hypertension related diseases are the leading cause (41%) of maternal mortality worldwide (2).

1.1 Hypertension in pregnancy: definition and classification

Hypertension during pregnancy is the most common gestational disorder affecting 10% of all pregnancies worldwide. Hypertension is diagnosed as a systolic blood pressure (SBP) ≥140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg and can be classified into three groups: chronic or essential hypertension (EH); gestational hypertension (GH) and preeclampsia (PE). In EH, hypertension was diagnosed before twenty weeks of gestation. With hypertension diagnosed after twenty weeks of gestation, GH is confirmed. If there is new onset proteinuria (≥300 mg/24 hours) on top of GH, the patient will be diagnosed with PE (3).
PE is a major obstetric complication with a high morbidity and mortality for both mother and child. It is a heterogeneous disease, occurring in humans, with different clinical features of either a maternal complication (such as HELLP, organ failure or peripheral edema) or a foetal intra-uterine growth restriction (IUGR) (4). The HELLP-syndrome is a severe complication of PE and is an acronym of the three main features of the syndrome: Haemolysis, Elevated Liver enzymes and Low Platelets.

PE has been subdivided into two different diseases: early-onset (EPE) and late onset PE (LPE). EPE is defined as PE before 34 weeks of gestation, and LPE will be diagnosed after 34 weeks of gestation. However, the clinical manifestations are comparable, although the pathophysiology is different. EPE is associated with a severe outcome for mother and child, compared to LPE.

PE is a severe complication that appears mostly in primigravid patients. There are several risk factors increasing the chance for developing PE. First, a high body mass index (BMI) is associated with a doubled risk for developing PE. Next, if PE occurred in a previous gestation or in a near family member, the risk of a new preeclamptic gestation will increase steeply (5). PE is a progressive disease for which there is currently no effective treatment. The disease can only be stopped by terminating the pregnancy, so the delivery of the placenta and foetus.

Over several decades, multiple hypotheses regarding the etiology of PE have been suggested. Nevertheless, the pathogenesis of PE is still unknown. One hypothesis is that PE is a systemic vascular disorder featured by shallow endovascular cytotrophoblast invasion in the spiral arteries, inappropriate endothelial cell activation and an exaggerated inflammatory response. In uncomplicated gestations, the placental cytotrophoblast will interact with the smooth muscles and endothelial layers of the maternal decidual arteries and start remodelling to provide adequate oxygenation and nutrition for the placenta and foetus (6). In PE, cytotrophoblasts only invade superficially, resulting in high-resistance spiral arteries (7). This abnormal placentation will release anti-angiogenic factors and placental debris into the maternal circulation, causing inflammation (8).

A more rare presentation of PE is postpartum preeclampsia. It can develop 48 hours postpartum and can last until maximum six weeks after childbearing. The prevalence of *de novo* postpartum hypertension ranges from 0.3% to 27.5%. A delayed mobilization of fluids received during labour, delivery and postpartum, into the intravascular space can play a role in the development of *de novo* postpartum hypertension (9).

1.2 Maternal cardiovascular system during pregnancy

During pregnancy the maternal system has to cope with an increased metabolic demand, due to an increased delivery of oxygenated blood to the peripheral tissues and foetus. Therefore, the maternal cardiovascular, haematological and hemodynamic system will accommodate to provide a suiting habitat for the foetus. In PE, it is known that several cardiovascular maladaptations occur. Recent studies showed that PE will increase the risk for developing chronic hypertension, ischaemic heart disease, stroke and venous thromboembolism in later life (10). It is likely that women with a history of PE will maintain these cardiovascular maladaptations and develop a pathological phenotype that puts these women at risk for developing these diseases.

1.2.1 Hemodynamic adaptations

1.2.1.1 Hemodynamic adaptations in uncomplicated pregnancy

A comprehensive understanding of the cardiovascular adaptations during pregnancy and postpartum is needed to unravel the underlying mechanisms in gestational complications.

First, in early pregnancy a decrease in total peripheral vascular resistance (PVR) and vasodilatation will develop, because of the interaction of placental vasoactive substances and hormones (nitric oxide, prostaglandins, endothelin, angiotensin and relaxine) (11)(12) with the endothelium of the blood vessels. Due to the maternal vasodilatation and plasma expansion, a blood flow increase will occur in the cutaneous, renal, and uteroplacental circulation.

Second, due to the decrease of PVR, the blood pressure (SBP and DBP) declines in early pregnancy until 20-24 weeks and increases until term pregnancy. The pressure parameters (SBP, DBP, mean arterial pressure (MAP)) will reach pre-pregnancy values at twelve weeks postpartum.
Third, an increase in heart rate (HR) is observed during the second week of gestation caused by a reduced parasympathetic modulation. This increased HR results in an augmentation of the left ventricle stroke volume (SV), which will reach a maximum at 24 weeks of gestation. The cardiac output (CO) (calculated as HR x SV) will thus increase and reaches its maximum at sixteen weeks of gestation. In the immediate postpartum period, the blood shifts from the empty uterus into the maternal circulation causing a 10-20% increase in CO. After four to six weeks, the CO returns to mid-pregnancy values (13).
The venous compartment is a considerable regulator of the CO, which is composed of a stressed volume (venous return to the heart) and an unstressed volume (reserve pool). In pregnancy, the venous compartment increases its expansibility, because of a decrease in PVR, which ameliorates the ability to regulate venous return and so maternal CO. First, the unstressed volume will increase. Second, the stressed volume expands and causes an overload of the venous bed and increase in preload. The role of the venous compartment to regulate CO is a relatively new area to explore, limited studies have been conducted to investigate this role. The kidneys and liver play important roles in volume homeostasis, therefore venous adaptation at the level of the renal interlobar vein and the hepatic vein are interesting to investigate during the course of pregnancy (14).

1.2.1.2 Hemodynamic adaptations in hypertensive gestations

Several cardiovascular maladaptations are well described in a preeclamptic gestation. First, vasoconstriction develops and results in an increase in blood pressure. Second, a shift from high CO and low PVR in early gestation to respectively low and high is seen after 24 weeks of gestation. The increase in total PVR is partly due to vasoconstriction. In EPE, myocardial contractility seems to be impaired, this is also reflected in a low cardiac index (15). Third, a reduction in velocity index (VI) and acceleration index (ACI) results from a decrease in aortic compliance and is seen in PE (16). Fourth, a maladaptation occurs in the arterial and venous system. The arterial distensibility is decreased in PE and is characterised by abnormal notching in the uterine arteries. A venous dysfunction is featured with an increase in the renal interlobar venous impedance index (RIVI) in patients with PE compared to uncomplicated pregnancies (17). A high percentage of RIVI is associated with a lower birth weight (BW) and higher proteinuria (18). It was also seen that RIVI is increased in EPE respectively to LPE. The same observation has been made for hepatic vein velocity index (HVI) (18). The venous pulse transit time (VPTT), which represents the venous rigidity, declines throughout an uncomplicated pregnancy. However in PE, this is significantly shorter compared to controls. A decrease in venous capacitance and compliance has also been monitored. These adaptations in the arterial and venous system can be found to five years postpartum. For example postpartum, an aberrant autonomic response to volume expansion (19) and exercise (20) is observed in women who previously had PE. This low venous capacitance persists postpartum and if pregnant again, this will continue to be chronically reduced, leading to a threefold higher risk to develop PE again(14).

1.2.2 Body fluid composition adaptations

1.2.2.1 Body fluid composition adaptations in uncomplicated pregnancy

Maternal weight gain is a biological phenomenon that supports the development of the foetus. This weight gain is influenced by changes in maternal physiology, metabolism but also by placental metabolism. The amount of weight gain during the pregnancy varies markedly interindividually between ten and sixteen kilogram in singleton gestations. This weight gain is partly maternal (water, mammary gland, blood, adipose tissue and uterus) and foetal (placenta, amniotic fluid, foetus).

The maternal body accumulates in weight in fat-free mass (FFM), fat mass (FM) and total body water (TBW). FFM is composed of bone minerals, proteins and TBW. TBW is composed of intracellular (ICW) and extracellular fluids (ECW), which is the sum of the interstitial fluid (fluid contained between cells), plasma fluid (fluid of the blood) and transcellular fluid (fluid within epithelial lined spaces).

In early pregnancy, a rapid increase of TBW occurs to irrigate the vascular beds of vital organs (placenta and foetus) and to prepare for the blood loss during delivery. It accounts for 50% of the total weight gain and increases seven to eight litre in singleton uncomplicated pregnancies. This increase is mediated through an elevated plasma renine, decreased anti-natriuretic peptide and vasodilation of the vascular system. The erythrocytes will increase slightly less in comparison with the plasma volume, causing dilatational anaemia. The biggest augmentation in TBW will proceed inside the plasma volume. During delivery, blood loss reduces the plasma volume and afterwards the fluids will shift from the ECW into the intravascular space (15).

1.2.2.2 Body fluid composition adaptations in hypertensive gestations

Women with hypertensive diseases differ from body composition in that their TBW and FM is increased compared to women with uncomplicated pregnancies. A study of da silva et al. demonstrated a significantly decrease in TBW, resulting in a decrease and increase in its subcomponents ICW and ECW respectively, which results in an increased ECW/ICW ratio (21). Another feature often observed in PE, is edema. This originates from the retention of abnormal fluid and is characterized as swollen ankles and wrists and an increase in excess ECW. The subcomponent of ECW: plasma volume, normally expands during pregnancy, but in PE a reduction is observed. This reduction is mediated by a fluid shift from plasma volume to interstitial space. This aberrant distribution is induced by an increased microvascular permeability (22).

1.3 Techniques to measure hemodynamic adaptations and changes in body composition

In order to obtain a hemodynamic and body composition profile during pregnancy and postpartum, different techniques are suitable. The main requirement is the non-invasiveness aspect of the techniques. Furthermore, the techniques have to be safe for both mother and child. Another demand is that the technique has to be easy to execute and should be validated. Last, the cost-effectiveness should also be taken into account. Based on these specifications, the following techniques were chosen above their alternatives: combined electrocardiography (ECG) with

Doppler ultrasonography, non-invasive continuous cardiac output monitoring (NICCOMO) using impedance cardiography (ICG) and bio-electrical impedance analysis (BIA).

1.3.1 Non-invasive techniques to obtain hemodynamic characteristics

To obtain hemodynamic alterations postpartum, ICG, also referred to as electrical impedance plethysmography is used. This technique uses four electrodes to send an electrical current throughout the body, to measure the thoracic blood flow. First, it registers the baseline resistance in the blood filled aorta, followed by registering the corresponding impedance changes with every heartbeat. This technique can be used in gynecology and has been validated by Gyselaers et al. (23).

Doppler ultrasonography obtains information on rigidity of the renal interlobar vein, hepatic veins and uterine artery. A probe sends out ultrasonic waves and picks up the reflection on red blood cells, thus creating and registering an image of blood flow. This technique has been proven to be effective in obstetrics and is validated by Gyselaers et al. (24).

1.3.2 Non-invasive techniques to obtain characteristics in body fluid composition

BIA provides information on the hydration status of a patient. It applies an electrical current to the body. This electrical current will be conducted by the electrolytes in body fluids. The cell membranes will behave as capacitors and permit the body to save electrical charges. BIA investigates the body's reactance, composed by the cell membranes of the body, and the resistance. The phase angle represents the relation between the reactance and resistance of the body. The current will pass more profoundly at a higher frequency into the tissue. With the use of multiple frequencies, different body compartments can be measured (25).

1.4 Aim of the study

Cardiovascular maladaptations may resolve or endure in the postpartum state. This evolution may relate to cardiovascular diseases in later life. Although different studies on cardiovascular parameters in pregnancy exist, little is known about these adjustments postpartum. Therefore, the first objective of this study is to evaluate the changes of the cardiovascular parameters in the immediate postpartum period. And the second objective is to investigate, if there are differences in the cardiovascular parameters between hypertensive and uncomplicated pregnancies.

2 Materials and methods

2.1 Ethics

An observational cross-sectional study was approved by the ethical committees of ZOL (Genk, Belgium) and Hasselt University (Hasselt, Belgium) (12/048U) before study onset.

2.2 Patients

Women admitted between 24/11/2014 and 10/03/2015 to the Fetal Maternal Medicine Unit of Ziekenhuis Oost Limburg (Genk, Belgium) for hypertension with singleton pregnancies >20 weeks were included. Exclusion criteria were age under 18 years, history of organ transplantation, women with concomitant diseases as diabetes, thyroid dysfunction, autoimmune disease, cholestasis nephritic syndrome, cardiac comorbidities or liver disease, abdominal masses and foetal abnormalities. This group was classified into (1) gestational hypertension (GH), (2) preeclampsia (PE). According to the criteria of the National High Blood Pressure Education Program Working Group, PE is defined as gestational hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) measured on at least two occasions with at least six hours in between measurements, with new onset proteinuria (≥300 mg/24 hours).

As a control group, patients with an uncomplicated pregnancy at a gestational age of ≥38 weeks and maternal age above eighteen years were included, while admitted for cardiotocography (CTG) in Ziekenhuis Oost Limburg (Genk, Belgium). The same exclusion criteria were obtained as in the cases group, with active hypertension as an additional exclusion criteria.

2.3 Data collection

After written and oral informed consent, measurements were performed in all patients of both groups (i.e. cases and controls) before delivery (day of admission or day of an ambulant foetal CTG for the cases or control group, respectively), 48-72 hours postpartum and six weeks postpartum. For each woman, data on demographics and perinatal outcome were recorded. Maternal demographic data include age (years), current BMI and BMI before pregnancy, smoking habits, parity, gravidity, the estimated date of delivery, and any drug use. Data on perinatal outcome comprise gestational age at delivery (weeks), birth weight (BW in g) and customized birth weight percentile (BW% in %).

2.4 Measurements

2.4.1 Doppler-ultrasound

A combined Doppler-ECG was obtained from the renal interlobar veins of the left and right kidney, the hepatic vein and the uterine arcuate artery. At all sites, three consecutive pictures were taken and stored on a hard disk for offline analysis later. All measurements were performed by the same sonographer (A.H.) using a 3.5-7 MHz probe (Toshiba AplioMX, United Medical Instruments Inc, San Jose, USA) and analysed by the same person (A.S.). All women were examined in a supine position irrespectively of the period of day or food intake. The kidneys were scanned in a transverse plane just above the renal hilus. Colour Doppler flow mapping was used to identify the arteries and veins. The relevance of holding breath during the measurements were explained and

demonstrated to the patients. After they were comfortable with the routine, a standard protocol was used, in which patients were asked to stop breathing after inspirations (18).

Maximum velocity (MxV) and minimum velocity (MnV) of the blood flow of the hepatic vein and the renal interlobar veins were measured using Doppler ultrasound. From these parameters, the RIVI is calculated as [(MxV- MinV)/MxV]. The maternal VPTT is the time interval between the atrial depolarization represented by the ECG P-wave and the reciprocal venous Doppler A-wave, corrected for the heart rate, expressed in msec. Next, the middle, left and right branch of the hepatovenous tree was visualized with colour Doppler flow mapping. The hepatic veins were distinguished from portal veins and the examination of the liver was performed according to the protocol reported (26). Next, the middle, left and right branch of the hepatovenous tree was visualized with colour Doppler flow mapping. The hepatic veins were distinguished from portal veins and the examination of the liver was performed according to the protocol reported (26).

Characteristics of the Doppler waveforms (A, X, V and Y) resemble those of the inferior vena cava. During atrial contraction blood flows away from the heart, representing in the A-deflection. After atrial relaxation forward cardiofugal flow will cause the X-deflection. The V-deflection is caused by the decelerated blood flow by the opening of the tricuspid valve. And the Y-deflection reflects the blood flow forward, which is caused due to ventricular relaxation (figure 1). The arterial rigidity can be estimated by looking at the venous pulse waves. According to the RIVI, the HVI is calculated as [(MxV- MinV)/MxV], with MxV the X-wave and MinV the A-wave (addendum II).

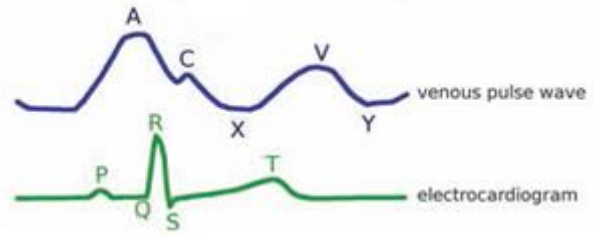


Figure 1: The blue line represents the hepatic venous pulse wave (A-wave = right atrial contraction, C-wave = reflection of the tricuspid valve that closes, X-base = right atrial relaxation and right ventricular systole, V-wave = filling state of the right atrium after the tricuspid valve has been closed, Y-base = tricuspid valve that opens). The green line reflects the electrocardiogram (P- wave = atrial depolarization, QRS-complex = ventricular depolarization, T-wave = ventricular repolarization).

Further, the uterine artery of the uterus was examined according to following protocol (16). Uterine arcuate arteries were selected, because of their intra-parenchymatous position. The Doppler ultrasound was performed at a maximum of 2 cm span of the bifurcation of the uterine artery. The maternal arterial pulse transit time (APTT) is known as the time interval between the ECG Q-wave and the start of systolic Doppler signal or end diastolic point D, corrected for heart rate (QD/RR). Arterial pulsatility (PI) and resistivity index (RI) were measured, defined as [(MxV–MnV)/mean velocity] and [(MxV–MnV)/MxV] respectively (addendum II).

2.4.2 Impedance cardiography

After Doppler-ultrasound, a standard protocol of ICG using the NICCOMO™ (Software version 3.0, Medis Medizinische Messtechnik GmbH, Ilmenau, Germany) was performed on all women in a supine and standing position (16). The ICG parameters are classified as pressure, time period, volume, contractility and resistance parameters. The pressure parameters are SBP; DBP; MAP which represents the average arterial pressure calculated as (MAP = DBP + PP/3) and pulse

pressure (PP), which is the pressure used by the heart to contract, calculated as (PP = SBP – DBP). All these parameters are expressed in mmHg. Left ventricular output parameters are SV in ml and CO in ml/min, which is calculated as (CO = HR x SV). The time period parameter consists of the heart rate (HR) in beats/min. Contractility parameters include ACI, which represents the maximal acceleration of aortic blood flow, expressed in $1/100/s^2$; VI in 1/1000/s is a measurement of myocardial contractility and heather index (HI) is the extent of ICG wave corrected for the required time the ventricle needs to eject maximally expressed in Ω/s. This factor is sensitive to changes in contractility. The resistance factors comprises thoracic fluid content (TFC) in 1/kΩ and is an indicator of total fluid volume in the thorax and total arterial compliance (TAC) in ml/mmHg calculated as (SV/PP) is a measurement of arterial expansibility.

2.4.3 Bio-electrical impedance analysis

Bio-electrical impedance analysis was determined using a tetrapolar multifrequency impedance analyser (BioScan 920-II, Maltron international Ltd, Essex, United Kingdom). All the women were normally clothed, their right sock and shoe were removed and they were placed in a supine position on a non-conductive table (figure 2). Electrodes were placed on the dorsal surfaces of the right hand and foot in contact with the skin. Bioelectrical impedance was measured at four different frequencies: 5 kHz, 50 kHZ, 100 kHZ and 200 kHZ during five seconds with a current of 0,6 mA. The current send out by the electrodes is send throughout the body at a constant flow and is received by the electrodes. The parameters obtained from BIA are presented in addendum I.

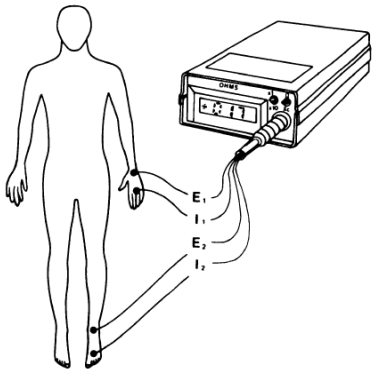


Figure 2: Bio-electrical impedance.

2.5 Statistics

A repeated measures analysis of variance (rm MANOVA) was applied to investigate the evolution of hemodynamic and body composition values between uncomplicated pregnancies (UP), gestational induced hypertensive pregnancies (GH) and preeclamptic pregnancies (PE), using SPSS software (version 22.00, SPSS inc., Chicago, IL, USA). Normality and sphericity of the data were checked using the Shapiro-Wilk test and Mauchly's test. The Bonferroni post hoc test was used to compare differences between the study groups. Paired T-tests were used for analysis of differences between different time points. The Wilcoxon signed-rank test was used in case the data were not normally divided. If p-value is <.05, data was considered statistically significant.

3 Results

3.1 Patients demographics

A total of 46 women were included in our study, between November 2014 and March 2015. Of these 46 women, 32 (69.56%) had an uneventful pregnancy (UP), 14 (30.44%) had a complicated pregnancy: gestational induced hypertension (GH) (n=5, 10.87%) or preeclamptic pregnancy (PE) (LPE=4 (8.70%), EPE=3 (6.52%), PE with additionally HELLP-syndrome=2 (4.35%)). Eight Women (2 GH, 6 HC) were excluded, because they did not attend the follow-up measurements. Table 1 represents patients demographics of the three study groups. Compared to UP, gestational age at inclusion is lower in PE and GH (p<.018 and .014, respectively). Gestational age at delivery is lower in PE compared to the other groups (p<.009 for UP and p<.012 for GH, respectively). The BW is lower in PE compared to UP (p<.014).

Table 1: Characteristics of the study groups: uncomplicated, gestational hypertensive and preeclamptic pregnancies.

	GH (n=3)	**P-value UP to GH**	**UP (n=26)**	**P-value UP to PE**	**PE (n=9)**
Maternal age (years)	28.00 ± 4.36	0.675	29.04 ± 4.51	0.645	28.33 ± 4.85
Pre-pregnancy BMI (kg/m^2)	30.10 ± 7.16	0.087	24.87 ± 4.79	0.480	26.08 ± 4.82
BMI at inclusion (kg/m^2)	35.10 ± 6.44	0.090	29.93 ± 4.86	0.368	31.55 ± 4.98
Weight gain (kg)	18.00 ± 7.21	0.172	13.42 ± 5.09	0.330	15.64 ± 6.80
Gestational age at inclusion (weeks)	36.76 (33.28; 38.00)	**0.014**	39.72 (38.57; 40.00)	**0.018**	34.83 ± 4.35
Gestational age at delivery (weeks)	39.76 ± 0.17	0.747	40.01 ± 1.46	**0.009**	35.21 ± 4.26
Gestation	1.00 ± 0.00	0.159	2.00	0.228	2.44 ± 1.59
Parity	0.00 ± 0.00	0.124	(1.00;3.00)	0.157	1.00 ± 1.00
Abortion	0.00 ± 0.00	0.104	0.00 ± 1.00	0.346	0.44 ± 0.73
			0.00 ± 1.00		
Infant birthweight (g)	3572.50 ± 1092.48	0.119	3836.46 ± 1892.13	**0.014**	2645.00 ± 1790.00

Data are represented as means ± standard deviation. If data are not-normally distributed, data is presented as median (interquartile range (IQR)). P-values are in reference to UP. Significant differences between PE and GH are underlined.

3.2 Hypertensive versus normotensive pregnancies

3.2.1 Central arterial hemodynamic system

3.2.1.1 Antepartum

The differences in the hemodynamic system between hypertensive and normotensive pregnancies are presented antepartum (table 2), two days postpartum (table 3) and six weeks postpartum (table 4). Antepartum, the pressure parameters (SBP, DBP, MAP) are higher in GH (p<.014; p<.000 and p<.001) and PE (p<.000; p<.000 and p<.000) compared to UP. No significant differences are found for CO, HR and SV antepartum between GH, PE and UP. The aortic compliance parameters (VI, ACI and HI) are lower in GH (p<.022; p<.023 and p<.003) and PE (p<.029; p<.048 and p<.015) compared to UP.

Table 2: Antepartum differences in the central arterial hemodynamic system between uncomplicated, gestational hypertensive and preeclamptic pregnancies.

Parameter	Timepoint	GH (n=3)	P-value UP to GH	UP (n=26)	P-value UP to PE	PE (n=9)
SBP (mmHg)	Antepartum	142.67 ± 10.22	**0.014**	122.80 ± 11.48	**0.000**	149.89 ± 15.83
DBP (mmHg)	Antepartum	101.33 ± 1.53	**0.000**	81.16 ± 7.92	**0.000**	98.11 ± 7.22
MAP (mmHg)	Antepartum	111.00 ± 4.58	**0.001**	91.64 ± 8.30	**0.000**	111.56 ± 8.70
PP (mmHg)	Antepartum	41.33 ± 9.29	0.893	41.64 ± 11.17	**0.038**	51.78 ± 11.19
CO (mL/min)	Antepartum	7.77 ± 0.42	0.744	8.00 ± 1.22	0.172	7.38 ± 0.96
HR (beats/min)	Antepartum	106.67 ± 22.55	0.207	93.64 ± 13.67	0.335	89.00 (83.50; 96.00)
SV (mL)	Antepartum	74.67 ±12.06	0.163	85.84 ± 12.76	0.823	86.78 ± 15.59
VI (1/1000/s)	Antepartum	39.00 ±17.52	**0.029**	65.64 ± 19.36	**0.022**	49.33 ± 11.72
ACI (1/100/s^2)	Antepartum	88.67 ±32.02	**0.048**	147.88 ± 48.76	**0.023**	105.89 ± 37.06
HI (Ω/s)	Antepartum	11.60 ± 2.17	**0.015**	18.63 ± 5.19	**0.003**	12.72 ± 3.86
TFC (1/kΩ)	Antepartum	24.07 ±3.35	0.349	26.17 ± 3.36	0.062	28.83 ± 4.78
TAC(mL/mmHg)	Antepartum	1.83 ±0.15	0.409	2.00 (1.62;2.40)	0.069	1.72 ± 0.36

Data are presented as means ± standard deviation, in case data are normally divided. Otherwise, data are presented as medians (IQR). Significant p-values are marked in bold. Significant differences between PE and GH are underlined. SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure; CO: cardiac output; HR: heart rate; SV: stroke volume; VI: velocity index; ACI: acceleration index; HI: heather index; TFC: thoracic fluid content; TAC: total arterial compliance.

3.2.1.2 Two days postpartum

After delivery of the baby, the pressure parameters (SBP, DBP and MAP) are still lower in UP compared to GH (p<.007; p<.006 and p<.000) and PE (p<.000; p<.000 and p<.000). The CO and HR are not different between hypertensive and normotensive pregnancies. However, there is a higher SV observed in PE compared to UP (p<.018). Also the aortic compliance parameters are still significantly lower in GH (p<.002; p<.013 and p<.011) and PE (p<.002; p<.038; p<.000) compared to UP. The TAC is higher in UP compared to PE (p<.000) (table 3).

Table 3: Differences between uncomplicated, gestational hypertensive and preeclamptic pregnancies in the cardiovascular system two days postpartum.

Parameter	Timepoint	GH (n=3)	P-value UP to GH	UP (n=26)	P-value UP to PE	PE (n=9)
SBP (mmHg)	2dPP	137.67 ± 6.66	**0.007**	119.92 ± 10.35	**0.000**	144.67 ± 17.18
DBP (mmHg)	2dPP	94.67 ± 0.58	**0.006**	79.24 ± 6.05	**0.000**	95.44 ± 9.23
MAP (mmHg)	2dPP	106.00 ±2.00	**0.000**	89.96 ± 6.48	**0.000**	106.00 ± 9.08
PP (mmHg)	2dPP	43.00 ±6.08	0.429	37.00 (35.00;44.75)	**0.017**	49.22 ± 10.49
CO (mL/min)	2dPP	8.10 ±1.28	0.889	8.01 ± 1.27	0.470	7.62 ± 1.49
HR (beats/min)	2dPP	114.33 ± 6.66	0.056	96.12 ± 15.25	0.070	105.00 (97.00; 123.50)
SV (mL)	2dPP	70.667 ± 7.09	0.119	84.56 ± 14.13	**0.018**	70.33 ± 15.07
VI (1/1000/s)	2dPP	42.33 ± 13.58	**0.002**	70.44 ± 13.12	**0.002**	53.11 ± 13.02
ACI (1/100/s^2)	2dPP	100.67 ± 32.88	**0.013**	163.32 ± 39.31	**0.038**	129.56 ± 43.76
HI (Ω/s)	2dPP	13.60 ± 1.99	**0.011**	19.51 ± 3.50	**0.000**	12.62 ± 4.36
TFC (1/kΩ)	2dPP	22.90 ±1.15	0.082	26.74 ± 3.43	0.269	29.53 ± 7.25

TAC(mL/mmHg)	2dPP	1.67 ± 0.31	0.102	2.14 ± 0.49	**0.000**	1.44 ± 0.29

Data are presented as means ± standard deviation, in case data are normally divided. Otherwise, data are presented as medians (IQR). Significant p-values are marked in bold. Significant differences between PE and GH are underlined. 2dPP: two days postpartum; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure; CO: cardiac output; HR: heart rate; SV: stroke volume; VI: velocity index; ACI: acceleration index; HI: heather index; TFC: thoracic fluid content; TAC: total arterial compliance.

3.2.1.3 Six weeks postpartum

Six weeks postpartum (table 4), several hemodynamic differences between hypertensive and normotensive pregnancies have diminished. However, the pressure parameters (SBP, DBP and MAP) are still increased in GH (p<.030; p<.048 and p<.034) compared to UP. And also the MAP is still higher in PE compared to UP (p<.046). No significant differences in CO, HR or SV are found. Despite a lower ACI for PE compared to UP (p<.027), no differences in aortic compliance parameters were found.

Table 4: Differences of the central arterial hemodynamic system in hypertensive and normotensive pregnancies at six weeks postpartum.

Parameter	**Timepoint**	**GH (n=3)**	**P-value UP to GH**	**UP (n=26)**	**P-value UP to PE**	**PE (n=9)**
SBP (mmHg)	6wPP	145.00 ± 21.21	**0.030**	113.67 ± 9.74	0.102	121.38 ± 15.03
DBP (mmHg)	6wPP	113.50 ± 2.12	**0.048**	76.33 ± 9.40	0.051	84.00 ± 8.77
MAP (mmHg)	6wPP	102.00 ± 7.07	**0.034**	86.42 ± 8.86	**0.046**	94.25 ± 10.32
PP (mmHg)	6wPP	37.33 ± 7.02	**0.043**	56.00 ± 15.56	0.760	34.00 (32.00; 41.50)
CO (mL/min)	6wPP	7.50 ± 1.27	0.192	6.63 ± 1.03	0.912	6.68 ± 0.92
HR (beats/min)	6wPP	101.00 ± 5.66	0.054	82.54 ± 11.84	0.208	88.75 ± 11.73
SV (mL)	6wPP	74.50 ± 16.26	0.563	81.50 ± 15.12	0.484	77.00 ± 16.85
VI (1/1000/s)	6wPP	61.00 ± 1.41	0.500	68.17 ± 16.24	0.068	56.38 ± 11.59
ACI (1/100/s^2)	6wPP	138.00 ± 0.00	0.564	154.54 ± 40.59	**0.027**	118.13 ± 30.24
HI (Ω/s)	6wPP	19.50 ± 2.83	0.773	19.39 ± 4.81	0.054	15.60 ± 3.98
TFC (1/kΩ)	6wPP	22.00 ± 1.56	0.531	23.02 ± 2.41	0.643	22.54 ± 2.79
TAC(mL/mmHg)	6wPP	1.40 ± 0.71	0.091	2.23 ± 0.51	0.094	2.04 ± 0.12

Data are presented as means ± standard deviation, in case data are normally divided. Otherwise, data are presented as medians (IQR). Significant p-values are marked in bold. Significant differences between PE and GH are underlined. 6wPP: six weeks postpartum; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure; CO: cardiac output; HR: heart rate; SV: stroke volume; VI: velocity index; ACI: acceleration index; HI: heather index; TFC: thoracic fluid content; TAC: total arterial compliance.

3.2.2 Venous hemodynamic system

3.2.2.1 Antepartum

Due to missing data, SPSS used only 21 subjects out of 26 for UP, 0 subjects out of 3 for GP and 5 subjects out of 9 for PE, for data analysis. As shown in table 5, the RIVI of the right kidney (p<.032), RI (p<.029), and PI (p<.034) of the right uterine arcuate artery are increased in PE compared to UP. A decrease was observed in APTT of the left (p<.032) and right uterine arcuate artery (p<.028).

Table 5: Antepartum differences in the venous hemodynamic system between uncomplicated, gestational hypertensive and preeclamptic pregnancies.

Parameter	Timepoint	UP (n=21)	P-value	PE (n=5)
LK-RIVI	Antepartum	0.33 ± 0.06	0.504	0.35 ± 0.12
RK-RIVI	Antepartum	0.27 ± 0.05	**0.032**	0.39 ± 0.13
HVI	Antepartum	0.33 (0.15;0.76)	0.487	0.54 ± 0.50
LK-VPTT	Antepartum	0.39 ± 0.08	0.105	0.33 ± 0.08
RK-VPTT	Antepartum	0.39 ± 0.09	0.130	0.34 ± 0.08
L-VPTT	Antepartum	0.25 (0.19;0.39)	0.288	0.25 ± 0.13
L-UtAA-RI	Antepartum	0.46 (0.42;0.55)	0.133	0.57 ± 0.17
L-UtAA-PI	Antepartum	0.78 (0.57;1.13)	0.139	0.58 (0.53;0.71)
R-UtAA-RI	Antepartum	0.43 ± 0.08	**0.029**	0.58 ± 0.17
R-UtAA-PI	Antepartum	0.56 ± 0.14	**0.034**	0.86 ± 0.35
L-UtAA-APTT	Antepartum	0.31 ± 0.06	**0.032**	0.26 ± 0.06
R-UtAA-APTT	Antepartum	0.32 ± 0.06	**0.028**	0.27 ± 0.06

Data are presented as means ± standard deviation, in case data are normally divided. Otherwise, data are presented as medians (IQR). Significant p-values are marked in bold. Significant differences between PE and GH are underlined. LK: left kidney; RK: right kidney; L: liver; L-UtAA: left uterine arcuate artery; R-UtAA: right uterine arcuate artery; RIVI: renal interlobar venous impedance index; HVI: hepatic venous impedance index; VPTT: venous pulse transit time; RI: resistance index; PI: pulsatility index and APTT: arterial pulse transit time.

3.2.2.2 Two days postpartum

Two days postpartum, the RIVI of the right kidney (p<.034) is higher in UP compared to PE. A smaller HVI (p<.010) and VPTT is observed for the left and right kidney (p<.029) (p<.006) in UP compared to PE (table 6).

Table 6: Differences between uncomplicated, gestational hypertensive and preeclamptic pregnancies in the cardiovascular system at two days postpartum.

Parameter	Timepoint	UP (n=21)	P-value	PE (n=5)
LK-RIVI	2dPP	0.41 ± 0.11	0.067	0.32 ± 0.10
RK-RIVI	2dPP	0.41 (0.33; 0.51)	**0.034**	0.32 ± 0.17
HVI	2dPP	0.33 (0.23;1.50)	**0.010**	0.67 (0.23; 1.50)
LK-VPTT	2dPP	0.31 ± 0.06	**0.029**	0.41 (0.38;0.43)
RK-VPTT	2dPP	0.31 ± 0.09	**0.006**	0.043 ± 0.08
L-VPTT	2dPP	0.22 ± 0.10	0.253	0.28 ± 0.14
L-UtAA-RI	2dPP	0.69 (0.58; 0.73)	0.366	0.60 ± 0.13
L-UtAA-PI	2dPP	0.98 ± 0.26	0.365	0.88 ± 0.26
R-UtAA-RI	2dPP	0.64 ± 0.12	0.916	0.66 (0.58; 0.70)
R-UtAA-PI	2dPP	0.96 ± 0.25	0.463	0.89 ± 0.17
L-UtAA-APTT	2dPP	0.27 ± 0.05	0.387	0.29 ± 0.04
R-UtAA-APTT	2dPP	0.27 ± 0.05	0.290	0.29 ± 0.06

Data are presented as means ± standard deviation, in case data are normally divided. Otherwise, data are presented as medians (IQR). Significant p-values are marked in bold. Significant differences between PE and GH are underlined. 2dPP: two days postpartum; LK: left kidney; RK: right kidney; L: liver; L-UtAA: left uterine arcuate artery; R-UtAA: right uterine arcuate artery; RIVI: renal interlobar venous impedance index; HVI: hepatic venous impedance index; VPTT: venous pulse transit time; RI: resistance index; PI: pulsatility index and APTT: arterial pulse transit time.

3.2.2.3 Six weeks postpartum

Despite the diminishing of the differences in central arterial hemodynamic between hypertensive and normotensive pregnancies, the venous system still contains some alterations. A significantly lower venous impedance index is observed in the right kidney (p<.028) and liver (p<.017) in PE.

Also the VPTT of the left kidney (p<.008) and liver (p<.009) are higher in women with PE compared to UP. This observation is also made for the APTT of the left (p<.014) and right (p<.006) uterine arcuate arteries (table 7).

Table 7: Differences of the venous hemodynamic system in hypertensive and normotensive pregnancies six weeks postpartum.

Parameter	Timepoint	UP (n=21)	P-value	PE (n=5)
LK-RIVI	6wPP	0.38 ± 0.08	0.302	0.34 ± 0.03
RK-RIVI	6wPP	0.40 ± 0.09	**0.028**	0.34 ± 0.04
HVI	6wPP	1.36 (0.67; 1.57)	**0.017**	0.54 ± 0.29
LK-VPTT	6wPP	0.28 (0.24; 0.34)	**0.008**	0.40 ± 0.03
RK-VPTT	6wPP	0.29 (0.25; 0.36)	0.051	0.38 ± 0.06
L-VPTT	6wPP	0.15 (0.12; 0.22)	**0.009**	0.29 (0.24; 0.45)
L-UtAA-RI	6wPP	0.71 ± 0.09	0.075	0.79 ± 0.07
L-UtAA-PI	6wPP	1.11 ± 0.21	0.066	1.30 ± 0.17
R-UtAA-RI	6wPP	0.69 ± 0.09	0.780	0.68 ± 0.08
R-UtAA-PI	6wPP	1.06 ± 0.21	0.749	1.03 ± 0.19
L-UtAA-APTT	6wPP	0.24 ± 0.04	**0.014**	0.29 ± 0.02
R-UtAA-APTT	6wPP	0.23 ± 0.04	**0.006**	0.23 (0.23; 0.27)

Data are presented as means ± standard deviation, in case data are normally divided. Otherwise, data are presented as medians (IQR). Significant p-values are marked in bold. Significant differences between PE and GH are underlined. 6wPP: six weeks postpartum; LK: left kidney; RK: right kidney; L: liver; L-UtAA: left uterine arcuate artery; R-UtAA: right uterine arcuate artery; RIVI: renal interlobar venous impedance index; HVI: hepatic venous impedance index; VPTT: venous pulse transit time; RI: resistance index; PI: pulsatility index and APTT: arterial pulse transit time.

3.2.3 Body fluid composition

3.2.3.1 Antepartum

The differences in body fluid composition between hypertensive and normotensive pregnancies are presented antepartum in table 8, two days postpartum in table 9 and six weeks postpartum in table 10. Antepartum, the weight is significantly higher in GH compared to UP (p<.030). This is due to a significantly higher level of FFM in GH (p<.020). This observation was also made for PE compared to UP (p<.016). Also differences in body fluids are registered: a higher TBW is seen in GH and PE compared to UP (p<.011)(p<.041). This increase is due to the increased ECW (p<.046), as ICW is not different between UP and PE (p<.064). However, in GH this increase is also mediated by an increase in ICW (p<.022). Also the three components of ECW (interstitial fluid, plasma fluid, and transcellular fluid) are significantly higher in GH and PE compared to UP (p<.017) (p<.046). A higher excess ECW was seen in prenatal PE compared to UP (p<.023). The same observation can be made for extracellular mass (ECM) in GH (p<.040) and PE (p<.046). A higher body cell mass (BCM) is observed for GH compared to UP (p<.023).

Table 8: Antepartum differences in body fluid composition between hypertensive and normotensive pregnancies.

Parameter	Timepoint	GH (n=3)	P-value UP to GH	UP (n=26)	P-value UP to PE	PE (n=9)
Weight (kg)	Antepartum	94.50 ± 13.44	**0.030**	83.05 ± 13.71	0.269	90.10 ± 15.44
FM (kg)	Antepartum	37.77 ± 10.20	0.059	31.88 ± 10.50	0.752	34.09 ± 12.43
FFM (kg)	Antepartum	58.07 ± 3.25	**0.020**	51.33 ± 4.62	**0.016**	56.14 ± 5.67
TBW (L)	Antepartum	44.017 ± 3.05	**0.011**	38.33 ± 3.57	**0.041**	43.39 ± 6.11

FFMH%	Antepartum	75.78 ± 2.56	0.300	74.66 ± 1.81	0.073	76.87 ± 3.27
ECW (L)	Antepartum	20.46 ± 1.63	**0.011**	17.40 ± 1.95	**0.046**	21.02 ± 4.59
ICW (L)	Antepartum	23.56 ± 1.50	**0.022**	20.93 ± 1.79	0.064	22.26 ± 1.65
ECW/ICW	Antepartum	0.87 ± 0.03	0.219	0.83 ± 0.05	0.072	0.94 ± 0.16
Excess ECW (L)	Antepartum	0.90 ± 0.91	0.272	0.31 (0.00; 0.69)	**0.023**	2.00 (0.19; 5.11)
Interstitial fluid (L)	Antepartum	14.87 ± 1.18	**0.011**	12.64 ± 1.41	**0.046**	15.28 ± 3.35
Plasma fluid (L)	Antepartum	4.25 ± 0.34	**0.011**	3.61 ± 0.40	**0.046**	4.36 ± 0.96
Transcellular fluid (L)	Antepartum	1.06 ± 0.9	**0.017**	0.90 ± 0.11	**0.046**	1.09 ± 0.24
ECM	Antepartum	25.08 ± 2.21	**0.040**	22.28 ± 2.22	**0.046**	25.15 ± 3.61
BCM	Antepartum	32.99 ± 2.08	**0.023**	29.05 ± 2.66	0.079	30.99 ± 2.45

Data are presented as means ± standard deviation, in case data are normally divided. Otherwise, data are presented as medians (IQR). Significant p-values are marked in bold. Significant differences between PE and GH are underlined. FM: fat mass; FFM: fat free mass; TBW: total body water; FFMH: fat free mass hydration; ECW: extracellular water; ICW: intracellular water; ECM: extracellular mass; BCM: body cell mass.

3.2.3.2 Two days postpartum

After delivery of the baby, the PE differences in body fluid are normalized. However, in GH pregnancies, there is still an absence of an aberrant body fluid composition (table 9). This is seen in an higher level of weight ($p<.035$) caused by a higher FFM ($p<.025$). A higher TBW in GH compared to UP is observed ($p<.017$). This is due to higher levels of the subcomponents of TBW: ICW ($p<.017$) and ECW ($p<.036$). This is also marked in higher levels of the subcomponents of ECW (interstitial fluid, plasma fluid and transcellular fluid) ($p<.036$; $p<.036$ and $p<.036$) A higher level of BCM is also seen in GH compared to UP ($p<.015$).

Table 9: Differences in uncomplicated, gestational hypertensive and preeclamptic pregnancies in the body fluid composition two days after parturition.

Parameter	Timepoint	GH (n=3)	P-value UP to GH	UP (n=26)	P-value UP to PE	PE (n=9)
Weight (kg)	2dPP	97.60 ± 20.50	**0.035**	78.90 ± 13.35	0.253	85.13 ± 15.48
FM (kg)	2dPP	40.34 ± 17.36	0.061	28.06 ± 9.76	0.553	30.39 ± 11.75
FFM (kg)	2dPP	57.26 ± 3.49	**0.025**	50.85 ± 4.49	0.179	54.74 ± 7.42
TBW (L)	2dPP	43.55 ± 2.60	**0.017**	38.20 ± 3.59	0.208	41.86 ± 7.80
FFMH%	2dPP	76.08 ± 2.01	0.431	75.12 ± 2.19	0.330	76.06 ± 4.08
ECW (L)	2dPP	20.28 ± 1.05	**0.036**	17.55 ± 2.16	0.214	20.15 ± 5.75
ICW (L)	2dPP	23.27 ± 1.55	**0.017**	20.66 ± 1.69	0.158	21.71 ± 2.22
ECW/ICW	2dPP	0.87 ± 0.01	0.115	0.85 ± 0.07	0.273	0.92 ± 0.17
Excess ECW (L)	2dPP	0.87 ± 0.77	0.551	0.43 (0.00; 1.43)	0.230	0.76 (0.00; 5.51)
Interstitial fluid (L)	2dPP	14.74 ± 0.76	**0.036**	12.75 ± 1.57	0.213	14.65 ± 4.19
Plasma fluid (L)	2dPP	4.21 ± 0.22	**0.036**	3.64 ± 0.45	0.213	4.19 ± 1.20
Transcellular fluid (L)	2dPP	1.05 ± 0.06	**0.036**	0.91 ± 0.11	0.214	1.04 ± 0.30
ECM	2dPP	24.69 ± 2.40	0.103	22.30 ± 2.28	0.158	24.66 ± 4.30
BCM	2dPP	32.57 ± 2.18	**0.015**	28.55 ± 2.59	0.173	30.09 ± 3.44

Data are presented as means ± standard deviation, in case data are normally divided. Otherwise, data are presented as medians (IQR). Significant p-values are marked in bold. Significant differences between PE and GH are underlined. 2dPP: two days postpartum; FM: fat mass; FFM: fat free mass; TBW: total body water; FFMH: fat free mass hydration; ECW: extracellular water; ICW: intracellular water; ECM: extracellular mass; BCM: body cell mass.

3.2.3.3 Six weeks postpartum

Six weeks postpartum the differences between hypertensive and normotensive pregnancies are diminished (table 10).

Table 10: The differences in body fluid composition between normotensive and hypertensive pregnancies at six weeks postpartum.

Parameter	Timepoint	GH (n=3)	P-value UP to GH	UP (n=26)	P-value UP to PE	PE (n=9)
Weight (kg)	6wPP	81.50 ± 13.44	0.354	73.34 ± 12.90	0.214	80.31 ± 15.49
FM (kg)	6wPP	28.76 ± 10.51	0.355	24.23 ± 9.42	0.224	29.30 ± 11.99
FFM (kg)	6wPP	52.74 ± 2.93	0.195	49.11 ± 4.58	0.314	51.01 ± 4.62
TBW (L)	6wPP	38.60 ± 0.48	0.195	36.38 ± 3.21	0.305	37.84 ± 4.17
FFMH%	6wPP	74.31 ± 1.67	0.517	73.27 ± 3.15	0.749	74.07 ± 2.35
ECW (L)	6wPP	17.00 ± 0.47	0.405	16.15 ± 1.92	0.382	16.89 ± 2.51
ICW (L)	6wPP	21.60 ± 0.95	0.195	20.35 ± 1.70	0.405	20.94 ± 1.86
ECW/ICW	6wPP	0.71 ± 0.06	0.926	0.78 (0.76; 0.80)	0.542	0.75 ± 0.04
Excess ECW (L)	6wPP	-0.01 ± 0.76	0.674	0.21 ± 0.59	0.935	0.19 ± 0.73
Interstitial fluid (L)	6wPP	12.36 ± 0.35	0.404	11.73 ± 1.40	0.380	12.28 ± 1.83
Plasma fluid (L)	6wPP	3.53 ± 0.10	0.404	3.35 ± 0.40	0.380	3.51 ± 0.52
Transcellular fluid (L)	6wPP	0.88 ± 0.03	0.404	0.83 ± 0.10	0.374	0.87 ± 0.13
ECM	6wPP	21.96 ± 2.22	0.287	20.13 ± 2.41	0.080	21.83 ± 1.93

BCM	6wPP	30.78 ± 0.71	0.165	28.98 ± 2.69	0.841	29.21 ± 2.95

Data are presented as means ± standard deviation, in case data are normally divided. Otherwise, data are presented as medians (IQR). Significant p-values are marked in bold. Significant differences between PE and GH are underlined. 6wPP: six weeks postpartum; FM: fat mass; FFM: fat free mass; TBW: total body water; FFMH: fat free mass hydration; ECW: extracellular water; ICW: intracellular water; ECM: extracellular mass; BCM: body cell mass.

3.3 Longitudinal evolution of the cardiovascular system

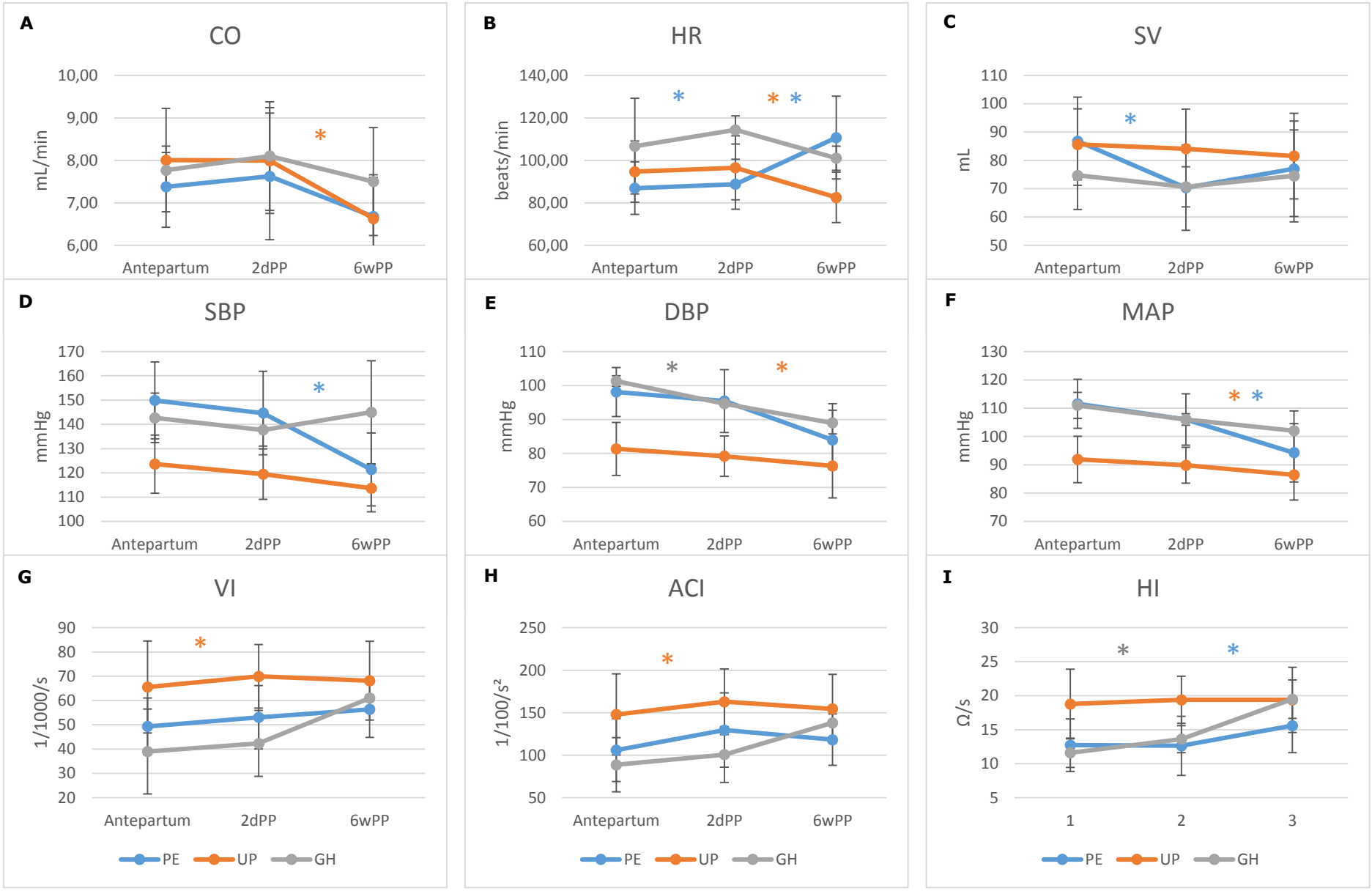
The differences between the study groups over the three time points in central arterial hemodynamic system, venous hemodynamic system and body fluid composition is presented in figure 3, respectively figure 4 and figure 5, in which the evolution of each parameter for each group over time is shown.

3.3.1 Longitudinal changes in the central arterial hemodynamic system

From two days postpartum (2dPP) to six weeks postpartum (6wPP) a significant decrease in UP for CO ($p<.000$) is found. This decrease is mainly due to a decrease in HR ($p<.000$). Despite decreases in HR for UP and GH, an increase ($p<.000$) is observed in PE between 2dPP and 6wPP. A significant decrease in PE for SV was found after parturition ($p<.004$).

Overall decreases in pressure parameters (SBP, DBP, MAP and PP) are found for each group, with the exceptions of an increase in SBP and PP between 2dPP and 6wPP for GH ($p<.500$) ($p<.341$).

After delivery, a global increase can be observed in aortic flow parameters (VI, ACI and HI), with significant differences for UP (VI and ACI) ($p<.039$ and $p<.011$, respectively) and GH (HI) ($p<.003$). Despite the lack of significant differences, an overall decrease and increase for respectively UP and GH are found between 2dPP and 6wPP. Between 2dPP and 6wPP an increase is found for PE ($p<.022$)(figure 3).


A
CO
mL/min
10,00
9,00
8,00
7,00
6,00
Antepartum
2dPP
6wPP
B
HR
beats/min
140,00
120,00
100,00
80,00
60,00
C
SV
mL
110
100
90
80
70
60
50
D
SBP
mmHg
170
160
150
140
130
120
110
100
E
DBP
mmHg
110
100
90
80
70
60
F
MAP
mmHg
130
120
110
100
90
80
70
G
VI
1/1000/s
90
80
70
60
50
40
30
20
H
ACI
1/100/s²
250
200
150
100
50
I
HI
Ω/s
30
25
20
15
10
5
1
2
3
PE
UP
GH

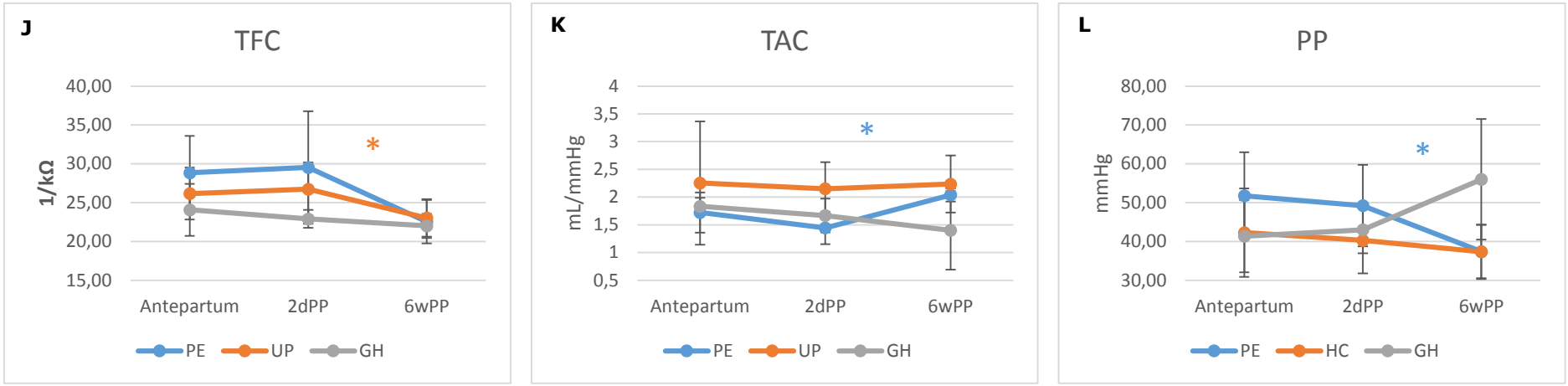


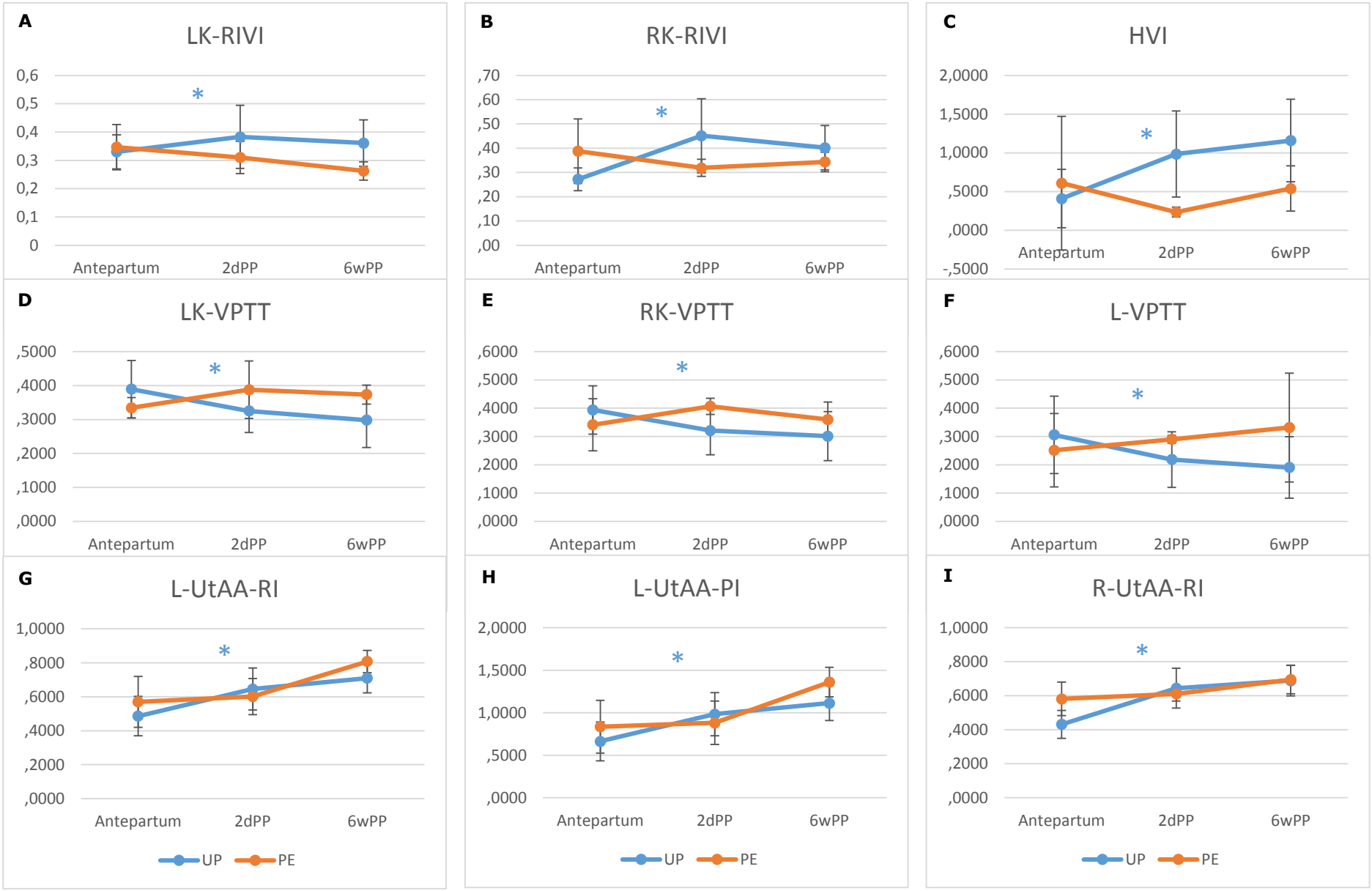
Figure 3: Graphical representation of the longitudinal changes of cardiovascular parameters in uncomplicated, preeclamptic and gestational hypertensive pregnancies, including cardiovascular parameters (HR (A), CO (B), SV (C), SBP (D), DBP (E), MAP (F), VI (G), ACI (H), HI (I), TFC (J), TAC (K), PP (L)). The measurements are shown in function of the measurement time point (antepartum, 48 hours postpartum and six weeks postpartum). The orange lines represent the uncomplicated pregnancies (n=26), the blue lines preeclamptic pregnancies (n=9) and the grey lines the gestational hypertensive pregnancies (n=3). HR: heart rate; CO: cardiac output; SV: stroke volume; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; VI: velocity index; ACI: acceleration index; HI: heather index; TFC: thoracic fluid content; TAC: transient arterial compliance; PP: pulse pressure.

3.3.2 Longitudinal changes in the venous hemodynamic system

After delivery, a global increase in venous impedance index (LK, RK and liver) (p<. 001, p<.000 and p<.000) and decrease in VPTT (LK, RK and liver) (p<.001, p<.000 and p<.001) was found in UP. No significant differences were found after delivery for HP. However, a tendency of a decrease in venous impedance index (LK, RK and liver) and increase in VPTT (LK, RK and liver) can be observed. No significant differences were found between 2dPP and 6wPP.

The left and right uterine arcuate artery 2dPP increases in resistive (p<.000 and p<.000) and pulsatory index (p<.000 and p<.000) and a decrease in APTT (p<.000 and p<.000) is found in UP. No significant alterations are found for HP after parturition.

At 6wPP a decrease in APTT is also observed in left (p<.032) and right (p<.001) uterine arcuate artery (figure 4) in UP.


A
LK-RIVI
0,6
0,5
0,4
0,3
0,2
0,1
0
*
Antepartum
2dPP
6wPP
B
RK-RIVI
,70
,60
,50
,40
,30
,20
,10
,00
*
Antepartum
2dPP
6wPP
C
HVI
2,0000
1,5000
1,0000
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,0000
-,5000
*
Antepartum
2dPP
6wPP
D
LK-VPTT
,5000
,4000
,3000
,2000
,1000
,0000
*
Antepartum
2dPP
6wPP
E
RK-VPTT
,6000
,5000
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,1000
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*
Antepartum
2dPP
6wPP
F
L-VPTT
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*
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6wPP
G
L-UtAA-RI
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Antepartum
2dPP
6wPP
UP
PE
H
L-UtAA-PI
2,0000
1,5000
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Antepartum
2dPP
6wPP
UP
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Antepartum
2dPP
6wPP
UP
PE

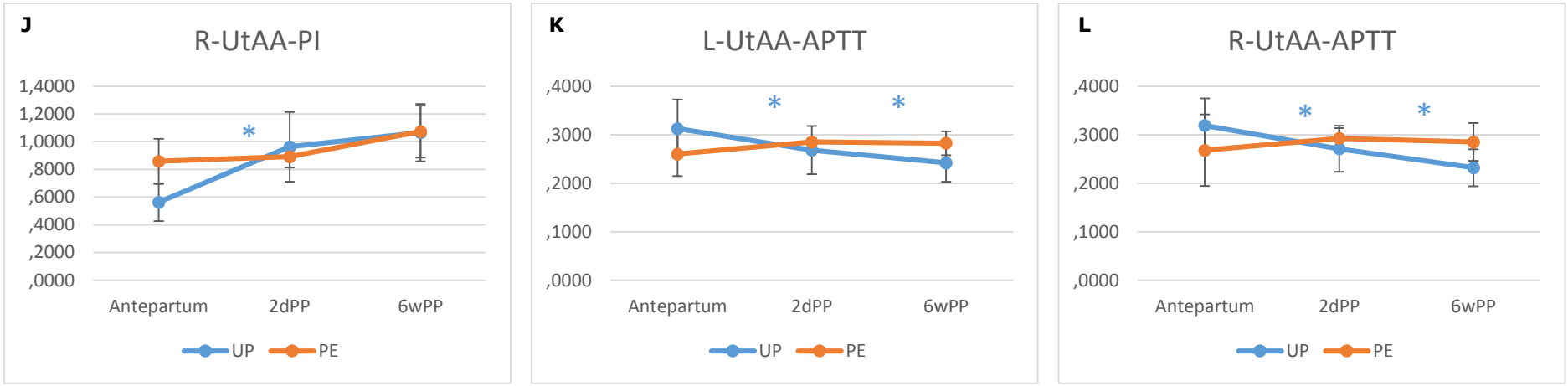
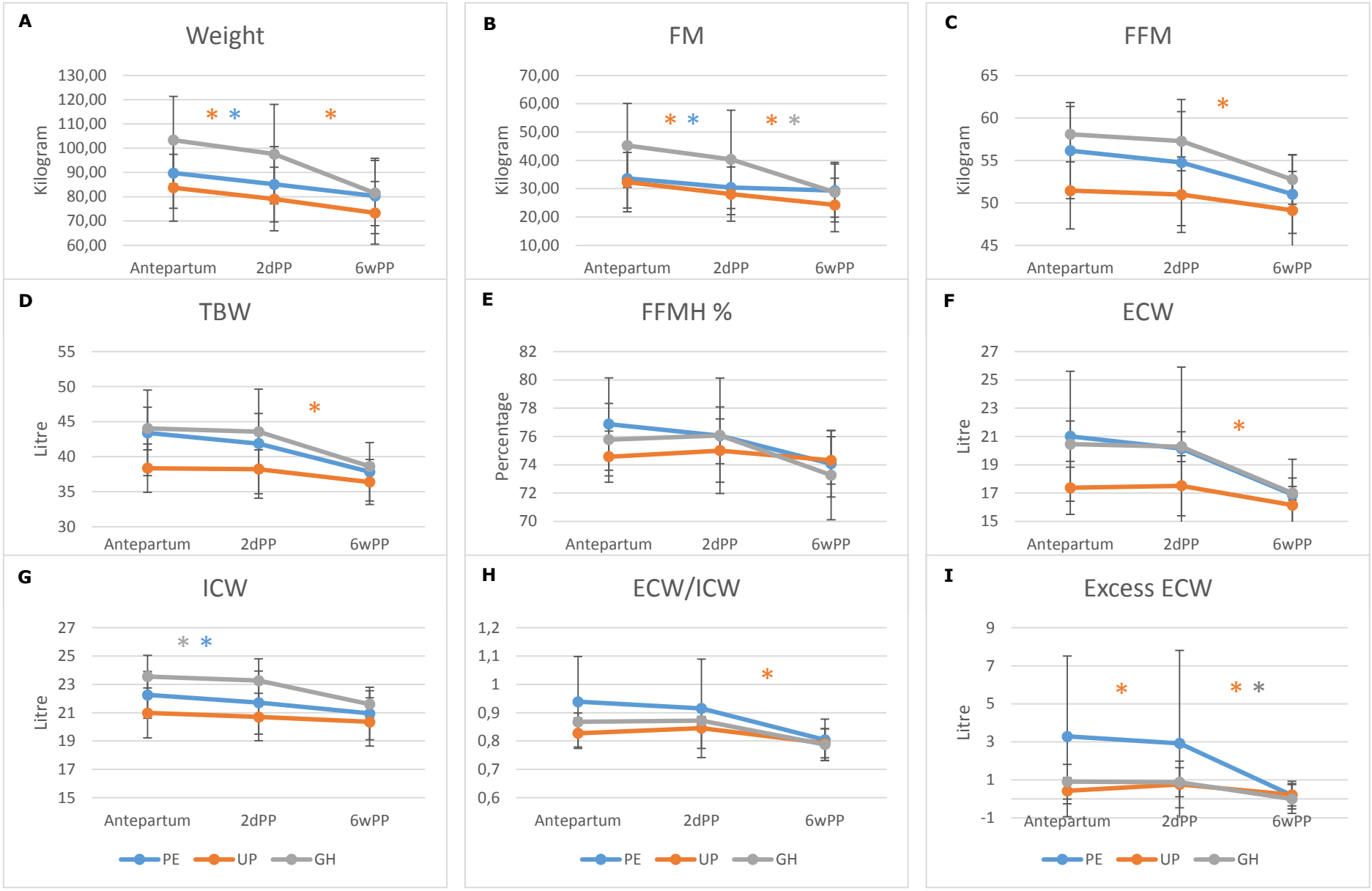


Figure 4: Graphical representation of the longitudinal changes of venous hemodynamic parameters in uncomplicated, preeclamptic and gestational hypertensive gestations (LK-RIVI (A), RK-RIVI (B), HVI (C), LK-VPTT (D), RK-VPTT (E), L-VPTT (F), L-UtAA-RI (G), L-UtAA-PI (H), R-UtAA-RI (I), R-UtAA-PI (J), L-UtAA-APTT (K), R-UtAA-APTT (L)). The measurements are shown in function of the measurement time point (antepartum, 48 hours postpartum and six weeks postpartum). The orange lines represent the uncomplicated pregnancies (n=26), the blue lines preeclamptic pregnancies (n=9) and the grey lines the gestational hypertensive pregnancies (n=3). LK-RIVI: left kidney renal interlobar venous impedance; RK-RIVI: right-kidney venous impedance; HVI: hepatic vein velocity index; LK-VPTT: left-kidney venous pulse transit time; RK-VPTT: right kidney venous pulse transit time; L-VPTT: liver venous pulse transit time; L-UtAA-RI: left uterine arcuate artery resistive index; L-UtAA-PI: left uterine arcuate artery pulsatory index; R-UtAA-RI: right uterine arcuate artery resistive index; R-UtAA-PI: right uterine arcuate artery pulsatory index; L-UtAA-APTT: left uterine arcuate artery arterial pulse transit time; R-UtAA-APTT: right uterine arcuate artery arterial pulse transit time.

3.3.3 Longitudinal changes in the body fluid composition

The weight loss 6wPP compared to the antepartum measurement is 4.65kg for UP, 5.73kg for GH and 4.63kg for PE. This weight loss after parturition is significant for UP and PE (p<.000 and p<.000, respectively). Corresponding with these results, a decrease for UP (p<. 000) and PE (p<.003) is also found in FM. Between 2dPP and 6wPP, a decrease in body fluid can be observed from a decrease in TBW in UP (p<.003). Since there is no significant decrease in ICW in UP (p<.068), this decrease is mainly due to a corresponding decrease in ECW, resulting in a decrease in ECW/ICW ratio (p<.001). This decrease is also noticeable in the subcomponents of ECW: interstitial fluid (p<.001), plasma fluid (p<.001) and transcellular fluid (p<.001).

This body fluid reduction can also be observed in ECM and BCM in UP (p<.000 and p<043, respectively). After delivery of the baby, a remarkable fluid retention is observed in UP (p<.040) from the increase in excess ECW. This fluid retention gradually decreases between 2dPP and 6wPP in UP and GH (p<.012, respectively p<.043) (figure 5).


A
Weight
Kilogram
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120,00
110,00
100,00
90,00
80,00
70,00
60,00
Antepartum
2dPP
6wPP
B
FM
Kilogram
70,00
60,00
50,00
40,00
30,00
20,00
10,00
Antepartum
2dPP
6wPP
C
FFM
Kilogram
65
60
55
50
45
Antepartum
2dPP
6wPP
D
TBW
Litre
55
50
45
40
35
30
Antepartum
2dPP
6wPP
E
FFMH %
Percentage
82
80
78
76
74
72
70
Antepartum
2dPP
6wPP
F
ECW
Litre
27
25
23
21
19
17
15
Antepartum
2dPP
6wPP
G
ICW
Litre
27
25
23
21
19
17
15
Antepartum
2dPP
6wPP
PE
UP
GH
H
ECW/ICW
1,2
1,1
1
0,9
0,8
0,7
0,6
Antepartum
2dPP
6wPP
PE
UP
GH
I
Excess ECW
Litre
9
7
5
3
1
-1
Antepartum
2dPP
6wPP
PE
UP
GH

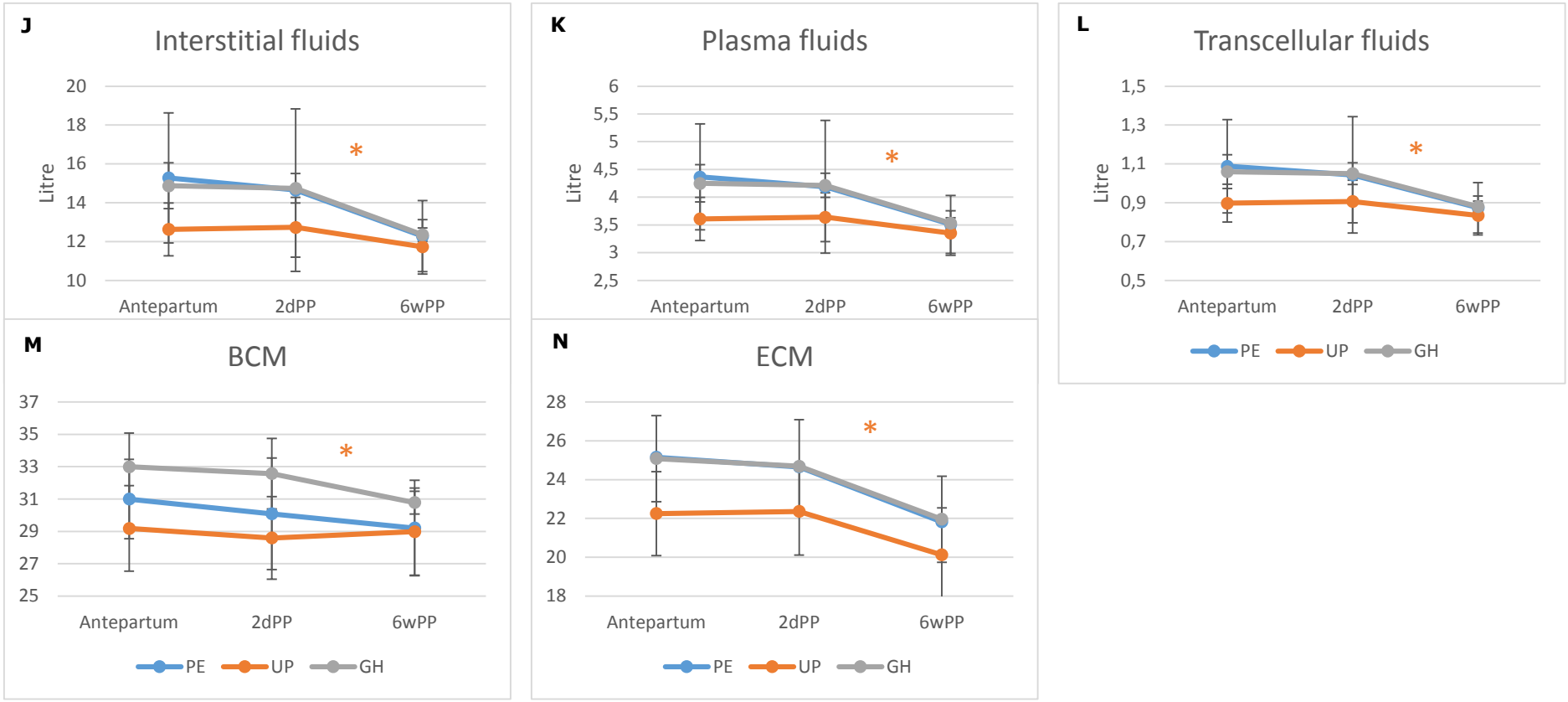


Figure 5: Graphical representation of the longitudinal changes of body composition in uncomplicated, preeclamptic and gestational hypertensive pregnancies, including body composition parameters (Weight (A), FM (B), FFM (C), TBW (D), FFMH% (E), ECW (F), ICW (G), ECW/ICW (H), Excess ECW (I), Interstitial fluid (J), Plasma fluid (K), Transcellular fluid (L), BCM (M), ECM (N). The measurements are shown in function of the measurement time point (antepartum, 48 hours postpartum and six weeks postpartum). The orange lines represent the uncomplicated pregnancies (n=26), the blue lines preeclamptic pregnancies (n=9) and the grey lines the gestational hypertensive pregnancies (n=3). FM: fat mass; FFM: fat-free mass; TBW: total body water; FFMH: fat-free mass hydrated; ECW: extracellular water; ICW: intracellular water; ECM: extracellular mass and BCM: body cell mass.

4 Discussion

From this observational cross-sectional study, it can be deduced that 1) antepartum an aberrant body fluid composition is present in hypertensive pregnancies and that this body fluid composition is normalized six weeks postpartum. 2) Antepartum, hypertensive pregnancies (PE and GH) are featured with a central arterial hemodynamic dysfunction. It is observed that these differences between normotensive and hypertensive pregnancies normalize six weeks postpartum. 3) Antepartum, also a venous hemodynamic dysfunction is present in HP and this aberrant alterations endure six weeks postpartum.

This is an original study, because literature on the postpartum evolution of body fluid composition and arterial and venous hemodynamic system in hypertensive and normotensive pregnancies is scarce. Another strength of the study is that every woman has been investigated in a non-invasive manner. These non-invasive techniques have been proven to be reliable, safe with known intra- and inter-observer correlation.

However, some limitations of the study should be noted. First, several study groups (GH (n=3) and PE (n=9)) have a limited sample size. Therefore, these data could have a large impact on the data analysis. Another consequence could be that due to lack of power, significant differences are withheld. Second, no distinction was made between EPE and LPE in the study group PE. Despite the similar features of the diseases, it is thought they have a different etiology. Therefore, it would be possible that they differ body fluid composition and hemodynamic system. Third, a previous pilot study showed a poor reliability for the body fluid composition parameter "plasma fluid". Therefore a validation study between the BIA and a golden standard (computed tomography imaging or isotype dilution with oxygen-18 or deuterium) should be performed in hypertensive pregnancies. Finally, there is a lack of correlation between arterial, venous hemodynamic system, and body fluid composition.

4.1 Central arterial hemodynamic system

Our results show antepartum an increase in pressure parameters (SBP, DBP, MAP and PP) in hypertensive pregnancies (GH and PE). This was also true two days after parturition and blood pressure was even still increased in GH gestations six weeks postpartum. According to literature, the pressure parameters remain decreased in UP until twelve weeks postpartum and will then increase until pre-pregnancy values (27). In hypertensive pregnancies, these parameters should diminish to baseline levels after five to seven days. If an increased SBP, DBP and MAP is maintained, this could lead to the diagnosis of EH. In a study of Evans et al. women with a history of PE still had a slight increased SBP and DBP compared to UP at sixteen months postpartum. However, the pressure parameters were well within range. They were still significantly higher in women with a history of PE compared to UP. This could indicate that women with a previous history of PE have a prehypertensive state, in which the likelihood to develop hypertension in later life, increases (28). Antepartum, hypertension is observed in PE and GH compared to UP. Corresponding with the literature, two days after parturition the hypertension is still present in PE and GH pregnancies. Six weeks after delivery, these pressure parameters are normalized for PE, except for MAP. Corresponding with the literature, the pressure parameters are well within range,

however, still slightly increased in PE (29). If, however, this latent prehypertension state is created by PE or was present before the pregnancy, is unclear. Six weeks after delivery of the baby, two out of three women with GH developed EH. This could explain the high pressure parameters at six weeks postpartum.

No significant differences in CO, HR, or SV between hypertensive and normotensive pregnancies were found at any point in time, except for a lower SV in PE after parturition. A significant decrease was found in CO after parturition in UP. Between two days and six weeks postpartum, a significant decrease was found in PE and UP. This corresponds with the known literature, which states that CO will increase to 80% postpartum and will gradually decline the following 24 hours, followed by a great fall after two weeks. This is similar for SV (13). The HR will increase in the immediate postpartum period and diminish to pre-pregnancy values two weeks postpartum. In PE, during pregnancy a shift from high CO and low PVR to respectively low and high is observed after 24 weeks (30). However this was not found antepartum. Literature states that certain subtypes of PE have low, normal or high CO. This correlates well with the BW of the child. Since no distinction was made between these subtypes, this could influence the results (31).

Our results showed a decrease in aortic flow parameters (VI, ACI and HI) in term pregnancy and after delivery of the baby in PE and GH. A high ACI and VI represents a strong ventricular ejection and high aortic compliance. A decrease in these parameters represent an impaired central arterial hemodynamic function in PE and GH (16). This impairment is associated with a left ventricular concentric hypertrophy of the heart (32). After parturition, a global increase can be observed in aortic flow parameters (VI, ACI and HI), with significant differences for UP (VI and ACI) and GH (HI). Despite the lack of significant differences, an overall decrease and increase for UP and PE respectively GH were found between 2dPP and 6wPP. Literature on postpartum ACI and VI is scarce. Since UP is associated with reversible left ventricular eccentric hypertrophy during pregnancy (32), an increase in VI and ACI is expected. Postpartum this remodeling will be reversed, resulting in a decrease, as seen in our results.

Although no significant differences were found between hypertensive and normotensive pregnancies for TFC, a tendency is found that TFC is higher antepartum and two days postpartum. Six weeks after delivery, this difference is diminished and for the three study groups the values are equal. According to literature, TFC is a measure for early signs of pulmonary edema and is increased in severe PE (33). Another study of Morris et al. also showed an increase in TFC between antepartum and two days after delivery of the baby in UP (34). However, no significant difference was found in this study, possibly due to presence of mild PE and the small number of PE included.

4.2 Venous hemodynamic system

Our results showed antepartum an increase in RI and PI of the R-UtAA and a lower APTT in the left and R-UtAA in PE, compared to UP. This difference is diminished after two days postpartum. Six weeks postpartum, the APTT is higher in R-UtAA and L-UtAA and the differences in RI and PI between UP and PE have diminished. According to literature, PE is featured with a high vascular stiffness rigidity and a low compliance as a result of vasoconstriction and an increase in PVR. This is reflected in a high RI and PI of the uterine arcuate arteries (16), as seen in our results. The APTT represents the time interval between departure and arrival of a pulse wave between two arterial

sites. A short APTT represents that the pulse wave travels faster, as a result of a higher vascular tone and is seen in PE (35). In our study, antepartum a lower APTT is also seen in PE compared to UP. During pregnancy an increase in distensibility and compliance is observed. This will decrease to pre-pregnant values within the first three months postpartum (36). In line with the literature, six weeks postpartum an increasing arterial stiffness in UP is observed and six weeks postpartum, a decrease in APTT is found as a result of a lower vascular tone reflecting in an increase in compliance (37). Estensen et al. investigated the arterial stiffness in normotensive and preeclamptic pregnancies at term pregnancy, six months postpartum and three years postpartum. An increased arterial rigidity was found at term and six months postpartum, due to left-ventricular impairment (37). Our results show no significant differences in RI and PI (L-UtAA and R-UtAA) between UP and PE at six weeks postpartum, but a tendency is seen that PE has a higher RI and PI (L-UtAA and R-UtAA) compared to UP. This could be a start of the aforementioned phenomena.

Antepartum, a higher venous impedance index was found in the right kidney in PE, compared to UP. This indicates a venous hemodynamic dysfunction in the right kidney. Literature states, that in PE a higher RIVI is found (18). This increase is associated with an increase in proteinuria (38). According to literature, an increase in blood pressure results in a higher vascular tone, which will decrease the VPTT (35). Since PE is associated with hypertension, a lower VPTT should be expected. A tendency that the VPTT is lower in PE compared to UP was found, however, this was not significantly different, this could be due to the small sample size of the group.
Our results showed a lower RK-RIVI and higher HVI, VPTT (LK and RK) in PE at two days postpartum. The differences between UP and PE have not diminished at six weeks postpartum and a global lower venous impedance index (RK and liver) and higher VPTT (LK and liver) is observed. This is contradictory with the known literature. Aardenburg et al. investigated whether a reduced plasma volume, is associated with a lower venous capacitance. The venous capacitance was measured before and after infusing 500 ml gelatin solution in 31 women with a previous history of PE. A reduced venous capacitance was found postpartum in women who had a lower plasma volume during pregnancy (39). A reduced venous capacitance is associated with an increased venous impedance index and a lower VPTT. However, our results show the opposite at two days and six weeks postpartum.

4.3 Body fluid composition

The weight loss between term pregnancy and two days postpartum was on average 4,65 kg (UP), 4,63 kg (PE), and 5,73 kg (GH). This decrease is more pronounced in FM, compared to FFM. This could partly be due to loss of the products of conception (fetus, placenta, amniotic fluid and uterine tissue). Cho et al. found that postpartum FM increases by 9,66% (40). They found that although the body weight decreases postpartum, an increase in FM was observed in UP, moreover visceral fat increases by 45%. A high deposition of visceral fat is associated with insulin resistance, diabetes mellitus, and cardiovascular disease (41). In concordance with the results of Cho et al. a decrease in FM was found in our study. At all three time points a significant decrease of TBW in UP was found, which is in line with the literature (42). Antepartum no significant decrease was found in its subcomponent ECW. However, there was a decrease in ICW for GH and PET, which also correlates with literature (40). ICW increases in term pregnancy due to changes in mammary and

uterine tissue. After parturition, the uterus loses its size and decreases. The other subcomponent of TBW, ECW decreases in UP between 2dPP and 6wPP. Corresponding with this decrease, the subcomponents of ECW (interstitial fluid, plasma fluid and transcellular fluid) all decline from 2dPP to 6wPP in UP. According to literature the plasma fluid should have normalized after 6wPP (43). An increase in excess ECW is observed after delivery in UP. This could indicate that there is an increase in edema after parturition in UP. A decrease in this factor is seen between 2dPP and 6wPP in UP and GH. A significant decrease was found between 2dPP and 6wPP in UP, this is corresponding with the decrease in FM.

There are multiple body fluid alterations between hypertensive and uncomplicated pregnancies antepartum. However, 2dPP and 6wPP no significant differences between the pregnancies for body fluids in PE were found, despite in GH there was. The clinical presentation of PE is mostly associated with peripheral edema (44). Edema was detected by an excess in ECW and is caused by an aberrant fluid retention. Our results showed an excessively high excess in ECW in PE compared to UP. An increase in TBW and corresponding FFMH% was observed antepartum. This observation was also found in a study of da Silva et al. (45), along with a decrease respectively increase in ICW and ECW antepartum, which is confirmed in our results. The increase and decrease in ECW and ICW respectively, cause an increase in the ECW/ICW ratio, which is also seen in the study of da Silva et al (45). Literature states that the subcomponents of ECW, interstitial fluid and transcellular fluid are increased in PE and plasma fluid is decreased. This decrease is originated from a fluid shift from plasma fluid to interstitial space, due to impaired microvascular permeability (22). However in our results, plasma fluid is increased in PE compared to UP, which is not according to the known physiology of PE. Further studies should be conducted to investigate the sensitivity and predictive values of BIA. It could be possible the amniotic fluid is included in the assessment of TBW and could falsify the values of ECW. An increase was also found in ECM and BCM, indicating an increased metabolic state in PE compared to UP.

5 Conclusion

This study showed antepartum an aberrant body fluid composition in hypertensive gestations. These differences will diminish over time in the postpartum period. Also central arterial and venous hemodynamic dysfunction is present in term pregnant women with PE. Six weeks postpartum, the arterial hemodynamic dysfunction has normalized, however alterations in the venous system endure. A longer follow-up period is needed to see if these changes alter postpartum. Future studies should also focus if there is an correlation between the antepartum aberrant body fluid composition and the hemodynamic dysfunction. The BIA gives valuable information on fluid change during pregnancy in a non-invasive manner, however a validation study should be conducted to investigate the reason for inconclusive data in the plasma fluid.

B Intrarectal pressure measurements: A validation study to monitor the intra-abdominal pressure

1 Introduction

1.1 Intra-abdominal pressure

In critically ill patients, 30-50% will develop intra-abdominal hypertension (IAH) and 3-4% abdominal compartment syndrome (ACS) (46). An intra-abdominal hypertension is defined by the World Society of Abdominal Compartment Syndrome as an increased intra-abdominal pressure (IAP)(>12 mmHg). The intra-abdominal pressure is the steady state pressure inside the abdominal cavity. ACS is a prolonged increase in IAP (>20 mmHg) with new onset organ failure (47). ACS has detrimental consequences such as acute renal failure and decreased blood flow to the organs. The diagnosis of IAH and ACS is made based on values of IAP. Therefore monitoring IAP has become an important indicator of hemodynamic instability in intensive care units (ICU).

1.2 Intra-abdominal pressure measuring techniques

As IAH is correlated with the patient's outcome, monitoring IAP on the ICU is recommended. Several measuring techniques are available these days. However, most of them are found to have a poor sensitivity and predictive values (48).

The abdomen is considered a closed area with a restricted capacity to expand. Therefore the fluids inside the abdominal cavity will follow Pascal's law. Subsequently, the IAP measured within the abdomen will represent the IAP throughout the abdomen and can be measured indirectly through gastric, rectal, uterine, inferior vena cava, intravesical and airway pressure monitoring.

The transvesicular route is most often used to measure IAP in critically ill patients and is seen as the non-invasive golden standard. The Foley manometer low volume (FMLV) is based on the use of urinary drainage tubing as a manometer to determine the height of the urine column above the bladder. The resulting column represents the IAP (figure 6) (49).

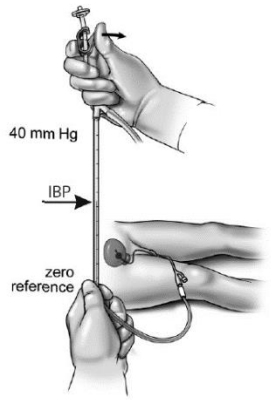


Figure 6: To measure the IAP, the FMLV is placed between the urinary drainage bag and the bladder catheter of the patient. The catheter is vertically placed with the zero reference placed at the midaxillary line that crosses the iliac crest. After opening the clamp, the height of the urine inside the urinary column, will represent the IAP (50).

The transgastric route is another route commonly used. The stomach lies at the proximal end of the abdominal cavity and is easily accessible for measuring IAP. Continuous intragastric pressure monitoring (CiMON) measures IAP through a nasogastric probe combining feeding, decompression and IAP measuring. The CiMON probe has a small air-filled balloon at the tip. The catheter is connected to a specialized monitor to supervise the IAP and abdominal perfusion pressure (figure 7) (49).

Because of the risk for infections or trauma, these two less-invasive techniques are still not appropriate to repeatedly measure IAP in a non-ICU setting. Therefore another possible route to

monitor IAP seems more appropriate: an intrarectal measurement. The rectum is considered a flexible structure and can represent the intra-abdominal cavity pressure. This technique is used in urodynamics to measure IAP.

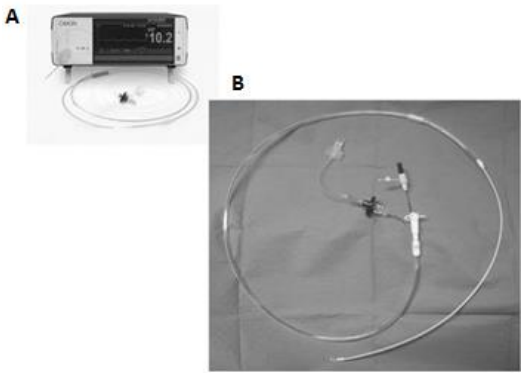


Figure 7: A monitor (A) is connected to a balloon tipped catheter (B) which will be inserted into the stomach (CiMON, PULSION Medical Inc., Munich, Germany). The monitor will continuously measure the IAP after zeroing automatically (51).

1.3 Intra-abdominal pressure in pregnancy

Several conditions lead to the augmentation of IAP. Pregnancy is considered a physiological state of hypertension. However, literature on IAP in pregnancy is scarce. The first to examine IAP in pregnancy was Paramore. He measured IAP in 24 pregnant women using a rectal catheter. His results showed that the IAP is increased throughout the course of pregnancy. Two of his patients had PE in whom an increased IAP was measured. Paramore hypothesized that these patients developed PE secondary to the increased IAP (52). Despite these explorations, research on IAP during pregnancy has only recently emerged.

Recently, Al-Khan et al. measured intermittently the IAP intravesical in 100 term healthy pregnant women prior to elective caesarean section after receiving spinal anaesthesia. They found an IAP in a leftward tilted position consisted of 22 mmHg (± 2.9 mmHg), which is within range of an ACS. Postpartum, the IAP decreased to values of 16 mmHg (range 11-24 mmHg), from which they concluded that IAP is physiologically increased during pregnancy and decreases after delivery (53). However, it was uncertain if the dermatome distribution from the spinal anaesthesia has an influence on the estimation of IAP and in which degree the patient had been leftward tilted. Furthermore, it is still unclear whether the weight of the gravid uterus causes an increased intravesical pressure measurement rather than the real IAP is increased.

Chun et al. measured IAP with a transurethral bladder catheter in 20 term patients under spinal anaesthesia in two different positions: supine and 10° left tilted. It was observed that the IAP was significantly increased in 10° left lateral tilt (8.9 mmHg) compared to the supine position (10.9 mmHg). They suggested that the abundant uterus exerts a pressure on the urinary bladder in supine position and therefore falsifies the actual IAP values (54).

Fuchs et al. measured the IAP using the FMLV in 70 patients at term in supine position after spinal anaesthesia. They found that IAP in pregnant women is increased compared to non-pregnant women, that obesity will interfere with IAP values and that IAP values will decrease slightly postpartum (55). As spinal anaesthesia might possibly interfere with the IAP, Staelens et al. reported IAP in term pregnant women, before any anaesthesia (56). According to their results, it can be confirmed that pregnancy is a physiological condition in which the IAP will give rise to IAH. Postpartum IAP will decrease to normal non-pregnant values. BW and foetal presentation influence IAP measurement in term pregnant women, probably because of the external pressure on the urinary bladder.

1.4 Intra-abdominal hypertension and preeclampsia: a similar pathophysiology?

The pathophysiology of PE resembles that of IAH in different ways. First, a decline in CO and increase in PVR are observed in both PE and IAH (13). A study of Bloomfield et al. inserted intra-abdominal balloons in dogs and inflated those over several weeks. The increasing volume was associated with a significant increase in IAP and hypertension that resolved with balloon deflation. Subsequently, the increased IAP caused an increased PVR and decrease in CO, which can be a plausible cause of hypertension associated with PE (57).

Secondly, diminished perfusion is present in both IAH and PE. Animal studies investigated the effect of IAP on visceral organ perfusion. Organ perfusion diminishes at a IAP of 10-15 mmHg, causing hypoxia, anaerobic metabolism and ischemia reperfusion injury (58). The first sign of increased IAP is decreased renal function indicated by oliguria which occurs if IAP >15 mmHg (59). An impaired renal blood flow due to obstruction of renal venal drainage is associated with proteinuria. The effect of an increased IAP on renal function can result in acute renal failure because of compression of the renal vessels, decreased CO and decreased glomerular filtration rate. Kirkpatrick et al. investigated the effect of an increasing IAP on renal vascular flow velocities on the renal arcuate artery and found that IAP and RI are linearly correlated (60). It is reported that liver perfusion is impaired at IAP of 10 mmHg (61). This will cause an obstruction of the portal vein and a decrease in the blood flow to the liver. Furthermore, Gyselaers et al. found a decreased hepatic venous velocimetry in preeclamptic patients (16). The HELLP syndrome occurring in 35% of preeclamptic women will have a decreased hepatic venous blood flow, causing hepatic ischemia and necrosis (62).

Third, a similarity of symptoms appear between PE and ACS. IAH and PE are most pronounced in the cardiac, renal and liver system. ACS results in a decline in end-organ oxygen delivery due to a reduction in blood flow to the abdominal organs. This could result in a reduced cardiovascular and renal function, causing multiple organ failure (63). In PE, a decreased CO is observed, which is caused by a decline in venous return and thus leading to a decreased preload, increased afterload and reduced end-organ oxygen delivery (13). Furthermore, IAH and PE have a common risk factor: obesity is associated with a twofold higher risk for developing PE (5), and with an increased IAP in pregnant and non-pregnant individuals (55) (64).

Some dramatic case reports documented the appearance of ACS in pregnant women. After delivery of the baby the ACS disappeared. Similarly, PE is mostly treated by delivery of the foetus and placenta.

Sugerman et al. hypothesized that an excessively high IAP compresses the venous system of the pregnant women, which might contribute to symptoms known as PE. The increased IAP could obstruct the inferior vena cava, causing a decreased venous return to the heart and thus inducing a decline in preload and subsequently in CO. Another repercussion of an increased IAP is the compression of the aorta and thereby increasing PVR. This causes an increased afterload and decreased CO, which is the opposite of the physiological adaptations during an uncomplicated pregnancy but is observed in preeclamptic women (65).

1.5 Aim of the study

The pathophysiology of PE might be associated with a maladaptation of the cardiovascular system due to an elevated IAP. Because of the gravid uterus, monitoring IAP in pregnancy faces different challenges of which developing an ideal measuring technique, is probably the toughest. As the experience and literature regarding rectal intra-abdominal pressure measurements are rather limited, a validation study is needed. Therefore, our objective is to validate the rectal intra-abdominal pressure measurement technique by comparing this with the intrabladder.

2 Materials and methods

2.1 Ethics

The validation study was performed at the Ziekenhuis Netwerk Antwerpen (Campus Stuivenberg, Antwerp, Belgium). Before study onset, the study was approved by the local ethical committee of ZNA Stuivenberg (IC Approval 3001). Oral and written informed consent was obtained from the relatives of all patients.

2.2 Patients

From December 2014 to May 2015, sedated and ventilated adult patients admitted on the ICU (Ziekenhuis Netwerk Antwerpen, Campus Stuivenberg, Antwerp, Belgium) were included. Exclusion criteria were age under 18 years and patients in whom there was a contraindication for intrarectal or urinary catheterisation.

2.3 Data collection

Demographic data were obtained for all patients. Different anthropomorphic data (figure 8) were recorded in supine position.

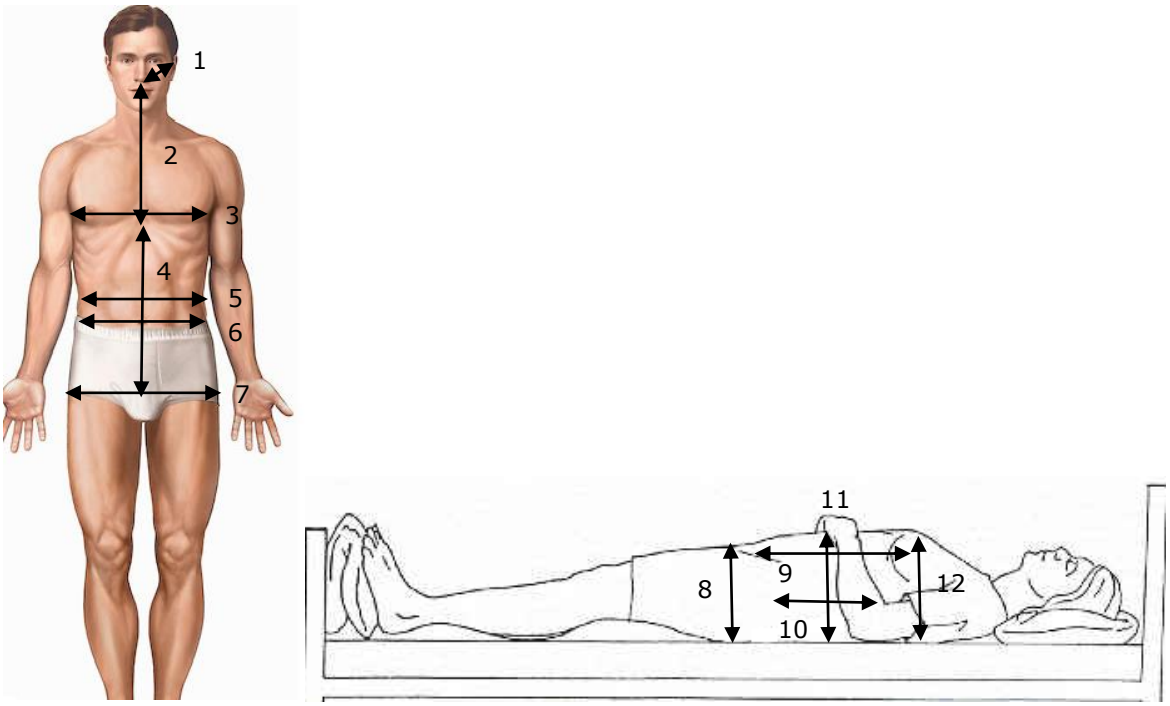


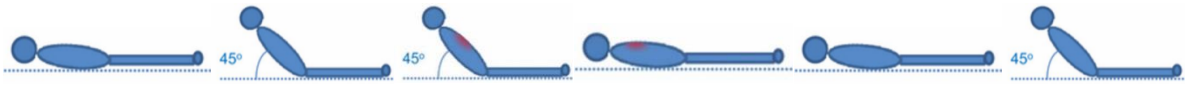
Figure 8: Anthropomorphic data represented in supine position. 1: Distance between ear-nose; 2: distance between the ear and xiphoid bone; 3: diameter of the rib cage and the circumference of the rib cage; 4: distance between xiphoid and pubic bone; 5: umbilical diameter and the abdominal circumference; 6: waist diameter and waist circumference 7: hip diameter and hip circumference; 8: hip height; 9: distance between xiphoid and pubic bone; 10: distance between bottom rib cage and iliac crest; 11: sagittal abdominal diameter; 12: rib cage height.

2.4 Intra-abdominal pressure measurements

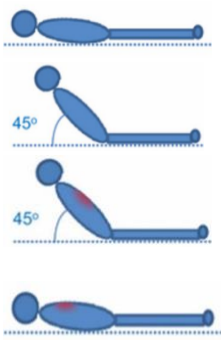
The rectal air-charged balloon catheter was validated through comparison of IAP values monitored with two different techniques in all patients: intravesical and intrarectal measurements.

2.4.1 Intravesicular pressure measurement

IAP was measured intermittently every four hours using a FMLV (Holtech, Medical, Charlottenlund, Denmark). FMLV was administered as standard care to critically ill patients on the ICU (Ziekenhuis Netwerk Antwerpen, Campus Stuivenberg, Antwerp, Belgium). FMLV was connected with the patient's bladder catheter and the urinary drainage tubing. If air-bubbles are present or the urinary bladder was empty, 0.9% sterile sodium chloride solution was injected at the sample port. The patient was measured in two different positions (supine or 45° semirecumbent) with and without an externally applied pressure (EAP) band, according to a standardized protocol (figure 9). The sample port was opened to ensure an open pressure conductive fluid column. The clamp below the bio filter is released, causing the pressure to equilibrate with atmospheric pressure within the tubing above the urine column. The IAP is measured by the extent between the midaxillary line that crosses the iliac crest and the meniscus as recommended by the World Society of Abdominal Compartment Syndrome (figure 6) (47).



Legend



: Supine

: 45° Semirecumbent

: Supine with EAP

: 45° Semirecumbent with EAP

Figure 9: Study design of intravesicular and intrarectal measurements. The patients were measured three times in two different positions (supine, 45° semirecumbent) with or without EAP (red).

2.4.2 Intrarectal pressure measurements

The IAP is also estimated using a rectal T-DOC 7 Fr abdominal air-charged balloon catheter (Laborie Medical Technologies, Sint-Niklaas, Belgium) connected to a T-DOC air-charged ARM transducer cable (Laborie Medical Technologies, Sint-Niklaas, Belgium) connected to a pressure monitoring device. The catheter consists a small air-filled balloon at the distal tip of the probe. The catheter was inserted 15 cm into the rectum, zeroed and charged with a constant volume of air (figure 10). The patient was measured in two different positions (supine and flexion of 45° in supine position) with and without EAP, according to the standardized protocol (figure 9).

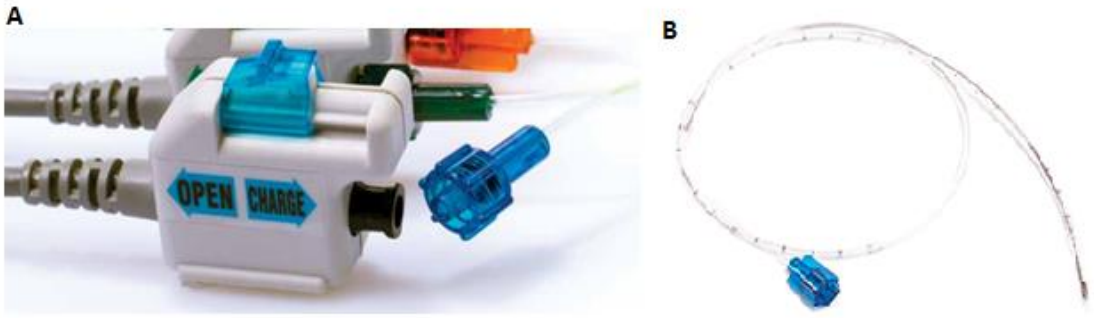


Figure 10: A T-DOC 7 Fr catheter (Laborie Medical Technologies, Sint-Niklaas, Belgium) with a small air-filled balloon at the distal tip is inserted 15 cm into the rectum (B). After inserting the catheter, the balloon is charged with air, mediated through the T-DOC air-charged ARM transducer cable (Laborie Medical Technologies, Sint-Niklaas, Belgium). The pressure monitoring device connected to the catheter would continuously measure the IAP (66).

2.5 Statistics

Normality was checked using the Shapiro-Wilk test. Correlations between intrarectal and intravesicular pressure were evaluated using univariate linear regression analysis using SPSS software (version 22.00, SPSS inc., Chicago, IL, USA). Feasibility was measured using the pearson correlations coefficients for normal divided data. In case of non-normality, the spearman correlation coefficient was used. The two measurement techniques were compared with the Bland-Altman plot using MedCalc (MedCalc BVBA, Software version 13.0.2, Ostend, Belgium). The Bland-Altman plots the difference of the FMLV and rectal catheter against the average of the two techniques.

3 Results

In total, IAP measurements were performed in fifteen patients. The IAP values in seven patients (46.67%) were proven to be invalid. The main reasons for exclusion of the patients are presented in table 11. An example of an invalid measurement is shown in figure 11. Due to placement of the rectal catheter along the internal anal sphincter, the IAP values represents the detrusor muscle activity and is therefore excessively increased. After passing the internal anal sphincter, the IAP signal became stable. The position of the patient was altered from 45° semirecumbent to supine and the observed IAP values were still balanced and the respiration cycle was still observed. Thereupon, a sudden increase and unstable IAP value was observed with absence of the respiration. The data of the eight (53.33%) valid IAP measurements were used for further assessment. An example of a successful measurement is seen in figure 12.

Table 11: Main reasons for exclusion of patients.

	Exclusion criteria
Subject 1	IAP fluctuations (profound diarrhea)
Subject 2	IAP fluctuations (Excess defecation)
Subject 3	IAP values out of physiological range
Subject 4	IAP values out of physiological range (Aberrant placement of rectal catheter)
Subject 5	IAP fluctuations
Subject 6	Lack of respiration cycle and IAP values out of physiological range
Subject 7	IAP fluctuations (Sub-conscious pressure counteraction of the patient)

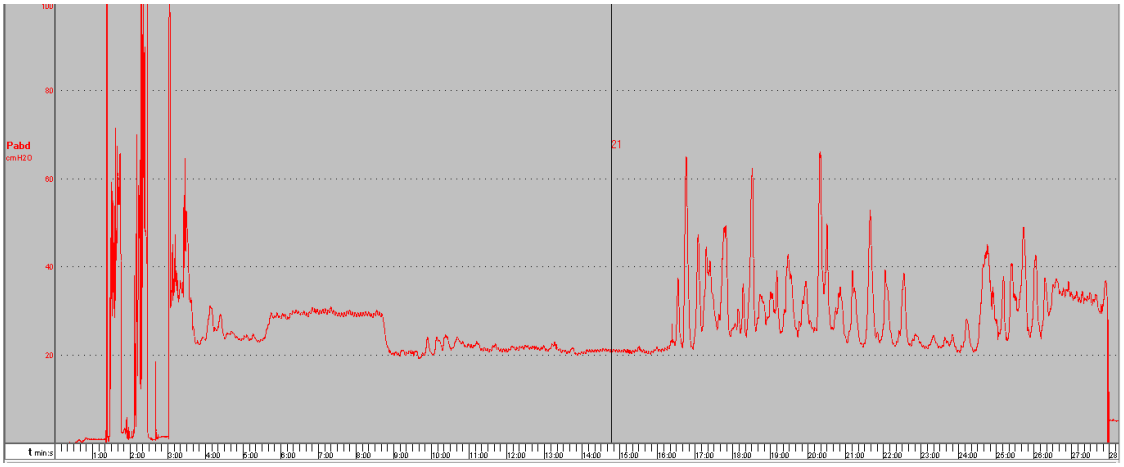


Figure 11: The intra-abdominal pressure measured in a supine and 45° semirecumbent position with or without an EAP. The x-axis represents the time in seconds and the y-axis represents the intra-abdominal pressure in cm H_2O.

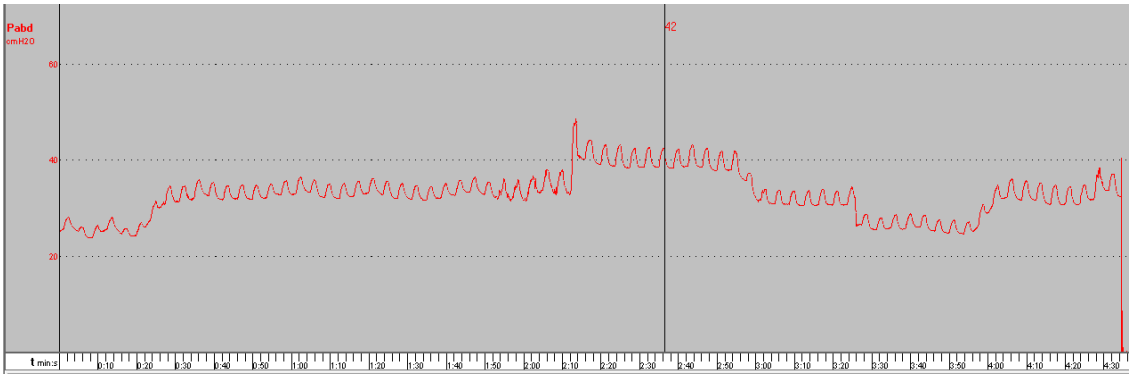


Figure 12: The intra-abdominal pressure measured in a supine and 45° semirecumbent position with or without EAP. The x-axis represents the time in seconds and the y-axis represents the intra-abdominal pressure in cm H_2O.

3.1 Demographics

In total, data of eight patients, admitted to ICU at ZNA Antwerp (53.33%) were analysed. Patients demographics and anthropomorphic data are represented in table 12. The mean age is 59 years (range 43-77), six patients were mechanically ventilated and two were spontaneously breathing at the time of IAP measurements.

Table 12: Patients demographics and anthropomorphic data.

Characteristics	Value	Anthropomorphic data	Value (cm)
Age (years)	59.00 ± 13.49	Distance ear-xiphoid	35.50 ± 2.93
Men to women ratio	7:1	Xiphoid-pubis	101.87 ± 5.22
Reason for admission to ICU	Sepsis;	Hip circumference	39.00 ± 3.51
	COPD;	Distance nose-ear	15.13 ± 0.99
	Pneumonia;	Rib cage diameter	37.25 ± 6.23
	Liver cirrhosis;	Umbilical diameter	39.63 ± 3.85
	Vascular disease	Waist diameter	38.00 (32.50; 38.75)
Mechanically ventilated (n)	6	Hip diameter	37,00 (35.50; 37.75)
		Xiphoid to pubic line	33.50 (32.25; 34.00)
		Rib cage height	21.81 ± 2.56
		Hip height	14.37 ± 2.33
		Rib cage to crista	16.88 ± 4.85
		Sagittal abdominal diameter	25.13 ± 3.27

Data are presented as means ± standard deviation. Not-normal divided data are presented as median (IQR). BMI: Body mass Index.

3.2 Intra-abdominal pressure measurements

In total, 38 IAP measurements were performed. The number of measurements in each patient was 5 ± 2 and were performed in two different positions (supine or 45° semirecumbent) with or without an EAP.

Table 13 presents the mean intravesical pressure (IVP) and intrarectal pressure (IRP) for two positions (supine and 45° semirecumbent) with or without EAP. Overall, a higher IRP is observed in any condition, with significant differences in supine ($p<.003$) and 45° semirecumbent ($p<.001$) position without EAP.

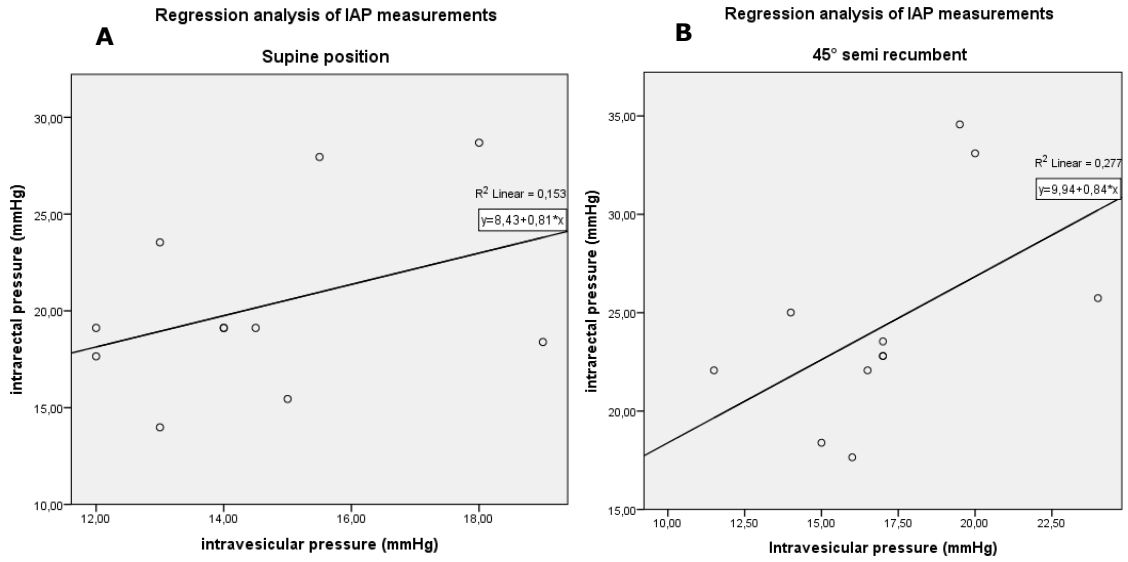
Table 13: Mean intrarectal and intravesicular pressure in different body positions with or without an EAP.

	Supine	45° semirecumbent	Supine with EAP	45° semirecumbent with EAP
IVP	15.58 ± 2.50	18.08 ± 3.77	18.42 ± 3.25	21.42 ± 4.78
IRP	21.33 ± 6.33	25.74 ± 7.10	25.99 ± 5.54	27.95 ± 6.46
P-value	0.003	0.001	0.628	0.077

Data are presented as mean ± standard deviation. Not-normally divided data are presented as median (IQR). IVP: Intravesical pressure and IRP: intrarectal pressure.

3.2.1 Feasibility and repeatability of intrarectal pressure measurement

A scatter plot was drawn using IRP and IVP (figure 13). A linear relationship between IRP and IVP was assumed and a regression line was drawn. The values for the slope of the line and the intercept were calculated. The regression analysis shows no correlations between IRP and IVP in supine and 45° semirecumbent position without (IRP = 8.43 + 0.81 IBP (R^2 = 0.153)) respectively (IRP = 9.94 + 8.84 IBP (R^2 = 0.277)) and with EAP (IRP = 5.92 + 1,05 IBP (R^2 = 0.370)) respectively (IRP = 17.06 + 0.51 IBP (R^2 = 0.142)).



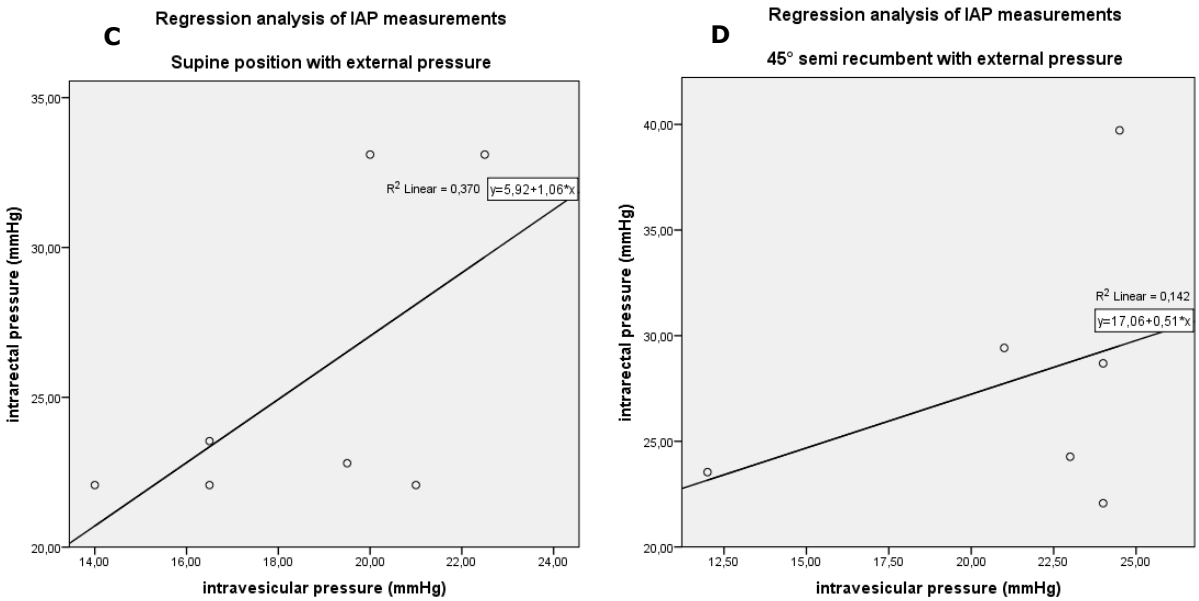


Figure 13: Regression analysis of IAP values measured through an urinary and rectal catheter. The x-axis represents the intrabladder pressure and the y-axis presents the intrarectal pressure, both expressed in mmHg. A) The patients were supine positioned. B) The patients were 45° semirecumbent positioned. C) An EAP was applied on these patients, while they lied in a supine position. D) An EAP was applied on these patients, while they lied in a 45° semirecumbent position.

Feasibility was analysed using the pearson correlation coefficient (PCC), if data are normal distributed, otherwise the Spearman correlation coefficient (SPCC) was calculated. The rectal catheter shows a low feasibility based on the PCC in supine (0.391 (p<.234)) and 45° semirecumbent (0.527 (p<.096)) position without EAP. The same observation can be made for IRP in a supine (SPCC = 0.510 (p<.242)) and 45° semirecumbent (SPCC = 0.348 (p<.499)) position with EAP (table 14).

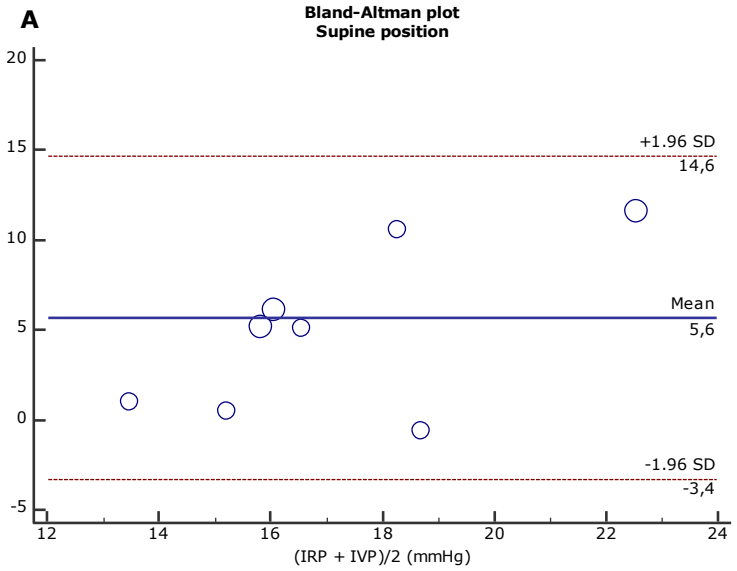
Table 14: Pearson and spearman correlation coefficients for IAP measurements in a supine or 45° tilted position with or without EAP.

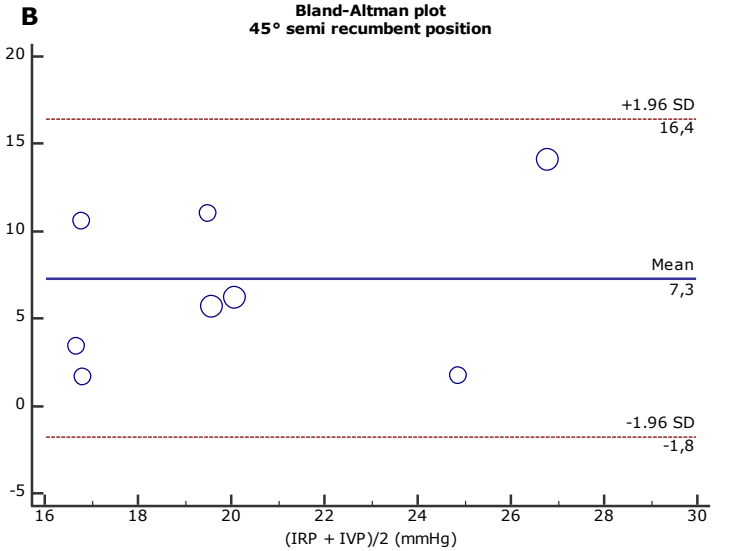
	Supine	**45° semirecumbent**	**Supine with EAP**	**45° semirecumbent with EAP**
PCC	0.391	0.527		
SPCC			0.510	0.348

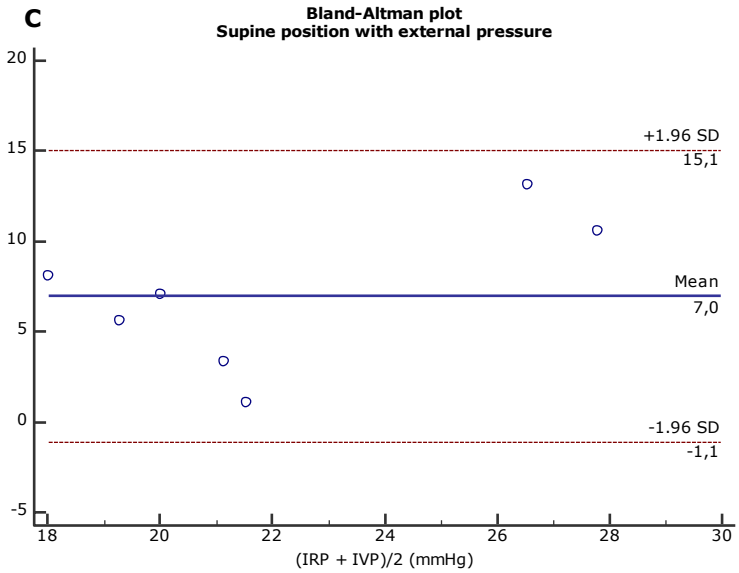
The pearson correlation coefficient was measured for normal divided data. For non-normal divided data the spearman correlation coefficient was used. PCC: Pearson correlation coefficient and SPCC: Spearman correlation coefficient.

3.2.2 Intravesicular versus intrarectal pressure

A comparison between the two techniques was made with Bland-Altman plots. The average of the IRP and IVP is plotted against the difference between the two methods. A small mean and limits of agreement indicate that the different techniques could be used interchangeable. The mean difference between IRP and IVP should abut to zero. However, our results show a mean difference of minimal 5.6 mmHg, indicating that the rectal catheter is unbiased. Another stipulation are narrow limits of agreement that contains all data. Although, the limits of agreement consist all data, the range is very broad (a minimum scatter from -3.4 mmHg to 14.6 mmHg). This means the two techniques cannot be used interchangeably.


A
Bland-Altman plot
Supine position
+1.96 SD
14,6
Mean
5,6
-1.96 SD
-3,4
(IRP + IVP)/2 (mmHg)


B
Bland-Altman plot
45° semi recumbent position
+1.96 SD
16,4
Mean
7,3
-1.96 SD
-1,8
(IRP + IVP)/2 (mmHg)


C
Bland-Altman plot
Supine position with external pressure
+1.96 SD
15,1
Mean
7,0
-1.96 SD
-1,1
(IRP + IVP)/2 (mmHg)

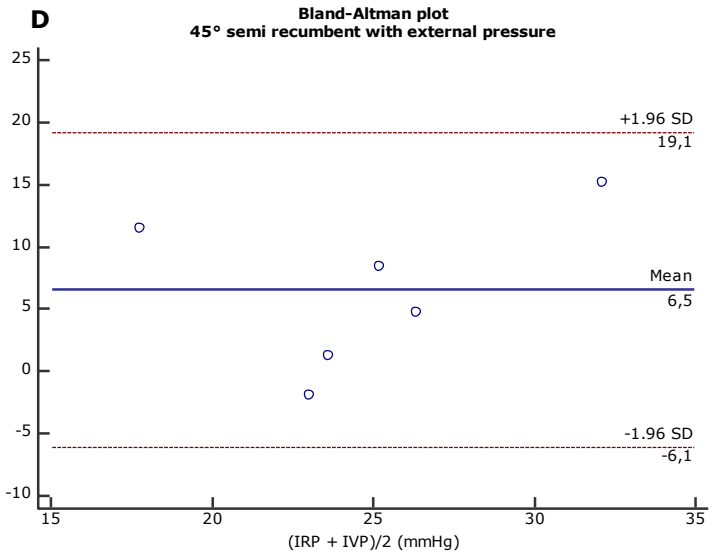


Figure 14: Bland-Altman plots for comparing intrarectal and intrabladder pressure. The x-axis presents the average of the intrarectal and intrabladder pressure and the y-axis represents the difference between the pressure in the rectum and in bladder. Both are expressed in mmHg. A) Bland-Altman plot of IRP and IBP in a supine position, with repeated measures. B) Bland-Altman plot of IRP and IBP in a 45° semirecumbent position, with repeated measures. C) Bland-Altman plot of IRP and IBP in a supine position with EAP. D) Bland-Altman plot of IRP and IBP in a 45° semirecumbent position with EAP.

4 Discussion

An increased IAP is associated with important morbidity and mortality in critically ill patients. New insights in the prevalence and detrimental consequences of IAH and ACS, raised new awareness for monitoring IAP in the past decades.

Multiple techniques were developed to administer IAP of which the intravesical approach is seen as the golden standard, however it is relatively invasive to use in a non-ICU setting. Therefore, we investigated a less invasive technique using an intrarectal approach and compared this with intravesical measurements. The intrarectal technique could be used as a standard procedure due to its easy approach, low risk for infection, and low invasiveness. Out of the fifteen patients included in this validation study, we found invalid measurements in seven patients (46.67%).

4.1 Exclusion criteria

Seven patients were excluded, due to IAP values out of the physiological range, or an instable measurement with fluctuating values. The excessive IAP values could be created by 1) an interference of faecal mass or bowel movement on the catheter-tip opening, or 2) a catheter's incorrect position at the level of the rectal sphincter. A possible explanation for the invalid data in these circumstances is that the faeces itself is a consealed area, closed from its environment and thus contains a different pressure inside. Measuring inside these concealed areas could lead to an IAP overestimation. The abdominal unit follows Pascal's law, which is $P_{hydr} = \rho.g.h$, where P_{hydr} is the hydrostatic pressure, ρ (rho) the density of fluid, g the standard acceleration of gravity and h the height. In a supine position, the effect of gravity should be minimal. However, it could be that the density of faeces differs from the density of fluids inside the abdomen, causing an overestimation of the IAP.

Next, 3) the abdominal muscle contraction of sub-conscious patients could also contribute to falsely elevated IAP values. Hence, it is shown that complete relaxation during the rectal IAP-measurement is required to avoid incorrect data. Another reason for the excessively high values of IAP is the aberrant placement of the catheter. Measuring before or at the level of the internal anal sphincter, obtains information regarding anorectal manometry, but not from IAP.

McCarthy et al. performed a validation study of the intrarectal pressure measurement in twelve patients who were undergoing laparascopic tubal coagulation. Intravesicular, intrarectal, and intra-abdominal pressure was measured and compared. Three patients (25.00%) were excluded due to lack of cough observation, an erratic abdominal traction and technical difficulties to insert the abdominal catheter. Excessive high intrarectal values were observed in one (11.11%) patient. McCarthy et al. state that the rectal catheter should be inserted at least 10 cm deep, otherwise the pressure changes inside the rectum would excel the simultaneously recorded intra-abdominal pressure (67).

4.2 Feasibility and repeatability of intrarectal measurements

When rectal IAP measurements seemed valid (n=8, 53.33%), data analysis was performed. First, regression analysis showed low R squares, indicating a low correlation between IVP and IRP. Our results confirm the results of Lacey et al., they evaluated different indirect techniques (inferior vena cava, bladder catheter, gastric, femoral artery, brachial artery, rectum) by comparing them

with the direct IAP measuring in seventeen white rabbits. A specially constructed prestrechted balloon catheter was placed into the peritoneal cavity and sequentially inflated with water. Instillation of water into the intra-abdominal balloon produced reproducible increases in IAP. Regression analysis was performed and a good correlation between the direct abdominal pressure measuring and inferior vena cava ($R<0,87$) and bladder catheter ($R>0,85$) was found, but a poor correlation between the direct abdominal pressure and rectal catheter ($R=0,1$) (68). Second, PCC and SPCC were calculated and presented a low feasibility for the rectal catheter. Lacey et al. also found a poor PCC for rectal IAP measurements. Third, Bland-Altman analysis was plotted, to compare the FMLV with the rectal catheter. A high bias (5,6 mmHg) and broad limits of agreements were found (-3,4 to 14,6 mmHg), indicating the obtained data differ greatly between the two measurement techniques. From this, we concluded that the validity of the rectal catheter technique is inadmissible.

If IAP is monitored through the rectum, certain stipulations need to be fulfilled. First, the rectal catheter should be inserted at a minimal distance of 10 cm into the rectum. Second, the patient should be calm, so no muscle contractions will interfere with IAP readings. Third, since defecation could influence the IAP readings, administering a fleet to remove possible faecal interference could avoid disproportionate IAP values.

5 Conclusion

Our data show that the IAP measured by the rectal catheter cannot replace the IAP monitoring by the FMLV, due to a poor feasibility and repeatability of this technique.

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Addendum

I Body fluid composition parameters

The body is composed of a fat free mass (FFM) and a fat mass (FM). The FM consists the amount of stored fat inside the body. Two types of fat exists: essential body fat and storage body fat.

The FFM is the total body mass including skin, bones, ligaments, organs and water content. It comprises a bone mineral component and the body cell mass (BCM). The BCM can be further elucidated into proteins and TBW.

TBW is the entire amount of water within the individual and is subdivided into the ECW and ICW. ECW is the sum of the interstitial fluid (fluid contained between cells), plasma fluid (fluid of the blood) and transcellular fluid (fluid within epithelial lined spaces). ICW contains the fluid within cells. The ratio of ECW/ICW represents the extracellular inward body fluid movements. The ions present in the ICW and ECW provide conduction throughout the body. The ECW contains mainly Na^+ and Cl^-, whereas ICW contains mostly K^+.

The hydrated fat-free mass percentage (FFMH %) contains the amount of water inside the FFM.

The excess of ECW represents the presence or absence (hydration of excess ECW) of edema. Edema is the accumulation ECW fluid.

Table 15: Formula for body composition parameters

Parameter	Formula
TBW	ECW + ICW
Fat free mass hydrated %	TBW/ FFM x 100
ECW/ICW ratio	ECW/ICW

TBW: total body water; ECW: extracellular water; ICW: intracellular water.

II Venous hemodynamic parameters

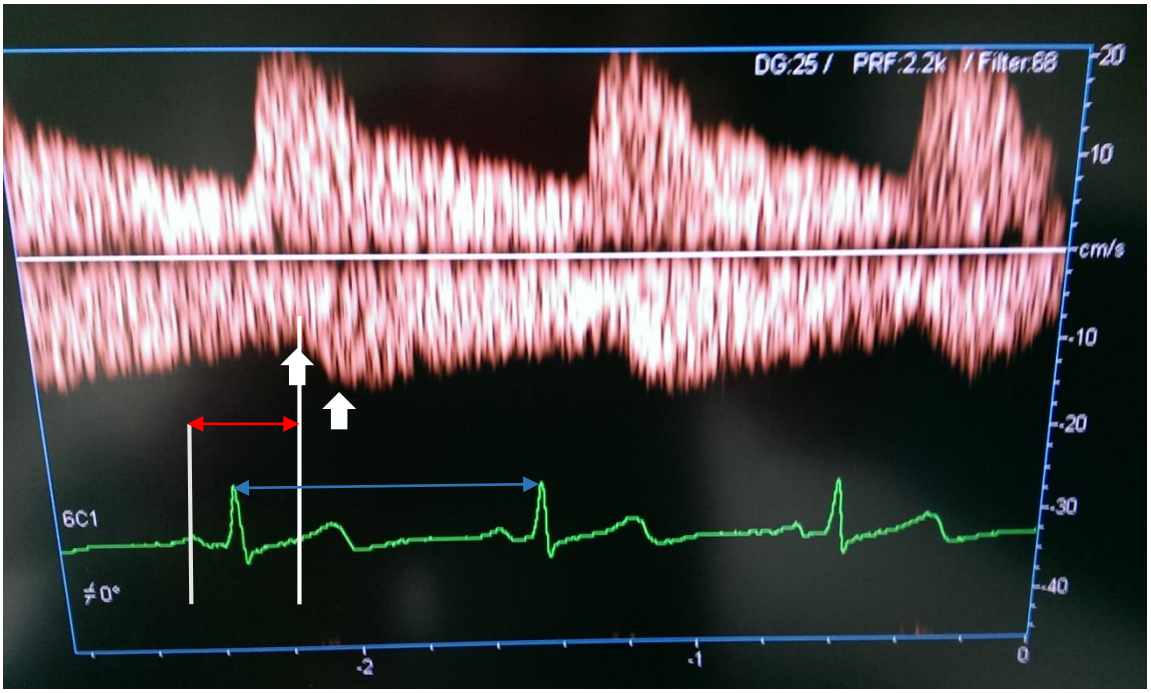

Figure 15: Pulse wave of the renal interlobar vein. Minimum velocity (left white arrow), maximum velocity (right white arrow), distance between two R tops (blue line), Distance between the P wave and the atrial contraction of the heart (red line). Venous pulse transit time: the time between contraction of the right atrium and the blood to arrive inside the vein accounted for the heart rate (PA/RR).

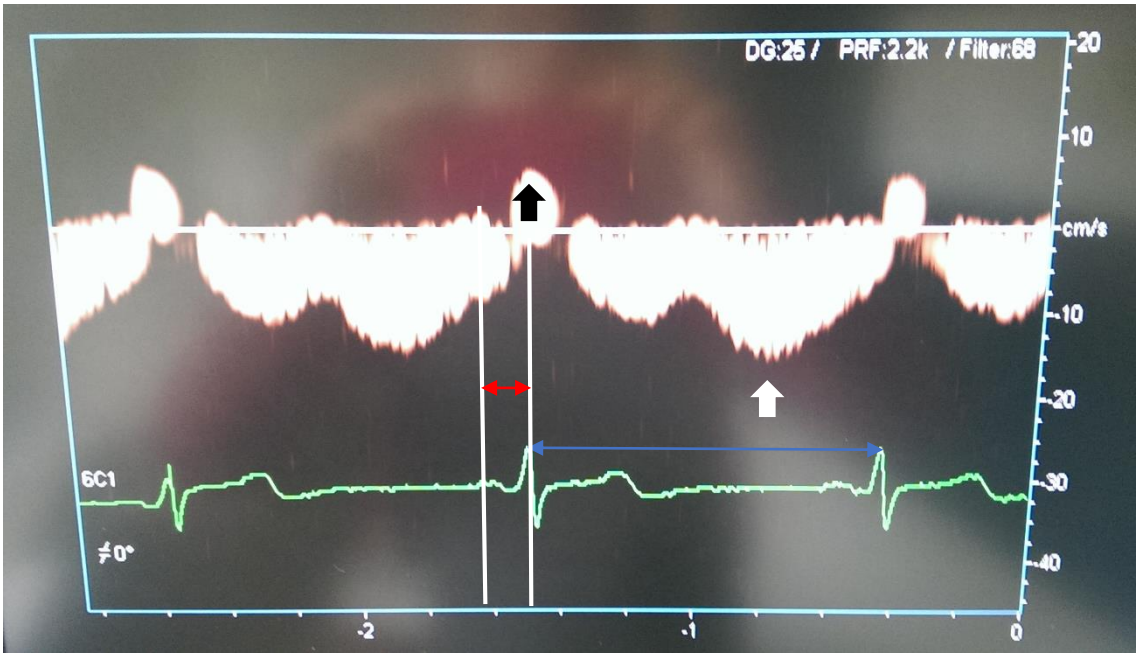

Figure 16: Pulse wave of a hepatic vein. Minimum velocity (black arrow), maximum velocity (white arrow), distance between two R tops (blue line), Distance between the P wave and the atrial contraction of the heart (red line). Venous pulse transit time: the time between contraction of the right atrium and the blood to arrive inside the vein accounted for the heart rate (PA/RR).

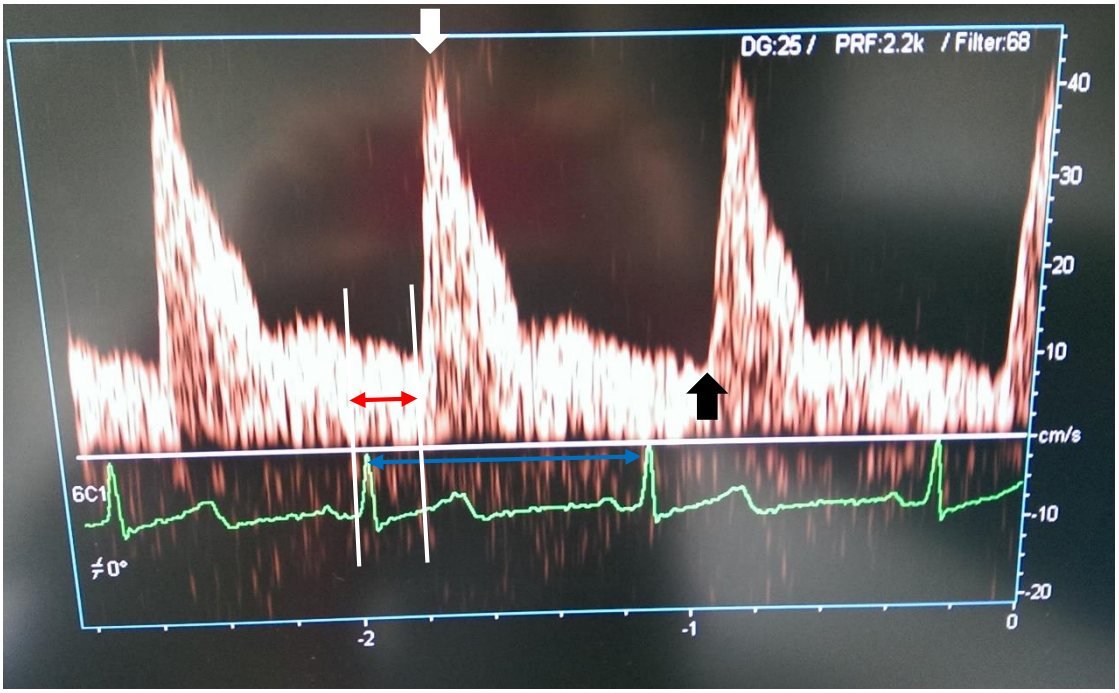

Figure 17: Pulse wave of the uterine artery. Minimum velocity (black arrow), maximum velocity (white arrow), distance between two R tops (blue line), Distance between the Q wave and the ventricle contraction of the heart (red line). Arterial pulse transit time: the time between contraction of the right atrium and the blood to arrive inside the vein accounted for the heart rate (QD/RR).

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Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
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Richting: **master in de biomedische wetenschappen-klinische moleculaire wetenschappen**
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Datum: **9/06/2015**