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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de biomedische wetenschappen

Masterproef

The relation between sleep-disordered breathing and gestational hypertensive complications

Promotor :
Prof. dr. Lena DE RYCK

Promotor :
prof. dr. W. GYSELAERS

Kimberly Dethier

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

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List of Abbreviations

AAI	Autonomic arousal index
AASM	American Academy of Sleep Medicine
ACI	Acceleration index
AHI	Apnea hypopnea index
APTT	Arterial pulse transit time
BMI	Body mass index
CI	Cardiac index
CO	Cardiac output
CPAP	Continuous positive airway pressure
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ESS	Epworth sleepiness scale
FRC	Functional residual capacity
GH	Gestational hypertension
GHD	Gestational hypertensive disorders
GPA	Gravid/para/abortus
Hb	Hemoglobin
HbO_2	Oxy-hemoglobin
HI	Heather index
HPD	Heart period duration
HR	Heart rate
HVI	Hepatic vein impedance index
ICG	Impedance cardiogram
LVET	Left ventricular ejection time
MAP	Mean arterial blood pressure
MAP	Multivariable apnea risk index
NICCOMO	Non-invasive continuous cardiac output monitor
NREM	Non-rapid eye movement
ODI	Oxygen desaturation index
OSAS	Obstructive sleep apnea syndrome
PAT	Peripheral arterial tonometry
PCC	Pearson correlation coefficient
PE	Preeclampsia
PEP	Pre-ejection period
PF	Pulse frequency
PI	Pulsatility index
PP	Pulse pressure
PPG	Photoplethysmogram

PWA	Pulse wave amplitude
RAAS	Renin angiotensin aldosterone system
RDI	Respiratory disturbance index
REM	Rapid eye movement
RI	Resistance index
RIVI	Renal interlobar vein impedance index
SBP	Systolic blood pressure
SDB	Sleep-disordered breathing
SI	Stroke volume index
STR	Systolic time ratio
SV	Stroke volume
TAC	Total arterial compliance
TACI	Total arterial compliance index
TFC	Thoracic fluid content
TFCI	Thoracic fluid content index
VI	Velocity index
VPTT	Venous pulse transit time

Abstract

BACKGROUND: Pregnancy is associated with many hormonal and physiological changes which have an effect on both the respiratory and the cardiovascular system. The respiratory-related changes increase the risk on developing or exacerbating sleep-disordered breathing (SDB). Emerging evidence suggests that pregnancies complicated with gestational hypertensive disorders (GDH) have a higher rate of SDB and additionally a maladapted cardiovascular system compared to normal pregnancies. Studies are needed to determine the possible causative association between SDB and cardiovascular dysfunction. The aims of the present study were 1) to evaluate the accuracy of the SomnoCheck Micro to measure sleep parameters and to optimize scoring of the obtained parameters 2) to compare the cardiorespiratory sleep pattern and the cardiovascular profile in both normotensive third-trimester pregnancies and pregnancies complicated with GHD 3) to investigate all possible associations between cardiorespiratory sleep parameters and cardiovascular maternal outcomes.

MATERIALS & METHODS: 1) To validate the SomnoCheck Micro, consisting of a nasal cannula and a fingertip photoplethysmography (PPG) sensor, ten patients slept with two devices during one night, one with nasal cannula and one without nasal cannula. The number of apneas and hypopneas were scored automatically and manually to discover the discrepancy. Additionally, manual respiratory event scoring was evaluated before and after training at the sleep laboratory. Moreover, respiratory event scoring was independently performed by two researchers and the interscorer correlation coefficient was calculated. 2) Sleep parameters were recorded by the use of the SomnoCheck Micro. Cardiovascular profiling was performed using combined ECG-Doppler ultrasonography and impedance cardiography. All parameters were compared between controls and cases. 3) The cardiorespiratory sleep parameters were correlated with cardiovascular parameters.

RESULTS: 1) A total of ten patients participated in the validation study. AHI_{manual} was significantly higher than AHI_{auto} ($p=0,007$) and RDI ($p=0,005$). AHI_{manual} was significantly lower after training than before training ($p<0,001$). The interscorer correlation coefficient was 0,635 ($p<0,001$). 2) 18 patients with GHD (cases) and 58 normotensive pregnancies (controls) were included for analysis. Snoring was significantly more prevalent in patients with GHD ($p=0,008$), but flow limitation was not significantly higher ($p=0,238$). AHI and oxygen desaturation index (ODI) were not significantly different between cases and controls ($p=0,175$ and $p=0,631$, respectively). 3) Snoring was significantly correlated with the systolic blood pressure. A significant negative correlation was present between snoring and both acceleration index (ACI) and velocity index (VI). Snoring was correlated with BMI and tended to be associated with gestational weight gain. The fluid content in the thorax was not correlated with obstructive events, including AHI, snoring and flow limitation.

CONCLUSION: Snoring was associated with a maladapted cardiovascular system due to its correlation with the systolic blood pressure and its negative correlation with VI and ACI. Associations between snoring and BMI were also demonstrated. These results suggest that snoring pregnant women with a high BMI are at risk for the development of GHD.

Samenvatting

ACHTERGROND: Zwangerschap gaat gepaard met een aantal hormonale en fysiologische veranderingen die een invloed hebben op zowel het ademhalingssysteem als het cardiovasculair systeem. De ademhalingsgerelateerde veranderingen verhogen het risico op *sleep-disordered breathing* (SDB). Uit onderzoek is gebleken dat zwangeren met hypertensie stoornissen (*gestational hypertensive disorders* (GHD)) te maken hebben met zowel een verstoord slaappatroon als een niet goed aangepast cardiovasculair systeem in vergelijking met normale zwangeren. Meer studies zijn nodig om een oorzakelijke associatie tussen SDB en cardiovasculaire dysfunctie aan te tonen. Het doel van deze studie was om 1) de accuraatheid van de SomnoCheck Micro voor het meten van slaapparameters te evalueren en het manueel scoren van de bekomen parameters te optimaliseren 2) het cardiorespiratoir slaappatroon en het cardiovasculair profiel in zowel normotensieve zwangeren als zwangeren met GHD te vergelijken 3) de associatie tussen slaap en cardiovasculaire parameters te beoordelen.

MATERIALEN & METHODEN: 1) Voor de validatie van de SomnoCheck Micro, bestaande uit een nasale canule en een fotoplethysmografie (PPG) sensor, sliepen patiënten met twee toestellen gedurende één nacht, één met en één zonder nasale canule. Het aantal apneus en hypopneus werden zowel automatisch als manueel geëvalueerd. Het manueel scoren van de respiratoire events werd geëvalueerd vóór en na training in het slaap laboratorium. Daarnaast werd het scoren van respiratoire events onafhankelijk uitgevoerd door twee onderzoekers en de interscorer correlatie coëfficiënt werd berekend. 2) Slaapparameters werden verzameld via de SomnoCheck Micro. Een cardiovasculair profiel werd opgesteld met behulp van gecombineerde ECG-Doppler ultrasonografie en impedantie cardiografie. Alle parameters werden vergeleken tussen normotensieve zwangeren en zwangeren met GHD. 3) De cardiorespiratoire slaapparameters werden gecorreleerd met cardiovasculaire parameters.

RESULTATEN: 1) Tien patiënten hebben deelgenomen aan de validatie studie. AHI_{maneel} was significant hoger dan AHI_{auto} ($p=0,007$) en RDI ($p=0,005$). $AHI_{manueel}$ was significant lager na training dan vóór training ($p<0,001$). De interscorer correlatie coëfficiënt was 0,635 ($p<0,001$). 2) 18 patiënten met GHD en 58 normotensieve zwangeren werden geïncludeerd in de analyse. Zwangeren met GHD snurkten significant meer dan de controle groep ($p=0,008$), maar flow limitatie was niet significant meer aanwezig bij zwangeren met GHD ($p=0,238$). De AHI en zuurstof desaturatie index waren niet significant verschillend tussen beide groepen ($p=0,175$ en $p=0,631$, respectievelijk). 3) Snurken was significant gecorreleerd met de systolische bloeddruk. Er was een significante negatieve correlatie tussen snurken en zowel de acceleratie index (ACI) als de velocity index (VI). Snurken was geassocieerd met BMI en er was een tendens naar een associatie met gewichtstoename.

CONCLUSIE: Snurken was geassocieerd met een stijf cardiovasculair systeem omwille van de correlatie met de systolische bloeddruk en de negatieve correlatie met VI en ACI. Associaties tussen snurken en BMI werden ook aangetoond. Deze resultaten suggereren dat snurkende zwangere vrouwen met een hoge BMI een verhoogd risico hebben op het ontwikkelen van hypertensie stoornissen.

1. Introduction

1.1 Sleep-disordered breathing in the non-pregnant population

1.1.1 Definition

Sleep-disordered breathing (SDB) refers to an array of breathing difficulties during sleep, ranging in severity from snoring to obstructive sleep apnea syndrome (OSAS). Snoring is the sound produced by vibrating respiratory structures due to increased upper airway resistance. OSAS is characterized by repeated narrowing of the upper airways, resulting in partial or nearly complete obstructions, occurring during sleep (1). Obstruction is the result of reduction of nasopharyngeal dimensions, most commonly caused by excessive fat deposits. Following obstructive events, blood oxygen levels reduce and arousal from sleep is necessary to restore normal airflow. This recurrent hypoxia and reoxygenation results in a disrupted sleep pattern, which leads to excessive sleepiness, unrefreshing sleep and disrupted daytime functioning. It is estimated that this disorder is prevalent in 2-10% of the middle-aged population worldwide (2, 3).

1.1.2 Risk factors

Obesity is the most important risk factor associated with SDB, which has a bidirectional relationship with obesity. On the one hand, obesity exacerbates SDB due to fat deposition in the upper airway. This facilitates the collapsibility and leads to obstructive events. Moreover, visceral fat distribution reduces chest compliance and functional residual capacity (FRC), resulting in the possibility for an increased oxygen demand. On the other hand, SDB gives rise to sleep deprivation, which leads to daytime somnolence and decreased physical activity, possibly resulting in weight gain. Additionally, sleep deprivation inhibits the production of leptin, which is a hormone produced by adipose tissue and is responsible for the sensation of satiety. Leptin also has a role in ventilatory control by directly stimulating the respiratory control centers (4). Severe and untreated SDB is considered as an important cardiovascular risk factor. SDB is strongly associated with systemic hypertension (5) and is an independent risk factor for congestive heart failure, strokes, atrial fibrillation, impaired glucose metabolism and insulin resistance. Other risk factors include age, male gender, smoking, chronic rhinitis, craniofacial anatomy and menopause (6).

1.2 Sleep-disordered breathing in the pregnant population

During pregnancy, many hormonal and physiological changes occur, which have an effect on both the respiratory and the cardiovascular system. These changes increase the risk on developing SDB and induce alternations in maternal sleep.

1.2.1 Hormonal and physiological changes: effect on respiratory system

Pregnancy is associated with marked hormonal augmentations. Both estrogen and progesterone influence the **respiratory physiology** during pregnancy. Progressive progesterone production causes an increase in the sensitivity to carbon dioxide in the respiratory center of the brain, resulting in an increased respiratory drive. Moreover, during pregnancy more metabolic carbon dioxide is produced, which also augments the minute ventilation. As result of this hyperventilation, excess carbon dioxide is exhaled, resulting in a respiratory alkalosis (7, 8). Similar to progesterone, estrogen is increased in the course of pregnancy. Estrogen induces vasodilatation and consequently decreases peripheral vascular resistance. This results in a lower blood pressure and a lower renal perfusion. As response, the renin-angiotensin-aldosterone system (RAAS) is stimulated, resulting in a higher sodium and water retention. The result of water retention is edema of the nasopharyngeal mucosa, leading to nasal obstruction and thus increased resistance to airflow. This estrogen-induced nasal obstruction, also called vasomotor rhinitis, is a common phenomena in the third trimester of pregnancy and disappears after delivery. It increases the risk of SDB, and more specifically snoring, in pregnant women (9).

Other respiratory-associated physiological changes are namely linked with progressive weight gain. The diaphragm is displaced upward with 4 cm, mediated by the growing uterus, resulting in reduction of the FRC by approximately 20 to 30%. In supine position during sleep, the upward diaphragm displacement is even more pronounced, leading to an additional fall in FRC (8, 10). The reduced FRC in combination with increased fetal and maternal oxygen consumption contributes to reduced maternal oxygen reserve. Consequently, respiratory events, such as apneas and hypopneas, which decrease oxygen delivery have a greater effect on the oxygen homeostasis in pregnancy (7).

Changes during pregnancy can be subdivided into factors with protective and exacerbating effects on SDB development. Protective changes include increased respiratory drive, preference for lateral position during sleep and reduction in rapid eye movement (REM) sleep (11). The latter, also called the dream sleep, is characterized by rapid eye movements, reduced muscle tone and increased brain activity. The estrogen-induced reduction in REM sleep is protective against SDB since obstructive events are more common during this stage of sleep (12). Changes which increase the risk on SDB include gestational weight gain, nasopharyngeal edema, decreased FRC and increased arousal from sleep (11).

1.2.2 Hormonal and physiological changes: effect on cardiovascular system

Many maternal cardiovascular changes take place in pregnancy which are needed to respond to the increased metabolic demands of the mother and the growing fetus. Due to the aforementioned water and sodium retention, maternal blood volume increases by 10-15% in early pregnancy and peaks at a 40% increase in the third trimester of pregnancy, compared to pre-pregnancy values (10). In response to the increased blood volume, the peripheral vascular resistance progressively decreases. This vasodilatory effect is induced by both nitric oxide and progesterone, which cause relaxation of the vascular smooth muscle (13). The increase in blood volume and the decrease in peripheral vascular resistance induce an increased preload and a decreased afterload, respectively, which leads to an augmentation of the stroke volume. The combination of an increased stroke volume and an increased maternal heart rate, results in an overall increased cardiac output (10, 14, 15). Blood volume expansion functions to increase uterus perfusion and compensates the high amount of blood loss in labor. Increased uterine blood flow functions to supply a sufficient amount of nutrition and oxygen to the growing fetus (10, 14).

1.2.3 Effect on maternal sleep

Most alternations in sleep have been reported to arise in the third trimester of pregnancy. Many pregnant women in this stage of pregnancy have complaints about difficulties with falling asleep or getting back to sleep. As result of insomnia, maternal sleep quality is significantly reduced (16). Third trimester sleep disturbance can be attributed to general physical discomfort, including backache, leg cramps, restless legs syndrome, heartburn, etc. Shortness of breath caused by upward displacement of the diaphragm and feeling hot are also commonly reported symptoms associated with pregnancy, which are also actively present at night. The large uterus causes compression of the bladder and increases the frequency to urinate, which results in more nocturnal awakening. Moreover, fetal movements and uterine activity might contribute to a disturbed sleep pattern by late pregnancy (16, 17). Sleep studies in pregnant women have been performed using polysomnography, which is a standard technique for analyzing different sleep stages. Sleep stages are divided into three major groups: REM sleep, stage 1-4 non-rapid eye movement (NREM) sleep and wakefulness. Measurements in the third trimester indicated decreased REM sleep, decreased stage 3 and 4 NREM sleep and increased stage 1 NREM sleep (18).

During pregnancy, there is an increase in frequency and severity of snoring, which is the most common symptom of SDB (19-23). Ursavas et al. performed a questionnaire-based study in 469 pregnant women and 208 non-pregnant women. This study showed that habitual snoring was reported in 11,7% of pregnant women in the third trimester, while 2,5% of these women snored before pregnancy, compared to only 1,9% of non-pregnant controls. Habitual snorers have been shown to have a higher neck circumference compared to non-snorers. Furthermore, Ursavas et al. showed that age, smoking during pregnancy and maternal obesity increase the risk for snoring (23). Another questionnaire-based study has been performed by O'Brien et al. This study included 1719 third-trimester pregnant women, of these, 34% reported snoring with 25% reporting pregnancy-onset snoring (24). Other studies (20, 21) supported this prevalence rate.

1.3 Diagnosis of SDB in pregnancy

SDB can be diagnosed by objective sleep pattern evaluation and subjective questionnaires. Currently, polysomnography is the gold standard for the diagnosis of SDB. During a polysomnography, recordings from electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), airflow, oxygen saturation and thoracic/abdominal movements are collected. Based on these signals, the apnea hypopnea index (AHI) can be calculated, which is an indicator for the severity of SDB. Since polysomnography is expensive, labor-intensive, has a limited availability and needs to be performed by experienced staff, several types of portable monitoring devices have been developed. A so-called type 2 device is the portable version of the polysomnography, which is a type 1 device, consisting of a minimum of seven channels. Polygraphy or cardiorespiratory sleep devices belong to the category of the type 3 devices. Airflow, respiratory movement, oxygen saturation and heart rate or ECG are measured using a minimum of four channels. Type 4 devices are the most simplified devices of all categories, recording only oxygen saturation and/or airflow (25). The SomnoCheck Micro belongs to this category and consists of a nasal cannula and a fingertip photoplethysmogram (PPG) (26). However, other type 4 devices have been developed, which additionally record peripheral arterial tonometry (PAT) and actigraphy, including the Watch_PAT100. Sleep/wake time is estimated from actigraphy signals, while peripheral arterial tone changes, heart rate and oxygen saturation are measured by the two finger sensors. Respiratory events induce sympathetic activation of α-adrenerge receptors, resulting in vasoconstriction and changed PAT signals. From these signals, respiratory disturbance index (RDI) and oxygen desaturation index (ODI) can be obtained, which are needed for the diagnosis of SDB. Due to the easy, non-invasive character, the Watch_PAT100 is an ideal screeningstool for SDB (27). Validation of the Watch_PAT100 against polysomnography in the nonpregnant population has already been performed in several studies and demonstrated strong correlations of respiratory event detection between both technologies (28, 29). In the pregnant population, both technologies have also been validated by O'Brien et al (30), which indicated that the Watch_PAT100 has an excellent sensitivity (88%) and specificity (86%) for SDB identification.

Subjective screening questionnaires have been used to identify the risk of having SDB based on self-reported symptoms. Both the Berlin questionnaire and Epworth Sleepiness Scale (ESS) have been validated against polysomnography and are used in the non-pregnant, middle-aged and elderly populations. The Berlin questionnaire asks about snoring, daytime sleepiness and hypertension, which are risk factors for sleep apnea, while the ESS asks about symptoms of daytime sleepiness (31). Two studies have evaluated the predictive capacity of these questionnaires in the pregnant population (32, 33). The Berlin Questionnaire and Multivariable Apnea Risk (MAP) index have also been evaluated against polysomnography in pregnancy. MAP index asks about the frequency of self-reported loud snoring, snorting or gasping and apneas to predict sleep apnea (34). They all concluded that these questionnaires poorly predict SDB in pregnancy due to overestimation of the true prevalence of SDB in pregnancy. Moreover, these questionnaires have been developed for predominantly male populations and males have been found to describe SDB symptoms differently than women. Questions regarding physical factors (obesity and neck circumference) and hypertension, rather than SDB symptoms, might have a better predictive value for the identification of SDB in pregnancy (32, 34).

1.4 Gestational hypertension and preeclampsia

Gestational hypertension (GH) is defined as pregnancy-induced hypertension, measured two times with minimum six hours in between, after twenty weeks of gestation in previously normotensive women. When accompanied by proteinuria, this condition is called preeclampsia (PE). These gestational hypertensive disorders (GHD) are the leading cause of maternal and fetal morbidity and mortality (35). An increased frequency of snoring has been observed in patients with GH and PE compared to normal pregnancies in several studies (19, 20, 23). In the study of Franklin et al., 10% and 14% of the habitual snorers developed GH and PE, compared to only 6% and 4% of the nonsnorers, respectively (20). Similar findings have been reported by Ursavas et al. (23). These findings might explain the observation that preeclamptic women have significantly narrower upper airways and larger neck circumferences. This is probably the result of edema or fat deposition in the pharynx (20, 23, 36).

Louis et al. showed that that obstructive sleep apnea (19%) and obesity (11%) is more present in preeclamptic patients, compared to normotensive individuals with normal weight (7%) (37). Both Champagne et al. and Reid et al. focused on the association between SDB and GH (38, 39). They both observed higher AHI values in hypertensive pregnant women compared to normotensive women. AHI is defined as the number of times the patient (nearly) stops breathing per hour sleep.

Diverse mechanisms are proposed to be involved in PE, which are suggested to be similar with the mechanism of the SDB effect on vascular disease.

(1) Intermittent hypoxia, as a result of obstructive apnea events, increases sympathetic nervous system activity, which leads to vasoconstriction by the activation of vascular smooth muscle and thus potential hypertension. (2) Another possibility leading to hypertension is the production of angiotensin II, upregulated by the sympathetic nervous system. Angiotensin II stimulates the production of renin in the kidney which has a vasoconstrictor function and thus affects the blood pressure. (3) An impaired baroreflex or the increased production of endothelin-1 by the vascular endothelial cells might also lead to increased vasoconstriction. (4) Intermittent hypoxia also stimulates the production of reactive oxygen species, which exacerbates endothelial dysfunction and impairs the nitric oxide availability. This latter functions as vasodilator (40). Oxygen saturation changes, caused by abnormal respiratory events, lead to recurrent placental hypoxia and reperfusion. Consequently, a cascade of events are initiated which result in endothelial dysfunction, peripheral vasoconstriction and high blood pressure (41).

1.5 Treatment of SDB in pregnancy

In normal pregnancy, nocturnal blood pressure is lower compared to the blood pressure during the daytime. However, pregnancies complicated with PE are associated with a reversal diurnal blood pressure rhythm, meaning that the blood pressure is higher during the night compared to the daytime (42). This reversed pattern has also been seen in snorers and patients with obstructive sleep apnea. Higher AHI values have been associated with increased nighttime/daytime and morning/evening blood pressure ratios (43). Therefore, Edwards et al. evaluated the effect of continuous positive airway pressure (CPAP) treatment on the nocturnal blood pressure in patients with PE. Polysomnography during the first night demonstrated that all eleven patients were affected by sleep-induced partial upper airway obstruction. Autosetting CPAP treatment in the second night resulted in nocturnal blood pressure reduction and elimination of the partial obstruction. Normalization of daytime hypertension, following CPAP treatment, was not evaluated in this study (44). The same authors evaluated the effect of CPAP on the cardiac output in a randomized controlled trial. Patients with PE were randomly assigned to receive CPAP (n=12) or no treatment (n=12) after a night of polysomnography. They found that reductions in cardiac output and increments in total vascular resistance during sleep in PE were minimized by CPAP treatment. These data suggest that the risk of fetal growth retardation associated with PE can be reduced by increasing the cardiac output (45). Both Guilleminault et al. (46) and Poyares et al. (47) focused on the potential benefit of early CPAP treatment in pregnant patients with risk factors for PE. In the prospective, longitudinal study of Guilleminault et al., pregnant women with risk factors for PE, including hypertension, obesity, or PE in a previous pregnancy, underwent a polysomnography. CPAP therapy was initiated only in patients with proven airflow limitation. CPAP started from the first trimester of pregnancy and was maintained during the whole pregnancy. This early CPAP intervention could unfortunately not prevent negative pregnancy outcomes, such as PE, early spontaneous abortion or premature births (46). In the study of Poyares et al. hypertensive patients and chronic snorers were randomized with CPAP treatment or no CPAP treatment, starting at a gestational age of eight weeks. In contrast to the control group, the treated group performed better blood pressure control and improved pregnancy outcomes (47). All together, these CPAP studies show conflicting results. CPAP does not seem to be able to solve the underlying cause of PE. Further research need to be done in larger, randomized controlled trials in order to investigate the potential use of CPAP in the treatment of PE (48).

1.6 Aims

The first aim of the present study was to evaluate the accuracy of a diagnostic sleep device, the SomnoCheck Micro, to measure sleep parameters and to optimize scoring of the obtained parameters. The second aim was to compare the cardiorespiratory sleep pattern and the cardiovascular profile in both normal pregnancies and pregnancies complicated with GH and PE in the third trimester. Finally, all possible associations between cardiorespiratory sleep parameters and cardiovascular maternal outcomes were investigated.

2. Materials and methods

2.1 Ethics Statement

Written informed consent was obtained from all participants. The experimental protocol was approved by the local Ethics Committee of Hasselt University and Ziekenhuis Oost-Limburg (CME ZOL reference 12/09 IU) and conformed to the Declaration of Helsinki (1964).

2.2 Quality tests/improvements of SomnoCheck Micro

2.2.1 Validation of the SomnoCheck Micro

A validation study was done with the SomnoCheck Micro in order to validate the accuracy of the device with or without nasal cannula to detect respiratory disturbance events. Patients were asked to sleep with two devices during one night, one with nasal cannula and one without nasal cannula. In one device AHI values were calculated based on both fingertip PPG and flow signals. In the other device RDI values were obtained since only PPG signals were recorded. The number of apneas and hypopneas were scored automatically and manually to discover the discrepancy. AHI_{manual} was compared with AHI_{auto} and RDI values. Statistics were performed using a One-sample Wilcoxon signed Rank Test at nominal level α = 0,05 using SPSS version 22.0 Statistical software (IBM SPSS Statistics).

2.2.2 Effect of training on respiratory event scoring

Respiratory events, i.e. apneas and hypopneas, measured by PPG and nasal cannula of the SomnoCheck Micro, were manually scored according to the American Academy of Sleep Medicine (AASM) standards. Based on the scored respiratory events, AHI values were calculated. Scoring was performed before and after an internship at the sleep laboratory campus Sint-Barbara in Lanaken, where manually scoring skills were acquired and trained by experienced employees. Training was focused on applying the ASSM scoring criteria correctly, as described in the AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Subsequently, AHI values before and after training were compared using a One-sample Wilcoxon signed Rank Test at nominal level α = 0,05 in SPSS version 22.0 Statistical software (IBM SPSS Statistics).

2.2.3 Inter- and intrascorer correlation coefficient

The reliability of manual respiratory event scoring (AHI_{manual}) between two researchers (JH and KD) was evaluated. Both researchers independently scored apneas and hypopneas, based on PPG and flow signals, according to the AASM standards and the calculated AHI values were compared. Respiratory event scoring was also performed twice, once before and once after training, by the same researcher (KD) and the calculated AHI values were correlated mutually. Both inter- and intrascorer correlation coefficients were obtained by calculating the Spearman's correlation coefficient in SPSS version 22.0 Statistical software (IBM SPSS Statistics).

2.3 Subjects

Subjects were divided into three groups: (1) the case group: pregnant patients complicated with GHD, (2) control group 1: pregnant patients with non-hypertensive complications and (3) control group 2: patients with uncomplicated normotensive pregnancies. Information about Gravida/Para/Abortus (GPA), expected date of delivery, BMI before and during pregnancy were gathered in each group.

The **case group** included women in the third trimester of pregnancy with GH or PE, admitted to the maternal intensive care unit (Ziekenhuis Oost-Limburg, Genk, Belgium). GH was characterized by repeated blood pressure measurements of >140/90 mmHg, diagnosed after a gestational age of twenty weeks in previously normotensive women, who received antihypertensive medication to control blood pressures. PE was defined as a pregnancy-induced hypertension of >140/90 mmHg, measured on at least two time points with minimum six hours in between. This rise in blood pressure is associated with *de novo* proteinuria of ≥300 mg per 24 h. Aside from those two strict diagnoses, no other pregnant women were enclosed in the case group.

Pregnant women hospitalized for other indications than PE and GH, such as placenta praevia, premature contractions or vaginal blood loss, were included in **control group 1**. Patients with strict bedrest, hyperemesis or nausea were excluded from the study.

The **second control group** contained normotensive pregnant volunteers in their third pregnancy trimester, which served as a non-hospitalized control group.

2.4 Study protocol

Each participant in the study went through a combination of tests: SomnoCheck Micro, cardiovascular examinations and questionnaire.

The SomnoCheck Micro is an easy, overnight device which measures the cardiorespiratory sleep pattern of the pregnant women, either in the hospital or at home. Patients were instructed on the proper use.

Either the day preceding or following the sleep test, patients underwent cardiovascular examinations, including combined ECG-Doppler ultrasonography and impedance cardiography (ICG). Those techniques visualize the cardiovascular profile of the pregnant women.

After accomplishing the nocturnal measurement, a non-validated questionnaire assessing sleep quality was completed by each patient.

These examinations are performed in order to find possible different relations between cardiorespiratory sleep parameters and cardiovascular parameters in both normal pregnancies and pregnancies complicated with GHD.

2.5 Techniques

2.5.1 SomnoCheck Micro

The SomnoCheck Micro is a wristband device consisting of a fingertip PPG sensor and a nasal cannula, able to record patients' sleep pattern (26). The PPG sensor is composed of an infrared light source and a photodetector (49). The infrared light illuminates the skin, which is absorbed by hemoglobin (Hb) and oxy-hemoglobin (HbO_2). Based on the relative difference in absorption of red light and infrared light by Hb and HbO_2, which is intercepted by the photodetector, the **blood oxygen saturation** can be calculated (49, 50). The blood oxygen saturation is defined as the percentage of Hb bindingsites occupied by oxygen. Beside oxygen saturation, the PPG sensor is able to measure the finger **pulse wave amplitude** (PWA) and the heart rate (26, 50). Pulsation of the blood flow in the vessels results in small variations in light intensity derived from the infrared light, which are detected by the photodetector. For example: a decrease in light intensity means an increase of blood volume (49, 50). These variations, caused by the wave-like motion of the blood, are represented by a PPG. The PPG waveform consists of a systolic (rising edge of the pulse) and a diastolic phase (falling edge of the pulse) with a systolic and a diastolic peak. The distance from the start of the systole to the end of the diastole is defined as the pulse rate or heart rate (Figure 1, left). The height of the systolic peak or the systolic amplitude is defined as the PWA (49). Changes in PWA can be used to determine the activation of the sympathetic nervous system (51). The PWA of each single PPG wave is extracted and plotted horizontally in function of the pulse rate (Figure 1, right) (26).

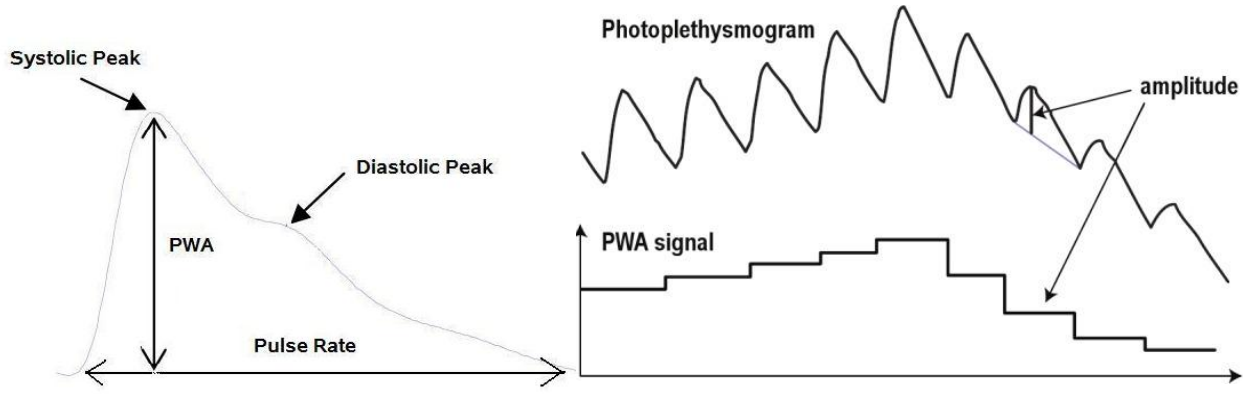

Figure 1: Photoplethysmogram from which PWA and pulse rate can be derived. Other components, including systolic peak and diastolic peak are indicated (left). The systolic amplitude from each pulse wave is plotted to obtain a PWA signal (right). The left and right figures are adapted from Elgendi et al. (49) and Sommermeyer et al. (26), respectively.

The second component of the SomnoCheck Micro device is the nasal cannula, which measures the **nasal airflow** (26). Detection of the inspiration and exhalation is possible by the generation of vacuum and overpressure, respectively. During inspiration, a negative pressure is experienced by the pressure sensor in the device, while a positive pressure is generated during exhalation. Not only nasal airflow, but also the presence of **snoring** is registered. Snoring events generate pressure fluctuations in the nostrils, which are transferred to the integrated pressure sensor via the nasal cannula (52). **Flow limitation** is differentiated from normal respiration based on the shape of the curve. Inspiratory flow limited-breaths are characterized by a cavity in the inspiratory curve,

also called flattening, while normal respiration is characterized by a sinusoidal shape. The flattening index is calculated by the Somnolab algorithm by the ratio of the area of the convex part of the curve (A1) and the sum of A1 and the area under the curve (A2) (Figure 2) (53). Both snoring and flow limitation percentages are calculated by dividing the sum of the duration of all snoring events and flow-limited breaths, respectively, by the good flow signal.

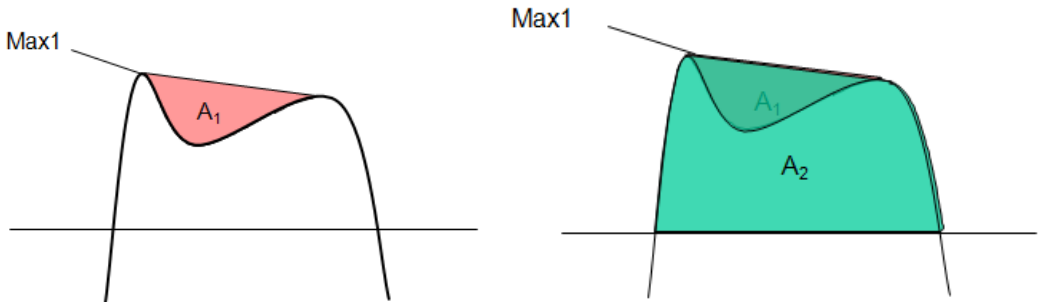

Figure 2 Illustration for the identification of flow limitation by the Somnolab algorithm. The flattening index is calculated by the ratio A_1/A_2 (53).

Based on the signals obtained from the PPG sensor and the nasal cannula, additional respiratory event parameters are automatically calculated by the Somnolab algorithm (26). The main parameters include AHI, RDI, ODI and autonomic arousal index (AAI). The risk on sleep apnea, sleep disturbances and sleep fragmentation depends on the values of AHI, RDI and AAI, which can be categorized as low, medium or high.

AHI is defined as the number of apneas and hypopneas per recorded hour of sleep and its calculation is based on both PPG and flow signals. Apneas and hypopneas are generally scored according to the definitions of the AASM scoring manual (54). An apnea is defined as a reduction in airflow of ≥90% compared to baseline for at least ten seconds. An hypopnea is scored when nasal airflow decreases with ≥30% compared to baseline lasting for at least ten seconds and accompanied by a ≥4% desaturation. Alternatively, an hypopnea is scored when nasal airflow decreases with ≥50% compared to baseline lasting for at least ten seconds and accompanied by a ≥3% desaturation or an arousal.

RDI includes the number of respiratory events per recorded hour of sleep, measured by the PPG sensor. When the nasal flow signal is insufficient, respiratory events are scored based on the PPG signals alone and a RDI value, instead of a AHI value, is given.

ODI is the number of times that the oxygen level in the blood decreases with more than 3-4% per recorded hour of sleep. Nocturnal oxygen desaturations are mostly the consequence of breathing disruptions i.e. apneas and hypopneas during sleep.

AAI represents the number of autonomic arousals per recorded hour of sleep. A combination of both a ≥15% pulse rate increase and a ≥35% PWA decrease is identified as an autonomic arousal. Autonomic arousals are also detected when the pulse rate increases with 20% or PWA decreases with 40%. Due to an autonomic arousal, the sympathetic nervous system is activated and the pulse rate is increased. Peripheral vasoconstriction, induced by sympathetic nervous system activation, leads to a gradual PWA decrease per hour sleep (26). Based on the presence or absence of a respiratory event, autonomic arousals are scored as respiratory-related or non-respiratory-related.

2.5.2 Combined ECG-Doppler ultrasonography

The arterial and venous function of the maternal body can be visualized through a combination of an ECG and a Doppler ultrasonography of kidneys, liver and uterus.

The ultrasonography was performed in supine position, using a 3.5 MHz transabdominal probe (Aplio Mx, Toshiba Medical Systems nv., Sint-Stevens-Woluwe, Belgium). The renal interlobar veins above the renal hilus (left and right) and the three hepatic vein branches were evaluated to represent the venous function. The arcuate branches of the left and right uterine arteries were evaluated for the arterial function. Corrections for breathing were made by breath holding during assessment (55).

For each kidney, liver and arcuate branches of both uterine arteries, three Doppler images were obtained and parameters were derived from it (55).

The **venous pulse transit time** (VPTT) is the time interval between the ECG P wave and the corresponding venous Doppler A wave (PA in milliseconds, Figure 3), adjusted for heart rate (PA/RR). In other words, it is the amount of time the pulse wave needs to move from the periphery to the heart. The transit time is influenced by the stiffness of the veins.

Arterial pulse transit time (APTT) is the arterial equivalent of the VPTT. It shows the time interval between the Q wave of the ECG signal and the start of the systolic Doppler signal or end-diastolic point D (QD in milliseconds, Figure 3), which is also corrected for heart rate (QD/RR). In other words, it is the amount of time the pulse wave needs to move from the heart to the periphery. The APTT gives an idea of the arterial stiffness.

Renal interlobar vein impedance index (RIVI) and **hepatic vein impedance index** (HVI) is calculated as [$velocity_{max}$-$velocity_{min}$]/$velocity_{max}$ (56) from blood flow velocities in the kidneys and liver, respectively.

The **arterial impedance indices** include pulsatility and resistance indices, labeled as PI and RI, respectively. PI is calculated as [peak systolic flow-end diastolic flow]/mean flow, while RI is calculated as [peak systolic flow-end diastolic flow]/peak systolic flow (57). Both PI and RI give information of the vascular resistance, which decreases in normal pregnancy.

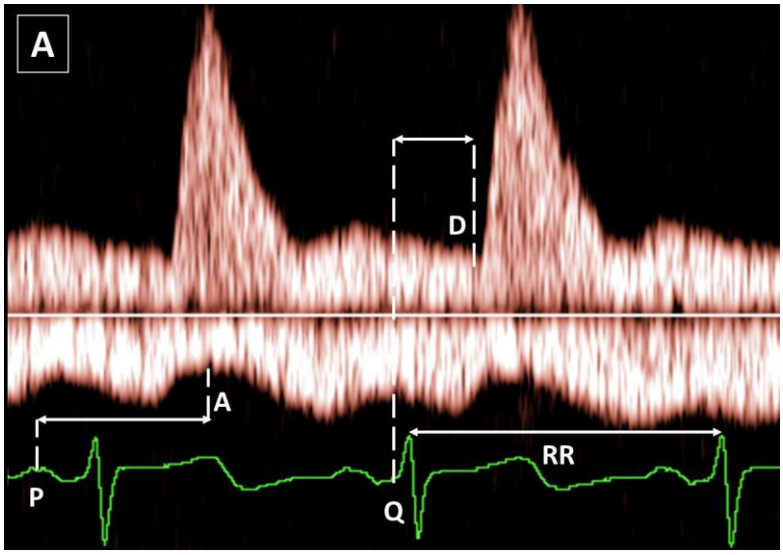

Figure 3: Combined ECG-Doppler ultrasonography signals. Both venous and arterial time intervals are indicated (PA and QD, respectively). Heart rate is represented by the RR interval. This figure is adapted from Oben et al. (58)

2.5.3 Impedance cardiography (NICCOMO)

ICG measurements were executed using the Non-Invasive Continuous Cardiac Output Monitor (NICCOMO; Software version 2.0; SonoSite, Medis Medizinische Messtechnik, Ilmenau, Germany). For this examination, two dual sensors are sticked to each side of the patient's neck and two to each side of the thorax along the midaxillary line (Figure 4). Each sensor has a stimulating electrode, most distal to the heart, and a measuring electrode, most proximal to the heart. From the stimulating electrode, an alternating current with a high frequency (60-100 kHz) and a low amplitude (1 mA) is transmitted. Voltage is produced due to the current flow through the thorax, which is measured by the measuring electrode (55). This electrode calculates the impedance. The impedance cardiogram (dZ/dt) is the first mathematical derivative of the change in thoracic impedance (Z) over time to this alternating current.

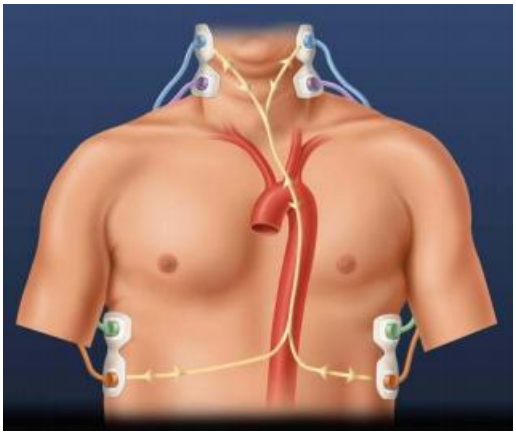

Figure 4: Electrode positions for the ICG examination. Two dual electrodes are placed to each side of the patient's neck and two dual electrodes are placed to each side of the thorax along the midaxillary line. This figure is adapted from http://impedancecardiography.com/icgover10.html.

Both ECG and ICG are generated by the device (Figure 5). The point at which the ventricles start to depolarize is represented by the Q-wave of the ECG, while the R-wave represents the point at which maximal depolarization is reached. Opening and closing of the aortic valve correspond to point B and point X of the ICG, respectively, while the maximal systolic flow corresponds to point C of the ICG (Figure 5). Through the combination of those signals, cardiovascular parameters are calculated by the device.

Every two seconds, ICG values were recorded and the blood pressure was measured every two minutes. Blood pressure measurements are integrated in the system and thus are automatically performed and recorded by the NICCOMO monitor. Data were collected over a timespan of one minute between the first and the second blood pressure measurement in both supine and standing position. The pressure parameters were derived from the first blood pressure measurement in standing position. All other parameters obtained in standing position were used for analysis (59).

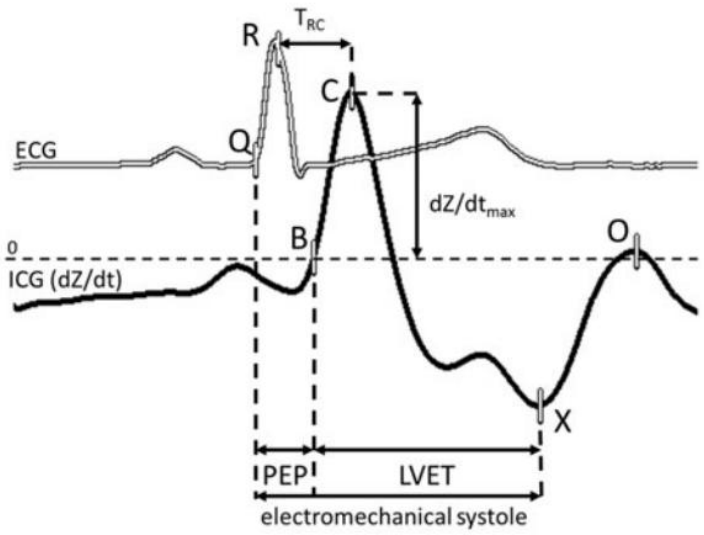

Figure 5: ECG and ICG signals. Q: start of ventricular depolarization, R: maximal ventricular depolarization, B: aortic valve opening, C: peak systolic flow, X: aortic valve closing, O: mitral valve opening, PEP: pre-ejection period, LVET: left ventricular ejection time, and T_{RC}: RC time interval. This figure is adapted from Oben et al. (58)

The measured parameters are classified into five major groups: pressures, left ventricular output parameters, cardiac cycle time intervals, aortic flow and thoracic fluid parameters (58, 59).

Pressures - Both systolic and diastolic blood pressures (SBP and DBP in mmHg) are automatically measured by the oscillometric sphygmomanometer of the NICCOMO device. From these pressures, pulse pressure (PP in mmHg) and mean arterial blood pressure (MAP in mmHg) are calculated. The difference between SBP and DBP is defined as PP, while MAP is the sum of DBP and PP/3 (58, 59).

Left ventricular output parameters - The heart period duration (HPD in ms) is derived from the RR-interval of the ECG signal, from which heart rate (HR in beats/min) is calculated. Using the Sramek-Bernstein formula, the stroke volume (SV in ml) is automatically calculated. Stroke volume index (SI in ml/m²) is SV divided by body surface area. This formula estimates the electrically participating chest tissue from the height, weight, age and gender of the patient. Cardiac output (CO in l/min) is the amount of blood pumped by the heart in one minute and is calculated as the product of heart rate and stroke volume. Cardiac index (CI in l/min/m²) is CO divided by body surface area (58, 59).

Cardiac cycle time intervals - The pre-ejection period (PEP in ms, Figure 5) corresponds to the electrical systole. On Figure 5, this is the time interval between the start of ventricular depolarization (Q-wave of the ECG) and the opening of the aortic valve (B-point of the ICG). It is the period needed for the ventricle to exceed the aortic pressure to open the valve and start ejection. The left ventricular ejection time (LVET in ms, Figure 5) corresponds to the mechanical systole or the duration of ejection. It is characterized by the time interval between opening (point B of the ICG) and closing of the aortic valve (point X of the ICG). Together, PEP and LVET represent the electromechanical systole. The ratio of the electrical and mechanical systole (PEP/LVET) is defined as the systolic time ratio (STR), which serves as a load-independent measure of beta-adrenergic sympathetic influence of the myocardium (58, 59).

Aortic flow parameters - The velocity of the aortic blood flow is represented by the velocity index (VI in 1/1000/s), which corresponds to point C of the ICG signal, i.e. the amplitude of the systolic wave. The maximum acceleration of blood flow in the aorta is represented by the acceleration index (ACI in 1/100/s²). Both VI and ACI give information about the contractility. The higher the VI and ACI amplitude, the higher the contractility. The Heather index (HI in Ω/s²) corresponds to the time interval between the R-wave of the ECG and the C-wave of the ICG. This parameter is a more sensitive measure for the contractility since the amplitude of the ICG wave is corrected for the time needed by the ventricle to reach maximum ejection. The total arterial compliance (TAC in ml/mmHg), which is a measure for the distensibility of the arteries, is calculated by dividing stroke volume by pulse pressure. The total arterial compliance index (TACI in ml/mmHg/m²) is calculated by dividing stroke volume index by pulse pressure (58, 59).

Thoracic fluid parameters - The overall impedance across the thorax is represented by the base impedance (Z0 in Ohm). The amount of conducting fluid in the thorax determines the base impedance and is expressed as the thoracic fluid content (TFC in 1/kΩ). TFC, normalized for body surface area, is defined as thoracic fluid content index (TFCI in 1/kΩ/m²) (58, 59).

2.6 Questionnaire

The subjective sleep evaluation questionnaire included six questions. Patients were asked if they slept the entire night with the device, how long it took to fall asleep starting from recording, how often they woke up and got up. Another question asked to which extent the night rest was disturbed in comparison to other nights, on a scale of 0 to 5, ranging from totally not to totally disturbed. The last question asked about the reason(s) for the disturbed night rest, if applicable. Possible reasons are the diagnostic sleep device, excessive thinking, uncomfortable hospital bed, noise, snoring of the bedpartner, pregnancy-related reasons, such as frequent nocturia, fetal movements, back pain and leg cramps.

2.7 Statistics

The cardiorespiratory sleep parameters (AHI, ODI, mean saturation and lowest saturation, AAI, % snoring, % flow limitation), NICCOMO parameters (HSBP, DBP, MAP, PP, TFC, TFCI, SV, SI, CO, CI, VI, ACI, HI) and all ECG-Doppler parameters (RIVI, RI, PI, VPTT, APTT) were compared between cases and controls, using the independent-samples T-test or non-parametric Mann-Whitney U-Test, depending on normality. The sleep parameters were correlated with both NICCOMO and ECG-Doppler parameters. Depending on normality, Pearson's or Spearman's correlation coefficient was calculated. A p-value of $< 0,05$ was used to indicate statistical significance. Statistical analyses were performed using SPSS version 22.0 Statistical software (IBM SPSS Statistics).

3. Results

3.1 Patient characteristics

Data was collected by two researchers, JH and KD. A total of 50 patients, recruited by JH, agreed to participate in the study in the period between February and April 2013. From this cohort, 32 patients in total were excluded for diverse reasons: insufficient analysis time (n=15), insufficient flow signal (n=8), labor activity (n=5), practical reasons (n=3) and HELLP syndrome (n=1).
A total of 101 patients, recruited by KD, agreed to participate in the study in the period between November 2013 and April 2014. From this cohort, 43 patients in total were excluded for diverse reasons: inconvenience of the sleep device (n=18), labor activity (n=5), insufficient flow signal (n=3), illness (n=3), practical reasons (n=6), HELLP syndrome (n=1), diabetes gravidarum (n=5), missing data (n=2).
Altogether, 76 sleep patterns were appropriate for analysis. In the case group, eighteen patients were diagnosed with GHD, i.e. thirteen patients complicated with PE and five patients complicated with GH. Control group 1 included initially 25 patients and control group 2 included 33 patients. Since none of the sleep and cardiovascular parameters were significantly different between both control groups, all 58 normotensive patients were considered as one control group. Data from combined ECG-Doppler ultrasonography and ICG was missing for three and seven normotensive patients, respectively. After delivery, ten of the 58 normotensive patients (17%) were diagnosed with IUGR. Among the cases, five pregnancies (28%) were additionally complicated with IUGR.
Patient characteristics such as maternal age, gestational age at inclusion, BMI and weight gain are summarized in Table 1. These parameters, except the gestational age, were not significantly different between controls and cases. Patients with GHD had slightly higher BMI before pregnancy and at inclusion compared to controls. Moreover, cases gained more weight during pregnancy compared to controls. Concerning the outcome characteristics (Table 1), birth weight, birth weight percentiles and gestational age at delivery were significantly lower in cases compared to controls. Exclusion of patients with IUGR still resulted in significantly lower birth weight in cases (p=0,039), but the birth weight percentiles were not significantly different between cases and controls (p=0,162).

Table 1: Patient and outcome characteristics of the study groups: normotensive pregnancies (controls) and gestational hypertensive and preeclamptic pregnancies (cases)

	Controls		Cases		
	(n=58)		(n=18)		P-value
Characteristics at inclusion					
Maternal age, years	29 ± 4	29 (27;32)	30 ± 5	31 (26;35)	0,499
Gestational age at inclusion, weeks	31 ± 3	31 (30;34)	34 ± 4	34 (30;37)	**0,013**
Pre-pregnancy BMI, kg/m²	24 ± 5	23 (21;26)	25 ± 4	25 (22;28)	0,189
Current BMI, kg/m²	28 ± 5	26 (24;30)	29 ± 5	28 (25;33)	0,094
Weight gain, kg	10 ± 6	10 (7;13)	13 ± 8	11 (7;16)	0,362
Outcome characteristics					
Birth weight, g	3010 ± 732	3010 (2639;3479)	2346 ± 850	2528 (1428;2928)	**0,002**
Birth weight, percentile	37,2 ± 26,9	35 (14,4;55,6)	26,4 ± 29,2	17,5 (5,0;26,3)	**0,048**
Gestational age at delivery, weeks	38 ± 3	39 (36;40)	36 ± 4	36 (32;39)	**0,006**

Data are presented as means ± standard deviation and medians (interquartile ranges). Differences between controls and cases are presented as p-values (α<0,05 was considered significant), calculated using independent-samples T-test or Mann-Whitney U-test, depending on normality. BMI: body mass index.

3.2 Quality tests/improvements of SomnoCheck Micro

3.2.1 Validation of the SomnoCheck Micro

To validate the SomnoCheck Micro, sixteen (three males, thirteen females) patients were evaluated. For six patients (38%) the cardiorespiratory sleep pattern registration failed due to (un)voluntary interruption or insufficient recording time. AHI_{manual} was significantly higher than AHI_{auto} (5,9 (2,0;8,9) events/h vs. 1,4 (0,8;5,5) events/h, p = 0,007) and AHI_{manual} was also significantly higher than RDI (5,9 (2,0;8,9) events/h vs. 1,5 (0;2,4) events/h, p = 0,005) (Figure 6).

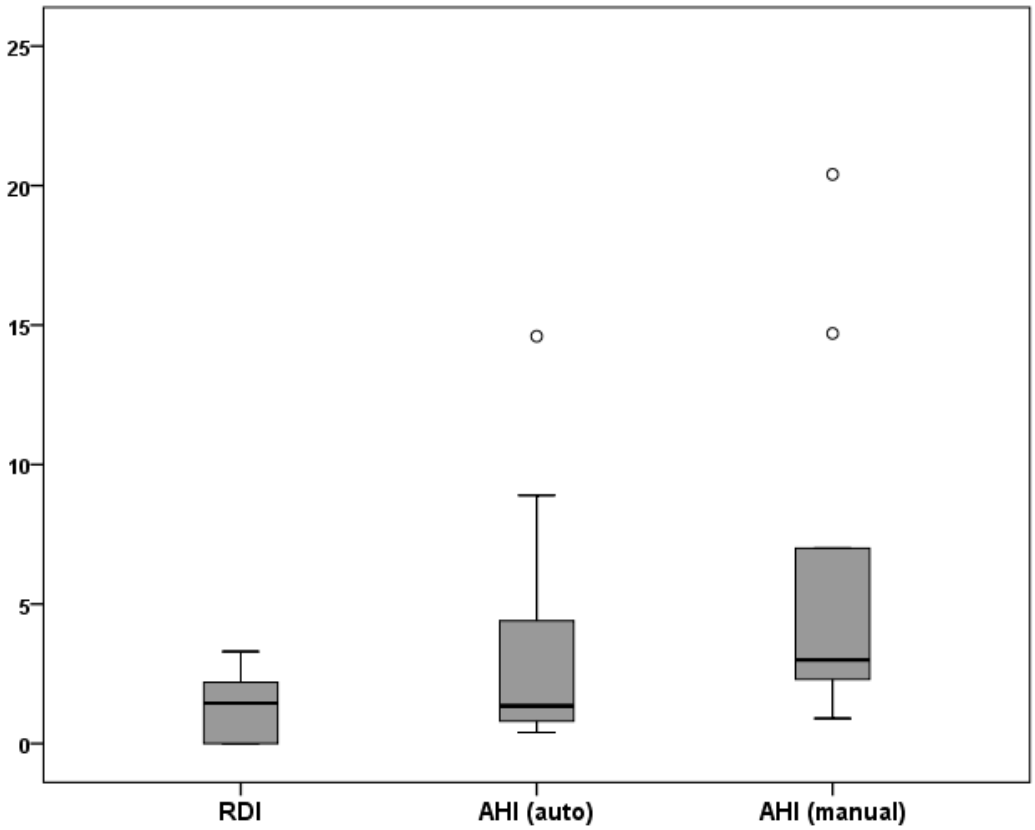

Figure 6 Boxplot for the validation of the SomnoCheck micro. The box represents median and interquartile range and the bars represent total ranges. Differences are given in manually scored AHI, automatically calculated AHI and RDI. Outliers, plotted as individual points, are present in AHI_{auto} and AHI_{manual} boxplots.

3.2.2 Effect of training on respiratory event scoring

The overnight respiratory pattern of eighteen patients (three males, fifteen females) was evaluated. The manually calculated AHI values were compared before and after training at the sleep laboratory. In all cases, the AHI value was lower after training than before training (2,6 (2,1;6,7) events/h vs. 5,9 (4,0;10,5), p<0,001).

3.2.3 Inter- and intrascorer correlation coefficient

Respiratory events in the sleep pattern of nineteen patients were independently scored by two researchers (JH and KD). AHI, scored by JH, was slightly higher than the AHI, scored by KD (2,3 (1,3;4,2) events/h vs. 1,9 (1,0;3,5) events/h, p=0,218). The inter- and intrascorer correlation coefficients were 0,635 (p=0,003) and 0,876 (p<0,001), respectively.

3.3 Sleep fragmentation

The level of sleep disturbance, expressed as autonomic arousal index, is classified as low, medium or high. Only one patient from the control group (2%) had a high sleep disturbance risk with a high AAI of 43 events/h. One patient from the case group (6%) and eight patients from the control group (14%) had an AAI between 30 and 40 and were therefore classified as having a medium sleep disturbance risk. An AAI below 30, indicating a low sleep disturbance risk, was measured in all other patients: seventeen patients in the case group (94%) and 49 patients in the control group (85%).

The AAI in all subjects was 19,2 (± 9,2) events/h. In all subjects, non-respiratory-related arousals were higher compared to the respiratory-related arousals (17,9 ± 8,7 events/h vs. 1,3 ± 1,7 events/h) (Table 2). This latter type of arousals compromises 8% of the total AAI in cases and 7% of the total AAI in controls. No significant difference was present between cases and controls for respiratory-related AAI (p=0,709), although AAI (p=0,095) and non-respiratory-related AAI (p=0,083) tended to significance (Table 2).

3.4 SDB and maternal outcome

Sleep apnea has the same risk classification system as sleep disturbance. A total of ten patients, six in the case group (33%) and four in the control group (7%), had an AHI above five events/h and were therefore classified as having a medium risk for sleep apnea. All other patients were classified as having a low risk for sleep apnea.

All averages and medians of the sleep parameters in the two patient groups are shown in Table 2. Only the percentage of snoring was significantly higher in patients with GHD compared to controls. Both AHI and ODI were higher in patients with GHD compared to controls, but no significant difference was reached. The average pulse frequency, mean and minimum oxygen saturation were similar in both groups of patients. Flow limitation, another form of upper airway obstruction, was also not significantly different between cases and controls.

Table 2: Comparison of sleep parameters between normotensive pregnancies (controls) and gestational hypertensive and preeclamptic pregnancies (cases)

Parameters	SomnoCheck Micro				
	Controls (n=58)		Cases (n=18)		p-value
AHI	2,2 ± 1,8	1,8 (1,0;2,6)	3,4 ± 2,7	2,2 (1,1;5,7)	0,175
ODI	0,5 ± 0,6	0,3 (0,1;0,6)	0,7 ± 0,9	0,4 (0;1,0)	0,631
Mean O_2 saturation %	96 ± 1	96 (95;97)	96 ± 2	96 (95;97)	0,217
Minimum O_2 saturation %	88 ± 5	88 (86;91)	88 ± 4	90 (86;92)	0,773
Snoring %	2,2 ± 4,0	0,4 (0;2,6)	7,5 ± 11,0	3,7 (0,3;9,3)	**0,008**
Flow limitation %	0,9 ± 2,1	0,3 (0,1;0,8)	1,8 ± 4,4	0,5 (0,1;1,2)	0,238
Average PF	76 ± 7	77 (73;81)	72 ± 12	71 (60;83)	0,119
AAI	20,2 ± 9,6	18,2 (12,5;28,1)	16,1 ± 6,9	15,9 (10,5;20,3)	0,095
AAI non-resp.	18,8 ± 9,1	17,4 (12,0;25,9)	14,8 ± 6,7	13,6 (9,6;19,4)	0,083
AAI resp.	1,4 ± 1,7	0,9 (0,5;1,6)	1,3 ± 1,5	0,8 (0,4;1,9)	0,709

Data are presented as means ± standard deviation and medians (interquartile ranges). Differences between controls and cases are presented as p-values (α<0,05 was considered significant), calculated using independent-samples T-test or Mann-Whitney U-test, depending on normality. AHI: apnea hypopnea index, ODI: oxygen desaturation index, PF: pulse frequency, AAI: autonomic arousals, AAI (non-)resp.: (non-) respiratory-related autonomic arousals.

3.5 Combined ECG-Doppler ultrasonography

Comparison of the combined ECG-Doppler parameters between controls and cases is shown in Table 3. Since all PTT intervals in renal veins, hepatic veins and uterine arteries showed a shorter pulse transit time in patients with GHD compared to controls, only statistical significance was reached for both renal VPTTs and uterine APTTs. Although HVI and RIVI in left and right kidney were higher in pregnancies complicated with GHD compared to normotensive controls, the difference was not significant. Furthermore, RI and PI of the left and right uterine arteries were significantly higher in cases compared to controls, except for the PI of the left uterine arteries.

Table 3: Comparison of combined ECG-Doppler parameters between normotensive pregnancies (controls) and gestational hypertensive and preeclamptic pregnancies (cases)

Parameters	ECG-Doppler ultrasonography				
	Controls (n=55)		Cases (n=18)		p-value
Renal veins					
Left RIVI	0,38 ± 0,10	0,37 (0,32;0,42)	0,41 ± 0,13	0,39 (0,32;0,49)	0,435
Right RIVI	0,34 ± 0,15	0,34 (0,28;0,39)	0,39 ± 0,11	0,37 (0,32;0,47)	0,087
Left VPTT	0,43 ± 0,14	0,40 (0,34;0,46)	0,34 ± 0,10	0,32 (0,25;0,43)	**0,021**
Right VPTT	0,39 ± 0,08	0,39 (0,34;0,44)	0,32 ± 0,08	0,30 (0,26;0,39)	**0,001**
Hepatic veins					
HVI	0,39 ± 0,46	0,22 (0,10;0,56)	0,57 ± 0,56	0,32 (0,15;0,77)	0,131
Liver VPTT	0,31 ± 0,16	0,30 (0,18;0,43)	0,28 ± 0,13	0,26 (0,16;0,38)	0,403
Uterine arteries					
Left RI	0,46 ± 0,14	0,45 (0,35;0,56)	0,57 ± 0,16	0,57 (0,48;0,68)	**0,011**
Right RI	0,41 ± 0,11	0,40 (0,31;0,47)	0,59 ± 0,26	0,47 (0,43;0,70)	**0,002**
Left PI	0,61 ± 0,24	0,56 (0,42;0,76)	0,70 ± 0,26	0,70 (0,50;0,86)	0,100
Right PI	0,52 ± 0,19	0,50 (0,35;0,63)	0,72 ± 0,25	0,62 (0,56;0,94)	**0,002**
Left APTT	0,36 ± 0,13	0,34 (0,29;0,38)	0,26 ± 0,06	0,25 (0,21;0,30)	**<0,001**
Right APTT	0,35 ± 0,07	0,34 (0,31;0,38)	0,26 ± 0,06	0,24 (0,21;0,30)	**<0,001**

Data are presented as means ± standard deviation and medians (interquartile ranges). Differences between controls and cases are presented as p-values (α<0,05 was considered significant), calculated using independent-samples T-test or Mann-Whitney U-test, depending on normality. RIVI: renal interlobar vein impedance index, VPTT: venous pulse transit time, HVI: hepatic vein impedance index, RI: resistive index, PI: pulsatility index, APTT: arterial pulse transit time.

3.6 Impedance cardiography

ICG parameters were compared in standing position between controls and cases (Table 4). SBP, DBP and MAP were significantly higher in pregnancies complicated with GHD than in pregnant controls. CO, CI and the aortic flow parameters VI, ACI and HI showed significantly lower values in hypertensive women than in uncomplicated pregnancies. TFC was significantly higher in cases than in controls and a tendency towards significance was seen in TFCI. Left ventricular output parameters SV and SI were lower in cases than in controls, but the difference was only significant for SI.

Table 4: Comparison of ICG parameters in standing position between normotensive pregnancies (controls) and gestational hypertensive and preeclamptic pregnancies (cases)

Parameters	Impedance cardiography				
	Controls (n=51)		Cases (n=18)		p-value
Pressures					
SBP, mmHg	122 ± 14	120 (109;130)	142 ± 16	141 (135;148)	**<0,001**
DBP, mmHg	76 ± 11	75 (69;82)	95 ± 11	94 (89;100)	**<0,001**
MAP, mmHg	86 ± 10	85 (79;92)	106 ± 11	106 (99;112)	**<0,001**
PP, mmHg	46 ± 11	46 (39;52)	48 ± 10	49 (38;53)	0,543
Left ventricular output parameters					
SV, ml	82 ± 21	80 (67;91)	75 ± 15	72 (65;85)	0,180
SI, ml/m²	45 ± 10	44 (37;50)	39 ± 6	40 (34;45)	**0,041**
CO, l/min	8,0 ± 1,9	7,7 (6,6;8,9)	7,0 ± 2,1	6,8 (5,3;7,8)	**0,030**
CI, l/min/m²	4,3 ± 0,7	4,2 (3,8;4,7)	3,7 ± 0,9	3,6 (2,9;4,4)	**0,007**
Aortic flow parameters					
VI, 1/1000/s	76 ± 21	74 (59;92)	48 ± 14	47 (40;56)	**<0,001**
ACI, 1/100/s²	153 ± 52	144 (107;191)	101 ± 43	96 (76;122)	**<0,001**
HI, Ω/s²	23,4 ± 7,6	22,4 (18,0;29,4)	12,1 ± 4,9	10,9 (9,2;14,7)	**<0,001**
Thoracic fluid parameters					
TFC, 1/kΩ	27,1 ± 3,9	27,0 (24,7;29,4)	31,0 ± 5,5	29,7 (26,7;35,0)	**0,002**
TFCI, 1/kΩ/m²	15,1 ± 2,8	15,0 (13,2;16,5)	16,7 ± 3,5	16,6 (13,6;19,5)	0,058

Data are presented as means ± standard deviation and medians (interquartile ranges). Differences between controls and cases are presented as p-values (α<0,05 was considered significant), calculated using independent-samples T-test or Mann-Whitney U-test, depending on normality. SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, PP: pulse pressure, SV: stroke volume, SI: stroke volume index, CO: cardiac output, CI: cardiac index, VI: velocity index, ACI: acceleration index, HI: Heather index, TFC: thoracic fluid content, TFCI: thoracic fluid content index.

3.7 Relation between sleep and cardiovascular parameters

Snoring was significantly correlated with systolic blood pressure (R=0,806, p<0,001) in pregnancies complicated with GHD (Figure 7). This correlation became slightly higher (R=0,823, p<0,001) when the outlier (◇) was removed. In normotensive pregnancies, this correlation was absent (R=0,144, p=0,313). In the control group, there was a significant association between snoring and gestational weight gain (R=0,371, p=0,004). Although this association was higher in the case group (R=0,445, p=0,064), there was only a tendency for significance. Snoring was significantly associated with BMI at inclusion (R=0,577, p=0,012 in cases and R=0,282, p=0,032 in controls). In GHD pregnancies, a significant negative correlation was present between snoring and ACI (R=-0,648, p=0,004) (Figure 8). Outlier (□) removal improved this correlation (R=-0,688, p=0,002), but removal of the other outlier (◇) resulted in an even stronger negative correlation (R=-0,771, p<0,001). Snoring and VI were also negatively correlated (R=-0,502, p=0,034) in GHD pregnancies (Figure 9). This correlation improved too after outlier (□) removal (R=-0,527, p=0,030), but removal of the other outlier (◇) resulted in a stronger correlation (R=-0,589, p=0,013). In controls, these parameters did not correlate. Flow limitation was not correlated with the systolic blood pressure (R=0,131, p=0,605 in cases and R=-0,073, p=0,612 in controls), BMI at inclusion (R=0,223, p=0,374 in cases and R=0,110, p=0,411 in controls), or gestational weight gain (R=-0,374, p=0,126 in cases and R=0,077, p=0,567 in controls). None of the other cardiovascular parameters were associated with an increased prevalence of snoring. Moreover, AAI was not associated with dysfunctional cardiovascular parameters. Finally, TFC in standing position could not be correlated with obstructive events, including AHI (R=0,049, p=0,848 in cases and R=0,068, p=0,637 in controls), snoring (R=-0,088, p=0,729 in cases and R=0,259, p=0,066 in controls) and flow limitation (R=0,107, p=0,671 in cases and R=0,215, p=0,129 in controls). Correlations between TFC in supine position and AHI, snoring or flow limitations were also absent.

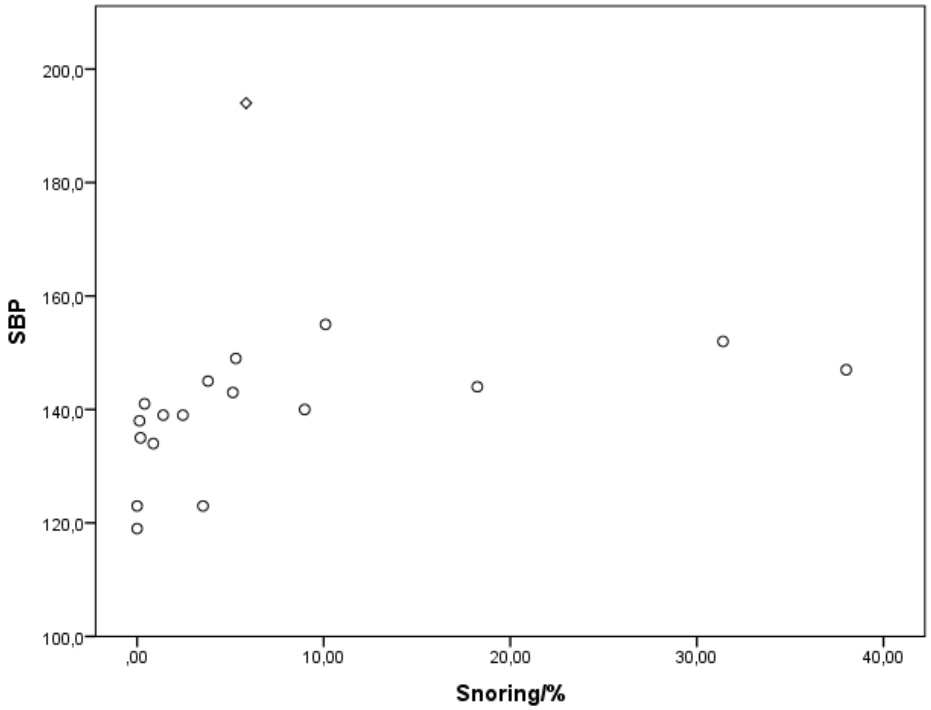

Figure 7 Scatterplot of snoring versus systolic blood pressure in pregnancies complicated with GHD. The outlier is presented as ◇.

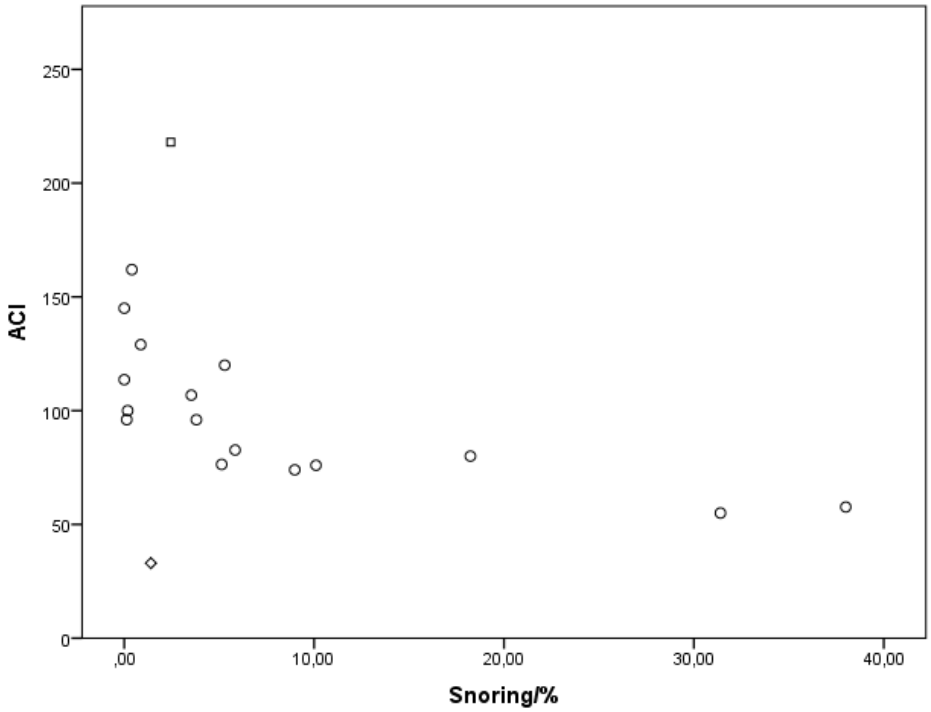

Figure 8 Scatterplot of snoring versus ACI in pregnancies complicated with GHD. The outliers are presented as ◇ and □.

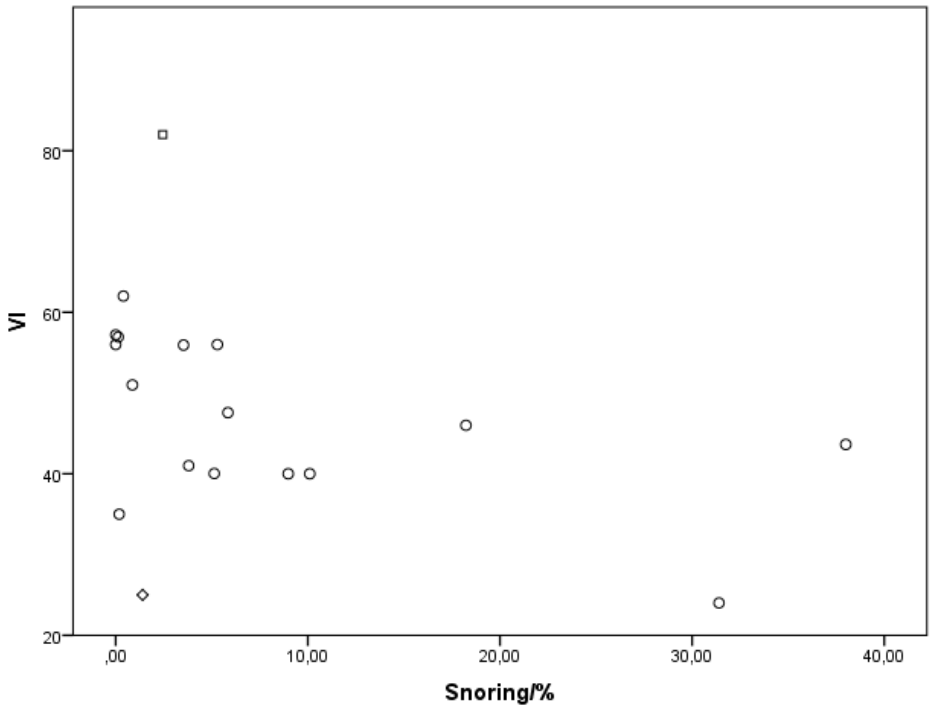

Figure 9 Scatterplot of snoring versus VI in pregnancies complicated with GHD. The outliers are presented as ◇ and □.

3.8 Questionnaire

A total of 73 patients completed a questionnaire to subjectively evaluate the sleep behavior during the night of recording. 59 subjects accomplished a valid sleep study, while fourteen measurements failed. The mean time to fall asleep was 37 minutes, 95% of the patients woke up during the night for approximately three times. In 62% of the time the patients actually got up during the night. Pregnancy-related reasons and the SomnoCheck Micro were most frequently reported to disturb the night rest during the night of recording (Figure 10). The majority of the valid measurements scored maximum three for the sleep disturbance score. High sleep disturbance scores of 3, 4 and 5 were given by patients who failed in completing the sleep study properly (Figure 11).

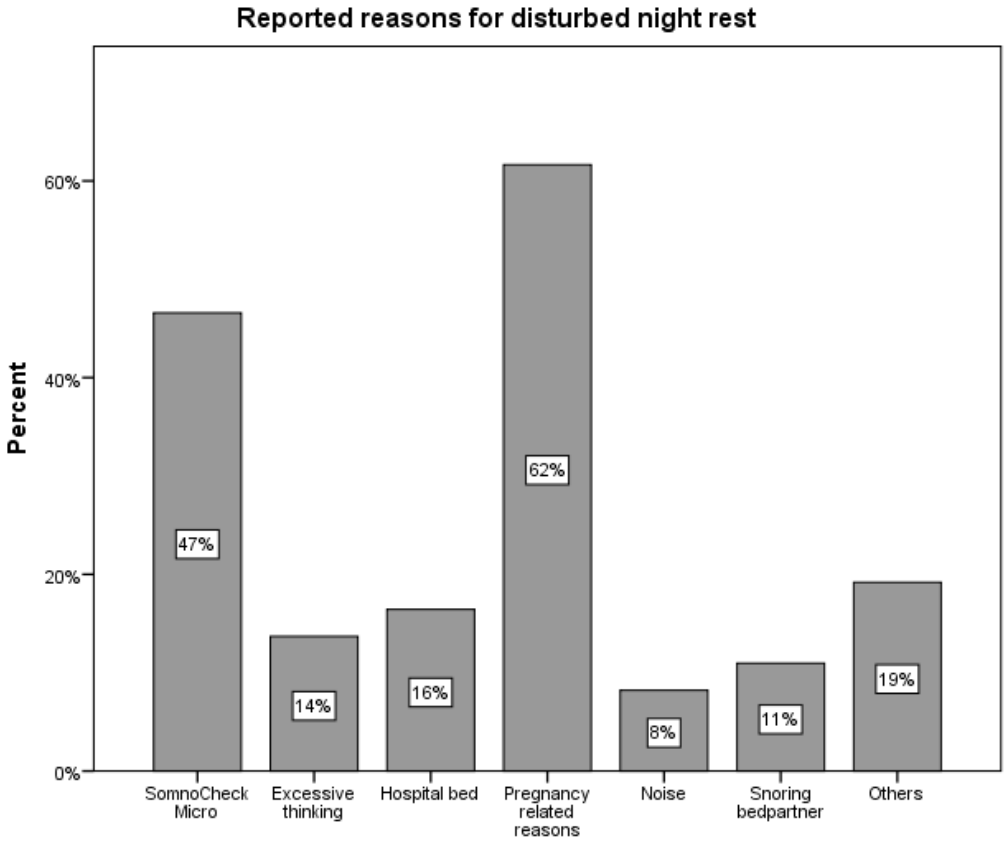

Figure 10 Percentage of pregnant women reporting various reasons for disturbed night rest

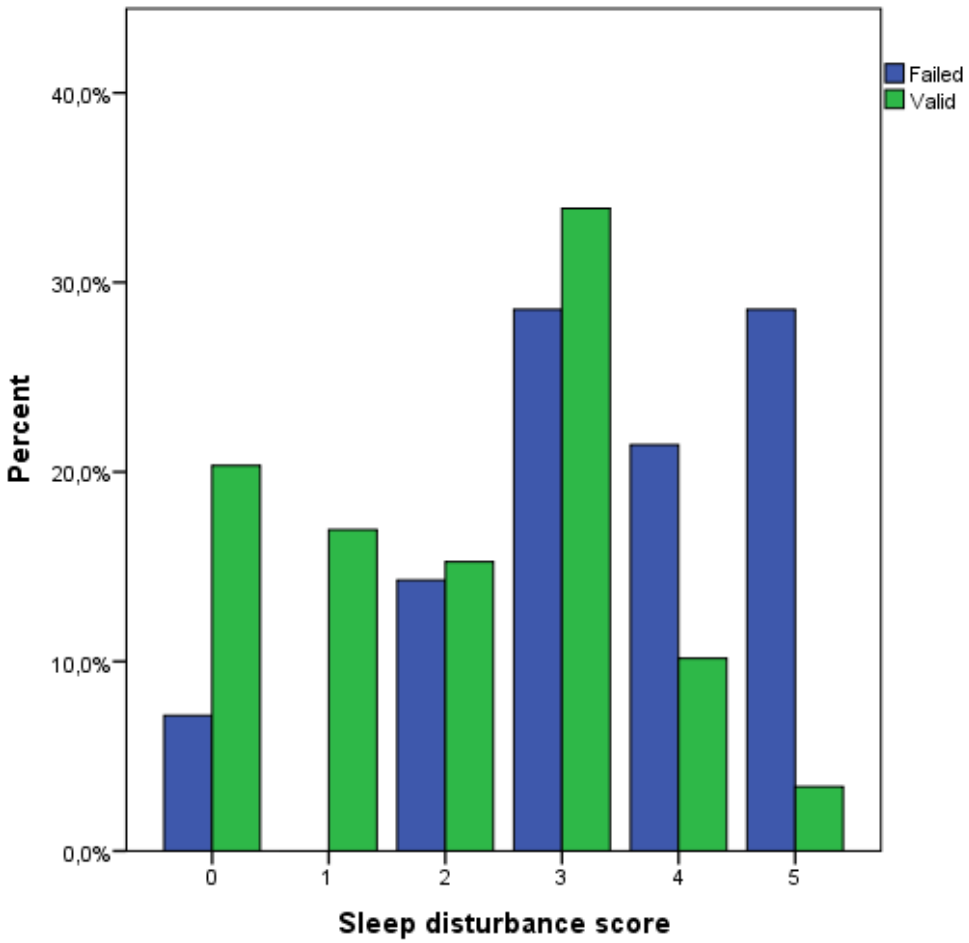

Figure 11 Percentage of pregnant women giving a sleep disturbance score of 0 (totally not disturbed) to 5 (totally disturbed) for both valid and failed measurements

4. Discussion

4.1 Quality tests/improvements of SomnoCheck Micro

4.1.1 Validation of the SomnoCheck Micro

The validation study of the SomnoCheck Micro included ten participating subjects, who slept with two devices at the same time, one with nasal cannula and PPG sensor and one with PPG sensor alone. Using only PPG, PWA and oxygen saturation were recorded. Whenever there was an oxygen desaturation, a respiratory event was scored by the Somnolab algorithm. However, it is not possible to distinguish between an apnea and a hypopnea with the PPG sensor alone. It is only possible to derive a RDI value, since an AHI value needs a flow signal. This validation study was to evaluate the accordance of a RDI value with the corresponding AHI value, since the nasal cannula encounters some discomforts: irritating, difficulties falling asleep, disturbed night rest. Moreover, a common reported reason why patients refused to participate in the study was the nasal cannula.

Cardiorespiratory sleep pattern analysis of the participating patients showed that a higher number of sleep-related respiratory events were detected in the presence of airflow than when the nasal cannula was removed. In the absence of nasal cannula, there was an underestimation of the true respiratory events. The reported differences confirm that measurements with or without nasal cannula has not the same sensitivity. From our data, it can be concluded that the nasal cannula is an essential part of the SomnoCheck Micro in order to collect the most proper data. However, as reported previously, another limited-channel diagnostic sleep device, i.e. the Watch_PAT100 does not make use of a nasal cannula to record patients' cardiorespiratory sleep pattern. Instead, beside oxygen saturation, other signals including PAT and actigraphy are recorded and contribute to the SDB risk determination. Similar to the PPG signals of the SomnoCheck Micro, PAT signals of the Watch_PAT100 reflect the pulsatile volume changes in the arteries in the finger. Respiratory events are indirectly detected based on the combination of PAT amplitude reduction and oxygen desaturation, pulse rate increase or wrist activity increase. PAT amplitude reduction occurs as response to an arousal and sympathetic activation, initiated by a respiratory event. Using actigraphy, a differentiation between wake and sleep is made based on the wrist activity and RDI is calculated based on the number of respiratory events in the PAT valid sleep time (27, 60). The actigraphy would have an additive value to the SomnoCheck Micro, since one of the limitations of the SomnoCheck Micro is the respiratory event detection during the entire recording night, independent of sleep or wakefulness. This would lead to an improvement of the reliability of the SDB diagnosis.

In all cases, manually scored AHI values were higher compared to automatically calculated AHI values. This variability might again be due to the underestimation of the Somnolab algorithm.

This validation study suggests that using isolated PPG signals with the SomnoCheck Micro device is not sufficient to make a good estimate of SDB severity. Cardiorespiratory sleep pattern analysis with this device should be performed with a combination of PPG signals and nasal cannula. Next to this, AHI values should be assessed manually since the Somnolab algorithm in the device is subject to under-interpretation.

4.1.2 Effect of training on respiratory event scoring

During a short internship at the sleep laboratory campus Sint-Barbara in Lanaken, all aspects of a polysomnography were illustrated. An essential part of the internship was learning the correct interpretation of the polysomnographic data. Similarly to the SomnoCheck Micro, the polysomnographic data were analyzed by an automatic algorithm and the automatically calculated respiratory events were manually revised by experienced sleep technicians. In contrast to the SomnoCheck Micro, the manually scored AHI value is generally not very different from the automatically calculated AHI value in polysomnography. However, in both SomnoCheck Micro and polysomnography, manual overview is recommended in order to make the diagnosis of sleep disorders as accurately as possible. Respiratory event scoring was performed according to the AASM standards and training was focused on using these standards properly. Beside airflow signals and oxygen saturation, many other signals are obtained from a polysomnography to evaluate the cardiorespiratory events during sleep. However, the data obtained from the SomnoCheck Micro is an abbreviated version of the polysomnograhy, which only records airflow, oxygen saturation and heart rate during sleep. These parameters are needed for registration of abnormal respiratory events. After training and practicing of manually scoring of AHI, a lower number of respiratory events were identified than before training. This was probably due to the incorrect use of the AASM standards.

4.1.3 Inter- and intrascorer correlation coefficient

Since scoring of respiratory events is subjective, the reliability of scoring by two researchers (JH and KD) was evaluated. Both researchers scored independently according to the AASM standards. The interscorer correlation coefficient was calculated, based on the manually calculated AHI values. A moderate interscorer correlation coefficient was obtained. The difference in scoring can be due to the fact that only one researcher (KD) followed an internship at a sleep laboratory to train the scoring of respiratory events, while the other researcher (JH) obtained scoring skills by practicing. Since the intrascorer correlation coefficient is high, it can be stated that the reliability of manual respiratory event scoring can improve by training. Training before data analysis of the SomnoCheck Micro is favorable for the interpretation, but it remains subjective.

4.2 Sleep fragmentation

In patients with OSAS, arousal from sleep is a common phenomena and serves to restore airflow after an obstructive event, which is an important survival reflex. These respiratory-related arousals cause shifts from deeper to lighter sleep stages. Recurrent arousals from sleep cause sleep fragmentation, which contributes to daytime sleepiness (61). Arousals are physiologically characterized by sudden shifts in the central nervous system activity, resulting in EEG activation and alternations in autonomic nervous system variables, including pulse rate, blood pressure, peripheral vascular resistance and ventilation (50). In polysomnography, arousals are scored during NREM stages of sleep when there is shift in EEG to a higher frequency lasting for at least three seconds. Arousal scoring during REM sleep requires a combination of an EEG shift and an increased EMG for at least one second. This arousal definition is in accordance with the AASM criteria (54). However, arousal detection by the SomnoCheck Micro differs from polysomnography. Here, autonomic arousals are detected, based on transient changes in autonomic parameters during sleep (50). In response to changes in pulse rate and PWA, measured by PPG, autonomic arousals are scored. Furthermore, in the SomnoCheck Micro a differentiation is made between respiratory-related arousals and non-respiratory-related arousals (spontaneous arousals). The spontaneous arousals were higher in all subjects than the arousals caused by a respiratory event. This could be due to the high number of pregnancy-related events, including urge to urinate and general physical discomfort, and the small number of apneas and hypopneas, according to the definition of SDB (AHI≥5), causing an arousal from sleep. Moreover, the overall high AAI in our pregnant population can also be attributed to the SomnoCheck Micro, causing more sleep fragmentation compared to non-recording nights. Similar AAI values were obtained in the study of Bourjeily et al. in both pregnant (20,1 ± 13,2 events/h) and non-pregnant subjects (20,0 ± 9,5 events/h) suspected of SDB (62). However, AHIs (5,2 ± 7,7 events/h in pregnant subjects and 9,1 ± 19,1 events/h) were higher compared to our study population, which probably results in more respiratory-related arousals. Compared to the AAIs in the present study, lower AAIs were measured in the studies of Reid et al. (10,3 ± 6,9 events/h) (63), Maasilta et al. (14,6 ± 1,0 events/h) (64), Wilson et al. (14,6 (10,7;18,9) events/h) (65) and Reid et al. (11,1 ± 7,0 events/h) (39) in third-trimester normotensive pregnancies. In these studies AAIs were measured using polysomnography. Furthermore, AAIs were reported to be lowest in non-pregnant state (8,8 (7,2;10,9) events/h (65), 5,6 ± 4,7 events/h (63) and increased from early (10,3 ± 0,8 events/h (64), 10,6 (7,6;15,8) events/h (65) to third-trimester pregnancy. In contrast to other studies, reporting higher AAIs in pregnancies complicated with GH (39, 63) and PE (66) compared to healthy subjects, lower AAIs were measured in cases compared to controls in the present study. This finding is in contrast to what we expected, which can be due to the difference in arousal detection or the difference in sample size. Since PE and GH are associated with sympathetic overactivity, superimposed on the already increased activity of the sympathetic nervous system, characteristic for normal pregnancy (67, 68), higher AAIs were expected to be present in this group of patients. The sympathetic overactivity partly explains the increased peripheral vascular tone, which is mediated by the sympathicus, in preeclamptic pregnancies (67). Similarly, in the non-pregnant population, both patients with hypertension and OSAS have higher AAIs compared to healthy controls due to increased sympathetic activity (69).

4.3 SDB and maternal outcome

Several SDB events, including apneas, hypopneas, oxygen desaturation, snoring and airflow limitations were evaluated using the SomnoCheck Micro in both normotensive pregnancies and pregnancies complicated with GHD.

4.3.1 Obstructive sleep apnea and oxygen desaturation

Our case group had AHIs far below the values presented by Yinon et al. (AHI 18,4 ± 8,4 events/h) and Champagne et al. (AHI 38,6 ± 36,7 events/h) (70). This might be due to the use of a different technology (SomnoCheck Micro vs. Watch_PAT100 and polysomnography), resulting in a difference in sensitivity. The measured AHIs in our pregnant case population were within normal range according to the definition of SDB (AHI ≥ 5). However, ten patients, six in the case group (33%) and four (7%) in the control group, had AHIs of more than 5. This indicates that overall higher AHIs were measured in cases compared to controls, but no significant difference was reached. This finding is consistent with the study of Facco et al., who used the Watch_PAT100 to measure RDI (71). In contrast, higher rates of SDB events among women with GH/PE compared to normotensive pregnant controls were reported by four case-control studies (38, 39, 70, 72). These reports demonstrated a strong relation between SDB and GHD. This relation is reported to be biologically plausible since, as described previously, SDB is known to predispose to hypertension in the non-pregnant population (5). Endothelial dysfunction, oxidative stress and inflammation are increased in both patients with SDB (73) or PE (74), but the underlying cause is different. In patients with SDB, these mechanisms take place in response to intermittent drops in maternal oxygen saturation caused by frequent apneas and hypopneas. In PE, endothelial dysfunction, oxidative stress and inflammation occur as a maternal response to maladapted spiral arterioles, caused by failed invasion of trophoblast cells (75). However, as mentioned before, AHIs were within normal range and therefore the oxygen saturation level remained stable during the night of recording. ODI, mean and lowest oxygen saturation were not significantly different between cases and controls. Similar results have been demonstrated by Reid et al. (39), Champagne et al. (38) and Bachour et al. (72), suggesting that oxygen saturation may not have a key role in adverse pregnancy outcomes. Contrary to oxygen saturation, other SDB events such as flow-limited breaths, snoring, arousals or poor sleep potentially have already proved adverse effects on the pregnancy outcome, such as GHDs (62).

4.3.2 Snoring

Pregnancy is associated with increased frequency of snoring due to a combination of pregnancy-induced changes, including weight gain, FRC decrease and estrogen-induced nasopharyngeal edema (19-23). Snoring has been reported to be significantly more prevalent in patients with PE and GH compared to normotensive pregnant controls by several studies (19, 20, 23, 24, 72) including our current study. However, the presence/absence of snoring was subjectively evaluated in these studies using questionnaires, including a five-point (19, 20, 24, 72) or four-point (23) Likert scale for snoring. The frequency of snoring before and during pregnancy was evaluated by a Likert scale ranging from zero (never) to four or five (every night). Other questions about snoring included the loudness of snoring, changes in snoring frequency in pregnancy (24, 72) and the beginning of snoring (24). This is in contrast with the objective recording using nasal cannula in the present study. The disadvantage of one-night recording is the possible underestimation of snoring, especially when the patients' sleep is disturbed by the sleep device, the hospital environment or when the nasal cannula releases slightly during the night of recording. In contrast, using sleep questionnaires an average of the degree of snoring is given. Moreover, questionnaires are easy accessible and applicable in contrast to sleep devices. For these reasons subjective surveys are most commonly used for the evaluation of snoring. The reason why patients with PE and GH significantly snore more than controls might be due to tissue edema, which is a clinical feature of PE. Tissue edema in the upper airways results in airway narrowing, thereby contributing to obstructive events during sleep (20, 36, 44, 72). As result of this tissue edema, preeclamptic patients have larger neck circumferences compared to healthy pregnant and non-pregnant controls. Moreover, weight gain during pregnancy can increase the neck circumference due to fat deposition around the upper airways. Excessive weight gain also causes a higher prevalence of GH and PE in obese pregnant women for this reason. (23, 36).

4.3.3 Flow limitation

Other obstructive events, including sleep-induced upper airflow limitations, were present in the majority of the pregnant patients in the current study. However, patients with GH with or without proteinuria did not present significantly more flow-limited breaths. This finding is in contrast with results obtained from the studies of Connolly et al. (76), Bachour et al. (72), Bourjeily et al. (62) and Edwards et al. (44) They all showed significantly more airflow limitations in preeclamptic or gestational hypertensive patients than in normal pregnant controls. The difference between our findings and those of the aforementioned studies could be due to the difference in the used device and the difference in the airflow limitation definition/detection. Both Connolly et al. and Bachour et al. derived the flattening index from the ratio inspiratory flow/inspiratory duration, using an Autoset portable device (72, 76). The threshold for significant flow limitation was a flattening index of <0,15. Bourjeily et al. evaluated the nocturnal nasal airflow by polysomnography and used two different methods for the identification of airflow limitations (62). Method 1 was based on the reduction in airflow amplitude, while method 2 included visual evaluation of the nasal airflow shape. This latter method has also been performed by Edwards et al. (44), which was based on the random selection of ten samples of thirty seconds for each of the four sleep stages (N1, N2, N3 and REM). In each of the samples, the percentage of flow-limited breaths, defined as the ratio flow-limited breath number/total breath number, was calculated. These studies, including ours, have in common that the airflow was measured with a nasal cannula. However, the gold standard technology for the detection of airflow limitations is the esophageal pressure measurement, which is an invasive technique. This method requires introduction of a pressure-tiped catheter into the pharynx and airflow limitations are identified when the pressure in the pharynx drops with at least one cm H_2O without a simultaneous airflow increase. Another method, which is less invasive, includes the measurement of flow rate by a nasal mask to which a pneumotach and a pressure transducer is connected, allowing the identification of flow-limited breaths (77). The disadvantage of measuring the nasal airflow solely, like the latter techniques, is that it can be influenced by mouth breathing. When the patient is mouth breathing during sleep, nasal airflow reduces consequently, which can be mistaken for inspiratory flow limitation. However, the differentiation between nasal and mouth breathing can usually be identified by experienced sleep technicians (62).

None of the studies about airflow limitations in pregnant women could give a definite reason why preeclamptic women have more airflow limitations than pregnant controls. However, two possible mechanisms have been proposed. Firstly, preeclamptic patients are reported to spent more time in deep NREM or slow wave sleep, during which more airflow limitations occur (66, 76). Secondly, as mentioned before, nasopharyngeal edema potentially induces airflow limitation due to upper airway narrowing (44, 72, 76).

4.4 Combined ECG-Doppler ultrasonography

During normal pregnancy, many cardiovascular adaptations take place, both at the level of the arteries and the veins. PE and GH are however the result of maladaptation to this hemodynamic process. The vascular tone is measurable with ECG-Doppler ultrasonography, including the venous and arterial abnormalities. The impedance index of the renal interlobar vein has been shown to reflect intrarenal venous vascular function in a reliable and reproducible manner (78, 79). The gradual decrease in RIVI, associated with uncomplicated pregnancy, is the consequence of both overall decreases in maximum and minimum flow velocity. On one hand, the improved renal perfusion and a resultant decrease in total peripheral vascular resistance cause the maximum flow velocity to fall. On the other hand, the minimum flow velocity decrease reflects the change in glomerular filtration rate and effective renal plasma flow. In contrast to normal pregnancy, both flow velocities are lower in PE, resulting in an overall RIVI increase, as confirmed by our results. This can be explained by the impaired glomerular filtration and the impeded venous drainage from the kidneys due to vascular abnormalities (78, 79). In both patients with or without PE, the VI was higher in the left kidney than in the right, due to the smaller pyelocalyceal diameter of the left kidney. This inter-kidney difference has been reported to be only present in the third trimester of pregnancy, since the compressive effect of the uterus on the renal venous vascularisation is more pronounced at this stage of pregnancy (80).

The effects of the reduced peripheral vascular resistance and increased blood volume are also measurable in the liver as flattening of the hepatic vein waveform, resulting in the reduction of HVI. Normal pregnancy progression is associated with the gradual disappearance of a so called venous preacceleration nadir (VPAN), which is characterized by the backflow of venous blood from the right atrium into the veins upon atrial contraction. The presence/absence of this mechanism is expressed as the presence/absence of an A-wave in the hepatic vein Doppler waveform. In preeclamptic pregnancies, this VPAN mechanism is still present, resulting in higher HVI compared to uncomplicated pregnancies, as confirmed by our results (81, 82).

Furthermore, the RI and PI of left and right uterine arteries were significantly higher in PE compared to normotensive pregnancies, except for the PI of the left uterine artery. This is due to the high uteroplacental vascular resistance, which is a well known characteristic of PE.

The PTT is a measure for the vascular reactivity, affected by the autonomic nervous system. A gradual increase in PTT reflects the gradual decrease in total peripheral resistance, associated with uncomplicated pregnancy. This reduction in arterial/venous wall stiffness is absent in PE, resulting in significantly lower PTTs at the level of left and right interlobar veins, hepatic veins, left and right arcuate arteries of the uterus (55). This process is in accordance with our results, aside the hepatic VPTT results. A probable explanation of the absent significance is the small sample size.

4.5 Impedance cardiography

ICG was used in parallel with ECG-Doppler ultrasonography to non-invasively evaluate the adaptation process in uncomplicated pregnancies and pregnancies complicated with GHD. Uncomplicated pregnancies were seen to be characterized with a decrease in systemic vascular resistance and plasma volume, which was absent in GHD pregnancies. This maladaptation results in a lower cardiac output. The increased vascular resistance is probably due to the endothelial dysfunction which functions as a regulator of the vascular tone, maintains the integrity of the blood vessels and prevents platelet adhesion (83). High vascular tone results in high blood pressures, which is the hallmark of PE and GH. Endothelial dysfunction is probably due to an increased inflammatory reaction. This results in an enhanced permeability of the capillary endothelial cells, leading to a reduction in intravascular volume and tissue edema. This explains the significantly higher TFC in GHD pregnancies (75).

Other cardiovascular impairments, associated with GHD, include the low VI, ACI and HI. These aortic flow parameters are related to the systolic function of the heart and the compliance of the aorta. Therefore, low VI, ACI and HI in pregnancies complicated with GHD implicate a cardiac systolic dysfunction and a low aortic compliance (58).

4.6 Relation between sleep and cardiovascular parameters

In this study, a significant association between snoring and a high systolic blood pressure in GHD pregnancies was demonstrated. This finding is consistent with other studies (20, 23, 37, 84, 85). However, in a recent study of Sarberg et al. no such association was found (86). It has been reported that a bidirectional interaction between snoring and GHD exists (39). As mentioned previously, both obesity and upper airway edema are common characteristics of GHD, leading to smaller upper airways and larger neck circumferences. GHD-mediated edema results in increased resistance to airflow, which is manifested as snoring and airflow limitations. Snoring and frequent partial upper airway obstruction can than further augment the already increased blood pressure in patients with GHD, due to an increased response of the sympathetic nervous system (36, 39, 44, 62). The potential exacerbating effect of snoring on the blood pressure has also been described by Franklin et al. (20). In his study, all habitually snoring subjects with PE started to snore before the presence of any clinical sign of hypertension or proteinuria. Since both GH and PE are complex disorders, which are until now not completely understood, snoring is not the sole cause of GHD.

Airflow limitations, belonging to the category of obstructive events, was however not significantly correlated with the systolic blood pressure in our case group. In contrast with our data, Edwards et al. recorded nocturnal blood pressure, beside snoring and airflow limitation, in women with PE and demonstrated that blood pressure increments were associated with obstructive events. The reason for this association is suggested to be result of the combination of an increase in CO_2, as a consequence of obstruction, and the increased peripheral vascular reactivity, leading to a high nocturnal blood pressure. Subsequent treatment with auto-CPAP reversed these upper airway obstructions and significantly reduced the associated blood pressure increments (44). However, as reported by Guilleminault et al., the underlying cause of PE and GH cannot be treated with CPAP, since early CPAP intervention in pregnant patients with risk factors for PE could not prevent the development of PE (46).

Further was snoring moderately correlated with both BMI at inclusion and total weight gain until measurement. More weight gain and a higher BMI during pregnancy increase the prevalence of snoring due to fat deposits around the upper airways, which induce a narrowing effect. All these parameters are also known important risk factors for adverse pregnancy outcomes, including GH and PE (23).

Furthermore, snoring was negatively correlated with ACI and VI. Both ACI and VI were significantly lower in patients with GH and PE. Other cardiovascular parameters such as CI, HI, RIVI, PTT, PI and RI were significantly different between cases and controls, but no correlation with snoring could be demonstrated. Snoring may contribute to the cardiovascular stiffness seen in patients with GH and PE (24). However, the causal relationship could not be completely proved in the present study, only NICCOMO parameters did show this relation. This could be explained by the sensitivity of the two techniques, by which we assume here that NICCOMO is more sensitive towards detecting blood vessel stiffness. Limited research has been done about the association between SDB and cardiovascular disease in the pregnant population. In the study of Yinon et al., both preeclamptic patients and uncomplicated normal pregnant women underwent a SDB evaluation, using Watch_PAT100, and an endothelial function testing, using the Endo_PAT device (70). A trend towards a negative correlation between respiratory abnormalities, i.e. RDI, and endothelial

dysfunction was demonstrated (R=-0,28, p<0,1). They speculated that respiratory abnormalities contribute to the functional abnormality of the blood vessels, which is characteristic for PE. However, using RDI, instead of AHI, can lead to an under-interpretation of the result. Conflicting results about the association between snoring and cardiovascular disease, in the non-pregnant population have been reported (87-89). Snoring is a marker of OSAS, but snores do not always have OSAS. Therefore, it is unknown whether snoring is a contributing factor for cardiovascular disease or whether the association is due to OSAS (90). Patients with OSAS have also been shown to exhibit increased aortic stiffness, decreased aortic distensibility and a mild decrease in both left ventricular systolic and diastolic function. It has been suggested that the reduced elastic properties of the aorta affect left ventricular function (91, 92). Sympathetic overactivity, oxidative stress and endothelial dysfunction, characteristic for both patients with OSAS and GHD, might be responsible for the arterial stiffness (high RIVI, PI and RI) and the left ventricular dysfunction (low ACI and VI) seen in our patients.

In the non-pregnant population, daytime sleepiness has also been associated with an increased risk of impaired cardiac function (89, 93). Frequent arousals from sleep contribute to daytime sleepiness and an increased sympathetic tone, affecting cardiac function (93). However, no association between the AAI and cardiovascular parameters could be demonstrated in the present study.

TFC did not correlate with obstructive events, including AHI, snoring and flow limitation, which is in contrast to what we expected. Diseases with excessive fluid retention, including heart failure and PE, contribute to the pathogenesis of OSAS. During daytime, the excessive fluid accumulates in lower extremities due to gravity. During the night, the fluid redistributes towards the thorax, thereby contributing to upper airway narrowing and increasing the risk of obstructive events (94).

4.7 Questionnaire

With the sleep questionnaire, we aimed to subjectively evaluate the night of recording in order to evaluate the extent of night rest disturbance due to the SomnoCheck Micro. The average time to fall asleep in our study population was 37 minutes, which is analogous with the data of Mindell et al. (95). In the questionnaire-based study of Mindell et al. (95), the mean time to sleep onset was 23,29 minutes in 25 to 28 weeks pregnant women and 39,72 minutes in 35 to 38 weeks pregnant women. Those data conclude that sleep behavior during pregnancy depends on the amount of pregnancy weeks. Almost all the third-trimester patients (95%) in our study awakened at night with an average of three times. This is in congruency with the study of Mindell et al., where 25-28 weeks and 35-38 weeks pregnant patients woke up 2,60 and 3,11 times, respectively (95). Moreover, as reported by Hutchison et al. (16), mean nocturnal waking progressively increases in the course of pregnancy, ranging from 2,1 wakings between week 28-32 to 3,4 wakings at or past 38 weeks. Similar results have been described by Hedman et al. (96) Since the time to fall asleep and the number of night awakenings is similarly to the ones obtained from the aforementioned sleep questionnaire-based studies, it can be stated that both parameters are not really affected by the SomnoCheck Micro. However, we need to add that questionnaire data of the present study is only based on a one night sleep, and no comparison with other nights was made. There is no information about the general sleep behavior. Two third of the patients got up during the night due to the urge to urinate, which is caused by the compression of the enlarged uterus on the bladder. The pregnancy-related problems were the most reported reasons for the disturbed night rest (62%). This is analogous with results from other sleep questionnaire-based studies (16, 95, 96). For example, more awakenings due to general physical discomfort, which worsens with pregnancy progression, results in a decline in maternal sleep quality. Although the SomnoCheck Micro is a limited-channel diagnostic sleep device, the corresponding nasal cannula was the second most reported reason for sleep disturbance. Other reasons, including excessive thinking, hospital bed, noise, snoring bedpartner, were less commonly reported. Patients who could not complete the overnight evaluation with the SomnoCheck Micro reported high sleep disturbance scores. This means that the SomnoCheck Micro, and more specifically the nasal cannula, was generally not well tolerated by these patients, resulting in early removal of the device during the night of recording. However, another reason for an invalid measurements was abrupt start of labor or illness, which was independent of the sleep device. The majority of the patients scored moderate on the disturbance question, whereby it can be stated that the SomnoCheck Micro has no extreme disturbance influence on the night rest of the patient. Even a moderate disturbance of sleep, caused by the SomnoCheck Micro, can lead to an underestimation of the respiratory events including snoring, flow limitation and apneas/hyponeas during sleep. Moreover, the number of autonomic arousals were possibly higher, compared to the nights when sleep is not recorded.

The sleep questionnaire has several limitations. First, the questionnaire was only based on a subjective evaluation of the night of recording. Secondly, no questions about the general sleep behavior of the patient or the change in sleep in the course of pregnancy were included. Moreover, the questionnaire has not been validated and included a limited number of questions. Until now there is no validated questionnaire for sleep disorders in pregnancy.

4.8 Strengths and limitations

Several limitations were faced in the course of the study. Instead of the gold standard technology, i.e. the polysomnography, an abbreviated version, i.e. the SomnoCheck Micro was used for the cardiorespiratory sleep pattern analysis in pregnancy. In contrast to the polysomnography, the SomnoCheck Micro is more ergonomic, not expensive, can be performed in home environment and the patients are able to apply the device themselves before bedtime after proper instruction. Unfortunately, in contrast to other limited-channel diagnostic sleep devices, including Watch_PAT100, the SomnoCheck Micro has not been validated against the gold standard polysomnography. Compared to the polysomnography, the SomnoCheck Micro has several limitations. First of all, the SomnoCheck Micro cannot differentiate between the different sleep stages (NREM vs. REM). Consequently, events are scored throughout the night, independently of the sleep stage. Moreover, it is not possible to know if the patient is awake or asleep with the SomnoCheck Micro. Therefore a questionnaire was completed to evaluate the sleep behavior of the according night. Still, it remains subjective and many patients had difficulties in answering the questions properly. Based on presence/absence of thoracic and abdominal movements, a distinction is made between central and obstructive apneas in polysomnography. However, using the SomnoCheck Micro, this distinction is based on fluctuations in the peripheral pulse wave by the PPG sensor. A constant PWA signal corresponds to an obstructive event, while a central event is classified when the PWA signal is reduced. In contrast to the SomnoCheck Micro, the polysomnography only classifies apneas and not hypopneas as obstructive or central. While additional information about leg movements, cardiac rhythm abnormalities and body position during sleep can be obtained from polysomnographic data, the SomnoCheck Micro is only able to analyze breathing irregularities. Based on limited data from nasal cannula and PPG sensor, cardiorespiratory events during sleep are measured. In contrast to the Watch_PAT100, the SomnoCheck Micro is able to record flow limitation and snoring. The objective evaluation of breathing abnormalities can be classified as a strength of this study, since many studies about sleep in pregnancy are based on subjective evaluation of sleep by questionnaires.

Compared to the number of subjects in the control group, the case group was too small. This was due to the small number of patients with GHD admitted at the Maternal Intensive Care in the course of the senior project. Moreover, difficulties in motivating the patients to participate in the study were encountered due to the unfavorable clinical and mental condition of the patients. Patients with a mild or severe type of PE were frequently delivered short after hospitalization and therefore these patients were not able to participate in the study. Other limitations of this study include the lack of data about the sleep pattern and the cardiovascular profile before, after and across the different trimesters of pregnancy. Moreover, the results, presented here, were based on the evaluation of sleep during one night recording. Performing several follow-up recordings can improve the reliability of the SDB diagnosis. Furthermore, since high neck circumference is reported to be a risk factor for snoring and SDB (23), this measurement should have been included.

5. Conclusion

In conclusion, this study suggests that the SomnoCheck Micro is a useful and simple diagnostic device for the evaluation of cardiorespiratory events during sleep. It was demonstrated from the validation study that information from finger PPG alone is not sufficient to make a good estimate of SDB severity. Rather, cardiorespiratory sleep pattern analysis should be performed with a combination of both nasal cannula and PPG sensor. Furthermore, respiratory events should be manually scored due to under-interpretation of the Somnolab algorithm. Manually scoring became more reliable by practicing or by education at a sleep laboratory.

This study also confirms that sleep is fragmented in women in the third trimester of pregnancy and that this sleep fragmentation mostly originates from pregnancy-related events than from respiratory events. However, the SomnoCheck Micro and especially the nasal cannula was also reported to be a disturbing element of sleep. The cardiorespiratory sleep pattern was only different in pregnancies complicated with GHD compared to normotensive pregnancies with respect to snoring. In pregnancies complicated with GHD, snoring and systolic blood pressure were associated and a negative correlation between snoring and dysfunctional aortic flow parameters ACI and VI was demonstrated. Cardiovascular parameters, obtained from combined ECG-Doppler ultrasonography, were not correlated with an increased prevalence of snoring. From these findings, we assume that NICCOMO is more sensitive towards detecting blood vessel stiffness. Snoring was significantly associated with BMI at inclusion and there was a tendency towards an association between snoring and gestational weight gain. More fluid content in the thorax was also not associated with more obstructive events, including AHI, snoring and flow limitation.

The simplicity and high accessibility of the SomnoCheck Micro, compared to polysomnography, opens perspectives for using as screening tool for SDB. Especially, pregnant patients with GH and PE form an important group for SDB screening. Subsequently, patients with high AHIs, increased snoring and flow limitation percentages could be treated with CPAP in order to modulate these obstructive events and to improve blood pressures during the pregnancy.

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Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
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Datum: **10/06/2014**