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Using critical flicker frequency in the evaluation of visual impairment in preeclamptic women

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ABSTRACT

Objective: To assess critical flicker frequency (CFF) in normal uneventful pregnancy and preeclampsia.
Study-design: Case-control observational study at the University Hospital Jena and Outpatient Institute for Prenatal Diagnosis and Preventive Medicine. 25 non-pregnant women, 75 uncomplicated pregnant women in first, second and third trimester, and 15 women with overt preeclampsia. For comparison with preeclamptic patients we matched 15 normal pregnant women (mNP) for age, parity, body mass index, current smoking and family history of cardiovascular disease (CVD). We measured CFF using the portable HEPAtonorm Analyzer (nevoLAB GmbH, Germany). This device generates a flickering red light, starting with a frequency of 60 Hz, giving the subjective an impression of a steady light. The participant signifies once the impression of a flickering light is recognized, and this CFF is recorded. Mean CFF and standard deviation is automatically calculated. Statistical analysis was performed using SPSS Version 22 for Windows. Following assessment of normal distribution with Kolmogorov-Smirnow test, comparisons were made with univariate and multivariate ANOVA and with unpaired and paired *t* test for continuous data and with χ^2 test for categorical data.
Results: Critical flicker frequency in healthy pregnant women does not differ from nonpregnant women. No significant differences in CFF measurements exist in first, second, and third trimester. In preeclampsia, CFF is significantly decreased compared to normal pregnant women (PE 38.80 ± 2.16 vs. mNP 46.23 ± 3.37; $p = 0.000$). This alteration persists even some weeks postpartum (PE 41.17 ± 1.13 vs. mNP 46.45 ± 3.44; $p = 0.003$).
Conclusion: In preeclamptic women, CFF is decreased indicating an altered endothelial situation. The finding that CFF remains reduced postpartum may be explained by either the effect of preeclampsia on maternal endothelium causing longer lasting damage or indicate a preexisting endothelial disorder. Up to this point, precise responsible mechanisms for altered CFF in preeclampsia are currently unclear and further studies are needed.

Introduction

Preeclampsia (PE) afflicts up to 5% of all pregnancies and is a leading cause of maternal and perinatal morbidity and mortality [1,2]. The main symptoms of preeclampsia are hypertension and proteinuria, but this systemic vascular disorder can also include maternal cardiovascular changes, hepatic impairment as well as cerebral manifestations with cognitive and visual changes [3–5]. The most common visual complaints are blurred vision and visual field defects [4,6]. Due to involvement of the occipital cortex, retina or optic nerve, complete blindness may be a rare complication as well [4]. Because of the serious consequences, immediate diagnosis and evaluation is mandatory [4,7]. Recent studies described mechanisms in PE such as retinal thickening [8], retinal oedema or increased intraocular pressure [9] which may lead to the mentioned visual alterations. Nevertheless, not all mechanisms are understood and further examinations are needed to detect visual disturbances and retinal alterations in normal pregnancy and consequently preeclampsia [10–12].

Previously, we could show, that retinal vascular response under the influence of flickering light is altered in women with

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preeclampsia, indicating a commenced retinal microvascular dysfunction [13]. A completely new method arises with the assessment of critical flicker frequency (CFF), a simple and objective method to assess the visual and cognitive function [14,15]. CFF is designed for bed-side use and is reported to be impaired in patients with hypertension, hepatic encephalopathy, and ocular disorders [14,16–19]. So far, measurement of CFF has never been performed in pregnancy nor PE. One advantage of this method is, that CFF is free from educational and cultural bias and thereby can be measured without preconditions [20]. Additionally, it is very simple to perform and easy to interpret [21], can be carried out by clinical personnel, and – as it is a simple device – the running costs are limited.

The aim of this study was to examine CFF for the first time in normal and preeclamptic pregnancies. As it has never been measured before in pregnancy, we investigated CFF in non-pregnant women during menstrual cycle, as well. To explore the development of CFF throughout gestation, we examined CFF in first, second and third trimester and postpartum. We hypothesized that CFF is altered in women suffering from preeclampsia compared to uncomplicated normal pregnant women.

Materials and methods

In this prospective study 120 women were included (Fig. 1). In study part A, 80 pregnant women were recruited, five of these women developed pregnancy complications (IUGR = 3 and HELLP syndrome = 2) and had to be excluded. Finally, 75 women with uncomplicated normal pregnancies (NP) were included (25 women each in 1st, 2nd, and 3rd trimester). 25 non-pregnant women (NC) without hormonal contraceptive use were measured on the 5th day of menstrual cycle, and matched for age, BMI, nulliparity, current smoking and family history of cardiovascular disease (CVD), including family history of hypertension, stroke, and myocardial infarction.

In study part B, 15 women with clinically evident preeclampsia (PE) were recruited, measured and matched with 15 normal pregnant women (mNP) from study group A for age, week of gestation, parity, BMI, current smoking and CVD and 15 non-pregnant women matched for age, parity, BMI, current smoking and CVD. For postpartum analysis (at least 8 weeks postpartum) 8 PE women and 10 mNP women remained (PE: 4 withdrawals and 3 relocations; NP: 2 withdrawals and 3 relocations).

Measurements in PE women had been performed prior to initiation of antihypertensive treatment and none of the subjects had severe preeclampsia.

Measurements were performed between 2013 and 2015 at the Dept. of Obstetrics, University Hospital Jena and at the Prenatal Diagnosis Center Erfurt, Germany. The Ethics Committee of the University of Jena approved the study (Number 3996-01/14).

Women with multiple pregnancy, chronic hypertension, renal disease, previous gestational or gestational hypertension, pregestational or gestational diabetes mellitus, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome and overt CVD were not included. None of the subjects had any visual symptoms or known ophthalmologic diseases.

According to the guideline of the International Society for the Study of Hypertension in Pregnancy (ISSHP), preeclampsia was defined as new onset of hypertension (≥140/90 mm Hg) with proteinuria ≥300 mg/d or ≥2+ on dipstick or as severe when systolic blood pressure (BP) was ≥160 mmHg and diastolic BP ≥ 110 mmHg and when massive proteinuria occurred (≥5000 mg/24 h) [22,23]. Following 10 min time for accommodation, systolic and diastolic blood pressure were measured on both upper arms with an automatic blood pressure (BP) monitoring device. Hypertensive readings were controlled and hypertension

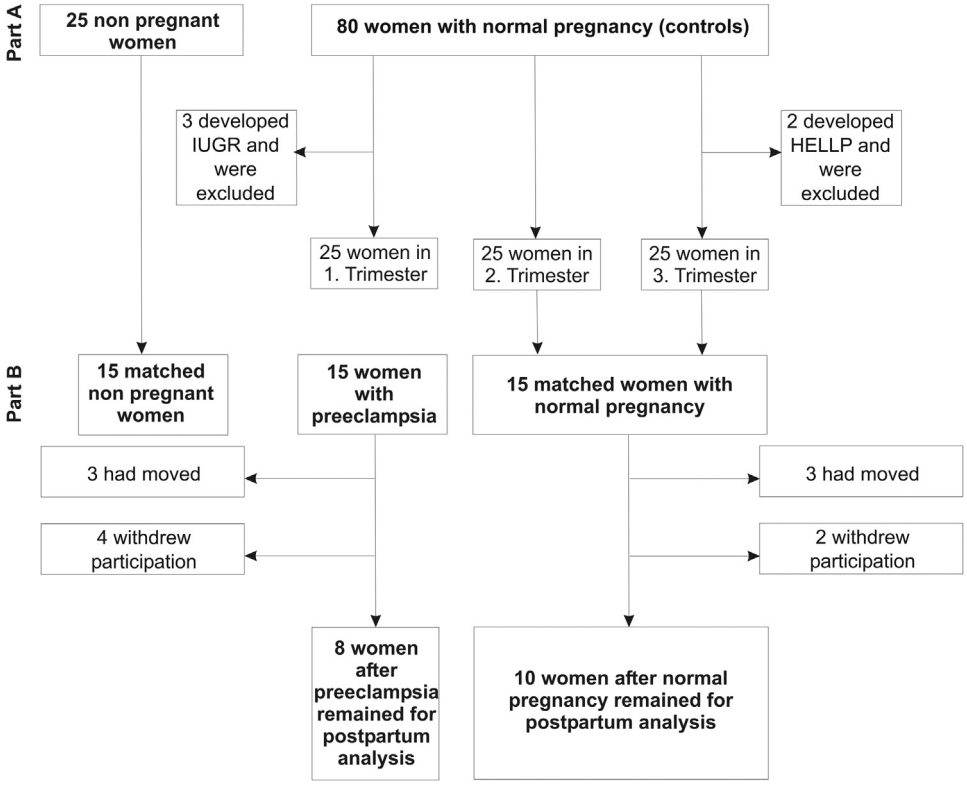

Fig. 1. Flow chart of women enrolled in this study, including 25 non-pregnant controls. Five were excluded from final analysis and 12 were lost of postpartum follow up.

confirmed in a second measurement 15 min later. Systolic BP and diastolic BP were averaged and mean arterial pressure (MAP) was calculated (MAP = [2xdiastolic BP + systolic BP]/3). Body mass index (BMI) was calculated from height and weight measurements.

CFF was measured with the validated portable HEPAtonorm™-Analyzer (nevoLAB GmbH, Germany) (Fig. 2) that comprises a remote controller, a head-mounted projection unit and a hand held micro-controller. The analyzer generates a flickering red light, starting with a frequency of 60 Hz, which gives the subjective impression of a steady light. The flicker frequency decreases then to a final frequency of 25 Hz. Once the impression of a flickering light is recognized, the participant indicates that by pressing the controller button, which thereby records the CFF. After a short briefing of 20 min, while the participants rested in a semi-dark room at normal room temperature, after 4 training recordings 8 measurements were performed. The analyzer automatically calculated mean CFF and standard deviation.

Statistical analyses

The data were analyzed using SPSS Version 22 for Windows. After assessment of normal distribution with Kolmogorov-Smirnow test, comparisons were made with univariate and multivariate ANOVA and with unpaired and paired *t* test for continuous data and with χ^2 test for categorical data between non-pregnant control women and uncomplicated pregnant women in each trimester, between PE, mNP, and NC, and between pregnancy and postpartum.

ANOVA analysis includes Bonferroni post hoc analysis for multiple comparisons. Adjustments in univariate and multivariate ANOVA were made for age and MAP, due to its known influence on CFF [16,24]. Data are expressed as mean (SD).

Results

Comparing the NP group in study part A, there were no differences between normal pregnant women at first, second and third trimester with respect to birth weight, birth centile, gestation at delivery, caesarean delivery, and MAP at measurement (Table 1). There was also no difference in MAP between non-pregnant women and healthy pregnant women in first, second and third trimester. No significant difference between CFF measurements in normal pregnancy (at each trimester) and non-pregnant women could be found, indicating that CFF is not altered by or throughout pregnancy (Table 4). There were no significant associations between CFF and age, smoking, BMI, MAP or family history of CVD in bivariate correlation analysis.

Preeclamptic women had children with lower birth weights and birth centiles, had to be delivered earlier and more often by caesarean section compared to the matched pregnant women. As by definition, a significant difference in blood pressure values could be found between normal pregnant women and women suffering from preeclampsia (Table 2). In addition, there was a significant difference between non-pregnant and preeclamptic women in mean arterial blood pressure (Table 1). Critical flicker frequency was significantly lower in PE compared to non-pregnant women and women with uncomplicated pregnancies (Table 4).

Postpartum analysis (PE: 15 ± 4 weeks; NP 20 ± 2 weeks): differences in blood pressure readings were no longer measurable between pregnant groups. In PE blood pressure readings dropped to normal values (Table 3). In PE women CFF seems to "recover" postpartal, but was still diminished in patients having suffered from preeclampsia compared to women with normal pregnancy and also to non-pregnant women (Table 4).

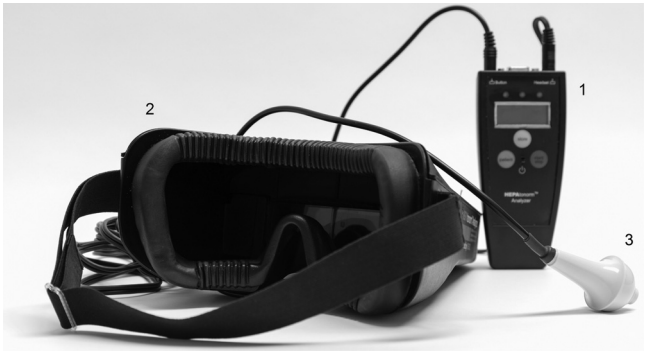

Fig. 2. HEPAtonorm Analyzer: 1 = remote control; 2 = head-mounted projection; 3 = button for the patient.

Comment

Our results show that CFF in healthy pregnant women differs not from non-pregnant women. In women suffering from PE, CFF was found to be significantly decreased compared to normal pregnant women. This alteration persists even some weeks postpartum.

The assessment of CFF is a very simple, fast and objective method to investigate the visual and cognitive function. The HEPAtonorm Analyzer is portable, adapted for a bedside use, the costs are limited and the measurement is easy to interpret. This is in contrast to the flicker analysis of our previous study, where we measured retinal vessels under the influence of flickering light, using a mydriatic fundus camera [13].

Numerous previous studies described mechanisms leading in clinically evident preeclampsia to alterations in the visual system, including decreased vision, visual field defects, and cortical blindness [4,7]. A method potentially being able to detect such alterations and abnormalities in visual signal processing is the critical flicker frequency [19,24]. This is a well-established, reproducible, sensitive and objective technique, with little bias for training effects. The method is dependent on visual function, particularly the retinal signalling cascade and includes interactions between photoreceptors, Müller cells and processes to blood vessels and axons [25]. Disturbances within this cascade may lead to visual dysfunction [25–28] and retinal tissue oedema with astrocyte swelling resulting in a deterioration of light guidance through the Müller cells [28,29]. Thickening of nerve fibre layer has been described in Glaucoma, which has been reported to have reduced CFF potentially due to selective loss of specific retinal signalling mechanisms within certain ganglion cells [30,31].

Due to the lack of other studies, which used CFF in pregnancy it is difficult to compare our results. But it is possible to compare the measurement of CFF with similar methods. In this regard, CFF seems to be a bedside test, which is easier and faster to perform as well as more economical. We suggest that the reduction in CFF in preeclampsia indicates a disturbed visual signal processing of the retina. In a recent study using a different method we could show, that retinal vascular response under the influence of flickering light is altered in women with preeclampsia, which indicates a commenced retinal microvascular dysfunction [13]. In hypertensive disorders such as preeclampsia, the effect of hypertension extends to involve the vasculature of the retina, choroids and optic nerve head [4]. The disruption of the blood-retinal barrier [32] leads to increased permeability [33], which results in retinal microvascular endothelial dysfunction, subretinal oedema, and impairment of the pigmented epithelium up to retinal detachment [4,10]. Resultant retinal changes may manifest as decreased retinal arteriolar to vein ratio, cotton wool spots, haemorrhages, Elschnig spots, and serous retinal detachments [4,34,35]. Oedematous

Table 1
Clinical characteristics of patients in study part A. Data are expressed as mean (SD) unless otherwise indicated. Comparisons were made with multivariate ANOVA (all data were normally distributed).

Variables	NC	NP			*p* value
	(n = 25)	I. trimester (n = 25)	II. trimester (n = 25)	III. trimester (n = 25)	
Gestational age at measurement (days) [weeks]		74 (2) [11]	142 (1) [20]	215 (5) [31]	
Maternal age (years)	29.36 (7.62)	32.24 (5.03)	30.20 (4.79)	32.00 (5.75)	0.247
BMI (kg/m^2)	23.2 (2.5)	23.5 (4.6)	25.1 (4.5)	25.9 (9.6)	0.291
Family history of CVD (n (%))	14 (56)	11 (44)	16 (64)	11 (44)	0.419
Nulliparous (n (%))	15 (60)	13 (52)	12 (48)	12 (48)	0.818
Current smokers (n (%))	2 (8)	3 (12)	0 (0)	1(4)	0.323
Birth weight (g)		3499 (332)	3418 (321)	3501 (470)	0.678
Birth centile		48 (22)	43 (24)	46 (26)	0.742
Gestational age at delivery (days) [weeks]		273 (2) [39]	275 (2) [39]	279 (1) [40]	0.130
Caesarean delivery (n (%))		7 (28.0)	6 (24.0)	8 (32.0)	0.826
MAP (mm Hg)	90 (7)	92 (11)	96 (9)	94 (15)	0.244

NC = non-pregnant controls; NP = normal pregnant women; BMI = body mass index; CVD, = cardiovascular disease; MAP = mean arterial pressure.

Table 2
Clinical characteristics of patients in study part B. Comparisons were made with unpaired *t*-test for continuous data and χ^2-test for categorical data and data are expressed as mean (SD), unless otherwise indicated.

Variables	mNP (n = 15)	PE (n = 15)	*p*-value
Maternal age (y)	31 (6)	30 (6)	0.505
BMI (kg/m^2)	23.4 (3.4)	24.7 (7.2)	0.246
SBP (mm Hg)	117(5)	136.53 (10)	0.000
DBP (mm Hg)	81 (7)	89 (11)	0.000
MAP (mm Hg)	100 (7)	105 (10)	0.000
Gestational age at measurement (days) [weeks]	218 (6) [31]	210 (5) [30]	0.691
Family history of CVD (n (%))	7 (46.7)	10 (66.7)	0.462
Nulliparous (n (%))	9 (60.0)	5 (33.3)	0.272
Current smokers (n (%))	1 (6.7)	1 (6.7)	1.000
Birth weight (g)	3536 (409)	2602 (936)	0.003
Birth centile	46 (31)	23 (30)	0.044
Gestational age at delivery (days) [weeks]	277(2) [40]	238 (4) [34]	0.000
Previous PE (n (%))	0 (0)	3 (20)	0.224
Caesarean delivery (n (%))	5 (33.3)	12 (80.0)	0.025

mNP = matched normal pregnant women, PE = preeclampsia; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; CVD = cardiovascular disease.

Table 3
Parameters postpartum in PE and mNP. Data are expressed as mean (SD). Comparisons were made with multivariate ANOVA (all data were normally distributed), adjusted for age and mean arterial pressure, unless otherwise indicated.

Variables	PE pp (n = 8)	mNP pp (N = 10)	*p-value*
BMI (kg/m^2)	24.50 (2.85)	23.44 (3.77)	0.522
SBP (mm Hg)	120.25 (6.92)	117.80 (4.85)	0.390
DBP (mm Hg)	73.00 (10.52)	80.20 (7.83)	0.115
MAP (mm Hg)	88.75 (8.06)	92.733 (5.76)	0.239

mNP = matched normal pregnant women; PE = women with preeclampsia; pp = postpartum; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure.

thickening of cornea, retina, and nerve fibre layer as well as increased IOP has been found in women with preeclampsia [8–10,36], all of them being possible explanations for altered CFF. Possibly, those retinal changes can be detected by CFF. Recent studies suggested that the cause of decrease in CFF may be due to vascular changes in parts of the choroidal circulation [37]. The severity of retinal arteriolar changes in PE is more closely related to the degree of underlying vasospasm. Previous studies showed that the level of retinopathy in patients with preeclampsia did not correspond to the severity of hypertension (systolic or diastolic). It has been suggested that retinal changes in preeclampsia may indirectly indicate the level of placental vascular status and, hence, placental insufficiency and foetal birth weight [4,34,35,38]. Other potential pathways causing reduced CFF in women with PE may be reduced production of vasoactive substances such as VEGF. The expression of VEGF by Müller cells is also required for endothelial cell survival [39] and the structural organization of the blood-retinal barrier [40], thereby reduced VEGF in preeclampsia may lead to Müller cell and photoreceptor apoptosis resulting in visual dysfunction [25]. Another possible explanation is, that CFF may already be reduced in early pregnancy or first trimester in women later developing PE. Even before pregnancy, CFF could be reduced in women destined to later develop preeclampsia. This hypothesis can be supported by the finding, that endothelial dysfunction has been already detected in the first trimester [41,42]. Endothelial factors like s-Flt and PlGF differ at this point significantly between healthy pregnant and preeclamptic women [43,44]. In preeclamptic women, CFF rises postpartum, but is still different from values measured in non-pregnant and healthy pregnant women. Compared to healthy pregnancy, it can be supposed that there is an altered endothelial situation in postpartum preeclamptic women. The finding that CFF remains reduced postpartum could be explained by either the effect of preeclampsia on maternal endothelium causing long lasting damage or on the other hand supports the possibility of an a priori damaged endothelium. Recent studies showed that women who had suffered from preeclampsia still have vascular, endothelial and metabolic dysfunction and higher cardiovascular risks than healthy pregnant

Table 4
CFF in studygroups. Data are expressed as mean (SD) unless otherwise indicated. Comparisons were made with multivariate ANOVA (all data were normally distributed).

	NC	NP			p-value[a]
		I. trimester	II. trimester	III. trimester	
n	25	25	25	25	
CFF (Hz)	44.46 (2.31)	44.36 (2.25)	43.35 (2.37)	44.50 (2.67)	0.283

	mNP	PE	mNP pp	PE pp	p-value[a]	p-value[b]	p-value[c]
n	15	15	10	8			
CFF (Hz)	46.23 (3.37)	38.80 (2.16)	46.45 (3.44)	41.17 (1.13)	0.000	0.010	0.003

NC = non-pregnant controls; NP = normal pregnant women; mNP = matched women with normal pregnancy; PE = women with preeclampsia; pp = postpartum; CFF = critical flicker frequency.
[a] PE versus mNP.
[b] PE pp versus mNP pp.
[c] PE versus PE pp.

women postpartum [45–47]. Preeclampsia is a – still under-recognized – risk factor for later chronic hypertension, peripheral vascular disease and even stroke and ischemic heart disease [47–49]. Recent studies hypothesized that the pre-existing tendency to increased cardiovascular risk or hypertension increases the risk of adverse pregnancy outcome and the susceptibility to develop preeclampsia [50–52]. But up to this point it is unclear, if endothelial dysfunction can be found in women destined to develop preeclampsia even before pregnancy [50,53].

One unanswered question is, that we do not know if there are pre-existing factors in preeclampsia. Is there an endothelial dysfunction or a pre-existing cardiovascular damage even before pregnancy in women which develop preeclampsia? Those alterations could be responsible for altered CFF, too. Another outstanding issue is the pathophysiology of altered CFF. We do not know which pathways or modifications lead to lower CFF values. As the measurement of CFF is a combined visual-cognitive test it is not clear if retinal changes or cognitive changes like reaction time are responsible.

Strengths and weaknesses of our study: We matched pairs for age, parity, body mass index, current smoking and family history of cardiovascular disease allowing better comparison of the results. Nevertheless, we are aware that the small patient numbers (especially postpartum) may hamper the interpretation of the results and further larger trials are necessary to validate our results. For the present, we did not include measurements of neuronal activity, parameters of cognition or the influence of vasoactive factors. Therefore, it is difficult to assess limitations of cognition and identify the main reason for altered CFF in preeclampsia. Additionally, we cannot exclude that pre-existing endothelial dysfunction are responsible for altered CFF in later preeclamptic women.

Conclusion

To the best of our knowledge, this is the first study that has examined critical flicker frequency in non-pregnant women, in pregnancy, and preeclampsia. Our results show that CFF is reduced in preeclampsia and remains reduced in the postpartum period. Further studies are needed to investigate CFF at different gestational ages throughout pregnancy to evaluate its potential for prediction of preeclampsia and in different hypertensive disorders, such as HELLP syndrome or pregnancy induced hypertension and especially in women with chronic hypertension. To investigate the assumption, that there is an endothelial damage even before pregnancy in preeclamptic women, we suggest to asses CFF in non-pregnant women aiming to become pregnant. This could be possibly identifying pre-existing endothelial dysfunction in women destined to develop preeclampsia in pregnancy.

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