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Preeclampsia postpartum: Impairment of cerebral autoregulation and reversible cerebral hyperperfusion

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ABSTRACT

Objectives: Preeclampsia is a pregnancy-related hypertensive disorder with endothelial dysfunction. Impaired cerebral autoregulation may lead to symptomatic cerebral hyperperfusion, which sometimes manifests not until after delivery. This study investigated, whether cerebral autoregulation was altered after delivery in healthy and preeclamptic women, and whether this associated with cerebral hyperperfusion.
Study design: In a prospective study, 35 preeclamptic and 35 healthy women were examined with transcranial Doppler within 10 days postpartum and 6 months later. Continuous arterial blood pressure and cerebral blood flow velocities (CBFV) in the middle (MCA) and posterior cerebral arteries (PCA) were recorded at rest.
Main outcome measures: Dynamic cerebral autoregulation was assessed upon regular breathing at 0.1 Hz via transfer function phase and gain between arterial blood pressure and CBFV oscillations.
Results: In preeclamptic women, phase was reduced after delivery in both, MCA and PCA. During the postpartum period, CBFV of the MCA, but not PCA, correlated with higher arterial blood pressure and poorer dynamic cerebral autoregulation. In healthy women with only moderately altered cerebral autoregulation, CBFV remained in the normal range. At both measurements, arterial blood pressure was higher in preeclamptic compared to healthy women.
Conclusions: Women with preeclampsia had poorer cerebral autoregulation and an increased risk of transient cerebral hyperperfusion after delivery.

1. Introduction

Preeclampsia, a hypertensive disorder affecting 3–5% of all pregnancies, remains a leading cause of maternal mortality worldwide [1]. Women with preeclampsia have an increased risk of hemorrhagic stroke during the postpartum period [2,3]. Cerebral blood flow is regulated by cerebral perfusion pressure and cerebrovascular resistance [4]. Cerebral perfusion pressure is increased in preeclamptic compared to healthy pregnant women [5,6]. During the postpartum period, mean cerebral blood flow velocities (CBFV) significantly increase in preeclamptic women with a maximum at day 5 after delivery, which, to a lesser extent, can also be demonstrated in healthy women [4]. Cerebral hyperperfusion and increased cerebral perfusion pressure both increase wall tension of cerebral vessels, and can therefore increase the risk of intracerebral hemorrhage [7].

Cerebral autoregulation is impaired in women with preeclampsia [8,9]. Reversible posterior encephalopathy syndrome with vasogenic edema is found in more than 10% of women with severe preeclampsia [10]. It results from cerebral hyperperfusion and disrupted blood-brain barrier in the context of generalized endothelial dysfunction [11,12]. It

Abbreviations: CBFV, cerebral blood flow velocitiy; MCA, middle cerebral artery; PCA, posterior cerebral artery; DCA, dynamic cerebral autoregulation; MAP, mean arterial blood pressure; IMT, intima-media thickness; Phase, phase shift between CBFV and MAP upon slow regular breathing; Gain, gain of the transfer function, normalized to MAP and CBFV; HELLP, hemolysis, elevated liver enzymes, low platelets

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Table 1
Baseline maternal demographics and clinical characteristics.

	n	P+	n	P−	p-value
Age, y	35	32.1 (± 4.5)	35	32.7 (± 4.9)	0.53
BMI before pregnancy, kg/m2	35	23.6 (± 3.6)	35	23.6 (± 5.4)	0.4
BMI 6 month postpartum, kg/m2	32	24.9 (± 4.4)	31	24.8 (± 5.0)	0.77
MAP ≤ 10 days postpartum, mmHg	35	103.5 (± 12.7)	35	87.3 (± 9.5)	< **0.001 (***)**
MAP 6 month postpartum, mmHg	32	88.6 (± 10.9)	30	81.9 (± 7.8)	**0.0087 (**)**
IMT ≤ 10 days postpartum, mm	26	4.6 (± 0.5)	26	4.5 (± 0.6)	0.2
IMT 6 month postpartum, mm	23	4.8 (± 0.6)	28	4.9 (± 0.5)	0.37
Day postpartum, d	35	5.9 (± 1.8)	35	4.5 (± 2.7)	**0.0047 (**)**
Pregnancy duration, d	35	228.7 (± 28.0)	35	273.8 (± 14.6)	< **0.001 (***)**
Primigravida, n (%)	35	28 (80%)	35	18 (51%)	**0.022 (*)**
Multiple pregnancy, n (%)	35	3 (8%)	35	1 (2%)	0.61
History of preeclampsia n (%)	35	2 (5%)	35	0 (0%)	0.49
Pre-existing hypertension, n (%)	35	6 (17%)	35	0 (0%)	**0.025 (*)**
HELLP, n (%)	35	15 (43%)	35	0 (0%)	< **0.001 (***)**
Migraine, n (%)	35	11 (31%)	35	5 (14%)	0.15
Neurological symptoms, n (%)	35	21 (60%)	35	6 (17%)	< **0.001 (***)**
Birth weight, g	38	1776 (± 835)	36	3304 (± 595)	< **0.001 (***)**
Birth weight percentile	38	25 (± 18)	36	51 (± 30)	< **0.001 (***)**

Data are given as mean ± standard deviation (SD) or absolute number (n). P+, preeclamptic women; P−, healthy women; y, years; BMI, body mass index; MAP_RR, mean arterial blood pressure; IMT, Intima Media Thickness; d, days; Notch, persistent bilateral postsystolic notching of uterine arteries in Doppler ultrasound examination during pregnancy; HELLP, HELLP-syndrome (acronym for hemolysis, elevated liver enzymes and low platelets); g, gram.

is not known, (I) how maternal cerebral autoregulation behaves after delivery, both, physiologically and in case of preeclampsia, and (II) how impaired cerebral autoregulation relates to the occurrence of cerebral hyperperfusion and clinical symptoms of pre-/eclampsia. In this prospective study, we analyzed cerebral hemodynamics and dynamic cerebral autoregulation (DCA) of middle and posterior cerebral arteries in women with severe preeclampsia and healthy mothers within 10 days postpartum and 6 months later.

2. Patients and methods

Over a period of 16 months (January 2014 to Mai 2015), 35 women with prepartal diagnosis of severe preeclampsia according to the criteria of the American Congress of Obstetrics and Gynecologists were recruited within 10 days after delivery and were compared to 35 healthy women within 10 days after delivery [13]. The study was approved by the Local Ethics Committee (UTN U1111-1152-5102), and written informed consent was obtained from all participants. Inclusion criteria were age 18–45 years, no stenosis of brain-supplying arteries, no disorders of the central nervous system and a normal temporal bone window for Doppler ultrasound. At study inclusion, all women underwent a neurological examination and a measurement of mean arterial blood pressure at rest (MAP) with the cuff at heart level. Software-aided assessment of intima-media thickness (IMT) of the common carotid artery was performed during routine extracranial ultasound examination (QLAB, Philips iU22, Bothell, WA, USA). A standardized questionnaire was applied to all participants regarding medical history, maternal and neonatal clinical characteristics and complications.

Cerebral hemodynamics were recorded in a dimmed room with the study participant in supine position with 60° inclination of the upper body. Using a headband with two 2-MHz transducers, CBFV of the right middle cerebral artery (MCA, M1 segment) and left posterior cerebral artery (PCA, P2 segment) were captured simultaneously by Doppler ultrasound through the temporal bone window (Multidop-X4, Compumedics DWL, Germany). Continuous noninvasive arterial blood pressure and heart rate were recorded from the left index finger with the hand positioned at heart level using a servo-controlled finger-plethysmograph (Finapres 2300, Ohmeda, Englewood, CO, USA). Via infrared nasal capnography (Normocap, Datex Instrumentarium Corporation, Helsinki, Finland) end-tidal CO2 partial pressure (PetCO2) was measured. Stable baseline values at normal breathing with closed eyes were captured, followed by 180 s of slow regular breathing at 0.1 Hz to induce sinusoidal oscillations of arterial blood pressure and CBFV [14]. Parameters were recorded at a sampling rate of 100 Hz (AcqKnowledge, Biopac Systems, Inc., Goleta, CA). Follow-up measurement was performed at 6 months (± 4 weeks) postpartum. At follow-up, MAP was measured at rest, medical history was updated.

For each measurement, parameters of DCA (phase and gain) were calculated between oscillations of arterial blood pressure and CBFV using transfer function analysis upon slow regular breathing at 0.1 Hz over a period of 180 s [15]. General hemodynamic data were assessed using custom-written software from baseline recordings, including CBFV and pulsatility index (PI) of right MCA and left PCA, and PetCO2.

Differences between both groups and between both measurements are depicted as mean +/- standard deviation. Linear and logistic regression was performed using the R software package, version 3.4.1 (2017-06-30). The correlations between CBFV and blood pressure values or phase, respectively, were calculated by Spearman's rank order. Statistical significance was assessed by Mann-Whitney-*U* test. Statistical significance was assessed by Wilcoxon tests or Fisher exact tests. Level of statistical significance was set at 0.05.

3. Results

3.1. Clinical characteristics (Table 1)

A total of 70 women (35 with severe preeclampsia, including 15 patients with concomitant HELLP-syndrome, and 35 healthy mothers) were recruited within 10 days after delivery. Both groups were similar regarding age and body mass index pre-pregnancy, but preeclamptic mothers were more often primiparous. During pregnancy, bilateral notching of the uterine arteries had been documented in 34% of preeclamptic women. Neurological symptoms, mostly headaches and blurred vision, were reported in 60% of preeclamptic, and 17% of control subjects. Pregnancy duration was shorter, and absolute neonatal birth weight, as well as the mean birth weight percentile, was lower in the preeclampsia group. MAP levels postpartum and 6 months later were significantly higher in preeclamptic women. Carotid IMT did not differ between groups.

3.2. General hemodynamics and cerebrovascular perfusion (Table 2)

After delivery, MAP values were significantly higher in preeclamptic patients, and heart rate was higher in healthy mothers. In both groups,

Table 2
Hemodynamics and cerebral autoregulation during early postpartum period and 6 months later.

		n	≤10 days postpartum	n	6 months postpartum	p-value
CAP (mmHg)	P+	35	84.6 (± 13.3)	32	80.1 (± 14.2)	0.11
	P−	34	77.8 (± 11.3)	31	76.5 (± 14.6)	0.48
P+ *versus* P−	p-value		**0.011 (*)**		0.28	
Heart rate (bpm)	P+	35	76.3 (± 15.7)	32	71.1 (± 13.5)	0.32
	P−	33	83.2 (± 11.6)	31	72.0 (± 7.4)	< **0.001 (***)**
P+ *versus* P−	p-value		**0.041 (*)**		0.93	
PetCO2 (mmHg)	P+	24	32.1 (± 2,9)	20	36.2 (± 5.3)	**0.0065 (**)**
	P−	24	32.7 (± 3,6)	20	35.8 (± 4.2)	**0.04 (*)**
P+ *versus* P−	p-value		0.40		0.53	
PI MCA	P+	35	0.61 (± 0.10)	32	0.61 (± 0.09)	0.89
	P−	35	0.68 (± 0.16)	31	0.70 (± 0.11)	0.22
P+ *versus* P−	p-value		**0.037 (*)**		**0.002 (**)**	
PI PCA	P+	35	0.56 (± 0.13)	32	0.56 (± 0.08)	0.45
	P−	35	0.57 (± 0.10)	31	0.64 (± 0.14)	**0.011 (*)**
P+ *versus* P−	p-value		0.34		**0.0047 (**)**	
CBFV MCA (cm/s)	P+	35	83.5 (± 18.2)	32	64.9 (± 11.1)	< **0.001 (***)**
	P−	34	64.3 (± 10.9)	31	60.4 (± 11.7)	0.16
P+ *versus* P−	p-value		< **0.001 (***)**		0.1	
CBFV PCA (cm/s)	P+	35	49.9 (± 11.2)	32	42.5 (± 6.5)	< **0.001 (***)**
	P−	34	44.9 (± 8.1)	31	41.0 (± 7.5)	0.056
P+ *versus* P−	p-value		0.065		0.21	
Phase MCA (°)	P+	33	21.4 (± 25.6)	32	43.9 (± 27.4)	< **0.001 (***)**
	P−	35	29.0 (± 20.4)	31	38.8 (± 17.2)	**0.028 (*)**
P+ *versus* P−	p-value		0.19		0.94	
Phase PCA (°)	P+	34	29.3 (± 25.4)	32	49.7 (± 25.6)	**0.0019 (**)**
	P−	35	37.5 (± 18.7)	30	42.6 (± 21.3)	0.37
P+ *versus* P−	p-value		0.063		0.25	
Gain MCA (%/%)	P+	33	0.94 (± 0.31)	32	0.79 (± 0.18)	0.075
	P−	35	0.85 (± 0.29)	31	0.81 (± 0.19)	0.93
P+ *versus* P−	p-value		0.26		0.44	
Gain PCA (%/%)	P+	34	0.91 (± 0.27)	32	0.86 (± 0.14)	0.80
	P−	35	0.91 (± 0.23)	30	0.89 (± 0.15)	0.67
P+ *versus* P−	p-value		0.78		0.42	

Data are given as mean ± standard deviation (SD). P+, preeclamptic women; P−, healthy women; n, number of eligible records; CAP, continuous arterial blood pressure; bpm, beats per minute; PetCO2, end-tidal CO2 partial pressure; PI, pulsatility index; MCA, right middle cerebral artery; PCA, left posterior cerebral artery; CBFV, cerebral blood flow velocity.

$P_{et}CO_2$ was significantly lower during the early postpartum period than 6 months later. PI of the MCA was lower in preeclamptic women ($p = 0.037$), whereas PI of the PCA was comparable in healthy and preeclamptic women. Mean CBFV of MCA was significantly higher in preeclamptic women postpartum (83.5 cm/s vs 64.3 cm/s, $p < 0.001$), mean CBFV of PCA to a lesser extent (49.9 cm/s vs 44.9 cm/s, $p = 0.065$).

At 6 months postpartum, CBFV, PI, MAP and heart rate had returned to normal values in healthy women [16]. PI of both, MCA and PCA, increased within 6 months only in healthy women, and was significantly lower in former preeclamptic women at the second measurement ($p = 0.002$ for MCA and $p = 0.0047$ for PCA). CBFV of MCA and PCA decreased in both groups, but more so in case of preeclampsia. At 6 months postpartum, there was no statistically significant difference of CBFV between healthy and preeclamptic women.

3.3. Dynamic cerebral autoregulation (Table 2)

In preeclamptic women, phase showed a significant reduction (i.e., impairment) after delivery. In healthy mothers, phase after delivery was also reduced, but to a lesser extent (see Fig. 1A and B). In the MCA, phase was clearly in the pathological range (< 20°) in 15/33 women (45%) with, and 12/35 women (34%) without preeclampsia ($p = 0.4579$ with Fisher's exact test, Fig. 1A) [17]. In the PCA, it was in the pathological range (< 20°) in 13/34 women (38%) with, and 5/34 women (15%) without preeclampsia ($p = 0.0526$ with Fisher's exact test, Fig. 1B). While numeric values were lower in women with preeclampsia, statistical intergroup comparisons (preeclamptic vs. healthy mothers) only showed a trend towards lower values in case of preeclampsia. Among women with preeclampsia, those with HELLP-syndrome did not show a stronger reduction of phase, and neurological symptoms did not correlate with impairment of cerebral autoregulation.

The autoregulatory parameter gain tended to be higher in the MCA in preeclamptic women postpartum, but this did not reach statistical significance (Fig. 1C and D).

Within 6 months postpartum, phase of MCA increased significantly in healthy and preeclamptic women ($p = 0.028$ and $p < 0.001$, respectively), and phase of PCA increased significantly in preeclamptic women ($p = 0.0019$). Increase of phase between both measurements was more pronounced in women with preeclampsia. At the second measurement, intergroup comparison showed no statistically significant difference of DCA between both groups, phase tended to be higher in former preeclamptic women.

3.4. Cerebral perfusion after delivery in MCA and PCA

CBFV after delivery correlated significantly with MAP, mainly in the MCA (adjusted $r^2 = 0.3534$, $p < 0.001$ in the MCA, and adjusted $r^2 = 0.1775$, $p = 0.293$ in the PCA). CBFV after delivery correlated inversely with phase in the MCA, but not in the PCA (adjusted $r^2 = -0.4557$, $p = 0.0039$ in the MCA and adjusted $r^2 = 0.0285$, $p = 0.9188$ in the PCA, Fig. 2). Multivariate analysis showed a statistically significant correlation of CBFV with MAP and (inversely) with phase only in the MCA, but not in the PCA (see Table 3).

4. Discussion

In this study, 35 preeclamptic and 35 healthy women within 10 days after delivery as well as 6 months postpartum were examined with

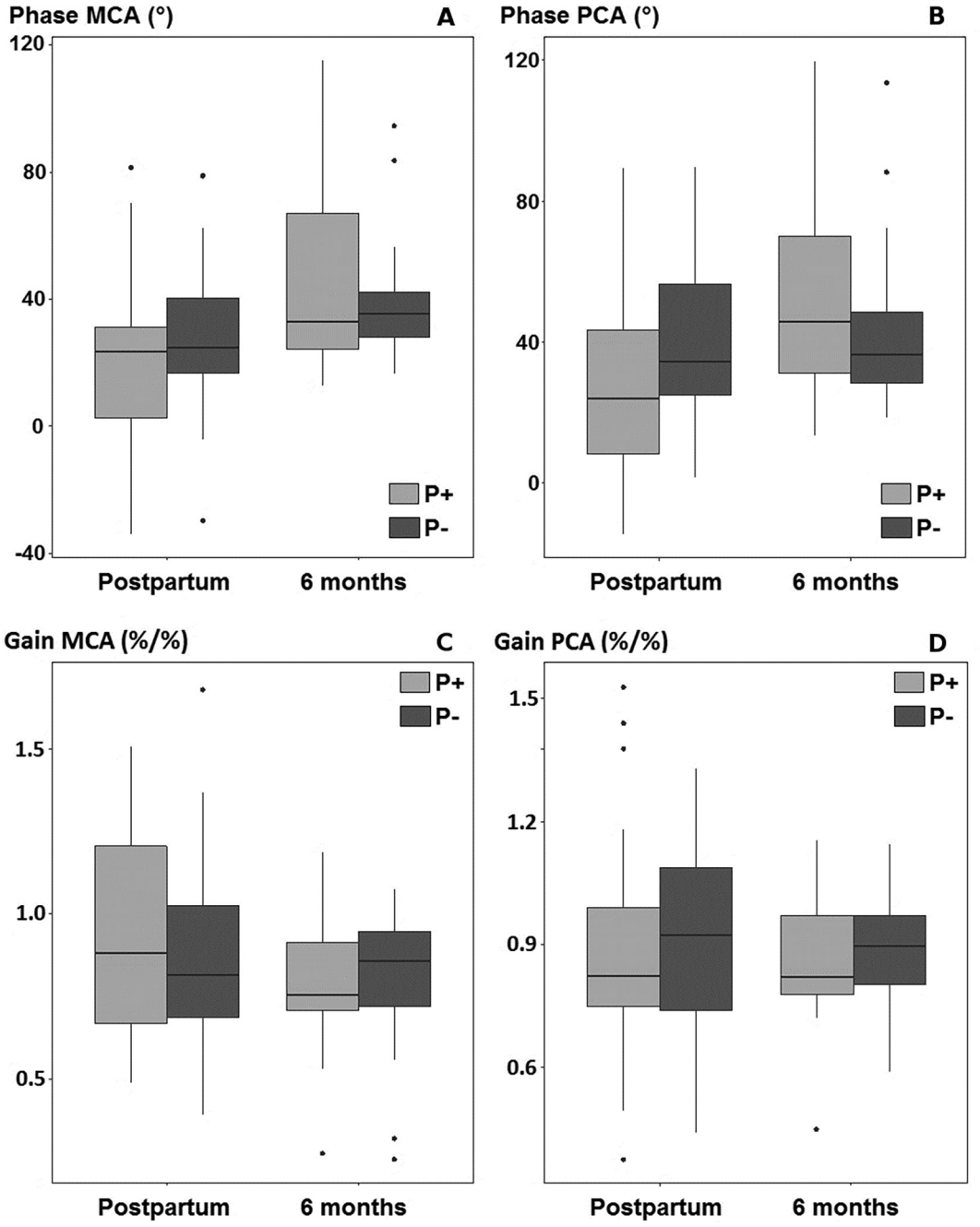

Fig. 1. Dynamic cerebral autoregulation in preeclamptic (P+) and healthy women (P−) within 10 days postpartum and 6 months later. Box plots for dynamic cerebral autoregulation parameters phase and gain of the right middle cerebral artery (MCA) and left posterior cerebral artery (PCA). Boxes denote the median, the lower and upper quartile; bars denote the 10th and 90th percentiles, dots denote outliers.

transcranial Doppler. Clinical data, basal hemodynamics and dynamic cerebral autoregulation were compared in both groups. Moreover, differences of cerebral blood flow regulation in the MCA and PCA were described.

During the early postpartum period, most of the preeclamptic women showed clinical signs of placental dysfunction (abnormal uterine Doppler ultrasound, prematurity, reduced neonatal birth weight) and neurological symptoms. MAP was significantly higher in preeclamptic women at both measurements and decreased significantly in both groups within 6 months. Heart rate was increased during the early postpartum period compared to the second measurement 6 months later only in healthy, but not in preeclamptic mothers. A study of cardiovascular function before, during and after pregnancy showed an increase of heart rate during pregnancy with highest heart rate at 38 weeks of gestation and a return to base line at 24 weeks postpartum, whereas vascular resistance remained lower and cardiac output remained higher up to one year after pregnancy [18]. A study comparing heart rates during the 48 h postpartum documented a mean heart rate value > 80/min during this period [19]. A higher heart rate during the early postpartum period could help to keep cerebral perfusion in the normal range after blood loss during delivery, which might not be required in case of arterial hypertension.

CBFV after delivery correlated with arterial blood pressure values. CBFV was markedly elevated in preeclamptic women during the early postpartum period. At 6 months postpartum, absolute values of CBFV were comparable to those of non-preeclamptic mothers and healthy non-pregnant women [16]. A high CBFV in preeclamptic women likely reflects an increase of cerebral blood flow, although other conditions

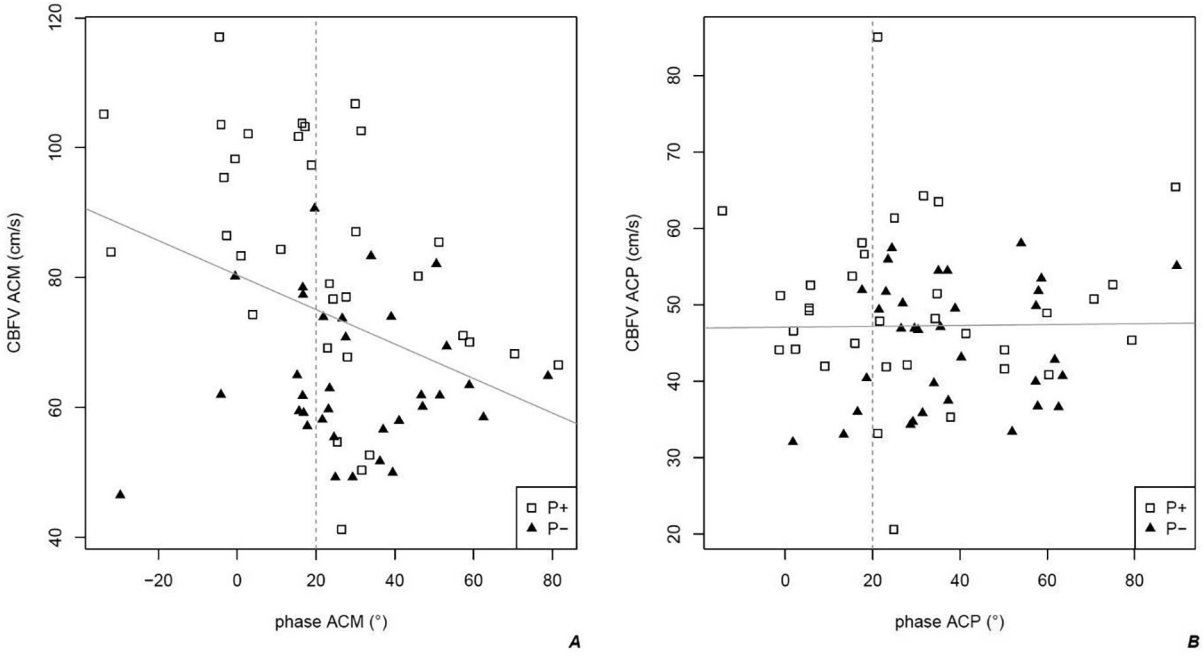

Fig. 2. Individual values of the dynamic cerebral autoregulation parameter phase of the right middle cerebral artery (MCA) and left posterior cerebral artery (PCA) in preeclamptic (P+) and healthy women (P−) within 10 days postpartum. Values less than 20° (left of the vertical line) are in the pathological range.

Table 3
Multivariate linear regression analysis of cerebral blood flow velocity of the middle cerebral artery and posterior cerebral artery within 10 days postpartum, with mean arterial blood pressure, and phase in the respective cerebral artery.

MCA	CBFV		PCA	CBFV	
n = 64	Beta (SD)	p-value	n = 65	Beta (SD)	p-value
MAP (mmHg)	0.553 (± 0.12)	**< 0.001 (***)**	MAP (mmHg)	0.076 (± 0.09)	0.398
Phase (°)	−0.253 (± 0.08)	**0.0024 (**)**	Phase (°)	0.010 (± 0.06)	0.862

Data are given as mean ± standard deviation (SD). MCA, right middle cerebral artery; PCA, left posterior cerebral artery; CBFV, cerebral blood flow velocity; n, number of eligible study participants including healthy and preeclamptic women; MAP, mean arterial blood pressure.

such as low hematocrit or vasospasm could also explain high CBFV measured with TCD [12,20,21]. Spontaneous intracranial hemorrhage is a multifactorial process involving numerous genetic and environmental risk factors, some of which are also associated with endothelial dysfunction [22,23]. Cerebral hyperperfusion and higher arterial blood pressure could additionally increase the risk of intracerebral hemorrhage in preeclamptic women during the early postpartum period [7].

In both, healthy and preeclamptic women, PaCO2 was reduced during the early postpartum period as compared to normal values at 6 months postpartum. Lower values of PaCO2 lead to a decrease of cerebral blood flow [24]. With regard to cerebral autoregulation, hypercapnia causes the autoregulatory plateau to steepen, with a shift of the lower limit towards the right, and a shift of the upper limit towards the left [25]. Mild respiratory hyperventilation during the early postpartum period could thus be a compensatory mechanism to counteract cerebral vasodilation but increases the risk of cerebral hyperperfusion at higher blood pressure levels.

During late pregnancy, cerebral autoregulation was impaired in preeclamptic women as compared to healthy pregnant women [9,26]. We demonstrated, that DCA in women with severe preeclampsia was also impaired within the first 10 days after delivery. In the MCA, phase correlated inversely with CBFV in both, preeclamptic and healthy women. Compared to healthy mothers, women with preeclampsia had lower cerebrovascular resistance (PI) and higher MAP after delivery. Preeclamptic women with impaired cerebral autoregulation are thus at an increased risk of symptomatic cerebral hyperperfusion, especially in case of higher arterial blood pressure values.

In the PCA, the correlation of CBFV with MAP values after delivery was much weaker than in the MCA. This could be explained by the better preserved DCA in the PCA as compared to the MCA. The susceptibility to edema formation during preeclampsia especially in posterior areas of the brain indicates that additional factors like reduced sympathetic innervation of the PCA might play a role [27–29]. Regional differences in cerebral autoregulation and vascular sympathetic innervation were also observed in pregnant rats [27]. In rats and in humans, cerebral autoregulation of anterior and posterior vascular territories is more effective during pregnancy than in the non-pregnant state [16]. Around delivery, this protective mechanism gets disrupted, especially in women with preeclampsia, but appears to be better preserved in the PCA than the MCA [8,9].

Of interest, DCA, mainly in the MCA, was not only impaired in preeclamptic, but also in one out of three healthy mothers within 10 days after delivery. Nevertheless, cerebral blood flow was still well preserved in most healthy women during the early postpartum period [12,20]. As CBFV correlated with arterial blood pressure values, cerebral blood flow could remain normal despite impaired DCA with normal MAP values. However, severe cerebral symptoms of preeclampsia, such as cerebral convulsions, manifest in 25% not until after delivery and often without preceding clinical signs of preeclampsia [30,31]. In the context of impaired cerebral autoregulation and low cerebrovascular resistance, a sudden increase of arterial blood pressure during the early postpartum period could lead to cerebral hyperperfusion and vasogenic edema even in previously healthy women.

In conclusion, the present study demonstrated that during the early postpartum period (I) cerebral blood flow velocities of the middle cerebral artery correlated with higher arterial blood pressure values, (II) dynamic cerebral autoregulation was impaired during the early postpartum period not only in preeclamptic, but also in healthy mothers, and (III) cerebral hyperperfusion in the middle but not the posterior cerebral artery was correlated with impaired dynamic cerebral autoregulation and higher arterial blood pressure.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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