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Cerebral perfusion pressure in pre-eclamptic patients is elevated even after treatment of elevated blood pressure.

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ABSTRACT

Background: Cerebral perfusion pressure (CPPe) is elevated in pre-eclampsia, and may predispose to cerebrovascular complications and progression to eclampsia.
Methods: We estimated zero flow pressure (ZFP) and CPPe using simultaneously obtained arterial blood pressure and middle cerebral artery blood flow velocity in 10 pre-eclamptic women, all treated with methyldopa, and 18 healthy pregnant controls.
Results: Mean (SD) ZFP was lower in patients than in controls (16.8 (10.9) versus 31.7 (15.0) mmHg, p=0.01) whereas CPPe was considerably higher (82.3 (17.7) versus 55.0 (11.7) mmHg, p<0.001), as was the cerebral flow index (41.9 (18.0) versus 25.6 (11.2), p=0.02). There was a significant correlation between blood pressure and CPPe in patients with pre-eclampsia, but not in controls.
Discussion: Pre-eclamptic women may have an increased cerebral perfusion due to a reduced ZFP and increased CPPe despite treatment with antihypertensive medication. More rigorous antihypertensive therapy, aimed at reducing CPPe, could result in a decrease in cerebral complications in pre-eclamptic patients.

Key Words: Pre-eclampsia, transcranial Doppler, zero flow pressure, cerebral perfusion, autoregulation

Abbreviations: CPPe, effective cerebral perfusion pressure; ZFP, zero flow pressure; ABP, arterial blood pressure; CFI, cerebral flow index; ISSHP, International Society for the Study of Hypertension in Pregnancy; CRF, case record form.

INTRODUCTION

Pre-eclampsia complicates 3% of pregnancies and is a major cause of maternal and foetal morbidity and mortality.(1) Cerebral infarction and haemorrhage account for the majority of maternal deaths from preeclampsia. The pathophysiology of cerebral damage in pre-eclampsia is unclear, but recent studies conducted with MRI have shown an increased cerebral blood flow in pre-eclamptic patients,(2) and Belfort *et al.* reported patients with severe pre-eclampsia have an increased effective cerebral perfusion pressure (CPPe).(3) High CPPe was also shown to be associated with pre-eclampsia related symptoms such as headache, and has also been reported in patients who subsequently developed eclamptic seizures.

Currently used drugs in patients with pre-eclampsia, such as labetalol and $MgSO_4$, tend to lower CPPe, while nimodipine is associated with a mild increase. Furthermore, a randomized study in pre-eclamptic patients reported that therapy with nimodipine is associated with more frequent eclamptic seizures in comparison with $MgSO_4$.(4) These findings may be explained by the different effects of these drugs on CPPe.

We aimed to investigate whether CPPe, as estimated using simultaneously measured arterial blood pressure (ABP) and middle cerebral artery blood flow velocity (V_{mca}), is elevated in pre-eclamptic patients, in whom blood pressure is adequately treated with antihypertensive medication.

MATERIAL AND METHODS

After obtaining informed consent, 10 pre-eclamptic patients and 18 healthy pregnant controls, admitted to the department of obstetrics of the Erasmus Medical Center, University Medical Center Rotterdam, were consecutively enrolled in this study. Preeclampsia was diagnosed according to the definition of the International Society for the Study of Hypertension in Pregnancy (ISSHP).(5) Pre-eclampsia was diagnosed as: hypertension in the presence of de novo proteinuria.(5) Severe preeclampsia was diagnosed if one or more of the following criteria were present: blood pressure of 160 mmHg systolic or higher than 110 mmHg diastolic or higher on two occasions at least 6 hours apart; proteinuria of 5 gram or more in a 24-hour urine specimen or dipstick urinalysis of 3+ or greater in two random urine samples collected at least 4 hours apart; oliguria of less than 500 mL in 24 hours; cerebral or visual disturbances; pulmonary edema or cyanosis; epigastric or right upper-quadrant pain; impaired liver function; thrombocytopenia; fetal growth restriction.(5) Exclusion criteria for this study were cerebral vascular disorders, diabetes mellitus, pre-existing hypertension and inadequate language skills. The study protocol was approved by the Institutional Review Board of the Erasmus MC University Medical Centre Rotterdam.

Transcranial Doppler measurements of the middle cerebral artery flow velocity (V_{MCA}) were conducted using a Digi-Lite monitoring system (RIMED, Jerusalem, Israel) using a 2 MHz probe after identification using imaging. Mean V_{MCA} was estimated as a weighted mean velocity. ABP was continuously measured non-invasively using a Finometer Midi (Finapres Medical Systems, Amsterdam, the Netherlands). The Finometer Midi allows for easy, non-invasive measurement of ABP using a finger cuff with a mounted infrared plethysmograph.(6) Expired CO_2 was measured using the Capnomac Ultima.

The zero-flow pressure (ZFP) in the circulation is the arterial pressure at which flow ceases. Dynamic pressure-flow-plots of the ABP and V_{MCA} have been used to extrapolate the ZFP of the cerebral circulation.(7, 8) During measurement sessions, a 2 to 5 minute time interval with stable measurements was specified on the CRF. For our analysis we used systolic, diastolic and mean values from up to 10 pulse waves (two respiratory cycles) to minimize the effect of breathing. ZFP was subsequently extrapolated by linear regression analysis through the individual measurements (figure 1). The CPPe was calculated as the difference between weighted mean ABP (MAP) and ZFP. CPP was also calculated using a formula proposed by Belfort et al.(3): CPPe = (meanV_{mca}/(mean V_{mca} – diastolic V_{mca})) x(mean ABP-diastolic ABP). Resistance area product (RAP) is an index of cerebrovascular resistance is obtained by dividing MAP by the mean V_{MCA} . Cerebral Flow Index (CFI), and index of total cerebral blood flow (CBF), was calculated as CFI = CPPe / RAP. (3)

SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. Results of continuous variables are presented as mean (standard deviation, SD) and results between groups were compared using t tests and chi square tests. All statistical tests were two-sided and were evaluated at 0.05 level of significance. The study protocol (MEC-2008-035) was approved by the Institutional Review Board of the Erasmus MC University Medical Center on April 29th 2008.

RESULTS

Age, parity and gestational age at inclusion were similar between patients and controls (table 1). Five patients had severe pre-eclampsia, and all patients were receiving methyldopa. One of the patients smoked during pregnancy, including the day that the measurements were performed, compared to none of the controls. Three patients were treated with a combination of methyldopa with nifedipine. None of the patients developed complications during follow-up. Gestational age at delivery for cases and controls was 32 (4.9) versus 37.4 (3.4) weeks (p = 0.012). Patients with pre-eclampsia had higher ABP and V_{MCA} than controls (table 1). End-tidal CO_2 did not differ between cases and controls (41.15 (2.52) versus 41.63 (2.97) mmHg, p=0.699). Pulsatility indices of the MCA were 0.47 and 0.40 in cases and controls (p=0.23).

Extrapolated ZFP was 16.8 (10.9) mmHg in pre-eclamptic women, compared to 31.7 (15.0) mmHg in controls (p = 0.01). Estimated CPPe was 82.3 (17.7) mmHg in patients compared to 55.0 (11.7) mmHg in controls (p< 0.001). Consequently, pre-eclamptic patients had a higher CFI than controls (41.9 (18.0) versus 25.6 (11.2), p = 0.02). We have also calculated CPPe using the method as proposed by Belfort et al. (3): the two measures of CPP are highly correlated (r = 0.659, p= 0.001). Patients also had higher CPPe than controls when estimated using the Belfort method: 87.1 (26.3) vs 70.7 (22.1) mmHg (p = 0.09).

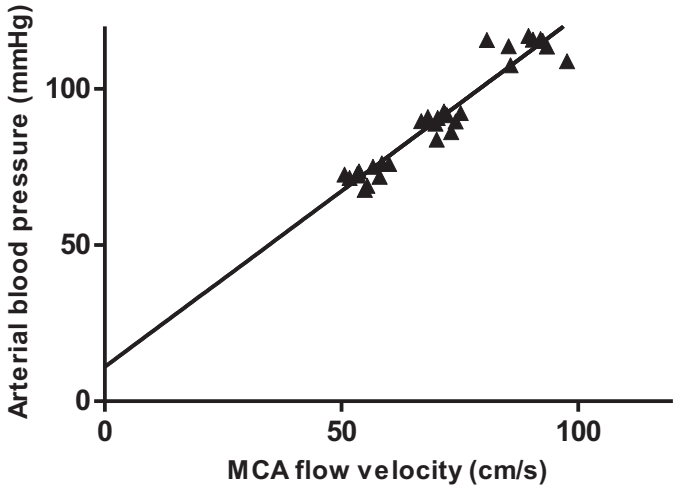
In a multivariate regression model adjusting for parity, gestational age at time of measurement and age at enrolment, patients with pre-eclampsia had higher CPP both when calculated using the regression method (adjusted CPPe 83.2 versus 54.5 mmHg, p<0.001) and the Belfort method (adjusted CPP 86.1 versus 69.6 mmHg, p=0.036).

In controls, there was no correlation between mean ABP and CPPe (r =- 0.004, p= 0.99), but in patients a distinct correlation was found between these parameters (r = 0.859, p = 0.001).

Table 1: A comparison of characteristics and measurements between cases and controls.

Patient characteristics	Patients (n=10)	Controls (n=18)	P-value
Demographics			
Age	29.9 (2.3)	32.4 (6.4)	0.14
Nulliparous	7 (70%)	10 (56%)	0.51
Severe pre-eclampsia	5 (50%)	-	
Gestational age	30.4 (3.2)	32.1 (3.2)	0.18
Blood pressure (mmHg)			
Systolic	123.8 (12.7)	101.5 (12.3)	<0.001
Mean	99.1 (9.1)	86.7 (9.3)	0.002
Diastolic	84.2 (7.7)	78.2 (10.3)	0.12
MCA flow velocity (cm/s)			
Systolic	65.4 (25.0)	49.2 (17.2)	0.05
Mean	50.7 (19.6)	38.8 (13.5)	0.07
Diastolic	41.5 (15.8)	33.8 (12.3)	0.16
Cerebral Perfusion			
Zero Flow Pressure	16.8 (10.9)	31.7 (15.0)	0.01
Cerebral Perfusion Pressure	82.3 (17.7)	55.0 (11.7)	<0.001
Cerebral Flow Index	41.9 (18.0)	25.6 (11.2)	0.02
Resistance are product	2.3 (1.21)	2.54 (1.04)	0.583

Mean levels of blood pressure, middle cerebral artery flow velocity, zero flow pressure, effective cerebral perfusion pressure and cerebral flow index. MCA, middle cerebral artery. Standard deviations are shown in brackets.



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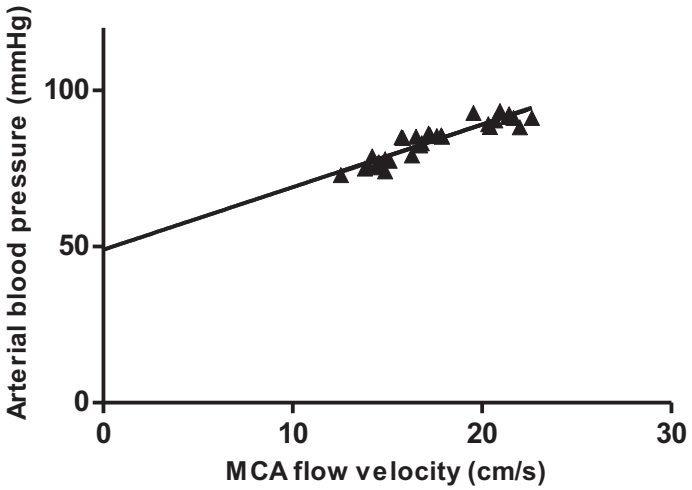

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Figure 1. Estimation of the zero flow pressure

by extrapolation of simultaneously measured beat-by-beat data on arterial blood pressure (systole and diastole) and middle cerebral artery blood flow velocity in a woman with preeclampsia (a) and a control woman (b). MCA, middle cerebral artery.

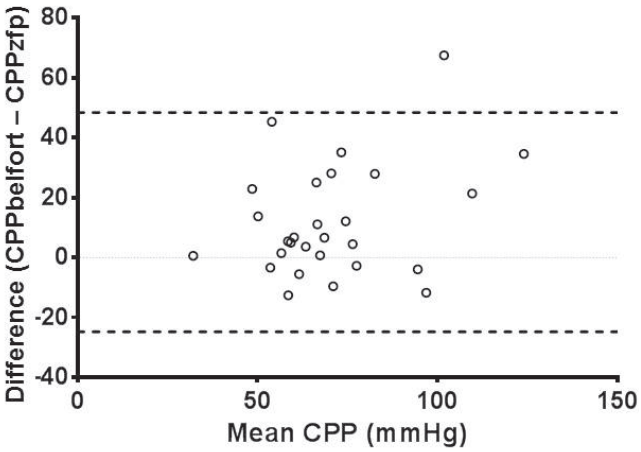

Figure 2. Bland–Altman comparison of the two methods for cerebral perfusion pressure estimation. Bold dashed lines represent the 95% confidence limits for the difference. CPPe, cerebral perfusion pressure.

DISCUSSION

The Dutch Maternal Mortality Committee reported cerebrovascular complications to be the major cause of death in hypertensive pregnant women.(9) Increased CPPe has been implicated as a possible mechanism to induce a cerebral hyperperfusion syndrome and subsequent cerebrovascular complications in pre-eclamptic patients.(2, 3) The CPPe in our healthily pregnant control group compares well with those from other reports, including large study by Belfort et al.(10) In the current study, we found that CPPe was elevated in pre-eclamptic patients after adequate treatment with antihypertensive therapy. Interestingly, this increase seems to be dependent upon a decrease in ZFP, as opposed to being merely an effect of the difference in blood pressure between patients and controls. The ZFP we found for healthy pregnant controls is compatible with earlier reports,(11) but whereas Sherman *et al.* found an increased ZFP in their population of untreated pre-eclamptics, we found a thoroughly decreased level in our study. A possible explanation for this discrepancy is the effect of medication on the ZFP: while the antihypertensive agents lowered blood pressure, other cerebrovascular mechanisms may have been induced that lowered ZFP, thereby maintaining an elevated cerebral perfusion pressure.(11) In our study we used methyldopa and nifedipine to lower blood pressure.

CPPe in patients with pre-eclampsia strongly correlates with ABP whereas this correlation is absent in healthy pregnant controls. The elevated CPPe was also accompanied by an increase in V_{mca} and CFI. Under normal circumstances, cerebrovascular autoregulation would maintain a stable cerebral blood flow, using cerebral vasoconstriction and a

subsequent change in ZFP, in the face of changes in the systemic circulation. Our findings therefore allude to a possible loss of cerebral autoregulation in pre-eclamptic patients.

A limitation of our study is that we used non-invasive methods for estimation of ZFP and CPPe. These methods have not been validated in vivo in humans. Given these limitations, we have chosen to use the two most often applied methods for estimation of CPPe and show that our findings are consistent irrespective of the method used, despite varying estimates observed across the methods (figure 2). The reason for the variation is currently unclear, and requires further investigation. Also, pre-eclamptics had a higher ABP than did the controls, despite antihypertensive therapy. This is in line with current treatment guidelines and therefore reflects clinical practice.(12)

In conclusion, the current study shows that in pre-eclamptic patients treated with antihypertensive therapy to reduce systolic ABP to <140 mmHg, in line with international and Dutch guidelines, CPPe and consequently cerebral perfusion are elevated. Possibly, more rigorous antihypertensive therapy, aimed at reducing CPPe, could therefore result in a decrease in cerebral complications in these patients although further studies are required to confirm this hypothesis. Future studies on elevated blood pressure control in pre-eclampsia should investigate the effect of reducing CPPe on the risk of cerebral complications in pre-eclampsia.

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