Cerebral haemodynamics in pregnancy and pre-eclampsia as assessed by transcranial Doppler ultrasonography


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Background. Altered cerebral circulation, as reported during normal pregnancy, and in patients with pre-eclampsia, can be associated with changes in cerebral vascular reactivity and/or cerebral autoregulation. The aim of our study was to perform a comparative assessment of cerebral haemodynamics, including vascular reactivity and autoregulation, in pre-eclamptic patients, healthy pregnant women, and healthy non-pregnant women.

Methods. Thirty patients with pre-eclampsia were recruited. Age- and height-matched healthy pregnant (n=30) and non-pregnant control (n=30) groups were also recruited. Monitoring included transcranial Doppler ultrasonography, end-tidal carbon dioxide and non-invasive arterial pressure measurement. Cerebral autoregulation was assessed by performing the transient hyperaemic response (THR) test. The cerebrovascular reactivity to carbon dioxide (CRCO₂) was assessed by measuring middle cerebral artery blood flow velocity (MCAFV) after induced changes in end-tidal carbon dioxide. Estimated cerebral perfusion pressure (eCPP) and critical closing pressure (CrCP) were calculated using established formulae. Statistical analysis included ANOVA with Tukey’s pairwise comparisons.

Results. Mean arterial pressure (MAP) was increased in pre-eclampsia (P<0.05). Mean MCAFV was lower in healthy pregnancy (P<0.05), but in pre-eclampsia it was similar to the non-pregnant group. When compared with the non-pregnant group, mean eCPP was higher in the healthy pregnant and pre-eclamptic groups (P<0.05). There were no meaningful differences in cerebral autoregulation or CRCO₂.

Conclusions. Healthy pregnancy increases eCPP, presumably by decreasing CrCP. In pre-eclampsia, eCPP is maintained at the same level as in healthy pregnancy despite an increased MAP. Pre-eclampsia has no significant effect on cerebral autoregulation or CRCO₂.

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Pregnancy induces widespread changes in the cardiovascular system.¹² Cerebral blood flow has been shown to be increased by up to 25% in the first trimester,³ but it reduces with increasing gestational age and, in the third trimester, it remains at up to 15% more than that in the non-pregnant state.⁴⁵ Pre-eclampsia has been shown to be associated with an increased middle cerebral artery blood flow velocity (MCAFV) and abnormal transcranial Doppler (TCD) findings compared with the healthy pregnant state.⁶ This increase in MCAFV is thought to be secondary to vasospasm and cerebral oedema.⁶⁷ During induction of anaesthesia, increases in MCAFV associated with increases in arterial pressure in pre-eclamptic patients have been reported to be significantly more than the increases seen in patients with a healthy pregnancy.⁸ Changes in vascular tone can affect cerebral perfusion pressure (CPP) by altering the critical closing pressure (CrCP) of cerebral arterioles.⁹ Despite reported changes in cerebral blood flow during
pregnancy and pre-eclampsia, the effects of pregnancy with or without pre-eclampsia on cerebral vascular reactivity, cerebral autoregulation, CPP, and CrCP have not been well documented.

Non-invasive assessment of cerebral haemodynamics using TCD ultrasonography has recently gained importance. Essentially, TCD measures flow velocity in the insonated vessel and the changes in flow velocity can be taken to reflect the changes in blood flow, assuming that the diameter of the insonated vessel remains constant. As TCD is easy to use and gives reproducible measurements, it has become a widely accepted method of assessing the cerebrovascular reactivity to carbon dioxide (CRCO\(_{2}\)), cerebral autoregulation, estimated (e)CPP, and CrCP. Knowledge of the effects of normal pregnancy and pre-eclampsia on cerebral haemodynamics is essential for appropriate management of these patients undergoing anaesthesia or in labour, particularly when vasoactive medications are administered.

The aim of the present study was to make a comparative assessment of cerebral haemodynamic variables such as cerebral autoregulation, CRCO\(_{2}\), eCPP, and CrCP, using TCD in pre-eclamptic patients, healthy pregnant women, and healthy non-pregnant women.

Materials and methods

After obtaining hospital ethics committee approval and written informed consent, we recruited 30 pre-eclamptic women, in the third trimester of pregnancy, from the obstetric unit. Pre-eclampsia was defined as an arterial pressure greater than 140/90 mm Hg on two separate occasions, with associated proteinuria (>2+ on dipstick and/or >0.3 g litre\(^{-1}\) on a 24-h collection), occurring after the 20th week of gestation. Healthy pregnant (third trimester; \(n=30\)) and non-pregnant women, matched for age and height to the pre-eclamptic women, were also recruited. Women with evidence of neurological disorder, recent head injury, pre-existing vascular disease, diabetes, renal disease, headache, and current vasoactive medication were excluded from the study.

Assessment of cerebrovascular haemodynamics was performed as soon as possible after the diagnosis of pre-eclampsia. Patients’ age, height, body mass index (BMI), gestational age (in pregnant patients), and arterial pressure were recorded. Before recruitment into the study, all the patients were fully assessed by obstetricians and those with severe pre-eclampsia (diastolic arterial pressure greater than 110 mm Hg and/or evidence of hyper-reflexia) were admitted immediately for anti-hypertensive therapy and/or induction of labour, and could not therefore be included in the study. The pre-eclamptic patients who were admitted to the study underwent carotid ultrasound scan to exclude any significant carotid artery disease.

All pre-eclamptic subjects were followed-up at 6 and/or 12 weeks post-partum to ensure that their arterial pressure had returned to normal levels, proteinuria had cleared, and that they had not suffered any neurological problems at any time during their stay in hospital or thereafter.

Study set-up

All subjects were studied in the supine position. The pregnant women were positioned with 15° left-lateral tilt to minimize any aortocaval compression. The left middle carotid artery (MCA) was identified using a 2 MHz-pulsed TCD probe (SciMed PCDop 842), and the position of the probe was fixed with a headband to ensure a constant angle of insonation during the period of the study. TCD measurements were recorded onto digital audiotape for subsequent analysis using specific software (SciMed UK). Following application of a nose clip, constant end-tidal carbon dioxide (\(\text{etCO}_{2}\)) monitoring was instituted via a mouthpiece connected to a Datex Capnomac monitor. The arterial pressure was measured at 1-min intervals with a non-invasive arterial pressure monitor (Dynamap) for the duration of the test. Further monitoring included heart rate and oxygen saturation measurements using pulse oximetry.

Following a period of acclimatization to the study apparatus, each subject’s baseline heart rate, arterial pressure, oxygen saturation, \(\text{etCO}_{2}\), and MCAFV were recorded.

TCD data

Cerebral autoregulation was assessed by the transient hyperaemic response (THR) test. This involved a 10-s compression of the ipsilateral common carotid artery (CCA) followed by sudden release of the compression, leading to hyperaemic flow in the MCA. Criteria for acceptance of a THR test were: (1) a sudden and maximal decrease in flow velocity at onset of the compression; (2) stable heart rate for the period of the compression; (3) steady TCD signal for the duration of the compression; and (4) absence of flow transients following release of the compression.

Two indices were used to analyse the THR test to assess autoregulation: the transient hyperaemic response ratio (THRR); and the strength of autoregulation (SA). To calculate these indices, three MCAFV waveforms were selected from the recordings during the THR test (Fig. 1): (1) the MCA waveform immediately before compression, F1; (2) the first waveform following compression, F2; and (3) the waveform immediately following release of compression, F3. The time-averaged mean of the outer envelope of the flow velocity profile was used for performing the analysis (Fig. 1). THRR was calculated as:
SA was calculated as: $SA=(F3 \times P2)/(MAP \times F1)$ where $P2$ is the greater value of either the estimated arterial pressure in the MCA at the onset of CCA compression, as calculated by $P2=MAP \times F2/F1$, or 60 mm Hg (the assumed lower limit of autoregulation). Details of the derivation of these formulae have been published elsewhere. \(^{12, 13}\)

The compression ratio (CR), a measure of the magnitude of decrease in flow velocity during the compression, was calculated using the formula: \(^{11}\)

$$CR\% = \left(\frac{F1-F2}{100/F1}\right)$$

CRCO\(_2\) was assessed by recording the MCAFV during induced hypocapnia (voluntary hyperventilation to an $E'_{CO2}$ of 1 kPa below baseline), and hypercapnia (addition of carbon dioxide to the inspired gases (oxygen-enriched air) to achieve an $E'_{CO2}$ of 1 kPa above baseline). CRCO\(_2\) was calculated as per cent change in MCAFV per kPa change in $E'_{CO2}$.

$$CRCO_{2} = 100 \times \frac{(MCAFV_{\text{high}CO2} - MCAFV_{\text{low}CO2})/MCAFV_{\text{low}CO2}}{E'_{CO2high} - E'_{CO2low}}$$

The eCPP and CrCP were calculated using the method described by Belfort and colleagues. \(^{7}\)

### Results

Thirty-five women with pre-eclampsia were enrolled into the study. Two were not included because of obstetric intervention before completion was possible, two because we were unable to identify a suitable MCA signal, and one because we were unable to perform a satisfactory THR test. None of the pre-eclamptic patients had a carotid artery atheromatous plaque.

The characteristics of the three groups of women included in the study are shown in Table 1. The groups were comparable for distribution of age and height; parity and gestation in healthy pregnant patients were similar to pre-eclamptics. Compared with non-pregnant subjects, the BMI in pre-eclamptic patients was significantly higher ($P<0.05$).

Baseline values for arterial pressure and $E'_{CO2}$ for the three groups are shown in Table 2. The systolic, diastolic, and mean arterial pressures (MAP) were significantly higher in the pre-eclamptic group ($P<0.05$) as compared with the healthy pregnant and non-pregnant control groups. The baseline $E'_{CO2}$ levels in the pre-eclamptic and healthy
pregnant groups were significantly lower than in the non-pregnant group (P<0.05).

The values of the cerebral haemodynamic variables are given in Table 3. Baseline MCAFV was significantly lower (P<0.05) in the healthy pregnant group compared with the pre-eclamptic and non-pregnant groups. There were no significant differences between the three groups for CR, THRR, SA, or CRCO₂. eCPP was significantly higher (P<0.05) in the pre-eclamptic and pregnant groups as compared with the non-pregnant control group. The CrCP was significantly lower in the healthy pregnant control group than the other two groups.

**Discussion**

We have shown that normal pregnancy is associated with a lower MCAFV as compared with non-pregnant women. However, MCAFV in pre-eclampsia is similar to that in non-pregnant women. The eCPP is higher in healthy pregnant women, as compared with non-pregnant women, and is maintained at this higher level during pre-eclampsia.

**Changes in MCAFV**

The effects of pregnancy and/or pre-eclampsia on MCAFV have been studied by other investigators. Ikeda and colleagues found little change in mean MCAFV during the first two trimesters but reduced values in the third trimester. Williams and Wilson showed that MCAFV fell significantly with advancing gestational age. In another study, Williams and Wilson used TCD to assess cerebral haemodynamics in 17 non-pregnant women, 17 normotensive pregnant women, 20 pregnant women with pre-existing hypertension, and 21 pre-eclamptic women. The pregnant women were all in their third trimester. There was no difference in mean MCAFV in healthy pregnancy compared with non-pregnant women and a small, but non-significant, increase in mean MCAFV in the hypertensive and pre-eclamptic women. Demarin and colleagues studied pre-eclamptic women before and after delivery and found a progressive increase in MCAFV during late pregnancy. Ohno and colleagues compared MCAFV in 35 healthy pregnant and 17 pre-eclamptic women. In this study, the mean MCAFV was significantly higher in the pre-eclamptic group. It has been suggested that these increases in MCAFV are because of a degree of vasospasm. The differences between the findings of various studies with regards to the changes in MCAFV in pre-eclampsia might be explained by the differences in the severity of pre-eclampsia between the studies. Some investigators have reported increased MCAFV in symptomatic, compared with asymptomatic pre-eclamptics.

In the present study, all our patients in the pre-eclampsia group were asymptomatic. We found that the values of MCAFV in pre-eclampsia, although similar to those in the non-pregnant group, were significantly higher than those seen in healthy pregnancy. These findings are in agreement with some of the previous reports. Overall, it would appear that MCAFV falls with advancing gestational age. An increase in late pregnancy to a level equal to, or greater than, normal non-pregnant velocities is suggestive of pre-eclampsia and probable underlying vasospasm.

**Cerebral autoregulation and carbon dioxide reactivity**

As far as we are aware, there are no previously reported studies using TCD, which have looked specifically at the effects of pregnancy and/or pre-eclampsia upon cerebral autoregulation or CRCO₂. It has been generally assumed that cerebral autoregulation remains intact during healthy pregnancy as the increase in cerebral blood flow is limited despite the raised cardiac output. With respect to pre-eclampsia, some investigators have suggested that the endothelial dysfunction seen in the pre-eclampsia/eclampsia syndrome may alter cerebral haemodynamics.

Our study confirms that cerebral autoregulation remains intact in healthy pregnancy, as we found no significant differences in THRR, SA, or CRCO₂ between the non-pregnant and healthy pregnant groups. In addition, perhaps surprisingly, we found no difference in these variables in patients with pre-eclampsia. This may be because all our pre-eclamptic patients were asymptomatic, and therefore, can be supposed to have had only mild disease. None of the pre-eclamptic women we studied went on to suffer an eclamptic seizure. Our study procedure required a carotid

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### Table 2

Baseline data. Values are mean (SD). *P<0.05 compared with the other two groups using ANOVA with Tukey’s test.

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-eclamptic (n=30)</th>
<th>Healthy pregnant (n=30)</th>
<th>Non-pregnant (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>149 (12)*</td>
<td>120 (11)</td>
<td>121 (11)</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>97 (10)*</td>
<td>76 (10)</td>
<td>77 (7)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>113 (11)*</td>
<td>90 (10)</td>
<td>89 (9)</td>
</tr>
<tr>
<td>eCO₂ (kPa)</td>
<td>4.3 (0.4)</td>
<td>4.2 (0.4)</td>
<td>5.1 (0.4)*</td>
</tr>
</tbody>
</table>

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### Table 3

Cerebral haemodynamic measurements and calculated variables. Mean (SD) values of MCAFV, CR, THRR, SA, CRCO₂, eCPP, and CrCP are given. *P<0.05 compared with the other two groups using ANOVA with Tukey’s test.

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-eclamptic (n=30)</th>
<th>Healthy pregnant (n=30)</th>
<th>Non-pregnant (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCAFV (cm s⁻¹)</td>
<td>67.9 (13.9)</td>
<td>56.7 (11.5)*</td>
<td>68.7 (14)</td>
</tr>
<tr>
<td>CR</td>
<td>32.3 (18.0)</td>
<td>34.9 (8.2)</td>
<td>34.3 (12.0)</td>
</tr>
<tr>
<td>THRR</td>
<td>1.68 (0.18)</td>
<td>1.64 (0.19)</td>
<td>1.57 (0.25)</td>
</tr>
<tr>
<td>SA</td>
<td>1.19 (0.29)</td>
<td>1.21 (0.19)</td>
<td>1.13 (0.20)</td>
</tr>
<tr>
<td>CRCO₂</td>
<td>26.6 (5.9)</td>
<td>27.7 (7.7)</td>
<td>28.0 (6.4)</td>
</tr>
<tr>
<td>eCPP (mm Hg)</td>
<td>65.4 (14.6)</td>
<td>60.3 (18.2)</td>
<td>43.3 (17.6)*</td>
</tr>
<tr>
<td>CrCP (mm Hg)</td>
<td>48.1 (16.1)</td>
<td>29.3 (20.1)*</td>
<td>44.5 (15.4)</td>
</tr>
</tbody>
</table>
ultrasound scan in the department of radiology before investigation of the patient’s cerebral haemodynamics. We were therefore unable to investigate severe pre-eclamptics as they were either confined to the labour suite, or underwent urgent Caesarean section. The carotid ultrasound scan in pre-eclamptic patients was performed to rule out the presence of any atheromatous plaques in the internal carotid artery, which in theory, could be dislodged during carotid compression for the THR test. The risk of developing atheromatous disease in pre-eclampsia has not been reported. We decided to screen pre-eclamptic patients as a matter of precaution because hypertension is one of the risk factors for developing atheromatous disease. Patients from other groups were not screened because they did not have any of the risk factors associated with atheromatous disease.

**CPP and CrCP**

Some studies have investigated eCPP in pre-eclamptic patients. Williams and Wilson found that mean eCPP was significantly lower in non-pregnant women compared with both healthy pregnant and (mild) pre-eclamptic women. Belfort and colleagues suggested that the brain can be ‘normally perfused, under-perfused or over-perfused’ in pre-eclampsia. In a different study, Belfort and colleagues also found that increasing severity of headache was associated with increasing eCPP.

We found a lower eCPP in non-pregnant women compared with healthy pregnant and pre-eclamptic women. There was no difference between healthy pregnancy and pre-eclampsia. These findings are similar to those of Williams and Wilson, although the absolute values of eCPP in our study are different. Previously reported results by Belfort and colleagues would suggest that the majority of the pre-eclamptics in our study had mild disease. The interpretation of the results of our study in conjunction with the previous studies would suggest that pregnancy leads to an increase in eCPP, with further increases in symptomatic, but not severe pre-eclampsia.

The only previously published data on cerebral CrCP in pregnancy comes from Belfort and colleagues in a study of general anaesthesia in severe preeclampsia. We found an increase in MAP is also associated with an increase in downstream pressure, therefore CPP is maintained. The hypotensive agents used in pre-eclampsia may affect CrCP in varying manner. It would be logical to use agents that affect MAP and CrCP in a similar fashion so the CPP is maintained. Therapies that reduce MAP but not CrCP will reduce cerebral perfusion. Further work needs to be done in this field, both to study the effects of severe/symptomatic pre-eclampsia upon the cerebral circulation, and the effects of the various anti-hypertensive drugs used in its treatment.

**Acknowledgement**

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**References**