Cerebral hemodynamics in normal and complicated pregnancy
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CHAPTER 4

CEREBRAL AUTOREGULATION IN NORMAL PREGNANCY AND PREECLAMPSIA

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ABSTRACT

Objective: Preeclampsia is associated with altered cerebral hemodynamics, and an increased risk for cerebrovascular complications. This is believed to be related to impaired autoregulation (AR), a physiological process that maintains blood flow at an appropriate level despite changes in blood pressure. Dynamic autoregulation has yet to be examined in women with untreated preeclampsia. The aim of this study was to test the hypothesis that preeclampsia is associated with impaired cerebral dynamic autoregulation (AR).

Methods: In a prospective cohort analysis cerebral blood flow velocity (CBFV) of the middle cerebral artery (determined by transcranial Doppler), blood pressure (determined by noninvasive arterial volume clamping), and end-tidal carbon dioxide (EtCO₂) were simultaneously collected during a 7-minute baseline periods of rest. The autoregulation index (ARI) was calculated. ARI values of 0 and 9 indicated absent and perfect autoregulation, respectively. Student’s t-test was used, with P<0.05 considered significant.

Results: Women with preeclampsia (prior to treatment, n=20) and their normotensive counterparts (n=20) did not differ with respect to baseline characteristics, except for earlier gestational age at delivery (363 (244–402) vs 392 (320–410), P<0.001), and higher blood pressure in women with preeclampsia. ARI during baseline was significantly reduced in preeclamptics compared with normotensive controls (5.5±1.7 vs. 6.7±0.6, P=0.004). There was no correlation between ARI and blood pressure.

Conclusion: Women with preeclampsia have impaired dynamic cerebral autoregulation. The fact that blood pressure does not correlate with autoregulation functionality may explain why cerebral complications such as eclampsia can occur without sudden and/or excessive elevation in blood pressure.
Chapter 4 - Cerebral autoregulation in normal pregnancy and preeclampsia

4.1 Introduction

During pregnancy, about 2-8% of women will be diagnosed with some form of hypertension or preeclampsia (PE). Complications of preeclampsia account for 16-38% of all maternal deaths,\(^1\)\(^2\) with cerebrovascular complications being the primary cause (38.7%).\(^1\)\(^2\) Preeclampsia has been implicated in hypertensive posterior reversible encephalopathy syndrome (PRES),\(^3\)\(^4\) which is hypothesized to be related to impaired autoregulation (AR), leading to either over- or underperfusion of the brain.\(^3\)\(^5\)\(^6\)

Cerebral autoregulation is a physiological process that maintains blood flow at an appropriate level, despite changes in blood pressure. Impairment of this function may explain why some patients develop cerebral edema and convulsions or cerebral hemorrhage, without significant hypertension.\(^7\)\(^8\)\(^9\) In previous studies using transcranial Doppler (TCD) the lack of increased resistance and the increased cerebral blood flow velocities, coupled with increased mean arterial pressure (MAP) in preeclamptic women, have been interpreted as dysfunctional autoregulation.\(^10\)\(^11\)\(^12\)\(^13\) Increased cerebral perfusion in preeclamptic patients was seen in studies using magnetic resonance imaging (MRI)\(^14\) supporting the concept that preeclampsia is associated with an overperfusion syndrome and disordered cerebral autoregulation. Cipolla et al. conducted multiple studies on the AR in rats, and found the upper limit of AR to be slightly shifted to the right in late pregnant rats, suggesting improved autoregulation. However, only the pregnant rats had significant cerebral edema in response to acute hypertension.\(^15\)

Transcranial Doppler (TCD) ultrasound makes it possible to study cerebral hemodynamics in pregnant women in a non-invasive fashion.\(^16\)\(^17\) When combined with a continuous non-invasive blood pressure measurement, dynamic cerebral AR (dCA) can be assessed at the bedside.\(^18\) The functionality of the dynamic AR can be expressed as the Autoregulation Index (ARI), with 0 representing absent and 9 perfect cerebral autoregulation.\(^19\) The cerebral blood flow velocity (CBFV) changes in response to BP perturbations caused by thigh cuff inflation, posture changes and drug effects have been used to study AR. However, these techniques are not suitable in pregnant patients for various logistic and practical reasons. Spontaneous fluctuation in
BP has been shown to correlate well with an induced decrease in BP with thigh cuffs for the estimation of ARI. This technique has been used in the study of cerebral autoregulation in stroke, hypertension and syncope. Studies of dynamic autoregulation in pregnancy are scarce. Only one study used a similar approach to examine dynamic autoregulation in 3 (pre)eclamptic women who were being treated with magnesium sulfate. They found reduced phase and elevated gain, indicating impaired autoregulation. No studies exist that compare normotensive pregnancy with preeclampsia before treatment with magnesium sulfate and/or antihypertensive medication. Therefore, our primary aim in this study was to test the hypothesis that preeclampsia is associated with impaired cerebral autoregulation.

4.2 Materials and Methods

We conducted a prospective cohort study over a six-month period (July 2012- February 2013). All subjects were non-laboring pregnant (or recently postpartum) women without a history of cerebrovascular disease. Women with preeclampsia (cases), were compared to a cohort of healthy normotensive pregnant women (controls). Preeclampsia was diagnosed according to ACOG guidelines. Although all patients had blood pressures and a physiologic state that met the diagnostic criteria for preeclampsia or normotensive pregnancy at the time of inclusion in the study, the blood pressures recorded at the time of the examination were not necessarily in this range. One examiner, with adequate training (TRVV) performed all the measurements, in some cases helped by an assistant (ACG). The Baylor College of Medicine Institutional Review Board approved this study, and informed consent was obtained from each participant prior to data collection.

Women were excluded from the control group if they had received any vasoactive medication, had greater than trace proteinuria, or had a blood pressure (BP) greater than 140 mmHg systolic and/or 90 mmHg diastolic at any point during their pregnancy. Furthermore, we excluded any patient who was included as a control but who later developed a hypertensive disease. Women in the preeclamptic group were excluded if (additional, in case of superimposed preeclampsia) antihypertensive therapy was initiated or magnesium sulfate (MgSO4)
was administered <48 hour before the examination.

Data were entered into a standardized database with the information being collected both from the medical record and from direct patient interview. The following maternal characteristics were based on self-report: race/ethnicity, height, current and prepregnancy weight, smoking and alcohol and illicit substance use. Gestational age was determined by menstrual dating. In cases of uncertain menstrual dates, ultrasound estimates of gestational age were used. The presence of neurological symptoms was abstracted from the medical record.

At the time of the TCD examination, brachial systolic (SBP) and diastolic (DBP) blood pressure were measured. Patients were studied in a semi-Fowlers position in a private room. Simultaneous transcranial Doppler (TCD) evaluation of both middle cerebral arteries (MCA) was carried out using 2 MHz pulsed, range gated transcranial Doppler probes (Spencer Technologies, Seattle, WA), held in place using a head frame. If only one MCA could be found, that one side was used in the analysis. The depth of insonation was set at 45 to 65 mm with slight anterior angulation (15-30 degrees) of the probe through the temporal window. The MCA was identified using M-mode to detect the MCA/ACA bifurcation, the expected velocity and the depth.

Blood pressure was continuously measured non-invasively using finger arterial volume clamping (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands) with the servo-adjust switched off. This was subsequently calibrated with the brachial BP. The BP tracing also served to mark each cardiac cycle. End-tidal CO₂ (EtCO₂) was measured with a nasal cannula (Nellcor Oximax N-85, Covidien, Mansfield, MA).

All data were recorded at 50 Hz, interpolated to 200 Hz and visually inspected during analysis to remove occasional large spikes. A median filter was used to remove small spikes and artifacts in the CBFV signal. All signals were then low-pass filtered with a Butterworth filter with a cutoff frequency of 20 Hz. Mean BP, bilateral CBFV, EtCO₂ and heart rate were then calculated for each beat. The critical closing pressure (CrCP) and resistance-area product (RAP) were obtained using the first harmonic of BP and CBFV of each cardiac cycle. All signals were then resampled at 5 Hz.

Cerebral autoregulation was determined from the CBFV
responses to spontaneous fluctuations in mean arterial BP as described previously.\textsuperscript{20} Segments consisting of 512 samples and 50\% superposition, were transformed with the fast Fourier transform (FFT) algorithm (Welch method), to obtain the transfer function parameters coherence, gain and phase in the low frequency range (<0.1 Hz). The inverse FFT was then performed to estimate the impulse and step responses. The CBFV step response to a sudden change in ABP was compared to 10 template curves proposed by Tiecks et al.\textsuperscript{19} and the best fit curve corresponded to the ARI autoregulation index.\textsuperscript{19,20} Measurements were rejected if coherence did not reach 0.5 for any frequency <0.25 Hz.

Baseline cerebral hemodynamic parameters are reported as the average over the 7 minute baseline recording.

Pulsatility (PI) and resistance (RI) indices and cerebral perfusion pressure (CPP) were calculated using the averages of the velocity and maternal blood pressure data as follows:

\begin{align*}
\text{PI} &= \frac{(\text{PSV}-\text{DV})}{\text{MV}} \\
\text{RI} &= \frac{(\text{PSV}-\text{DV})}{\text{PSV}} \\
\text{CPP} &= \frac{\text{[MV/MV-DV]}(\text{MAP-DBP})}{\text{}}
\end{align*}

All data sets were checked for normalcy of distribution (Kolmogorov-Smirnov test). Data are reported as mean and standard deviation, or median and [range] as appropriate. Analyses were performed using student t test or Mann-Whitney Rank Sum test. (Sigmastat 2004, Systat Software, Richmond, CA). P < 0.05 was used to indicate statistical significance.

Prior ARI studies have in general used 15-30 patients and one study showed that 45 patients are needed to show a ARI difference of 1.0;\textsuperscript{25} however, given that these were in non-pregnant women, who are expected to have a lower baseline ARI due to higher EtCO\textsubscript{2}, we could not reliably use their information for our sample size calculation. Accordingly, in this study, using a baseline mean ARI of 6.5 with an expected standard deviation of 1.0 (obtained from an initial cohort of 5 healthy pregnant women), we calculated a
necessary sample size of 16 in each group to provide approximately 80% power for detection of a 1.0 difference in group means (alpha=0.05). However, given that prior ARI studies have used more patients, we increased our sample size to remain consistent.

4.3 Results

A total of 42 patients were enrolled, and 40 successfully underwent dCA evaluation. There were 20 patients in the preeclampsia group, which was made up of 12 women with mild disease (5 of whom progressed to severe disease later in pregnancy), 3 patients with severe disease at the time of inclusion, and 5 with superimposed preeclampsia. Of these 20 patients, 4 (25%) reported a history of PE or gestational hypertension in a previous pregnancy. Twenty-two women were enrolled in the control group. One patient was excluded due to insufficient coherence, and one due to frequent extrasystoles (every 4th to 6th beat). Demographic data of the 40 patients used in the analysis are presented in Table 1. The patient in the control group who delivered at 32 weeks had monoamniotic monochorionic twins.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Preeclampsia (n=20)</th>
<th>Control (n=20)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Maternal age (years)</td>
<td>32 (18-43)</td>
<td>30 (19-36)</td>
<td>0.425</td>
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<tr>
<td>EGA at study (weekday)</td>
<td>35\textsuperscript{5} (24\textsuperscript{1} – 40\textsuperscript{5}) + 1 patient 4 days PP</td>
<td>37\textsuperscript{0} (24\textsuperscript{4} – 40\textsuperscript{3})</td>
<td>0.232</td>
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<tr>
<td>Prepregnancy BMI (kg/m\textsuperscript{2})</td>
<td>29 ± 8</td>
<td>27 ± 6</td>
<td>0.33</td>
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<tr>
<td>Current smoking</td>
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<td>1</td>
<td>1.00</td>
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<tr>
<td>Nulliparous</td>
<td>14</td>
<td>11</td>
<td>0.514</td>
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<tr>
<td>EGA at delivery (weekday)</td>
<td>36\textsuperscript{3} (24\textsuperscript{4} – 40\textsuperscript{2})</td>
<td>39\textsuperscript{2} (32\textsuperscript{0} – 41\textsuperscript{9})</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1: Demographic data

Figure 1 shows representative CBFV, BP and CBFV step response data from two patients. The upper panels depict 50 second segments of baseline CBFV and BP data from two patients (one with good AR
(control group, panel A) and one with impaired AR (preeclamptic group, panel C) and show the responses to a spontaneous decrease in BP. The lower panels (B and D) show the average step response of the 7 minutes baseline, with a good response (ARI = 7.0) in panel B and an abnormal response (ARI = 2.6) in panel D. In the patient with good functioning AR (panels A and B), the decrease in BP is accompanied by a smaller amplitude change in CBFV, an earlier nadir in CBFV, and a more rapid return to baseline (with an overshoot) as compared to the tracings seen in panel C. The CBFV step response, which reflects the effect of a sudden change in BP on the CBFV, also shows this fast recovery with overcorrection. The CBFV response in panel C mimics the BP, the recovery of the CBFV starts after the recovery of the BP, and the CBFV does initially not return to baseline. This pattern indicates impaired AR (ARI=2.6), and the CBFV step response reflects this by not returning to baseline.

Preeclamptic women had a significantly lower ARI (Figure 2), PI and RI, and higher CPP and RAP when compared with the control patients (Table 2). There was no significant correlation between ARI and PI, RI, CPP or RAP. However, the ranges of the cerebrovascular parameters were wider in the preeclamptic group, suggesting less homogeneity.

A subgroup analysis was performed comparing those preeclamptic women with an ARI above the mean ARI of the control group (ARI > 6.7), with those preeclamptic women who had an ARI at least 2 points lower (ARI <4.7). The two groups, which both consisted of 6 patients, were no different in terms of the type of hypertension (3 superimposed and 3 mild PE versus 1 superimposed, 2 mild, 2 severe and 1 postpartum PE), neurological symptoms, MAP, or CBFV. However, the three patients with the worst ARI (ARI < 3), all had chronic hypertension with superimposed preeclampsia, and required ≥ 2 antihypertensive drugs to control their BP. Only one other patient had a history of chronic hypertension and antihypertensive medication use (ARI = 7.7)
Figure 1) Example of good functioning AR (panel A) and corresponding step response (panel B, ARI = 7.0) and impaired AR (panels C and D, ARI = 2.6) during baseline measurement.

Figure 2) Average CBFV step responses of the preeclamptic (ARI = 5.5 ± 1.7) and the control group (ARI = 6.7 ± 0.6). Error bars represent largest ±1 S.E.M.
### Table 2: Hemodynamic data
ARI: Autoregulation index; BP: blood pressure; MAP: mean arterial pressure; EtCO₂: end-tidal CO₂; CPP: Cerebral Perfusion Pressure; CrCP: critical closing pressure
4.4 Discussion

The primary aim of this study was to test the hypothesis that preeclampsia is associated with impaired cerebral autoregulation and the data presented support the premise that preeclamptic patients have impaired dynamic cerebral autoregulation when compared to normotensive pregnant controls.

This study adds to the existing literature on cerebral hemodynamic abnormalities in preeclampsia. Dynamic cerebral autoregulation is abnormal in preeclampsia, and it does not directly correlate with blood pressure. This may indirectly explain the development of eclampsia, by means of autoregulatory breakthrough and hyperperfusion, without sudden and/or excessive elevation in blood pressure. In this study only 2 preeclamptic patients had a systolic BP > 160 mmHg, and none had a diastolic BP > 100 mmHg and yet dynamic cerebral autoregulation was abnormal. The mean BP in the subgroups with the best and worst ARI were not significantly different.

Aside from ARI, we also found statistically significant differences in RI, PI, RAP and CPP, but not in flow velocities or CrCP. These results are in agreement with previous studies. The increase in RAP suggests an increase in the myogenic activity, while the metabolic control, as indicated by CrCP was not different. The hemodynamic characteristics (e.g. ARI and blood flow velocities) of the control group were rather homogenous, the same could not be said for the cases. These hemodynamic variations reflect the wide array of presentations and varying (and multifactorial) underlying causes.

Clinical symptoms (especially visual disturbances and headache) have previously been shown to be associated with autoregulatory dysfunction in preeclampsia. In the current study, those women with the most dysfunctional AR could not be identified based on clinical characteristics, (degree of proteinuria, presence of severe clinical symptoms (e.g. headache), laboratory abnormalities (data not shown), or blood pressure). However, the groups are too small to draw any definitive conclusions.

Although the normal values of ARI are not defined, the ARI in the control group now described seems to be in the high normal range when compared to published data from non-pregnant subjects in an age range of 20-56 years, which have been reported to range
between 5.5 and 6.8. The higher ARI might be caused by the relative hypocapnia seen in pregnancy, which is known to cause physiologic vasoconstriction, a reduction in CBF and improved autoregulatory capacity.

This study has some limitations, which merit discussion. The study has a small sample size, which hindered any detailed subgroup analysis. The cases included few patients with severe laboratory abnormalities, or with neurological symptoms, which prohibited any analyses of correlation between these parameters and ARI. The data only represent a 7 minute period. While the reliability of the method has been proved in a longitudinal fashion in non-pregnant subjects, this might not hold true for preeclampsia, where blood pressure can be very labile. Due to the inherent limitations associated with the study design, assessment of ARI changes (if any) with advancing gestational age was not possible. Longitudinal studies in the future are necessary to assess this impact. Lastly, the MCA was studied because of its anatomical characteristics. However, the visual disturbances seen in preeclampsia and the fact that neuroimaging reveals that lesions consistent with PRES are generally seen in the posterior cortex implicate involvement of the posterior circulation. It is possible that local cerebral autoregulation is different in this part of the cerebrovascular system.

In conclusion, this study suggests the presence of impaired dynamic cerebral autoregulation in preeclamptic patients compared to their healthy counterparts. The paucity of data addressing the cerebral hemodynamic and autoregulation changes in preeclampsia underscore the need for further research in this area.
Chapter 4 - Cerebral autoregulation in normal pregnancy and preeclampsia

References


