CHAPTER 6

CEREBRAL AUTOREGULATION IN DIFFERENT HYPERTENSIVE DISORDERS OF PREGNANCY

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Cerebral hemodynamics in normal and complicated pregnancy

ABSTRACT

Objective: Cerebrovascular complications associated with hypertensive disorders of pregnancy (preeclampsia (PE), chronic hypertension (CHTN) and gestational hypertension (GHTN)) are believed to be associated with impaired cerebral autoregulation (AR), a physiological process that maintains blood flow at an appropriate level despite changes in blood pressure. The nature of AR dysfunction in these conditions is unclear. We therefore evaluated AR in 30 patients with PE, 30 with CHTN and 20 with GHTN, and compared them to a control group of 30 normal pregnant women.

Study design: The autoregulation index (ARI) was calculated using simultaneously recorded cerebral blood flow velocity in the middle cerebral artery (transcranial Doppler ultrasound), blood pressure (noninvasive arterial volume clamping), and end-tidal carbon dioxide during a 7-minute period of rest. ARI values of 0 and 9 indicate absent and perfect autoregulation, respectively. Statistics: ANOVA with Bonferroni test versus control group. Data are presented as mean±SD.

Results: ARI was significantly reduced in PE (ARI 5.5±1.6, P=0.002) and CHTN (5.6±1.7, P=0.004) but not in GHTN (6.7±0.8, P=1.0) when compared to controls (6.7±0.8). ARI was more decreased in patients with CHTN who subsequently developed PE than in those who did not (3.9±1.9 vs. 6.1±1.2, P=0.001). This was not true for women with GHTN or controls who later developed PE.

Conclusion: Pregnant women with CHTN or PE (even after excluding superimposed PE) have impaired AR when compared to women with GHTN or normal pregnancy. Whether the decreased ARI in patients with CHTN who later develop PE is due to preexistent differences or early affected cerebral circulation remains to be determined.
6.1 **INTRODUCTION**

Hypertension is one of the most common medical complications of pregnancy, accounting for 16-38% of all maternal deaths. While multiple maternal organs can be affected, cerebrovascular involvement is one of the more serious ones as it can lead to death or long-term morbidity due to cerebrovascular hemorrhage or edema. The cerebral manifestations in these patients are similar to those seen in the posterior reversible encephalopathy syndrome (PRES), which is hypothesized to be related to impaired autoregulation (AR), leading to either over- or underperfusion of the brain.

Hypertensive disorders of pregnancy range in a spectrum from chronic hypertension (CHTN) to gestational hypertension (GHTN), preeclampsia (PE), and super-imposed preeclampsia in the setting of chronic hypertension (SiPE). Women with CHTN have an increased risk of developing SiPE. The incidence has been reported to be between 12 and 29% from the first trimester. The risk for cerebrovascular complications during pregnancy is increased with all hypertensive disorders, but is most pronounced with severe preeclampsia and SiPE. These complications are believed to be caused by impaired cerebral autoregulation, related to endothelial dysfunction.

Cerebral autoregulation (AR) is the ability of the cerebral vasculature to maintain adequate cerebral perfusion despite changes in blood pressure. The cerebral AR can be assessed by using a combination of transcranial Doppler (TCD) and continuous non-invasive blood pressure measurement. The functionality of the AR can be expressed as the Autoregulation Index (ARI), with 0 being absent and 9 perfect cerebral autoregulation. This ARI has been shown to be lower in PE when compared to normotensive controls. The ARI was independent of blood pressure and clinical symptoms, which may explain why cerebral complications such as eclampsia and cerebrovascular hemorrhage can occur without sudden and/or excessive elevation in blood pressure. The ARI of the other hypertensive disorders in pregnancy is not known. Based on the increased risks of cerebrovascular complications seen in pregnancies complicated by CHTN and PE, but not in GHTN, we hypothesize that the AR is
impaired in CHTN (as has been shown for PE), but not in GHTN.

Consequently, the aim of this study was to evaluate cerebral autoregulation in hypertensive disorders of pregnancy (SiPE, PE, CHTN and GHTN), and compare this with a control group of normal pregnant women. Furthermore, we measured the more traditional parameters cerebral blood flow velocity, critical closing pressure and resistance-area-product to gain additional insight in the pathophysiology.

6.2 Materials and Methods

We conducted a prospective cohort study in non-laboring pregnant women recruited between 20 and 41 weeks gestation. The Institutional Review Boards at Baylor College of Medicine in Houston, Texas and North Austin Medical Center in Austin, Texas approved this study, and informed consent was obtained from each participant prior to data collection.

Patients were recruited and tested at Texas Children’s Pavilion for Women in Houston and North Austin Maternal-Fetal Medicine in Austin, Texas, either at the time of admission to the hospital for management of a hypertensive disorder, or at the time of routine prenatal care. Inclusion criteria were maternal age greater than 18 years and absence of a history of cerebrovascular disease or epilepsy. Hypertensive diagnoses were based on ACOG guidelines.17, 18 Exclusion criteria consisted of smoking, drugs use and the initiation of antihypertensive therapy or treatment with magnesium sulfate <48 hour before the examination.

Using a standard data collection sheet, demographic characteristics and obstetrical data were abstracted from patient interviews and medical records. The following maternal characteristics were based on self-report: race/ethnicity, height, current and pre-pregnancy 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. Patients were followed until 6 weeks postpartum.

At time of TCD examination, brachial systolic and diastolic blood pressures were measured. With the patients in semi-Fowlers position, bilateral maternal transcranial Doppler (TCD) examinations
of the middle cerebral artery (MCA) were carried out using 2 MHz pulsed, range gated transcranial Doppler probes (Spencer Technologies, Seattle, WA), held in place using a head frame.

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, and was afterwards calibrated with the brachial BP. The BP tracing also served to mark each cardiac cycle. End-tidal CO$_2$ (EtCO$_2$) was measured with a nasal cannula (Nellcor Oximax N-85, Covidien, Mansfield, MA), and linearly interpolated at the end of each expiratory phase.

Patients were measured only once for a period of 7 minutes. All data were recorded at 50 Hz, interpolated to 200 Hz and visually inspected during analysis to remove large spikes. A median filter was used to remove small spikes and artifacts in the cerebral blood flow velocity (CBFV) signal. All signals were then low-pass filtered with a Butterworth filter with a cutoff frequency of 20 Hz. Mean BP, bilateral CBFV, EtCO$_2$ 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. Segments of 512 samples and 50% superposition were transformed with the fast Fourier transform (FFT) algorithm, using the 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 BP was compared to 10 template curves proposed by Tiecks et al. and the best-fit curve corresponded to the ARI autoregulation index. A value of ARI=9 represents the best observed cerebral autoregulation. Measurements were rejected if coherence did not reach 0.5 for any frequency <0.25 Hz. Reported baseline CBFV, BP, RAP and CrCP were the averages over the 7 minute baseline recording.

All data sets were checked for normalcy of distribution (Sigmastat 2004, Systat Software, Richmond, CA). Data are reported
as mean and standard deviation, or median with the corresponding range as appropriate. Analyses were performed using ANOVA with Bonferroni’s post-hoc test, ANOVA on Ranks with Dunn’s post hoc test (both comparisons versus the control group) and a second analysis using multiple linear regression including pre-pregnancy BMI and gestational age at study was performed to control for these potential confounders.

Chi-square without Yates correction was used for analysis between groups. Student t test or Mann-Whitney Rank Sum test were used for subgroup analysis. Univariate regression analysis was used to assess the relationship between autoregulation parameters and blood pressure. A two tailed p < 0.05 was used to indicate statistical significance.

6.3 RESULTS

A total of 30 patients with preeclampsia (PE, 23 new onset, 7 superimposed PE (SiPE, confirmed PE at the time of measurement)), 30 with chronic hypertension (CHTN, 16 with and 14 without antihypertensive treatment), 20 with gestational hypertension (GHTN), and 30 controls were enrolled. Of the women with CHTN who had antihypertensive therapy, twelve used only labetalol, and two had labetalol combined with either hydralazine/furosemide or nifedipine. The other two women received metoprolol for blood pressure control.

Seven patients (23%) with CHTN (5 with and 2 without medication), 3 (10%) of the control group and 5 (25%) patients with GHTN later developed PE.

Maternal demographics were similar for both groups, except for gestational age at examination and delivery, pre-gestational BMI and parity (table 1).

Women with PE/SiPE (ARI 5.5 ± 1.6) or CHTN (ARI 5.6 ± 1.7) had a significantly lower ARI than the control group (ARI 6.7 ± 0.8), while GHTN (ARI 6.7 ± 0.8) was not associated with an altered ARI (Figure 1, table 2). There was no difference in ARI between women with CHTN with and without medication (ARI = 5.4 ± 1.9 vs. 5.8 ± 1.4, P=0.55). These outcomes did not change after adjusting for pre-pregnancy BMI and gestational age at the time of study.
Table 1) Demographic data. EGA: Estimated gestational age; PE: preeclampsia; CHTN: Chronic hypertension; GHTN: gestational hypertension; BMI: Body mass index. Data are mean ± SD, median (range) or number (%). Indicated P-values by ANOVA, ANOVA on ranks or Chi-square. *P < 0.001 vs. control (ANOVA with Bonferroni test); †P < 0.05 vs. control (ANOVA on Ranks with Dunn’s test).

<table>
<thead>
<tr>
<th></th>
<th>PE (n=30)</th>
<th>CHTN (n=30)</th>
<th>GHTN (n=20)</th>
<th>Control (n=30)</th>
<th>P-value (ANOVA)</th>
</tr>
</thead>
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<tr>
<td>Maternal age (years)</td>
<td>30 ± 7</td>
<td>29 ± 6</td>
<td>31 ± 5</td>
<td>30 ± 6</td>
<td>0.83</td>
</tr>
<tr>
<td>Pre-gestational BMI (kg/m²)</td>
<td>29 ± 8</td>
<td>36 ± 9*</td>
<td>31 ± 8</td>
<td>31 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus Type 2</td>
<td>6 (20%)</td>
<td>6 (20%)</td>
<td>2 (10%)</td>
<td>0</td>
<td>0.061</td>
</tr>
<tr>
<td>Gestational</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (13%)</td>
<td>4 (13%)</td>
<td>2 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>5 (17%)</td>
<td>0</td>
<td>3 (15%)</td>
<td>2 (7%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>23 (77%)†</td>
<td>11 (37%)</td>
<td>12 (60%)</td>
<td>17 (57%)</td>
<td>0.020</td>
</tr>
<tr>
<td>EGA at study (weekday)</td>
<td>35⁴ (24¹ – 40³)</td>
<td>33⁴ (20⁰ – 38²)</td>
<td>37¹ (27⁰ – 38⁰)</td>
<td>36⁰ (23³ – 40⁴)</td>
<td>0.002</td>
</tr>
<tr>
<td>EGA at delivery (weekday)</td>
<td>35⁵ (24³ – 40²)</td>
<td>37² (24³ – 39¹)</td>
<td>38⁰ (28⁰ – 39⁹)</td>
<td>39¹ (33³ – 41⁰)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 1) Average cerebral blood flow velocity (CBFV) step responses of all groups. PE: Preeclampsia; CHTN: Chronic hypertension; GHTN: gestational hypertension; a.u. arbitrary unit. Error bars represent largest ± standard error of the mean.
The ARI of women with SiPE was significantly lower than in those with new onset PE (3.9 ± 2.2 vs. 6.0 ± 1.1, P=0.002, Figure 2), but the ARI in new onset PE was still decreased when compared to the control group (6.0 ± 1.1 vs. 6.7 ± 0.8, P=0.007). RAP was significantly higher in PE and GHTN than in the controls, and even higher in the patients with SiPE. CrCP was lower in GHTN than in controls, but although there was a trend to a lower CrCP in PE, this difference did not reach significance.

ARI, RAP and CrCP were not significantly associated with MAP in women with preeclampsia. However, in both CHTN and control pregnant women, BP was positively associated with RAP (resp. P<0.0001 and P=0.014 respectively). Women with GHTN demonstrated a MAP positive association with CrCP and ARI (P=0.026 and P=0.037).

In subgroup analysis of women who did or did not develop preeclampsia (Table 2), the ARI was significantly lower in women with CHTN who subsequently developed SiPE versus those that did not. This was not seen in the GHTN group or controls. The time between the measurements and the development of PE varied widely, but was not different between the three groups. (Table 2)
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Table 2) Hemodynamic data: PE: preeclampsia; SiPE: Superimposed preeclampsia; CHTN: Chronic hypertension; GHTN: gestational hypertension; ARI: autoregulation index; MAP: Mean arterial pressure; EtCO$_2$: End-tidal CO$_2$; CBFV: Cerebral blood flow velocity; CrCP: Critical closing pressure; RAP: Resistance area product. Data are mean ± SD, or median (range). Indicated P-values by ANOVA or ANOVA on ranks. Adjusted P value is adjusted for BMI and gestational age at measurement. *P < 0.05; †P < 0.01 and ‡P ≤ 0.001 vs. control (ANOVA with Bonferroni test); §P < 0.05 (ANOVA on Ranks with Dunn’s test); ||P < 0.05; and ¶P < 0.01 vs. new PE or no later PE (t-test or Mann-Whitney U test).

6.4 Comment
In this study, we examined the autoregulation functionality in different hypertensive states of pregnancy, and compared them with those seen in pregnant normotensive controls. Our findings indicate that cerebral autoregulation is impaired in pregnant women with chronic hypertension and preeclampsia, and even more so in patients...
with superimposed preeclampsia. Cerebral autoregulation is, however, independent from the actual blood pressure values. Furthermore, the functionality of autoregulation is impaired in pregnant women with chronic hypertension, who subsequently developed superimposed preeclampsia when compared to women who did not develop SiPE. These results may explain why women with CHTN or PE have an increased risk of developing cerebral complications or stroke during pregnancy, even without sudden or excessive elevation in blood pressure.\textsuperscript{11-13}

Previous studies also have shown abnormal cerebral hemodynamics in PE, SiPE and CHTN,\textsuperscript{6, 21-23} and interpreted the finding of increased cerebral perfusion pressure (CPP) or CBFV as impaired autoregulation. However, none of these measured CBFV and BP simultaneously, and therefore could not assess the dynamic cerebral autoregulation. More recently, our group demonstrated decreased autoregulation index (ARI) in women with preeclampsia when compared to normotensive controls,\textsuperscript{5} with the largest degree of impairment in women with SiPE who required ≥ 2 antihypertensive drugs to control their BP. In this study, we also found a significant difference between SiPE and new onset PE. Indeed, the ARI of patients with new onset PE was not much different from the ARI of CHTN (5.9 ± 1.3 vs 5.6 ± 1.7, P=0.48). But in both groups, the large range in ARI indicates non-homogeneity in disease severity and possibly pathophysiology. In addition, women with CHTN who subsequently developed SiPE had a significantly lower ARI than those who did not progress to this disease, while the ARI in the GHTN and control groups were similar for those who did and did not progress to preeclampsia.

The spectrum of conditions, ranging from SiPE, PE and CHTN to GHTN and controls, along with their associated spectrum in ARI, might reflect a range of endothelial impairment. Scientific evidence suggests that altered expression of angiogenic factors produce systemic endothelial dysfunction and play an important role in the pathogenesis of preeclampsia.\textsuperscript{14} The extent of these deviations depends on the type of hypertensive disorder, being more pronounced in PE than in CHTN and GHTN when compared to controls.\textsuperscript{24-26} Another study found an altered angiogenic balance in PE, but not in GHTN.\textsuperscript{27}
These results are in agreement with our study. We also found that the ARI was lowest in the PE group, while the ARI in GHTN was similar to the control group. The proteinuria seen in PE is caused by renal endothelial dysfunction and is also related to this angiogenic imbalance.\(^ {14}\)

The increase in RAP seen in GHTN and PE is in accordance with a previous study, suggesting that RAP might reflect myogenic activity.\(^ {28}\) Interestingly, CrCP, which is more indicative of metabolic control,\(^ {28}\) appears to be decreased in both PE and GHTN, counteracting the effect of RAP. This suggests an abnormal neurovascular coupling, which was also seen in former (pre)eclamptic women.\(^ {29}\) Further work is required to establish the interpretation and significance of this difference.

Women with CHTN who subsequently did develop SiPE had a significantly decreased ARI. Their ARI was comparable to patients who already had SiPE. This can be explained in two possible ways. First, it is possible that the changes in cerebral autoregulation occur before clinical symptoms of SiPE appear, reflecting early manifestation of disease or the underlying pathophysiology. This possibility is further supported by the finding that CHTN outside of pregnancy does not appear to alter cerebral autoregulation, even in sustained untreated middle-aged and older people.\(^ {30-32}\) Furthermore, previous research has demonstrated that decreased maternal MCA resistance in the second trimester was predictive of subsequent preeclampsia in low-risk pregnant women, who can be expected to have no endothelial dysfunction at the time of the TCD examination.\(^ {33}\) These findings, coupled with evidence that angiogenic factors have been detected in maternal serum 5 to 10 weeks before the onset of preeclampsia, suggest that ARI may indeed be impaired in these cases well before the clinical manifestation of disease.\(^ {14, 24, 27}\) If this is in fact true, the ARI could have the potential of being used as a screening tool.

A second hypothesis is that the reduced ARI is an indication of baseline endothelial dysfunction, making pregnant women with CHTN more susceptible for developing SiPE. This is supported by the fact that women with CHTN or diabetes develop PE at a lower level of angiogenic disturbance,\(^ {25}\) and would also explain why the ARI in women with GHTN and controls was normal. In CHTN, endothelial
function is already impaired, and the angiogenic imbalance causes a second hit and SiPE. This theory is in agreement with Noori et al., who found impaired endothelial function in the brachial artery before angiogenic factors were altered.\textsuperscript{27}

One of the strengths of this study is the inclusion of patients with multiple hypertensive disorders of pregnancy and a pregnant control group, who were all studied in an identical setting. Further, none of the women received magnesium sulfate or had recent changes in antihypertensive therapy at time of the measurement.

This study also has some limitations, which merit discussion. A limitation of using TCD is that only the cerebral blood flow velocity (CBFV) can be obtained, and therefore relies on the assumption that changes in CBFV are directly proportional to changes in CBF. 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 pressures can be very labile. The study has a small sample size, predominantly in the SiPE, and GHTN groups, and in the comparison of those who did versus those who did not develop PE later during their pregnancy, which precluded any detailed subgroup analysis on severity of preeclampsia, laboratory abnormalities or neurological symptoms. The incidence and severity of adverse events in CHTN is related to the duration of the disease and the severity and control of the hypertension,\textsuperscript{7} but we do not have information on this from our patients. Finally, the women with chronic hypertension had a significant higher pre-gestational BMI and were studied at a younger gestational age, but controlling for this possible confounder in a multiple regression analysis did not change the results.

In conclusion, our findings suggest the presence of impaired dynamic cerebral autoregulation in patients with PE, particularly in those with SiPE, when compared to their GHTN or normotensive counterparts. The autoregulation is impaired in patients with CHTN who subsequently develop SiPE, but not in normotensive pregnant women or women with GHTN who subsequently develop PE. Whether this disparity is due to preexistent differences or early affected cerebral circulation in pregnant women with CHTN remains to be determined.
# References

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