CHAPTER 5

EFFECT OF BREATH HOLDING ON CEREBRO-VASCULAR HEMODYNAMICS IN NORMAL PREGNANCY AND PREECLAMPSIA

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ABSTRACT

Preeclampsia (PE) is associated with endothelial dysfunction and impaired autonomic function, which is hypothesized to cause cerebral hemodynamic abnormalities. Our aim was to test this hypothesis by estimating the difference in the cerebrovascular response to breath holding (BH) (known to cause sympathetic stimulation) between women with preeclampsia and a group of normotensive controls.

In a prospective cohort analysis, cerebral blood flow velocity (CBFV) in the middle cerebral artery (transcranial Doppler), blood pressure (BP, noninvasive arterial volume clamping), and end-tidal carbon dioxide (EtCO₂) were simultaneously recorded during a 20 second breath hold maneuver. CBFV changes were broken down into standardized subcomponents describing the relative contributions of BP, cerebrovascular resistance index (CVRi), critical closing pressure (CrCP) and resistance area product (RAP). The area-under-the-curve (AUC) was calculated for changes in relation to baseline values.

A total of 25 preeclamptic (prior to treatment), and 25 normotensive women in the second half of pregnancy were enrolled, and respectively 22 and 21 patients were included in the analysis. The increase in CBFV and EtCO₂ was similar in both groups. However, the AUC for CVRi and RAP during BH was significantly different between the groups (3.05±2.97 vs.-0.82±4.98, P=0.006 and 2.01±4.49 vs.-2.02±7.20, P=0.037), indicating an early, transient increase in CVRi and RAP in the control group, which was absent in PE. BP had an equal contribution in both groups.

Women with preeclampsia have an altered initial CVRi response to the BH maneuver. We propose that this is due to blunted sympathetic or myogenic cerebrovascular response in women with preeclampsia.
5.1 Introduction

Preeclampsia (PE) is a systemic disease occurring in the second half of pregnancy, complicating 2–8% of pregnancies, and among the leading causes of maternal mortality and severe morbidity. PE is generally defined as new hypertension and proteinuria. The exact pathophysiology of preeclampsia remains unclear, but leading hypotheses are based on disturbed placental function in early pregnancy, causing endothelial dysfunction that can affect several organs, including the brain.\(^1\) Cerebral manifestations include headache, hypertensive encephalopathy, eclampsia, and cortical blindness, and are believed to be caused by impaired cerebral blood flow regulation.\(^2\) Cerebral autoregulation (AR) is the ability of the cerebral vasculature to maintain adequate cerebral perfusion despite changes in blood pressure, and can be affected by a variety of factors such as partial pressure of carbon dioxide (PaCO\(_2\)), extreme hypo- or hypertension, mental activation and intracranial pressure.

Deep breath holding is associated with complex chemical (PaCO\(_2\)), mechanical (changes in BP and heart rate (HR)), and neural consequences (autonomic nervous system), all of which affect cerebral blood flow (CBF). Deep breath holding induces changes in the autonomic nervous system, which is thought to result in a redistribution of blood flow to the cerebral circulation.\(^3,4\) This physiological response is known as the diving response, and characterized by a rapid onset bradycardia.\(^3\)

The hypercapnia that occurs as a result of breath holding leads to cerebral vasodilation and increased CBF, and reflects the ability of the vascular endothelium to adapt to changes in metabolic activity. This vasoreactivity is impaired in patients who have a predisposition to cerebrovascular diseases, such as hypertension,\(^5,6\) diabetes\(^5,7\) or carotid artery stenosis.\(^5,8\) The proposed hypothesis to explain the response has to date been based on endothelial dysfunction.\(^5,7\)

Previous studies on vasoreactivity in women with preeclampsia have shown conflicting results, with either impaired\(^9,10\) or unaffected\(^11\) vasoreactivity. However, none of these studies measured the CBF velocity (CBFV) or the blood pressure (BP) continuously, and thus lacked the ability to define the temporal pattern of the physiologic changes associated with hypercapnia.
Using multivariate models of the CBFV response to breath holding, the independent contributions of (a) BP and cerebrovascular resistance (CVR) and (b) BP, critical closing pressure (CrCP) and resistance area product (RAP), to changes in CBFV can be analyzed. While resistance (CVR) has traditionally been used to indicate vasodilation or vasoconstriction, a two-parameter model, using CrCP and RAP can give more information, possibly reflecting different regulatory pathways in the cerebral circulation. It has been suggested that CrCP is mainly influenced by metabolic pathways, while RAP is thought to largely reflect myogenic activity in response to BP transients.\textsuperscript{12,13} By separating the different systemic and cerebral influences that account for the CBF response, more insight into the pathophysiology of preeclampsia will be gained.

Therefore, our primary aim in this study was to test the hypothesis that preeclampsia is associated with an altered cerebrovascular response to breath holding when compared to their normotensive counterparts.

### 5.2 Methods

We conducted a prospective cohort study in non-laboring pregnant women without a history of cerebrovascular disease. Women with preeclampsia (cases), were compared to a cohort of healthy normotensive pregnant women (controls).

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 preeclampsia, or at the time of routine prenatal care. Preeclampsia was diagnosed according to ACOG guidelines.\textsuperscript{14} One examiner (TRVV) performed all the measurements. The Institutional Review Boards at Baylor College of Medicine in Houston, Texas and North Austin Medical Center in Austin, Texas approved the study, and informed consent was obtained from each participant prior to data collection.

Women were excluded from the control group if they had a history of a chronic disease, had received any vasoactive medication, had greater than trace proteinuria, or had blood pressure (BP) greater than 140 mmHg systolic and/or 90 mmHg diastolic at any point.
during their pregnancy. Inability to perform the breath holding maneuver, or an incorrectly performed maneuver were also exclusion criteria. Furthermore, we excluded any patient who was included as a control but who later in pregnancy developed a hypertensive disease or diabetes. Women with preeclampsia were excluded if antihypertensive therapy was initiated, or magnesium sulfate (MgSO4) was administered <48 hour before the examination.

Data were entered into a standardized database with background 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 pre-pregnancy weight, smoking, 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. Blood pressure was continuously measured non-invasively using finger arterial volume clamping (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands) with the servo-adjust control switched off. This was subsequently 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.

After an acclimatization period of at least 10 minutes, patients were asked to take a breath and hold it for 20 seconds (or for as long as possible if they were unable to achieve a 20 second breath hold). This was followed by a 2 minute recovery period during which they breathed normally. The initial small BP peak at the start of the BH maneuver was used as point of synchronism and as the beginning of the 20 second analysis interval.
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 cerebrovascular resistance index (CVRi) was estimated by the ratio meanABP/meanCBFV of each cardiac cycle and critical closing pressure (CrCP) and resistance-area product (RAP) were obtained using the first harmonic of BP and CBFV. All signals were then resampled at 5 Hz.

To identify the different systemic and cerebral contributions to the total change in CBFV induced by breath holding, the total percentage change in CBFV was broken down into standardized subcomponents describing the relative contributions of BP, CVRi, CrCP and RAP. The subcomponent analysis was represented in two ways: 1) as the sum of simultaneous changes in BP, CrCP and RAP; and 2) as the sum of changes in BP and CVRi, resulting in

1) \( \Delta v = V_{BP} + V_{CrCP} + V_{RAP} \) and

2) \( \Delta v = V_{BP} + V_{CVRi} \)

where \( \Delta v \) is the change in CBFV in percent of baseline values and \( V_{ABP} \), \( V_{CrCP} \), \( V_{RAP} \) and \( V_{CVRi} \) are its subcomponents due to concomitant changes in ABP, CrCP, and RAP, respectively, which are also expressed in % change in velocity.

With this analysis, RAP, CVRi and CrCP will appear inverted since their increases will lead to reductions in CBFV.

The area-under-the-curve (AUC) of these parameters was calculated for changes in relation to baseline values. A low-pass filter with a cutoff frequency of 0.15 Hz was used for the graphs. The baseline values reflect the average over a one-minute period before the breath holding maneuver.

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, Mann-Whitney Rank Sum test or Fisher’s exact test. (Sigmastat 2004, Systat Software, Richmond, CA). A P-value of < 0.05 was used to indicate statistical significance.

5.3 RESULTS

A total of 25 patients were enrolled in each group and included in the analysis. After visual inspection of the heart rate response, 3 women with preeclampsia and 4 normotensive women were excluded because they showed an acceleration in HR during the breath holding maneuver, suggesting an incorrectly performed breath hold maneuver. One patient with severe post-partum preeclampsia was excluded to eliminate the effect higher PaCO\textsubscript{2} postpartum when compared to pregnancy. The preeclampsia group was made up of 12 women with mild disease (3 of whom progressed to severe disease later in pregnancy), 3 patients with severe disease at the time of inclusion, and 6 with superimposed preeclampsia. Four patients with PE had diabetes, all were monitored very closely, 3 were diet controlled and none had any signs of end-organ damage. The two groups did not differ with respect to demographic features except for earlier gestational age at delivery in the subjects with preeclampsia (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Preeclampsia (n=21)</th>
<th>Control (n=21)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>30.9 ± 6.2</td>
<td>30.5 ± 4.9</td>
<td>0.83</td>
</tr>
<tr>
<td>Pre-gestational BMI (kg/m\textsuperscript{2})</td>
<td>30.7 ± 8.2</td>
<td>26.3 ± 6.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Current smoking (n (%))</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Nulliparous (n (%))</td>
<td>14 (67%)</td>
<td>13 (62%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Multiple gestation (n (%))</td>
<td>5 (24%)</td>
<td>1 (4%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Diabetes Mellitus (n (%))</td>
<td>4 (19%)</td>
<td>0</td>
<td>0.11</td>
</tr>
<tr>
<td>EGA at study (week\textsubscript{day})</td>
<td>35\textsuperscript{4} (24\textsuperscript{1} – 40\textsuperscript{1})</td>
<td>37\textsuperscript{2} (24\textsuperscript{4} – 40\textsuperscript{3})</td>
<td>0.07</td>
</tr>
<tr>
<td>EGA at delivery (week\textsubscript{day})</td>
<td>35\textsuperscript{5} (24\textsuperscript{3} – 40\textsuperscript{2})</td>
<td>39\textsuperscript{9} (32\textsuperscript{0} – 41\textsuperscript{1})</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1) Demographic data BMI: body mass index; EGA: estimated gestational age; PP: postpartum Data are median (range), mean ± standard deviation, or n(%).
Baseline CBFV, BP, CVRi and RAP were significantly higher in women with preeclampsia (Table 2).

<table>
<thead>
<tr>
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<th>Preeclampsia (n=21)</th>
<th>Control (n=21)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBFV (cm/s)</td>
<td>76.0 ± 18.0</td>
<td>65.5 ± 8.4</td>
<td>0.016</td>
</tr>
<tr>
<td>CVRi (mmHg.s.cm(^{-1}))</td>
<td>1.50 ± 0.39</td>
<td>1.28 ± 0.24</td>
<td>0.039</td>
</tr>
<tr>
<td>CrCP (mmHg)</td>
<td>3.71 (0 – 40)</td>
<td>10.6 (0 – 25)</td>
<td>0.58</td>
</tr>
<tr>
<td>RAP (mmHg.s.cm(^{-1}))</td>
<td>1.37 ± 0.44</td>
<td>1.14 ± 0.27</td>
<td>0.033</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>108.3 ± 12.6</td>
<td>82.0 ± 9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>87.2 ± 8.6</td>
<td>84.5 ± 11.9</td>
<td>0.40</td>
</tr>
<tr>
<td>EtCO(_2) (mmHg)</td>
<td>33.6 ± 2.1</td>
<td>34.5 ± 1.6</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Table 2: Baseline hemodynamic values. CBFV: Cerebral blood flow velocity; CVRi: cerebrovascular resistance index; CrCP: Critical closing pressure; RAP: resistance area product; MAP: mean arterial pressure; HR: heart rate; EtCO\(_2\): End tidal carbon dioxide. Data are median (range) or mean ± standard deviation.

In both groups, the breath holding maneuver resulted in a typical pattern, consisting of bradycardia (Figure 1), followed by the following pattern in BP and CBFV: initial increase, subsequent decrease, and final slow rise preceding the peak immediately after the end of breath hold (Figure 2).

Figure 1: Changes in heart rate (HR) and end-tidal CO\(_2\) (EtCO\(_2\)) during the breath hold maneuver (gray bar) for the two groups BPM: beats per minute; Gray bar: breath hold maneuver.
The change in CBFV (Δv), expressed in percent of baseline values, during breath holding for each group is presented in Figures 2 and 3. This change is the sum of simultaneous changes in BP and CVRi (Figure 2) or BP, CrCP and RAP (Figure 3).

BP had an equal contribution in both groups (-1.84 ± 4.46 vs. 0.70 ± 5.24, P=0.08), but the AUC for CVRi and RAP during BH were significantly different between the groups (3.05 ± 2.97 vs. -0.82 ± 4.98, P=0.006 and 2.01 ± 4.49 vs. -2.02 ± 7.2, P=0.037, Table 3).
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<th>Preeclampsia (n=21)</th>
<th>Control (n=21)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>CBFV (%)</td>
<td>1.24 ± 3.5</td>
<td>-0.02 ± 4.3</td>
<td>0.43</td>
</tr>
<tr>
<td>CVRi (%)</td>
<td>3.05 ± 2.97</td>
<td>-0.82 ± 4.98</td>
<td>0.006</td>
</tr>
<tr>
<td>CrCP (%)</td>
<td>1.33 ± 3.17</td>
<td>1.38 ± 3.76</td>
<td>0.88</td>
</tr>
<tr>
<td>RAP (%)</td>
<td>2.01 ± 4.49</td>
<td>-2.02 ± 7.2</td>
<td>0.037</td>
</tr>
<tr>
<td>MAP (%)</td>
<td>-1.84 ± 4.46</td>
<td>0.70 ± 5.24</td>
<td>0.08</td>
</tr>
<tr>
<td>EtCO2 (mmHg)</td>
<td>35.9 ± 2.4</td>
<td>36.5 ± 2.2</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Table 3) Area under the curve for subcomponents of CBFV variation during breath holding. For abbreviations, see Table 1.

Figure 4 shows the average percentage of the CVRi contribution for the two groups, in absolute values (A) and as a component of the CBFV change (B), with the AUC indicated by the shaded areas. This figure also shows a second transient increase in CVRi in the control group, leading to a negative reflection in the subcomponent analysis (increased CVRi decreases the CBFV, Figure 4B). This transient change was absent in women with preeclampsia.

Visual inspection of the measurements showed that 81% of the tracings in the control group had a second peak, while only 41% of the tracings of women with preeclampsia demonstrated this peak (P=0.005).

![Figure 4](image-url)  
*Figure 4* Group averages of CVRi during breath holding.  
A: absolute CVRi values, showing an absent transient increase in the PE group. B: Subcomponent analysis of CVRi, indicating the percentage contribution of CVRi to the CBFV response. Positive changes in VRAP and VCrCP are caused by reductions in RAP and CrCP, leading to increases in CBFV. The shaded areas indicate the area under the curve used for analysis. CVRi: Cerebrovascular resistance index; PE: Preeclampsia.
5.4 Discussion

This study shows that women with preeclampsia have an altered cerebrovascular response to breath holding when compared to normotensive pregnant women. Even though the CBFV and BP response, and the peak CBFV, BP and CVRi are similar in both groups, the group with preeclampsia lacks a transient increase in both CVRi and RAP during the initial phase of the BH maneuver. We hypothesize that this is due to a blunted sympathetic or impaired myogenic cerebral vasoconstriction response in women with preeclampsia.

Besides influencing PaCO$_2$, deep breath holding also affects the sympathetic nervous system via the diving reflex.$^3$ This reflex is characterized by peripheral sympathetic stimulation, leading to vasoconstriction and increased blood pressure (BP) along with a parasympathetic induced heart rate reduction,$^3$ which can also be elicited by immersion of the face in cold water. The combination of apnea with stimulation of facial cold receptors attenuates the response.$^3$ Although the exact role of the autonomic nervous system on the regulation of CBF remains controversial,$^{16}$ recent studies do suggest an autonomic, mainly sympathetic, role in cerebral blood flow control.$^{17, 18}$

Little is known about the CBF response to the diving reflex. PaCO$_2$ is a potent vasodilator, for which the vasculature of the brain is more sensitive than the systemic circulation,$^{3, 4, 19, 20}$ causing a redistribution of blood to the brain. The effect of BP, sympathetic stimulation and CVR in this sequence of events is largely unknown. Palada et al. saw an initial increase in CVRi during breath holding, before becoming negative.$^{20}$ Brown et al. applied a cold stimulus in eucapnic conditions, and showed an increase in CVRi until the stimulus was removed.$^{21}$ They interpreted this as sympathetic induced vasoconstriction.

In this study, the transient increase in CVRi and RAP in the early, eucapnic stage of breath holding might indicate a transient sympathetic effect initiated by the diving reflex, before the effect of the increased PaCO$_2$ dominates, causing vasodilation and thus decreasing CVR. The patients with preeclampsia did not show this initial response, and the CVRi seemed to be mainly influenced by the BP and PaCO$_2$. The precise mechanism for this cannot be determined.
from our study, but potential explanations are a diminished sensitivity of the cerebral vasculature to sympathetic activity or impairment of the vessels’ response to this activity (possibly due to increased sympathetic activity or increased CVRi at baseline).22

Another explanation could be impairment of the myogenic pathway. Salinet et al. showed a similar response in patients with a recent ischemic stroke.23 In those patients, the RAP followed the BP, instead of the metabolic demand during passive arm movement, while the CrCP response was similar to controls.23 The authors interpreted this as the result of a damaged myogenic pathway.23

The similar subcomponent peak of CrCP between the groups in our study suggests that the metabolic pathway is intact, at least during the relatively small demand of a short breath hold. The contribution of the metabolic versus myogenic effect of sympathetic stimulation is not known.

One of the strengths of this study is the inclusion of patients with PE who were not treated with magnesium sulfate or had recent changes in antihypertensive therapy at time of the measurement. This study has some limitations, which also merit discussion. The small sample size hindered any detailed subgroup analysis. The cases included few patients with severe laboratory abnormalities, or with neurological symptoms, which precluded any analyses of correlation between these parameters and the CVRi pattern.

Another potential limitation relates to the measurement technology that was used to measure CBFV (TCD) and BP (finger arterial volume clamping). TCD measured blood flow-velocity can only reliably be interpreted as CBF if the diameter of the MCA remains constant. However, studies have shown that the MCA does not change diameter despite significant changes in CO₂.24, 25 If the MCA diameter were reduced, it would lead to an overestimation of the CBFV and RAP changes, but changes in CrCP would not be affected. Estimates of cerebral hemodynamic parameters from noninvasive BP measurement in the finger are comparable to those estimated using intra-arterial measurements in the ascending aorta.26 However, in the case of peripheral vasomotor regulation during breath holding, and the subsequent sympathetic stimulation of the diving reflex, this might not be the case. This is because the diving reflex has a graded
response and may cause a greater vasoconstrictor response in the fingers than in the forearm.  

In conclusion, this study suggests that the cerebral circulation of women with preeclampsia has a reduced vasoconstrictor response, similar to what is seen in acute stroke patients. Further research is needed to get a better understanding of the influence of the sympathetic nervous system and the myogenic pathways on the cerebral complications seen in preeclampsia.
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References
