Effect of breath holding on cerebrovascular hemodynamics in normal pregnancy and preeclampsia

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Preeclampsia (PE) is a systemic disease occurring in the second half of pregnancy, complicating 2–8% of pregnancies, and is among the leading causes of maternal mortality and severe morbidity. PE is generally defined as new hypertension and proteinuria in the second half of pregnancy. 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 (23). Cerebral manifestations include headache, hypertensive encephalopathy, eclampsia, and cortical blindness, and are believed to be caused by impaired cerebral blood flow regulation (26). Cerebral auto-regulation (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 (PaCO2), extreme hypotension, mental activation, and intracranial pressure.

Deep breath holding is associated with complex chemical (PaCO2), 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, 11). 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 (8, 9), diabetes (7, 8), or carotid artery stenosis (8, 22). The proposed hypothesis to explain the response has to date been based on endothelial dysfunction (7, 8).

Previous studies on vasoreactivity in women with preeclampsia have shown conflicting results, with either impaired (16, 18) or unaffected (25) 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.

By using multivariate models of the CBFV response to breath holding, the independent contributions of 1) BP and cerebrovascular resistance (CVR) and 2) BP, critical closing pressure (CrCP), and resistance area product (RAP) to changes in CBFV can be analyzed. Although 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, whereas RAP is thought to largely reflect myogenic activity in response to BP transients (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 compared with their normotensive counterparts.
Table 1. Demographic data

<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, yr</td>
<td>30.9 ± 6.2</td>
<td>30.5 ± 4.9</td>
<td>0.83</td>
</tr>
<tr>
<td>Premedication BMI, kg/m^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 (0%)</td>
<td>0.11</td>
</tr>
<tr>
<td>EGA at study, weekday</td>
<td>35^s (24^s-40^s)</td>
<td>37^s (24^s-40^s)</td>
<td>0.07</td>
</tr>
<tr>
<td>EGA at delivery, weekday</td>
<td>35^s (24^s-40^s)</td>
<td>39^s (32-41^1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are median (range), mean ± SD, or n, BMI, body mass index; EGA, estimated gestational age.

METHODS

We conducted a prospective cohort study in nonlaboring pregnant women without a history of cerebrovascular disease. Women with preeclampsia (cases) were compared with 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 American Congress of Obstetricians and Gynecologists guidelines (1).

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 written informed consent was obtained from each participant before 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 h before the examination.

Data were entered into a standardized database, with background information being collected from both 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, 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 transcranial Doppler (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 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 noninvasively 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 CO2 (EtCO2) 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 min, patients were asked to take a breath and hold it for 20 s (or for as long as possible if they were unable to achieve a 20-s breath hold). This was followed by a 2-min 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-s 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 (14). 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 (13); (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 ΔV = VBP + VCrCP + VRAP and 2) ΔV = VBP + VCrCP, where ΔV is the change in CBFV in percent of baseline values and VABP, VCrCP, VRAP, and VCVRi are its subcomponents due to concomitant changes in ABP, CrCP, and RAP, respectively, which are also expressed in %change in velocity (12).

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

Table 2. Baseline hemodynamic values

<table>
<thead>
<tr>
<th></th>
<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>
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<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, beats/min</td>
<td>87.2 ± 8.6</td>
<td>84.5 ± 11.9</td>
<td>0.40</td>
</tr>
<tr>
<td>etCO2, mmHg</td>
<td>33.6 ± 2.1</td>
<td>34.5 ± 1.6</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Data are median (range) or mean ± SD. CBFV, cerebral blood flow velocity; CVRi, cerebrovascular resistance index; CrCP, critical closing pressure; RAP, resistance area product; MAP, mean arterial pressure; HR, heart rate; etCO2, end tidal carbon dioxide.

Fig. 1. Changes in heart rate (HR) during the breath hold maneuver (gray bar) for the 2 groups. BPM, beats per minute.
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 1-min 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’s $t$-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.

RESULTS

A total of 25 patients was enrolled in each group and included in the analysis. After visual inspection of the heart rate response, three women with preeclampsia and four 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 postpartum preeclampsia was excluded to eliminate the effect higher PaCO2 postpartum compared with pregnancy. The preeclampsia group was made up of 12 women with mild disease (3 of whom progressed to severe disease later in pregnancy), three patients with severe disease at the time of inclusion, and six with superimposed preeclampsia. Four patients with PE had diabetes, all were monitored very closely, three 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).

Baseline CBFV, BP, CVRI, and RAP were significantly higher in women with preeclampsia (Table 2).

In both groups, the breath holding maneuver resulted in a typical pattern, consisting of bradycardia (Fig. 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 (Fig. 2).

The change in CBFV ($\Delta v$), expressed in percent of baseline values, during breath holding for each group is presented in Figs. 2 and 3. This change is the sum of simultaneous changes in BP and CVRI (Fig. 2) or BP, CrCP, and RAP (Fig. 3).

BP had an equal contribution in both groups ($-1.84 \pm 4.46$ vs. $0.70 \pm 5.24$, $P = 0.08$), but the AUC for CVRI and RAP during BH were significantly different between the groups ($3.05 \pm 2.97$ vs. $-0.82 \pm 4.98$, $P = 0.006$ and $2.01 \pm 4.49$ vs. $-2.02 \pm 7.2$, $P = 0.037$, Table 3). 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, Fig. 4B). This transient change was absent in women with preeclampsia.

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Fig. 2. Group average components of CBFV change during breath holding in percentage change in the control group (A) and the preeclampsia group (B) for the CVRI model. Change in cerebral blood flow velocity (CBFV) is the sum of simultaneous changes in mean arterial pressure (MAP) and cerebrovascular resistance index (CVRI). Gray bar, breath hold maneuver. Error bars represent largest ± S.E.M.

Fig. 3. Group average components of CBFV change during breath holding in percentage change in the control group (A) and the preeclampsia group (B) for the critical closing pressure + resistance area product (CrCP+RAP) model. The change in CBFV is the sum of simultaneous changes in blood pressure (BP), critical closing pressure (CrCP), and resistance area product (RAP). Gray bar, breath hold maneuver. Error bars represent largest ± S.E.M.
Table 3. Area under the curve for subcomponents of CBFV variation during breath holding

<table>
<thead>
<tr>
<th></th>
<th>Preeclampsia(n = 21)</th>
<th>Control(n = 21)</th>
<th>P Value</th>
</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>

Data are mean ± SD.

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

DISCUSSION

This study shows that women with preeclampsia have an altered cerebrovascular response to breath holding compared with normotensive pregnant women. Although 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.

In addition to influencing PaCO₂, 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 (20), recent studies do suggest an autonomic, mainly sympathetic, role in cerebral blood flow control (5, 27).

Little is known about the CBF response to the diving reflex. PaCO₂ is a potent vasodilator, for which the vasculature of the brain is more sensitive than the systemic circulation (3, 10, 11, 24), 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. (10) saw an initial increase in CVRi during breath holding, before becoming negative. Brown et al. (2) applied a cold stimulus in eucapnic conditions and showed an increase in CVRi until the stimulus was removed (2). 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 PaCO₂ 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 PaCO₂. 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) (19).

Another explanation could be impairment of the myogenic pathway. Salinet et al. (17) showed a similar response in patients with a recent ischemic stroke (17). In those patients, the RAP followed the BP instead of the metabolic demand during passive arm movement, whereas the CrCP response was similar to controls (17). The authors interpreted this as the result of a damaged myogenic pathway (17).

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 vs. 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 the 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 (4, 21). 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 with those estimated using intra-arterial measurements in the ascending aorta (15). 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 (6).

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.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

REFERENCES