Hypertension Impairs Vascular Reactivity in the Pediatric Brain

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Background and Purpose—Chronic hypertension impairs cerebrovascular regulation in adults, but its effects on the pediatric population are unknown. The objective of this study was to investigate cerebrovascular abnormalities in hypertensive children and adolescents.

Methods—Sixty-four children and adolescents aged 7 to 20 years underwent transcranial Doppler examinations of the middle cerebral artery at the time of rebreathing CO2. Time-averaged maximum mean cerebral blood flow velocity and end-tidal CO2 were used to quantify cerebrovascular reactivity during hypercapnia. Patients were clinically categorized as hypertensive, prehypertensive, or white coat hypertensive based on 24-hour ambulatory blood pressure measurements. Their reactivities were compared with 9 normotensive control subjects and evaluated against baseline mean blood pressure z-scores and loads.

Results—Untreated hypertensive children had significantly lower hypercapnic reactivity than normotensive children (2.556 \( \pm \) 1.832 cm/s \( \pm \) 85.28 mm Hg versus 4.256 \( \pm \) 1.334 cm/s \( \pm \) 85.28 mm Hg, \( P < 0.05 \)). Baseline mean diastolic blood pressure z-scores (\( r = -0.331, P = 0.037 \)) and diastolic blood pressure loads (\( r = -0.351, P = 0.026 \)) were inversely related to reactivity.

Conclusions—Untreated hypertensive children and adolescents have blunted reactivity to hypercapnia, indicating deranged vasodilatory reactivity. The inverse relationship between diastolic blood pressure indices and reactivity suggests that diastolic blood pressure may be a better predictor of cerebral end organ damage than systolic blood pressure. (Stroke. 2011;42:000–000.)

Key Words: cerebral blood flow • cerebrovascular reactivity • hypercapnia • hypertension • pediatric • transcranial Doppler

Although adult hypertension is associated with tangible consequences, including stroke, vascular dementia, heart failure, and renal disease, evidence of target organ damage in mild to moderate childhood hypertension has only recently been elucidated. Consequently, pediatric hypertension is defined statistically, instead of functionally, as the top fifth percentile of blood pressure values by age, height, and gender.

Attempts to define hypertensive end organ damage in the pediatric brain document an association between pediatric essential hypertension and decreased cognitive function as evaluated with neuropsychological testing. However, these reports lack evidence of a physiological substrate for the cognitive changes that are found with modest blood pressure elevation. In adults, findings support a relationship between long-standing hypertension with the presence of altered cerebral autoregulation, decreased cerebral microvascular reactivity, and white matter lesions. Similar changes in hypertensive children have not been described.

The objective of this study was to investigate cerebrovascular abnormalities in hypertensive children. We hypothesize that chronic essential hypertension in children results in impaired cerebrovascular reactivity, whose effects on white matter may explain the cognitive changes seen in these children. We assessed cerebrovascular regulatory capacity by measuring the response of cerebral blood flow velocities (CBFV) to hypercapnia in children and adolescents with hypertension, prehypertension, and white coat hypertension compared with normotensive control subjects.

Materials and Methods

Study Design and Methods

Patients between 7 and 20 years old were recruited after referral to the pediatric nephrology clinic for elevated blood pressure (BP)
readings. Those with secondary hypertension, seizure disorders, kidney disease, and diabetes mellitus Type II were excluded. The study protocol was approved by the Maimonides Medical Center Institutional Review Board. All of the parents and participants gave informed and written consent and assent.

Patients were evaluated using manual BP measurements and 24-hour ambulatory blood pressure monitoring (ABPM; Model 90217; Spacelabs Medical, Issaquah, WA). Each subject’s arm circumference was measured and an appropriately sized cuff was selected according to Fourth Report recommendations.19 Daytime measurements were taken every 20 minutes from 6 AM to 12 AM and nighttime measurements were taken every 30 minutes from 12 AM to 6 AM. Sleep state during the nighttime measurement period was confirmed with the patient. A successful study was defined as having >40 readings over the 24-hour period. If this criterion was not met, the study was repeated. Patients were diagnosed with hypertension, nocturnal hypertension, prehypertension, and white coat hypertension by comparing their ABPM readings with the 95th percentile cutoff values by height and gender from the normative population.19 Hypertensive children were divided into untreated and treated groups. From the ABPM results, both the mean systolic BP and the systolic BP load were assessed. The mean systolic BP was a simple average of the systolic BPs taken during the 24-hour period. The BP load is defined as the percentage of BP readings during the 24-hour diagnostic period that exceeded the respective 95th percentile cutoff values by height and gender. Hypertensive patients had a mean systolic BP ≥95th percentile and a systolic BP load ≥25%. Nocturnal hypertensive patients had a nighttime mean systolic BP ≥95th percentile and a nighttime systolic BP load ≥25% but were normotensive during the daytime. Prehypertensive patients were defined as having a mean systolic BP <95th percentile and a systolic BP load between 25% and 50%. White coat hypertensive patients had normal ABPM results with a mean systolic BP <95th percentile and a systolic BP load <25%.3

Three patients in the untreated hypertensive group repeated the study protocol as treated hypertensive patients after at least 6 months of treatment. Of the 7 treated hypertensive patients, 5 were taking enalapril and 2 were taking enalapril/hydrochlorothiazide. Control group patients were recruited from a normal school cohort, had no history of hypertension, and had a manual BP taken at the time of the transcranial Doppler that was <90th percentile for gender, age, and height.2

Subjects were placed in a comfortable sitting position and an initial manual BP was taken. Each subject wore a nose clip and was instructed to breathe normally into a mouthpiece with the proximal end connected to a capnometer detecting end-tidal CO2 (ETCO2; BCI Capnocheck-Capnograph; DRE, Louisville, KY) and the distal end attached to a sealed plastic bag. The middle cerebral artery was evaluated using a Smart-Lite transcranial Doppler (Rimed LTD, Raaana, Israel) through the temporal window to measure time-averaged maximum mean velocity at baseline in room air19 and then during hypercapnia as the patient rebreathed air from the sealed bag.15,16 Time-averaged maximum mean velocity measurements were obtained with increasing ETCO2 at 10-second intervals. Each patient underwent this protocol for 80 to 260 seconds. Each session was stopped when the ETCO2 reached a plateau or if the patient could no longer tolerate the procedure.16

Data Analysis

First, patients’ data were excluded from the analysis if there was difficulty in detecting the appropriate signal during the transcranial Doppler or intolerance to the procedure by the subject. If adequate transcranial Doppler measurements were obtained from both sides of a patient, the side with the higher correlation coefficient was used. The basic data record was a linear fit of the time-averaged maximum mean velocity against ETCO2, and patients’ data were also excluded from the analysis if the linear regression explained <50% of the variance. Eight patients were excluded from the analysis due to inadequate data: 3 untreated hypertensives, 1 prehypertensive, and 4 normotensive control subjects. For the final analysis, the untreated hypertension group consisted of 11 with untreated hypertension and 2 with untreated nocturnal hypertension.

Statistical analysis was performed using SigmaPlot for Windows Version 11.0 (Systat Software, Inc, Chicago, IL) and JMP (SAS Institute, Cary, NC). The time-averaged maximum mean velocity versus ETCO2 relationship was characterized by a slope calculated using simple linear regression (Figure 1). Some patients showed asymptotic approach at higher ETCO2 values of the reactivity curve. Here, points with stable CO2 values outside of 1 SD of the regression line were excluded. Reactivity values were compared across groups using the Kruskal-Wallis 1-way analysis of variance on ranks to account for a nonnormal distribution with pairwise post hoc tests calculated using the Dunn method. A probability value of <0.05 was considered statistically significant.

Z-scores of the mean arterial pressure, mean systolic, and mean diastolic BP were calculated from the 24-hour ABPM data using the LMS method, which accounts for degrees of skewness (L), distribution median (M), and coefficient of variation (S) of the ABPM reference population.17,18 The BP Z-scores and load values for untreated hypertensives, prehypertensives, and white coat hypertensives were then used to assess the relationship between BP and reactivity. Due to the nonnormal distribution and heterogeneous distribution of the reactivity slopes, these values were transformed to a log scale for linear regression analysis. Unless otherwise specified, all correlations refer to the simple linear Pearson coefficient.
A total of 56 participants remained after 8 were excluded as explained previously (mean age±SD, 15±3 years; 43 males and 13 females). There was no difference between genders with respect to age (P=0.382) and gender did not differ among groups (P=0.503). Also, the patient groups did not differ from each other with respect to age (F=1.802, 4 df, P=0.143), height (F=0.976, 3 df, P=0.413), weight (F=1.419, 3 df, P=0.250), and body mass index (F=2.329, 3 df, P=0.250). The control subjects were not matched for body mass index. The time-averaged maximum mean velocity–ETCO2 reactivity slope was not significantly affected by age (r=0.178, P=0.189), body mass index (r=0.213, P=0.151), weight (r=0.256, P=0.083), or height (r=0.195, P=0.189).

Hypercapnic reactivity differed significantly among diagnostic groups (H=8.028, 3 df, P=0.045; Table; Figure 2). Post hoc analysis revealed that untreated hypertensives had lower reactivity than control subjects (2.556±1.832 versus 4.256±1.334 cm/s·mm Hg, Q=2.778, P<0.05). Reactivity of prehypertensives and white coat hypertensives, although also lower than control subjects, did not reach statistical significance. The treated hypertension group was not included in this analysis because of the small size of this subgroup.

The 24-hour mean diastolic BP z-score was negatively correlated to the log-transformed reactivity (r=−0.331, P=0.037; Figure 3). The 24-hour diastolic load showed a similar negative linear correlation (r=−0.351, P=0.026; Figure 4). Although the 24-hour mean systolic BP z-score, 24-hour systolic load, and mean arterial pressure z-score tended toward a negative relationship with the reactivity slope, the data were underpowered to detect a statistically significant relationship.

### Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Untreated Hypertension</th>
<th>Prehypertension</th>
<th>White Coat Hypertension</th>
<th>Treated Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAMM–ETCO2 slope, cm/sec·mm Hg</td>
<td>4.256±1.334</td>
<td>2.556±1.832</td>
<td>2.770±1.069</td>
<td>3.422±1.966</td>
<td>2.715±1.297</td>
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<tr>
<td>No.</td>
<td>9</td>
<td>13</td>
<td>9</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>10</td>
<td>8</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Age, y</td>
<td>15.8±2.4</td>
<td>13.9±3.0</td>
<td>14.6±3.6</td>
<td>13.6±3.2</td>
<td>16.6±1.5</td>
</tr>
<tr>
<td>Age range, y</td>
<td>13–20</td>
<td>8–17</td>
<td>7–19</td>
<td>8–17</td>
<td>14–18</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>N/A</td>
<td>87.9±31.6</td>
<td>84.2±14.9</td>
<td>74.5±25.7</td>
<td>96.8±28.2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>N/A</td>
<td>160.3±13.3</td>
<td>169.7±15.5</td>
<td>161.4±15.4</td>
<td>164.8±6.2</td>
</tr>
<tr>
<td>BMI, kg/cm²</td>
<td>N/A</td>
<td>33.7±10.8</td>
<td>29.3±4.4</td>
<td>27.8±6.4</td>
<td>35.6±9.6</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD.

TAMM indicates time-averaged maximum mean velocity; ETCO2, end-tidal CO2; BMI, body mass index; N/A, not available.

### Discussion

Our results indicate that children and adolescents with untreated essential hypertension have decreased CBFV augment-
tation with hypercapnia compared with normotensive control subjects. Furthermore, the reactivity slope is negatively correlated with mean diastolic BP and diastolic load regardless of patient diagnosis.

In hypertensive adults, the static cerebral autoregulatory curve is shifted to higher limits. Both hypertrophy and remodeling of the cerebral artery walls have been proposed as the mechanisms behind this adjustment, resulting in wall thickening, luminal narrowing, and decreased compliance of the vessels. Furthermore, in both adult and adolescent hypertensive patients, studies have demonstrated abnormal responses of the cerebral vessels to hypercapnia and hypocapnia, presumably as a result of increased arteriolar vascular resistance. We hypothesize that hypertension has similar effects on the small vessels in children, resulting in increased cerebrovascular resistance and decreased compliance, thereby explaining the decreased hypercapnic reactivity. Several analyses in adults using different hypercapnic reactivity stimuli and different measures of cerebral blood flow have attempted to characterize the physiological association between hypertension and cerebral reactivity with conflicting results. However, an important distinction is that children do not typically have similar effects of age, atherosclerosis, and cerebrovascular disease to confound this relationship.

Several studies in adults reveal an association among hypertension, white matter abnormalities, and impaired cognitive function. More specifically, a study by Raz et al suggests larger effects of hypertension on prefrontal regions and executive function. Although analogous imaging studies in hypertensive children are lacking, investigation of cerebral damage has been approached from the cognitive standpoint. Parental history of hypertension and elevated systolic BP were correlated with lower scores on neurocognitive tests in French-Canadian 14-year-old boys. A study by Lande et al found that hypertensive children were scored lower by their parents on scales of executive function when compared with normotensives. Their group also found that learning disabilities were more frequent in hypertensive children. Future investigations are planned to correlate our present finding of abnormal cerebral reactivity to cognitive dysfunction.

We did not find a statistically significant difference between the hypercapnic reactivity of white coat hypertensive patients and normotensives, contrary to a previous investigation by Pall et al, in which hypercapnic reactivity was assessed with breath-holding. Two important factors in CBFV measurement and patient categorization may account for this different finding in white coat hypertensives. First, although they quantified cerebral reactivity as a percent change between 2 ETCO₂ points, we examined continuous change in CBFV over a range of ETCO₂. Second, Pall et al classified all patients with a mean systolic BP <95th percentile as white coat hypertensives, whereas we further divided these patients into white coat hypertensives and prehypertensives based on systolic BP load.

Diagnosis of pediatric hypertension based on ABPM uses systolic BP parameters, and many studies show a positive correlation between cardiovascular end organ damage and systolic BP. However, in our analysis, hypercapnic reactivity was significantly correlated with the 24-hour mean ambulatory systolic BP and diastolic load, rather than the systolic BP parameters, suggesting that diastolic BP may be a preferred indicator of physiological changes in pediatric CBFV. In our cohort, some prehypertensive patients have the same 24-hour mean diastolic BP z-scores as some hypertensive patients, although their 24-hour mean systolic BP levels are less than the corresponding 95th percentile values by height and gender. Under current guidelines, these patients are diagnosed or treated as hypertensives only when their systolic BP values reach their respective 95th percentile threshold. Currently the identification of prehypertensive children emphasizes the increased risk of progression to hypertension in adulthood. However, our results suggest that cerebral small vessel changes may already be occurring in these prehypertensive patients.

In adults and the aged, a relationship between diastolic BP and cognitive impairment has been documented. However, a comparable relationship between diastolic BP and cognitive function has not been previously found in children. In a study using the National Health and Nutrition Examination Survey III data, neuropsychological testing scores from normotensive children were compared with those from children with systolic BP values >90th percentile by gender, age, and height. Within this cohort, children with higher systolic, rather than diastolic, BP had significantly lower scores on tests of memory, attention, and concentration. However, unlike our study in which we treated diastolic BP as a continuous variable, their analysis evaluated diastolic BP as a dichotomous variable, collecting all participants with diastolic BP values <90th percentile into 1 group. Using their approach, the relationship between diastolic BP and cognitive function may have been diluted.

Limitations of our study include several factors. Although control subjects were normotensive at recruitment, they were not evaluated by ABPM; therefore, the small possibility exists that control subjects had masked hypertension. In addition, none of the control subjects were overweight or obese, so they could not be matched with patients for body
mass index. Other measures of CBFV reactivity during rapid changes in BP such as using squat–stand maneuvers were not used. A full sigmoid reactivity curve was not obtained for each patient, and as a result, we had to compare a linear representation of the data rather than a sigmoid representation. Because essential hypertension does not have overt symptoms at onset, the duration of the disease in each patient is unknown. Finally, an intrinsic limitation of pediatric hypertension research is its gross underdiagnosis.

Conclusions
Cerebrovascular reactivity to hypercapnia in hypertensive children is blunted. Whether these abnormalities are reversible is not known. Our data, although showing a trend, did not find a significant difference between the treated hypertensives versus the control subjects. Additional investigations are ongoing following hypertensive patients serially before and after treatment. These studies will further elucidate the hypothesis that cognitive abnormalities are related to vascular abnormalities as defined by cerebral reactivity dysfunction.

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Disclosures
None.

References
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