Effects of Childhood Primary Hypertension on Carotid Intima Media Thickness
A Matched Controlled Study

Marc B. Lande, Nancy L. Carson, Jason Roy, Cecilia C. Meagher

Abstract—To determine whether carotid intima media thickness is increased in children with primary hypertension, the current study compared carotid intima media thickness in hypertensive children with that of normotensive control subjects matched closely for body mass index and determined the relationship between carotid intima media thickness and hypertension severity determined by ambulatory blood pressure monitoring. Children with newly diagnosed office hypertension (n=28) had carotid intima media thickness, left ventricular mass index, and ambulatory blood pressure monitoring performed. Carotid intima media thickness was performed in normotensive control subjects (n=28) matched pairwise to hypertensive subjects for age (±1 year), gender, and body mass index (±10%). Eighty-two percent of subjects were overweight or obese (body mass index ≥85th percentile). The median carotid intima media thickness of hypertensive subjects was greater than that of matched controls (0.67 versus 0.63 mm; P=0.045). In the hypertensive subjects, carotid intima media thickness correlated strongly with several ambulatory blood pressure monitoring parameters, with the strongest correlation for daytime systolic blood pressure index (r=0.57; P=0.003). In the hypertensive group, the prevalence of left ventricular hypertrophy was 32%, but unlike carotid intima media thickness, left ventricular mass index did not correlate with ambulatory blood pressure monitoring. Together, the findings that hypertensive subjects had increased carotid intima media thickness compared with matched controls and that higher carotid intima media thickness correlated with more severe hypertension by ambulatory blood pressure monitoring provide strong evidence that carotid intima media thickness is increased in childhood primary hypertension, independent of the effects of obesity. (Hypertension. 2006;48:40-44.)

Key Words: carotid arteries ■ children ■ hypertension, obesity

End-organ damage is common in children with primary hypertension.1,2 Increased left ventricular mass, the best-studied marker of cardiovascular end-organ damage, is present in approximately 40% of hypertensive children.4 Despite these findings, the level and duration of blood pressure elevation that results in hypertensive end-organ damage in children remains poorly defined.1 Additional markers of hypertensive end-organ damage are needed to determine outcomes and guide management.5 Recently, carotid artery intima media thickness (cIMT), as measured by vascular ultrasound, has emerged as a potential marker of hypertensive vascular damage. In adults, increased cIMT is an indicator of generalized atherosclerosis and a strong predictor of future cardiovascular morbidity and mortality.6,7

Previous reports have shown that cIMT is increased in several childhood diseases that increase cardiovascular risk, including diabetes,8 familial hypercholesterolemia,9 and end-stage kidney disease.10,11 Recent studies have investigated whether cIMT is also increased in childhood primary hypertension.12-17 However, these reports have been confounded by the high proportion of hypertensive subjects with obesity, itself an independent risk factor for increased cIMT.18-22 Consequently, after adjusting for body mass index (BMI), previous studies have been inconsistent in showing increased cIMT in hypertensive children and have failed to demonstrate office blood pressure (BP) as an independent predictor of cIMT. Given such limitations, the recent Fourth Report from The Working Group on High Blood Pressure in Children and Adolescents1 stated that further research is needed to determine the clinical use of cIMT as a measure of hypertensive end-organ damage in children.

The objectives of the current study were as follows: (1) to determine whether cIMT is increased in children with primary hypertension after prospectively controlling for obesity by pairing hypertensive subjects with normotensive controls matched for BMI; and (2) to investigate the relationship among cIMT, left ventricular mass index (LVMI), and hypertension severity as measured by 24-hour ambulatory BP monitoring (ABPM).

Methods

Subjects
Newly diagnosed, untreated hypertensive subjects were recruited from children referred to the Pediatric Nephrology Clinic or the...
Pediatric Hypertension Clinic (created during the recruitment period) at the University of Rochester. All of the hypertensive subjects had office systolic and/or diastolic BP ≥95th percentile for age, gender, and height on ≥3 occasions (office hypertension). The diagnosis of hypertension was confirmed by ABPM, where hypertension was defined as average daytime and/or nighttime BP ≥95th percentile for gender and height for ABPM pediatric norms. Children with average BP <95th percentile for both day and night were considered to have white-coat hypertension (WCH) and were not included in the hypertension group. Subjects were limited to children aged 10 to 18 years of age without evidence of secondary hypertension. Secondary causes of hypertension were excluded by history, physical examination, urinalysis, serum chemistries, renal ultrasonography, and other tests as indicated, according to guidelines from the Working Group on High Blood Pressure in Children and Adolescents. For each hypertensive subject, a matched healthy, normotensive control subject was recruited from the General Pediatric Clinic at the University of Rochester. Control and hypertensive subjects were matched pairwise for gender, age (±1 year), and BMI (±10%). Control subjects were required to have 2 office BP readings with systolic and diastolic BP <90th percentile within the preceding 6 months. The study protocol was approved by the Research Subjects Review Board at the University of Rochester. All of the parents and participants >12 years of age gave informed, written consent.

ABPM
Office hypertension subjects had ABPM to confirm hypertension and to characterize the severity of BP elevation. An appropriate cuff size was placed on the nondominant arm. Spacelabs monitors 90217 (Spacelabs Medical) were used. Monitors were programmed to obtain BP readings every 20 minutes during the day (8:00 AM to 10:00 PM) and every 30 minutes at night (10:00 PM to 8:00 AM). Wake/sleep periods for ABPM analysis were determined by the patient’s self-report. BPs were analyzed using Spacelabs software (ABP Report Management System, version 1.03.16). To be considered adequate, ABPM needed to have a minimum of 40 readings with ≥2 hours between successful readings. BP load was defined as the percent of BP readings ≥95th percentile, and BP index was defined as the average BP divided by the 95th percentile. BP load and index were calculated for systolic and diastolic BP for 24-hour, daytime, and nighttime intervals. The percentage of day–night systolic BP fall (diP) was defined as the percentage decrease in average systolic BP from day to night.

Carotid Ultrasonography
Carotid IMT was determined in both hypertensive and control subjects using a high-resolution M12L matrix transducer on the GE Logic 700 ultrasound machine. On longitudinal 2D ultrasound images of the carotid artery, the near and far arterial walls are displayed as 2 echogenic lines, the adventitia and intima, separated by the hypoechoic media. The distance between the leading edge of the first bright line on the far wall (lumen–intima interface) and the leading edge of the second bright line (media–adventitia interface) indicates the IMT. Measurements of the far wall were made 1 cm proximal to the bifurcation of the left carotid artery, with the subject’s head turned 45° toward the right. The mean of 3 measurements was used for each subject. All of the measurements were performed by a single experienced sonographer (N.L.C.) who was blinded to the subject’s BP status. Carotid ultrasonography was performed within 1 month of echocardiography and before the initiation of antihypertensive therapy. Intraobserver reproducibility of cIMT measurements was determined by measuring cIMT twice, 2 weeks apart, in 6 healthy children, aged 10 to 16 years. The average difference between cIMT measures was <4%.

Echocardiography
All of the hypertensive patients underwent a complete 2D echocardiogram with M-mode and Doppler study (Acuson Sequoia or Aspen, Siemens). No patients were found to have coarctation of the aorta, and all had structurally normal hearts. 2D left ventricular mass by the area–length method was measured according to standards published by the American Society of Echocardiography. Measurements obtained were reviewed on digitally stored images and confirmed by an experienced physician echocardiographer (C.C.M.) blinded to the BP and cIMT data from the patients using a Siemens KinetDx workstation 3000, version 4.0.0. Left ventricular mass was indexed to height to correct for the effect of body size on assessment of left ventricular hypertrophy (LVH). LVH was defined as LVMI ≥95th percentile, which was 39.36 g/m² for boys and 36.88 g/m² for girls, respectively.

Data Analysis
Data are expressed as mean±SD or median and range, where appropriate. Statistical analysis was performed using SAS for Windows 9.1 (SAS Institute, Inc.). McNemar’s test was used to evaluate the difference in group proportions. Pearson correlation coefficients were used for correlations with the hypertensive group. Spearman correlation coefficients were used for correlations with the groups combined, because the control group was not normally distributed. The Wilcoxon rank sum test was used to examine differences between the hypertensive and control groups. P values <0.05 were considered significant for all analyses.

Results

Baseline Demographics
Thirty-five patients with office hypertension had cIMT measured. Of these, 25 had hypertension confirmed by ABPM, and 7 had WCH. Another 3 subjects with office hypertension had inadequate ABPM but had stage 2 office hypertension requiring antihypertensive medication. These 3 subjects were included in the hypertension group, giving a total of 28 hypertensive subjects. Twenty-eight normotensive controls were matched to the 28 hypertensive subjects. Of the 25 hypertension subjects with adequate ABPM monitoring, 21 had isolated systolic hypertension, and 4 had combined systolic and diastolic hypertension by ABPM. All had 24-hour systolic BP (SBP) load >30%. Fourteen (56%) had a nocturnal hypertension component. Fifteen (54%) of 28 of hypertension subjects were African American compared with 17 (61%) of 28 normotensive controls (P=0.52). Of the 28 hypertension subjects, 10 (36%) had a BMI between the 85th and 95th percentile, and 13 (46%) had a BMI ≥95th percentile. These BMI proportions were identical in the matched normotensive group. Table 1 shows matched demographic characteristics and average office BP for hypertensive and normotensive subjects. Table 2 shows ABPM parameters for the 25 hypertension subjects with ABPM.

Echocardiography
All of the hypertension subjects had echocardiography. Mean LVMI was 36.0±7.1 g/m² (range, 24.0 to 51.0 g/m²). Nine (32%) of 28 had LVH. Only 1 subject had an LVMI of 51 g/m², and no subject had LVMI above this value. LVMI did not correlate with office systolic or diastolic BP, ABPM parameters, age, weight, BMI, or BMI z score.

Carotid Ultrasonography
For all of the subjects combined (hypertension, 28; control, 28; WCH, 7), cIMT correlated with BMI (r=0.33; P=0.008) and BMI z score (r=0.26; P=0.04) but not office SBP, diastolic BP (DBP), age, height, or lean body mass. The lower and upper quartiles for cIMT, based on measurements of the normotensive subjects, was ≤0.58 mm and ≥0.67 mm, respectively.

Carotid IMT in hypertension subjects (n=28) did not correlate with age, height, weight, BMI, BMI z score, office systolic or diastolic BP, or office pulse pressure. Carotid IMT did not
correlate with LVMI \((P=0.92)\). By contrast, among hypertensive subjects with ABPM \((n=25)\), there was significant positive correlation between cIMT and several ABPM parameters, with the strongest correlation for daytime systolic index \((r=0.57; P=0.003; \text{Figure})\). Other significant correlations between cIMT and ABPM parameters included daytime systolic load \((r=0.54; P=0.005)\), daytime diastolic load \((r=0.56; P=0.004)\), daytime diastolic index \((0.54; P=0.005)\), daytime mean DBP \((r=0.54; P=0.005)\), 24-hour SBP load \((r=0.51; P=0.009)\), 24-hour DBP load \((r=0.50; P=0.01)\), daytime mean SBP \((r=0.43; P=0.03)\), and nighttime SBP index \((r=0.40; P=0.04)\). Fifteen \((60\%)\) of 25 hypertension subjects with ABPM had 24-hour systolic load \(\geq 50\%\), a value associated previously with higher risk of cardiovascular end-organ damage in pediatric primary hypertension. \(^{29}\) Fourteen hypertension subjects with ABPM had cIMT in the upper quartile. Of these, 9 \((64\%)\) had 24-hour systolic load \(\geq 50\%\).

Comparison of groups showed that the median cIMT was significantly greater for hypertensive subjects compared with that of normotensive control subjects, 0.67 mm versus 0.63 mm, respectively \((P=0.045)\). The range for cIMT for hypertensive subjects was 0.53 to 0.77 mm and for normotensive controls, 0.53 to 0.93 mm. Seventeen \((61\%)\) of 28 hypertensive subjects had cIMT measurements at or above the upper quartile compared with only 9 \((32\%)\) of 28 control subjects \((P=0.032)\). The control group contained 2 subjects with cIMT measurements greater than the maximum value for the hypertensive group. Both of these control subjects were significantly overweight, with BMI values \(>98\text{th}\) percentile for age and gender \((\text{BMI z scores of 2.13 and 2.31})\).

### Discussion

Children with primary hypertension are frequently overweight. As a result, all previous studies comparing cIMT in hypertensive and normal children have had a disproportionately high number of children with obesity in the hypertensive study group compared with the normotensive control group. This difference has led to difficulty in discerning the possible effects of hypertension on the vasculature from the strong association between obesity and increased cIMT. \(^{13}\) Previous reports have controlled for this confounding effect of obesity by adjusting for BMI with multiple regression or by analyzing overweight and normal weight subjects separately, when comparing cIMT in hypertensive and normotensive groups. \(^{12–17}\) Results have been variable, with some investigators reporting an association between childhood primary hypertension and increased cIMT \(^{13}\) and others failing to find such an effect, after adjusting for BMI. \(^{14–17}\)

### TABLE 1. Matched Demographic Characteristics and Office BP of HTN Subjects and Controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HTN Subjects ((n=28))</th>
<th>Controls ((n=28))</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>14.9 (\pm) 2.3</td>
<td>14.6 (\pm) 2.1 ((10 \text{ to } 18))</td>
<td>0.60</td>
</tr>
<tr>
<td>BMI, kg/m (^2) (range)</td>
<td>27.7 (\pm) 6.1 ((19.6 \text{ to } 39.6))</td>
<td>27.9 (\pm) 5.8 ((19.2 \text{ to } 38.2))</td>
<td>0.80</td>
</tr>
<tr>
<td>BMI z score (range)</td>
<td>1.54 (\pm) 0.81 ((-0.47 \text{ to } 2.68))</td>
<td>1.60 (\pm) 0.79 ((-0.65 \text{ to } 2.62))</td>
<td>0.84</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>22 ((79%))</td>
<td>22 ((79%))</td>
<td>N/A</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>144 (\pm) 12</td>
<td>120 (\pm) 8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>77 (\pm) 10</td>
<td>64 (\pm) 8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HTN indicates hypertension; N/A, not applicable.

### TABLE 2. ABPM Parameters for the 25 Subjects With ABPM-Confirmed Hypertension

<table>
<thead>
<tr>
<th>ABPM Parameter</th>
<th>Mean (\pm) SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h SBP load, % (range)</td>
<td>59 (\pm) 18 ((33 \text{ to } 100))</td>
</tr>
<tr>
<td>24-h DBP load, % (range)</td>
<td>27 (\pm) 25 ((2 \text{ to } 98))</td>
</tr>
<tr>
<td>Daytime SBP</td>
<td></td>
</tr>
<tr>
<td>Mean, mm Hg</td>
<td>137 (\pm) 7</td>
</tr>
<tr>
<td>Index</td>
<td>1.02 (\pm) 0.05</td>
</tr>
<tr>
<td>Load, %</td>
<td>58 (\pm) 20</td>
</tr>
<tr>
<td>Daytime DBP</td>
<td></td>
</tr>
<tr>
<td>Mean, mm Hg</td>
<td>77 (\pm) 10</td>
</tr>
<tr>
<td>Index</td>
<td>0.91 (\pm) 0.11</td>
</tr>
<tr>
<td>Load, %</td>
<td>25 (\pm) 25</td>
</tr>
<tr>
<td>Nighttime SBP</td>
<td></td>
</tr>
<tr>
<td>Mean, mm Hg</td>
<td>121 (\pm) 9</td>
</tr>
<tr>
<td>Index</td>
<td>1.03 (\pm) 0.08</td>
</tr>
<tr>
<td>Load, %</td>
<td>58 (\pm) 29</td>
</tr>
<tr>
<td>Nighttime DBP</td>
<td></td>
</tr>
<tr>
<td>Mean, mm Hg</td>
<td>64 (\pm) 10</td>
</tr>
<tr>
<td>Index</td>
<td>0.96 (\pm) 0.15</td>
</tr>
<tr>
<td>Load, %</td>
<td>31 (\pm) 31</td>
</tr>
<tr>
<td>Systolic dip, %</td>
<td>12 (\pm) 5</td>
</tr>
</tbody>
</table>

Relationship between cIMT and daytime SBP index.
The current study was designed to control directly for the strong confounding effect of obesity on cIMT. It is the first study of cIMT to match hypertensive and control subjects closely for BMI. Our results showed that cIMT was increased in hypertensive children compared with normotensive controls. This finding is particularly remarkable given that 82% of all subjects were either overweight or obese, a factor that would tend to overshadow any potential difference in groups because of hypertension. The current finding of increased cIMT in the hypertensive group provides further evidence that primary hypertension can lead to vascular abnormalities in childhood. The result is consistent with previous autopsy studies that showed early atherosclerotic changes of the aorta and coronary arteries associated with hypertension in adolescence.30,31 The current study also demonstrates the limitations of using cIMT as a marker of hypertensive end-organ damage in children with primary hypertension who are also overweight. There was considerable overlap in the range of cIMT of the hypertensive and normotensive study groups, and the highest individual cIMT measurements were in 2 obese normotensive subjects. These findings are in agreement with previous studies demonstrating the association between obesity and increased cIMT18–22 and underscore the importance of childhood obesity as an independent cardiovascular risk factor.

Studies in both adults and children with hypertension have shown that ABPM is superior to office BP as a predictor of hypertensive end-organ damage.28 Consistent with this observation, previous studies of cIMT in childhood primary hypertension failed to show a correlation between office systolic or diastolic BP and cIMT, after adjusting for BMI. The current study also failed to show a correlation between office BP and cIMT. By contrast, we found a strong correlation between cIMT and several ABPM parameters. The relationship was particularly strong for daytime systolic BP load and daytime systolic BP index, parameters that measure the percentage of BP readings over normal and the degree of BP elevation over the normal range, respectively. Considered together, BP load and BP index provide an ABPM expression of the severity of hypertension that has been shown previously to correlate with end-organ damage in hypertensive children.29 The finding of significant correlation between increased hypertension severity by ABPM and higher cIMT suggests a dose effect of hypertension on cIMT and provides further evidence that primary hypertension can lead to vascular end-organ damage in childhood. However, because of the cross-sectional nature of the current study, one cannot assume that the association between hypertension severity and increased cIMT is causative.

In the current study, 32% of the hypertensive subjects had LVH by echocardiography, but there was no correlation between LVMI and severity of hypertension by office BP or ABPM. These findings are consistent with a previous report by Belsha et al32 in which 35% of children with primary hypertension had LVH, but ABPM parameters did not differ between hypertensive children with and without LVH. By contrast, Sorof et al30 reported a strong correlation between LVMI and ABPM parameters in pediatric primary hypertension. In that study, a relatively high proportion of children had LVMI >51 g/m2, a value that is predictive of cardiovascular morbidity in hypertensive adults and greater than the 99th percentile for LVMI in normal children. Regardless, the current finding of a positive correlation of ABPM parameters with cIMT, but not with LVMI, has potentially important implications. This result suggests that, in the subjects studied, the presence of increased cIMT was complementary to the presence of LVH in the detection of children with hypertensive end-organ damage. In addition, the current study found that cIMT did not correlate with LVMI, a result that differs from a previous report by Sorof et al.12 This disparity in results may be because of potential differences between studies in the severity of hypertension, the duration of hypertension before referral, or differences in subject genetic predisposition to hypertensive end-organ damage. The difference in results may also be because of potential differences between studies in the type of hypertension present (systolic, diastolic, or combined systolic and diastolic). Further study of the vascular effects of primary hypertension in childhood may help clarify the relationship between the level of BP elevation, the duration of hypertension, and the development of hypertensive end-organ damage.

The current study has several limitations. The sample size is relatively small, limiting power for subgroup analysis. For example, BMI was significantly correlated with cIMT for all of the subjects combined, but not for the HTN subjects and control subjects when analyzed separately. Furthermore, ABPM was not performed in the control subjects to document normotension. Although 2 normal office BP readings were required, some of the control subjects may have had masked hypertension (normal office BP but elevated ABPM), an entity that may represent increased cardiovascular risk.33 In addition, there were potential differences in the quality of the office BP assessments. Hypertensive subjects had more office BP readings and had their BP measured in a hypertension subspecialty clinic, where the method for BP measurement may have been more standardized. Control subjects also did not have echocardiography, so the differences between hypertensive and control LVMI could not be assessed. Lastly, the majority of subjects were overweight, limiting analysis of the effects of hypertension on cIMT in normal weight children.

Perspectives
The current study showed that cIMT was increased in hypertensive children compared with controls matched for BMI and that higher cIMT correlated with more severe hypertension as determined by ABPM. These findings provide further evidence that childhood primary hypertension is associated with vascular pathology, independent of the effects of obesity. Used together with echocardiography, measures of vascular damage may help identify hypertensive children who are at increased cardiovascular risk. Our findings confirm that hypertension-associated vascular pathology can occur in childhood and suggest that future research directed at the mechanisms of vascular damage associated with childhood primary hypertension may lead to improved cardiovascular outcomes.
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Disclosures

None.

References

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