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Left Ventricular Hypertrophy in Hypertensive Adolescents Analysis of Risk by 2004 National High Blood Pressure Education Program Working Group Staging Criteria

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Abstract

The National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents recently recommended staging hypertension (HTN) in children and adolescents based on blood pressure severity. The use of blood pressure staging and its corresponding therapeutic approach was examined in this pooled analysis assessing the risk for end-organ damage, specifically left ventricular hypertrophy among hypertensive adolescents stratified by working group criteria. Newly diagnosed hypertensive adolescents and normotensive control subjects similar in age, race/ethnicity, gender, and body mass index completed casual and 24-hour ambulatory blood pressure measurements, M-mode echocardiography, and fasting serum laboratories. Hypertensive subjects had higher insulin and cholesterol but similar glucose levels as

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compared with control subjects. Among subjects with stage 1 HTN by casual blood pressure, 34% had white-coat HTN as opposed to 15% of stage 2 hypertensive subjects. Of the subjects with normal casual measurements, 20% had HTN by ambulatory monitoring. Subjects with stage 2 HTN by casual measurement alone (odds ratio: 4.13; 95% CI: 1.04 to 16.48) and after 24-hour ambulatory confirmation (odds ratio: 7.23; 95% CI: 1.28 to 40.68) had increased odds for left ventricular hypertrophy. In addition, the risk for left ventricular hypertrophy was similar for subjects with masked and confirmed stage 1 HTN, whereas subjects with white-coat HTN had a risk comparable to normotensive subjects. Thus, recommendations that adolescents with stage 2 HTN by casual measurements alone receive medication initially along with therapeutic lifestyle counseling are reasonable, though ambulatory blood pressure monitoring remains a valuable tool for evaluating children with stage 2 HTN, because >10% have white-coat HTN.

Keywords

hypertension; left ventricular hypertrophy; echocardiography; ambulatory blood pressure monitoring; white-coat hypertension; masked hypertension; adolescents

In 2004, the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (working group)[1] published new guidelines regarding the diagnosis and management of pediatric patients with hypertension (HTN). In addition to updating normative tables, these recommendations called for the staging of hypertensive children based on blood pressure (BP) severity and provided different treatment strategies for each stage.

Although treatment recommendations for hypertensive adults are based on studies demonstrating an increased risk of cardiovascular morbidity and mortality, similar studies in children are not practical because of the extended time required for such outcomes to occur. Left ventricular hypertrophy (LVH) has been shown to confer added risk to hypertensive adults,[2–4] is easily measurable in children and adolescents, and has, thus, become a surrogate marker for hypertensive end-organ damage in children. In fact, previous studies have shown a correlation between BP severity by ambulatory BP monitoring (ABPM) and the presence of LVH.[5] The goal of the current study then was to assess the risk for LVH among hypertensive adolescents categorized by working group staging criteria to validate this staging scheme and current guidelines recommending different treatment strategies for each group.

Methods

A retrospective pooled analysis of data collected from 2 cross-sectional studies performed between January 2002 and October 2005 was conducted. Both studies had as primary original objectives to measure differences in target organ abnormalities between hypertensive and nonhypertensive adolescents recruited from a hypertensive referral clinic or through school screening. There were, however, slight variations between these studies in enrollment criteria, specific outcomes, and targeted confounding variables. All of the hypertensive subjects had a history of casual BP readings ≥95th percentile for age, height, and gender compared with normative tables at the time of enrollment on 3 occasions before entry and were naïve to antihypertensive medications. In addition, subjects later found to have a secondary cause of HTN were excluded from analysis. The following data were extracted for each subject. First, was demographic information, including age, gender, and race/ethnicity. Second were anthropometric measures, including height, weight, and body mass index (BMI).

Third was casual BP at study entry. All of the BP measurements were taken in the right arm after 5 minutes of rest with an appropriately sized cuff for measured arm circumference. The mean of 3 auscultatory readings taken with a mercury manometer or the last 3 of 4 oscillometric readings (Spacelabs 90217) was used for BP staging. Auscultatory BP was used for subjects when both techniques were used. Casual BP status was defined per working group criteria as nonhypertensive (<95th percentile for age, height, and gender), stage 1 HTN (≥95th percentile to 99th percentile + 5 mm Hg), and stage 2 HTN (≥99th percentile+5 mm Hg). BP index (mean casual BP/95th percentile) was calculated for each subject to allow for comparison between individuals.

Fourth were ABPM parameters, including systolic BP and diastolic BP 24-hour, day, and night mean and load (percentage of BP measurements ≥95th percentile for height and gender by ABPM normative values[6]) measured using Space Labs 90217. White-coat HTN was defined as those with stage 1 or stage 2 HTN but 24-hour mean systolic BP and diastolic BP <95th percentile[6] and load <25%. Masked HTN was defined as casual BP <95th percentile with mean 24-hour systolic BP or diastolic BP ≥95th percentile or load >50%, because these limits have been shown previously to most closely correlate with LVH in adolescents.[5]

Fifth were M-mode measurements obtained during diastole via transthoracic echocardiography, including intraventricular septal wall thickness, left ventricular (LV) end-diastolic dimension, and LV posterior wall thickness. LV mass (LVM) and LVM index (LVMI) were calculated per working group recommendations using the equation of Devereux et al[7]: {LVM (g)=0.80 [1.04 (intraventricular septal thickness+LV end-diastolic dimension+LV PWT)^3−(LV end-diastolic dimension)^3] + 0.6} with measurements (in centimeters) obtained according to the criteria of the American Society of Echocardiography.[8] Height (meters$^{2.7}$) was used for LVMI as described by de Simone et al[9] to standardize LVM for body size, and LVH was defined as LVMI >51 g/m$^{2.7}$ as recommended by the working group.

Finally, fasting serum laboratories including glucose, insulin, and complete lipid panel were recorded. The Quantitative Insulin Sensitivity Check Index of insulin resistance was calculated as 1/[Log (insulin)+Log (glucose)].

All of the protocols were approved by the University of Texas-Houston Health Science Center Committee for the Protection of Human Subjects, and informed consent/assent was obtained from subjects and parents. Analysis was performed using Stata 9.2. Results are reported as mean±SD or percentage as appropriate. Differences between groups were evaluated by contingency table analysis and ANOVA or Kruskal-Wallis tests when variances were not equivalent across groups, as well as a nonparametric test for trend across ordered groups. Crude and adjusted odds ratios (ORs) were calculated via logistic regression models. Covariates assessed for inclusion in logistic models included age, gender, ethnicity, BMI, and fasting chemistries and were retained in final models if they were original matching variables or if they were independently associated with both LVH and BP and their addition to the crude logistic model resulted in at least a 10% change in the OR for 1 BP category. Values are reported as OR (95% CI).

Results

A total of 163 adolescents who had complete causal BP, ABPM, echocardiography, and fasting laboratory measurements available were included in the pooled analysis. Demographic information and initial measurements are provided in Table 1. Groups were similar in terms of age, gender, and BMI, although racial distribution varied between the groups with more white and less Hispanic adolescents in the nonhypertensive group. As

expected, both systolic and diastolic BP indexes differed between the groups, and a larger number of adolescents with stage 1 HTN by casual BP had white-coat HTN as compared with those with stage 2 HTN. Twenty percent of nonhypertensive subjects had masked HTN. Fasting insulin, total cholesterol, and triglycerides were also significantly higher in those with HTN as compared with those without HTN, whereas the Quantitative Insulin Sensitivity Check Index was lower in the hypertensive population.

The presence of LV abnormalities by casual BP classification is shown in Table 2. A total of 9.1% of subjects in the nonhypertensive category were found to have LVH. All but 1 of these subjects had BMI >95th percentile for age and gender, highlighting the known association between obesity and LVH,[10–12] and half were ultimately found to have masked HTN. LVMI did not differ significantly between groups, though LVH prevalence did increase significantly across categories, and subjects with stage 2 HTN had an increased risk of LVH before and after adjusting for age, gender, race/ethnicity, and BMI. Although several metabolic parameters varied between the hypertensive groups, none ultimately met criteria to be included in the final regression models.

The presence of LV abnormalities by groups following reclassification of subjects considering ABPM is shown in Table 3. Again, LVH prevalence but not LVMI differed between groups, with the greatest risk for LVH seen among those with stage 2 HTN. Although it did not reach statistical significance, the risk among subjects with white-coat HTN more closely resembled the risk in the nonhypertensive group, and those with masked HTN had a risk similar to those with stage 1 HTN.

Discussion

Appropriately classifying and identifying children with elevated BP who carry an added risk of long-term hypertensive disease is challenging, because the natural history of this disease expresses itself over decades. Although LVH has been shown to confer added risk among adults,[2–4] the long-term studies validating that it confers added risk among hypertensive children have yet to be conducted. In addition, LVH is not specific to hypertensive disease, because it has also been associated with a number of other conditions independent of BP, including obesity[10–12] and chronic kidney disease.[13–15] Despite these concerns, LVH remains to date the most well-documented end-organ manifestation of hypertensive disease in the younger population.

Accurately identifying children at risk is essential for the determination of indications for the initiation of antihypertensive therapy, particularly pharmacological therapy. The 2004 working group recently recommended that, in the absence of LVH or compelling indications, such as diabetes or chronic kidney disease, children and adolescents with stage 1 HTN initially be treated with therapeutic lifestyle changes. In contrast, those with LVH and all children with stage 2 HTN should have pharmacological therapy initiated. Assuming that LVH is in fact a marker for poor outcomes in children, the current study provides support for these recommendations. The statistically significant increased risk of LVH among those presenting with stage 2 HTN suggests that this group has a higher risk for hypertensive sequelae than those with stage 1 HTN who did not have an increased risk for LVH when compared with normotensive subjects. Whether this is a consequence of BP severity or perhaps length of disease leading to both higher BP and LVH needs to be evaluated.

Although casual BP measurements did independently predict LVH among patients with stage 2 HTN, this relationship was strengthened when participants with white-coat HTN and masked HTN were considered separately. It has been shown previously that ABPM values more closely correlate with LVMI.[5] Despite using staging criteria to classify casual BP by

severity, ABPM continues to provide added information regarding hypertensive risk, because those with white-coat HTN appear to have a rate of LVH similar to that of nonhypertensive subjects, whereas those with masked HTN more closely resemble individuals with stage 1 HTN. A larger sample of adolescents with white-coat and masked HTN will be necessary to confirm this finding, because calculated confidence intervals in this study were quite wide. However, these findings are consistent with those of Stabouli et al,[16] who have shown similar correlations between these groups among 85 patients referred for evaluation of suspected HTN. Thus, ABPM appears to remain an important diagnostic tool for assessing risk of hypertensive disease among children.

This study was limited as a secondary pooled analysis of 2 studies of which the primary hypotheses were not to determine the association between LVH and BP staging. Rather, these studies were originally designed to assess the risk for end-organ damage in adolescents with HTN stratified and matched to control subjects based on obesity status, as well as to determine the ability of casual BP as compared with ABPM to predict end-organ damage. Thus, the control group had a higher proportion of obese individuals than would be seen in the general population. As has been mentioned, obesity is, itself, associated with LVH, and its increased prevalence among control subjects may have contributed to an increased rate of LVH compared with what would be expected in this group. With a more representative sample of normotensive adolescents, the association between LVH and hypertensive stage may be more evident. Finally, subjects were recruited before the publication of the working group report; thus, patients with pre-HTN were recruited in insufficient numbers to be considered in this analysis. This is a group of potentially at-risk individuals who will definitely require further evaluation in the future.

Despite these limitations, these data provide indirect validation of the 2004 working group staging criteria and their associated treatment recommendations, especially for adolescents with stage 2 HTN. However, casual BP measurements alone continue to be a less specific marker for hypertensive end-organ damage, particularly in those with milder disease. Further research to examine the association between pre-HTN and end-organ damage, as well as other markers of such damage, is needed to validate the working group recommendations.

Perspectives

The pattern of increased risk of LVH among hypertensive patients included in this study provides support for the 2004 working group staging criteria and their associated treatment recommendations, especially for adolescents with stage 2 HTN. Casual BP measurements alone continue to be less specific than when combined with ABPM.

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References

1. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004; 114:555–576. [PubMed: 15286277]

2. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990; 322:1561–1566. [PubMed: 2139921]

3. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med. 1991; 114:345–352. [PubMed: 1825164]

4. Brown DW, Giles WH, Croft BC. Left ventricular hypertrophy as a predictor of coronary heart disease mortality and the effect of hypertension. Am Heart J. 2000; 140:848–856. [PubMed: 11099987]

5. Sorof JM, Cardwell G, Franco K, Portman RJ. Ambulatory blood pressure and left ventricular mass index in hypertensive children. Hypertension. 2002; 39:903–908. [PubMed: 11967247]

6. Soergel M, Kirschstein M, Busch C, Danne T, Gellermann J, Holl R, Krull F, Reichert H, Reusz GS, Rascher W. Oscillometric twenty-four-hour ambulatory blood pressure values in healthy children and adolescents: a multicenter trial including 1141 subjects. J Pediatr. 1997; 130:178–184. [PubMed: 9042117]

7. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol. 1986; 57:450–458. [PubMed: 2936235]

8. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommnedations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation. 1978; 58:1072–1083. [PubMed: 709763]

9. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman JM, de Divitiis O, Alderman MH. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol. 1992; 20:1251–1260. [PubMed: 1401629]

10. Urbina EM, Gidding SS, Bao W, Pickoff AS, Berdusis K, Berenson GS. Effect of body size, ponderosity, and blood pressure on left ventricular growth in children and young adults in the Bogalusa Heart Study. Circulation. 1995; 91:2400–2406. [PubMed: 7729027]

11. Murdison KA, Treiber FA, Mensah G, Davis H, Thompson W, Strong WB. Prediction of left ventricular mass in youth with family histories of essential hypertension. Am J Med Sci. 1998; 315:118–123. [PubMed: 9472911]

12. Friberg P, Allansdotter-Johnsson A, Ambring A, Ahl R, Arheden H, Framme J, Johansson A, Holmgren D, Wahlander H, Marild S. Increased left ventricular mass in obese adolescents. Eur Heart J. 2004; 25:987–992. [PubMed: 15172471]

13. Johnstone LM, Jones CL, Grigg LE, Wilkinson JL, Walker RG, Powell HR. Left ventricular abnormalities in children, adolescents and young adults with renal disease. Kindey Int. 1996; 50:998–1006.

14. Palcoux JB, Palcoux MC, Jouan JP, Gourgand JM, Cassagnes J, Malpuech G. Echocardiographic patterns in infants and children with chronic renal failure. Int J Pediatr Nephrol. 1982; 3:311–314. [PubMed: 7166455]

15. Mitsnefes MM, Kimball TR, Witt SA, Glascock BJ, Khoury PR, Daniels SR. Left ventricular mass and systolic performance in pediatric patients with chronic renal failure. Circulation. 2003; 107:864–868. [PubMed: 12591757]

16. Stabouli S, Kotsis V, Toumanidis S, Papamichael C, Constantopoulos A, Zakopoulos N. White-coat and masked hypertension in children: association with target-organ damage. Pediatr Nephrol. 2005; 20:1151–1155. [PubMed: 15947982]

Table 1
Demographics and Baseline Measurements

Baseline Measure	Normal Casual BP (n=44)	Stage 1 HTN (n=76)	Stage 2 HTN (n=40)	*P*
Age, y	12.8±2.81	12.4±2.50	12.4±2.48	0.63*
Male, %	77%	61%	60%	0.13†
Racial distribution, %				<0.001‡
White	50%	28%	35%	…
Black	43%	33%	23%	…
Hispanic	7%	39%	42%	…
BMI	23.6±7.07	26.8±6.65	25.4±6.84	0.21*
Obesity prevalence, %	36%	55%	50%	0.13†
Systolic BP index	0.92±0.060	1.04±0.040	1.15±0.053	<0.001§
Diastolic BP index	0.85±0.093	0.92±0.129	1.00±0.161	<0.001§
Presence of WCH, *n* (%)	…	26 (34)	6 (15)	…
Presence of masked HTN	9 (20%)	…	…	…
Fasting glucose, mg/dL	78.6±17.71	80.9±26.56	81.9±12.69	0.82§
Fasting insulin (n=123), IU/mL	9.1 ±6.32	15.0±10.25	14.5±13.02	0.01§
QUICKI (n=123)	0.37±0.047	0.34±0.047	0.35±0.040	0.02*
Total cholesterol, mg/dL	156.7±20.07	167.6±36.22	173.1 ±25.27	0.02§
Triglycerides, mg/dL	70.8±48.41	101.0±71.55	110.1 ±75.52	<0.01§

QUICKI indicates Quantitative Insulin Sensitivity Check Index; WCH, white-coat HTN.

*ANOVA.

†χ^2.

‡Fisher's exact.

§Kruskal-Wallis.

Table 2

LV Abnormalities by Casual BP

LV Abnormality/Associated OR	Normal Casual BP (n=44)	Stage 1 HTN (n=76)	Stage 2 HTN (n=40)	*P*
LVMI, $g/m^{2.7}$	35.5±11.36	38.0±12.39	40.9±17.93	0.20 *
LVH prevalence, %	9.1	14.5	30	0.01 †
Crude OR (95% CI)	1.0 (reference)	1.69 (0.50 to 5.68)	4.29 (1.25 to 14.67)	
Adjusted OR (95% CI) ‡	1.0 (reference)	1.21 (0.31 to 4.68)	4.13 (1.04 to 16.48)	

* ANOVA.

† Nonparametric test for trend across ordered groups.

‡ Adjusted for age, gender, race/ethnicity, and BMI.

Table 3

LV Abnormalities by Casual BP and ABPM

LV Abnormality/Associated OR	Normal BP (n=35)	White-Coat HTN (n=32)	Masked HTN (n=9)	Stage 1 HTN (n=50)	Stage 2 HTN (n=34)	*P*
LVMI, g/m$^{2.7}$	33.8±10.81	35.8±13.15	42.3±11.51	39.7±13.07	41.1 ±17.36	0.11*
LVH prevalence, %	5.7	9.4	22.2	18.0	32.4	<0.01†
Crude OR (95% CI)	1.0 (reference)	1.71 (0.27 to 10.94)	(0.56 to 39.39)	3.62 (0.73 to 17.92)	7.89 (1.60 to 39.01)	
Adjusted OR (95% CI)‡	1.0	1.30 (0.17 to 9.79)	6.43 (0.61 to 67.62)	2.68 (0.47 to 17.49)	7.23 (1.28 to 40.68)	

*ANOVA.

†Nonparametric test for trend across ordered groups.

‡Adjusted for age, gender, race/ethnicity, and BMI.