

Left Ventricular Hypertrophy Phenotype in Childhood-Onset Essential Hypertension

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The aim of this study was to determine the risk factors associated with left ventricular (LV) hypertrophy (LVH) among 89 untreated children with primary hypertension. Clinic hypertension was confirmed by 24-hour ambulatory blood pressure (BP) monitoring. LV mass (LVM) index was calculated as LVM (g)/height (m)^{2.7} and LVH was defined as LVM index >95th percentile. Children with (n=32) and without (n=57) LVH were compared. Both obesity and systolic BP were independently associated with LVH, with

a higher contribution by body mass index. Obesity contributed significantly, with a nearly nine-fold increased risk of LVH. There was evidence of effect modification by the presence or absence of obesity on the relationship between systolic BP and LVH, whereby the relationship existed mainly in nonobese rather than obese children. Hence, to achieve reversal of LVH, clinicians should take into account both BP control and weight management. *J Clin Hypertens (Greenwich)*. 2016;18:449–455. © 2015 Wiley Periodicals, Inc.

Primary hypertension or essential hypertension (EH) can lead to cardiovascular changes in childhood, including subclinical hypertensive cardiomyopathy,^{1–3} aortopathy,⁴ and vasculopathy.^{5,6} Left ventricular (LV) hypertrophy (LVH), as demonstrated by an increase in LV mass (LVM) on echocardiography, is the most common surrogate marker of end-organ damage from EH^{7–9} on echocardiography. Blood pressure (BP) levels alone cannot predict LVH and, hence, echocardiography is recommended in all children with hypertension.¹⁰ Presence of LVH in adults with EH has been associated with impaired LV systolic¹¹ and diastolic function¹² and thus overall worse cardiovascular morbidity and mortality.^{13–20} Therefore, early detection and treatment of LVH in childhood is crucial to prevent cardiovascular events in adult life. Moreover, investigating end-organ damage in childhood can give further information on the origins of subclinical hypertensive cardiomyopathy in humans.

Multiple risk factors, both genetic and environmental, have been associated with the LVH phenotype in adults and children with EH. The LVH phenotype in children has been associated with family history of EH,²¹ with multiple markers of the child's BP such as diagnosis of hypertension,² systolic BP,^{22,23} diastolic BP,^{22,24} ambulatory BP,^{25–27} nocturnal systolic BP,^{28,29} and daytime systolic variability,²⁹ as well as with metabolic markers such as body mass index,^{22–24,26,30} obesity,^{27,31,32} body

fatness,²⁷ lean tissue mass,²⁷ insulin resistance,³¹ C-reactive protein,²³ and microalbuminuria.²³

BP levels have been shown to explain only about 40% of the variability in LVM among adults with untreated EH.³³ Controlling BP has been shown to decrease LVH in both adults and children with hypertension,³⁴ but weight loss can also decrease LVH in those who do not have hypertension.³⁵ Among children with EH, it is unknown which has the greater influence on LVH—BP or weight. The aim of this study was to examine the contributory factors associated with LVH phenotype in childhood-onset EH and determine individual contributions by weight and BP on LVH.

METHODS

Institutional Approval

The study was approved by the Institutional Committee for the Protection of Human Subjects at the University of Texas Health Science Center and Children's Memorial Hermann Hospital, Texas Medical Center. All participants and parents gave informed assent and consent, respectively, for this study.

Patient Population

This was a single-center, case-control study of children who were diagnosed with elevated BP prior to antihypertensive therapy. We prospectively enrolled children aged 9 to 18 years from our tertiary pediatric hypertension clinic whereby they were referred or recruited as follows: (1) *Referral Study Population*: These patients were referred to the clinic after detection of elevated BP from either an ambulatory setting by a primary care provider or an inpatient setting. (2) *Recruited Study Population*: Patients recruited by screening comprised a small proportion of patients in our clinic and were identified by systematic school-based screening for

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hypertension in students aged 11 to 18 years in Houston area public schools.³⁶ Patients recruited by these two methods, ie, school screening or referral as described above, have been reported to be similar in a prior publication;³⁶ this was confirmed in our current data set during this analysis. All enrolled children underwent further evaluation including ambulatory BP monitoring (ABPM) as described further below. Demographic and anthropometric data were collected on all participants at study entry. Obesity was defined as body mass index (BMI) at or above 95th percentile for age and sex.

BP Protocol

Children with untreated newly diagnosed EH without any identifiable etiology for the hypertension were enrolled in the study. BP was reported as the participant's BP factored by their age-, sex-, and height-specific 95th percentile (BP index). Hypertension status was evaluated by both clinic and ambulatory BP monitoring for 24 hours in all children as follows: clinic hypertensive status was diagnosed when three separate measurements of systolic and/or diastolic BP >95th percentile for height, age, and sex per the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (Fourth Report)³⁷ were recorded and elevated BP by Critikon oscillometric monitor (Tampa, FL) was determined at the first visit to the hypertension clinic. The hypertension in clinic was confirmed by manual auscultation with a mercury sphygmomanometer by trained personnel using methods recommended by the Fourth Report.³⁷ Clinic BP measurements considered the average of the last three of four BP measurements performed by oscillometric monitor after 5 minutes of rest. Prehypertension, stage I hypertension, and stage II hypertension were classified per the Fourth Report.³⁷ Children who were older than 5 years underwent ABPM using Spacelabs oscillometric monitors (Spacelabs, Inc, Redmond, WA). The children along with their families were instructed on avoidance of caffeinated beverages or supplements, any medications, herbal or over-the-counter products, smoking, and alcohol for 24 hours prior to and during the ABPM. While undergoing ABPM, BP was measured every 20 minutes for 24 hours. Children with casual hypertension but with 24-hour systolic BP and diastolic BP less than the pediatric 95th percentile and BP load <25% were considered to have white-coat hypertension. Children with mean 24-hour systolic BP or diastolic BP greater than the pediatric 95th percentile or BP load (percentage of BP values exceeding the 95th percentile for the 24-hour period) >25% were considered to have ambulatory hypertension.³⁸

Diagnosis of EH

Once hypertension was confirmed, the diagnosis of primary hypertension or EH was made by extensive evaluation per recommendations by the Fourth Report,³⁷ including a urinary evaluation, blood tests,

renal ultrasound, and echocardiography. Children with congenital cardiac disease including bicuspid aortic valve were excluded from this study. Criteria for the diagnosis of EH were: (1) clinic BP elevation above the 95th percentile on three previous occasions, (2) absence of secondary causes of hypertension, and (3) no concurrent medication with the potential to raise BP (eg, steroids, central stimulants).

Echocardiography and Vascular Ultrasound Protocol

All children underwent transthoracic echocardiography and vascular ultrasound and the measurements were made in a manner-blinded fashion. The reproducibility of measurements for both were determined by repeat assessments for 10 values by the same sonographer and by two sonographers independently, yielding kappa values >0.8. The echocardiographic studies were performed for all participants using an Acuson Sequoia 512 ultrasound machine (Siemens, Malvern, PA) by trained pediatric sonographers using a standard protocol to evaluate congenital cardiac disease³⁹ and LVH.^{40,41} Quantification of LVM was made from two-dimensionally guided M-mode measurements during diastole of the LV internal dimension, interventricular septal thickness, and posterior wall thickness according to methods established by the American Society of Echocardiography.^{40,41} LVM was calculated using the equation reported by Devereux and colleagues.⁴² LVM index (LVMI^{2.7}) was calculated by dividing LVM by height in meters to the 2.7th power to minimize the effect of age, sex, ethnicity, and overweight status.^{43,44} For this study, LVH was defined as an LVMI 38.6 g/m^{2.7}, a value reported to represent the pediatric 95th percentile of LVMI^{2.7} in normotensive healthy children.⁴³⁻⁴⁵ Because the quantiles of LVMI^{2.7} vary only a little after the age of 9 years, we did not use these in our cohort of children since they were 9 years and older.⁴⁶ Eccentric and concentric hypertrophy was defined similarly to that previously reported in the literature.⁹ The measurements of diastolic function (peak E and A velocities, E/A ratio, isovolumic relaxation time, and deceleration times) were made by simultaneous transmitral and transaortic spectral Doppler flow velocities.⁴¹ Carotid artery duplex ultrasound was performed by protocol to measure carotid intima-media thickness (CIMT) by experienced vascular sonographers in a standard manner.⁴⁷ The thickest IMT complex of the far wall of the distal common carotid artery was measured in the longitudinal B-mode section using a high-resolution 8 MHz transducer. The values of right and left CIMT were averaged for the purpose of this study.

Statistical Analysis

Patients with LVH and no LVH were compared. Data from the medical records was abstracted and tabulated. Mean (standard deviations [SDs]) and medians (interquartile ranges) for continuous variables were compared between groups using parametric (*t* tests, analysis

of variance with post hoc Tukey) and nonparametric (Mann-Whitney, Kruskal-Wallis) tests, depending on the distribution of the variable. Chi-square tests were used to compare categorical variables across groups. Multivariable logistic regression analyses were performed to assess odds of LVH relative to differences in demographic, anthropometric, BP, laboratory, and vascular ultrasound parameters. Backward stepwise selection was used to optimize the regression model and calculate the odds ratios (ORs) along with 95% confidence intervals (CIs). All analyses were performed with STATA version 11 (StataCorp, College Station, TX). Statistical significance was assumed at a type I error rate of .05.

RESULTS

Children with EH (n=89, males 65%, mean age 13.5 years, SD 1.8 years) were enrolled in the study. Eight (9%) of the children were diagnosed with prehypertension, 23 (26%) with stage I hypertension, and 58 (65%) with stage II hypertension in the clinic. LVH was detected in 32 (36%) children, with eccentric LVH in 25 (78%) and concentric LVH in seven (22%) of these patients. Their demographic (Table I), anthropometric (Table I), BP (Table II), laboratory (Table III), vascular ultrasound (Table III), and echocardiographic (Table IV) parameters are summarized.

In univariable analysis, LVH was significantly associated with weight/BMI but not with BP (Table I and Table II). CIMT, triglyceride levels, and isovolumic

relaxation time were significantly higher among hypertensive children with LVH compared with those without LVH (Table III and Table IV). Overall, the BMI z scores were significantly higher in children with LVH (mean, 1.9; SD, 0.6) than in those without LVH (mean, 1.2; SD, 0.9; $P=.0002$) (Figure 1, Table I). In addition, univariable analysis of the degree of obesity showed that the odds of LVH was significantly higher in obese compared with normal-weight children with EH (OR, 8.9; 95% CI, 2.3–34.3; $P=.002$). A similar trend but of a lower magnitude was observed in overweight children compared with normal-weight children with EH; however, the trend failed to reach statistical significance (OR, 3.6; 95% CI, 0.8–16.0; $P=.096$).

Various multivariable models were assessed to identify the factors associated with LVH. Multivariable logistic regression analyses were performed to assess odds of LVH relative to differences in demographic (age, sex, ethnicity), anthropometric (weight, BMI, BMI z score), BP, laboratory, and vascular ultrasound parameters. From all the variables selected, only weight and/or BMI measurements were significantly associated with LVH. Adjusted for mean 24-hour ambulatory systolic BP, the BMI z scores were significantly associated with LVH (OR, 5.69; 95% CI, 2.10–15.44; $P=.001$). Thus, for every incremental increase in SD of the BMI z score, the odds of LVH increased by more than five-fold. The same models also showed that for every 10-unit increase in mean 24-hour ambulatory systolic BP, the odds of LVH approximately doubled (OR, 2.16; 95% CI, 1.04–4.49; $P=.039$).

There was, however, evidence of effect modification by the presence or absence of obesity on this relationship between systolic BP and LVH. Among the nonobese children, mean 24-hour ambulatory systolic BP was significantly higher in children with LVH compared with those without LVH (mean 132 mm Hg, SD 10 vs mean 123 mm Hg, SD 7, respectively; $P=.003$) (Figure 2). In comparison, the obese children demonstrated similar levels of mean 24-hour ambulatory systolic BP between the two LVH groups (mean 122 mm Hg, SD 9 vs mean 120 mm Hg, SD 9, respectively; $P=.659$) (Figure 2). Based on multivariable analysis, for every 10-mm Hg increase in mean 24-hour ambulatory systolic BP, the odds of LVH was much higher in the nonobese population (OR, 5.91; 95% CI, 1.18–29.6; $P=.030$) than in the obese population (OR, 1.23; 95% CI, 0.44–3.37; $P=.693$). This differential effect of obesity was also observed in the relationship of systolic BP measurements (in 10-mm Hg increments) in the clinic and LVH, with a stronger association in obese (OR, 2.43; 95% CI, 1.07–5.52; $P=.033$) than in nonobese (OR, 1.29; 95% CI, 0.67–2.48; $P=.453$) children with EH.

DISCUSSION

In this study, we identified that among hypertensive children, BMI had a stronger independent effect on

TABLE I. Demographic and Laboratory Profiles of Children With Childhood-Onset Essential Hypertension With and Without Left Ventricular Hypertrophy

	Left Ventricular Hypertrophy		P Value
	No	Yes	
Number	57	32	
Age, y	13.5 (1.7)	13.6 (2.0)	.796
Male, No. (%)	34 (60)	24 (75)	.145
Ethnicity, No. (%)			
NHW	23 (40)	6 (19)	.175
Black	19 (33)	12 (37)	
Hispanic	14 (25)	13 (41)	
Asian	1 (2)	1 (3)	
Weight, kg	69.1 (20.2)	85.1 (18.7)	.0004
Height, m	1.6 (0.1)	1.7 (0.1)	.202
BMI, kg/m ²	25.6 (6.9)	30.6 (6.5)	.001
BMI z score	1.2 (0.9)	1.9 (0.6)	.0002
Weight status, No. (%)			
Normal	23 (41)	3 (9)	.002
Overweight	15 (26)	7 (22)	
Obese	19 (33)	22 (69)	

Abbreviations: BMI, body mass index; NHW, non-Hispanic white. All values are expressed as mean (standard deviation) unless otherwise indicated.

TABLE II. BP Profile of Children With Childhood-Onset Essential Hypertension With and Without LVH

	Systolic			Diastolic		
	No LVH	LVH	P Value	No LVH	LVH	P Value
Clinic BP, mm Hg ^a	134.3 (9.0)	138.8 (13.8)	.064	75.7 (11.8)	79.7 (8.6)	.091
Clinic BP Index	1.1 (0.1)	1.1 (0.1)	.464	0.9 (0.1)	1.0 (0.1)	.195
Ambulatory BP, mm Hg						
Total	121.8 (7.4)	124.6 (10.3)	.205	68.5 (6.4)	68.4 (7.3)	.921
Waking	128 (7.3)	130.9 (9.8)	.177	74.4 (7.3)	73.5 (9.2)	.686
Sleeping	111.3 (8.3)	113.3 (10.7)	.395	58.6 (6.1)	59.2 (7.7)	.719
Ambulatory BP index						
Total	1.0 (0.1)	1.0 (0.1)	.528	0.9 (0.1)	0.9 (0.1)	.758
Waking	1.0 (0.1)	1.0 (0.1)	.426	0.9 (0.1)	0.9 (0.1)	.638
Sleeping	1.0 (0.1)	1.0 (0.1)	.804	0.9 (0.1)	0.9 (0.1)	.771
Ambulatory BP load, %						
Total	34.4 (24)	43 (27.8)	.186	19 (17.4)	20.6 (20.7)	.735
Waking	36.2 (24.5)	43.9 (27.9)	.241	18.8 (17.3)	20.8 (22.4)	.676
Sleeping	30.3 (27)	32.8 (30.7)	.728	18.4 (20)	20.9 (25.1)	.65
Ambulatory BP dip, %	10.1 (7)	10 (7.9)	.986	16.3 (10.1)	14.2 (12.7)	.399
Ambulatory BP nondippers, No. (%)	10 (23)	6 (25)	.833	1 (2)	3 (12.5)	.122

Abbreviation: LVH, left ventricular hypertrophy. All values are expressed as mean (standard deviation). ^aClinic blood pressure (BP) is the average of three measurements.

TABLE III. Vascular Ultrasound and Laboratory Profiles in Childhood-Onset Essential Hypertension With and Without Left Ventricular Hypertrophy

	Left Ventricular Hypertrophy		P Value
	No	Yes	
Carotid intima-media thickness, mm	0.56 (0.08)	0.64 (0.03)	.002
Total cholesterol, mg/dL	169.1 (32.2)	173.2 (29.8)	.646
High-density lipoprotein, mg/dL	38.2 (8.7)	35.4 (8.6)	.279
Low-density lipoprotein, mg/dL	112.1 (28.6)	103.6 (32.6)	.348
Triglycerides, mg/dL	95.1 (59.9)	148.7 (110.0)	.018
Fasting glucose, mg/dL	88.2 (9.9)	89.6 (11.2)	.632
Fasting insulin, IU/L	13.1 (6.2)	17.4 (9.8)	.110
Urine albumin/creatinine	0.07 (0.11)	0.04 (0.03)	.144

All values are expressed as mean (standard deviation).

TABLE IV. Echocardiographic Profile in Childhood-Onset Essential Hypertension With and Without Left Ventricular Hypertrophy

	Left Ventricular Hypertrophy		
	No	Yes	P Value
Heart rate, beats per min	74.4 (13.4)	72.7 (13.6)	.5877
Left ventricular mass, g	121 (29.5)	178.7 (30)	<.0001
Left ventricular mass index, g/body surface area	68.8 (12.3)	90.8 (12.2)	<.0001
Left ventricular mass index, g/cm ^{2.7}	31.7 (5.3)	44.9 (4.6)	<.0001
Relative wall thickness	0.3 (0.04)	0.4 (0.05)	<.0001
Shortening fraction, %	41.2 (9.3)	50.8 (13.7)	.0002
Ejection fraction, %	78.2 (10.2)	85.5 (9.4)	.0016
Mitral valve E wave, cm/s	98.4 (17.3)	99.7 (28.2)	.7986
Mitral valve A wave, cm/s	52.5 (13.2)	55 (16.1)	.4540
Mitral valve E/A	2.0 (0.5)	1.9 (0.4)	.3403
Velocity of circumferential fiber shortening, circ/s	422.5 (19.1)	426.1 (27.3)	.5374
Mitral valve deceleration time, ms	183.0 (35.6)	180.5 (36.1)	.7557
Mitral valve acceleration time, ms	90.5 (15.4)	96.8 (23.7)	.1471
Isovolumic relaxation time, ms	69.7 (12.8)	79.6 (21)	.0081
Left ventricular ejection time, ms	295.6 (22.4)	296.5 (28.5)	.8683

Values are expressed as mean (standard deviation) unless otherwise indicated.

LVH than BP measures, both clinic systolic BP and mean 24-hour ambulatory systolic BP. In addition, we identified the presence of effect modification by BMI on the association between LVH and BP.

Similar to previous reports,^{22–24,27,48} and after robust analysis, both BMI and systolic BPs were shown in our study to contribute to the LVH phenotype in children with EH. However, we have demonstrated that BMI has a higher contribution toward the presence of LVH. There was a nearly nine-fold increased risk in the development of LVH among obese children compared with normal-weight children with EH. In our study, for every 10-mm Hg increase in the 24-hour ambulatory mean systolic BP, the odds of LVH approximately

doubled. Comparatively, the odds of LVH increased more than five-fold for every unit increase in BMI z score.

We further identified that in childhood-onset EH, both obesity and systolic BP were independently associated with LVH. Interestingly, the relationship between systolic BP and LVH in our study was modified by the presence of obesity, whereby the relationship existed mainly in the nonobese rather than the obese children with EH (Figure 2). Thus, the systolic BP values were significantly different between those with and those without LVH in the nonobese hypertensive children, with higher systolic BP values in those with LVH (Figure 2). However, the systolic BP values were not significantly different between those with and without LVH among the obese hypertensive children (Figure 2). In a study among African American adolescents, both obesity and high BP were found to be independently associated with elevated LVMI.³² Our finding has implications on clinical management of these children

and may indicate that even when the systolic BP is controlled, the child may continue to have LVH if he or she is obese, although this needs to be determined by a longitudinal study. It is possible that management of systolic BP alone in obese children would not result in complete resolution of LVH unless weight is also controlled. Comparatively, in nonobese children, BP control may provide a beneficial outcome with respect to resolution of their LVH.

We found that LVH phenotype was significantly associated with higher body size, triglycerides, and arterial thickening. From previous studies, we know that LVH is prevalent among obese children and is seen in association with both elevated BP^{49,50} and without elevated BP.^{27,48,51} Therefore, it is not surprising that even in children with EH in our study, obesity plays a role in the development of LVH. In our previous study, after multivariate analysis, we demonstrated that LV compliance indices correlated significantly with serum insulin levels in nondiabetic children with EH.¹ Obesity along with elevated triglycerides was seen in association with LVH in our current study, indicating a potential role of cardiometabolic phenotype⁵¹ in the development of LVH among children with EH.

We also found abnormal diastolic distensibility or ventricular relaxation as evidenced by prolongation of the isovolumic relaxation time of the left ventricle in association with LVH in childhood-onset EH. An alteration in LV filling with myocardial fibrosis and ischemia has been demonstrated in adults with hypertension. This diastolic dysfunction is related to inappropriately high levels of LVM, disproportionate to the hemodynamic load predicted by the individual body size and cardiac load. Delayed LV relaxation has been independently associated with concentric LV geometry in hypertensive adults, including obese patients.

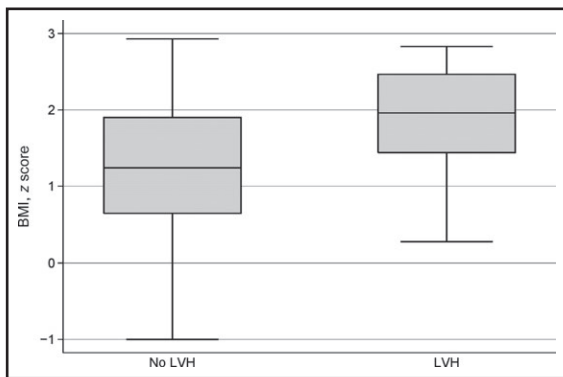


FIGURE 1. Box plots showing the distribution of body mass index (BMI) z scores in hypertensive children with and without left ventricular hypertrophy (LVH) ($P=.0002$).

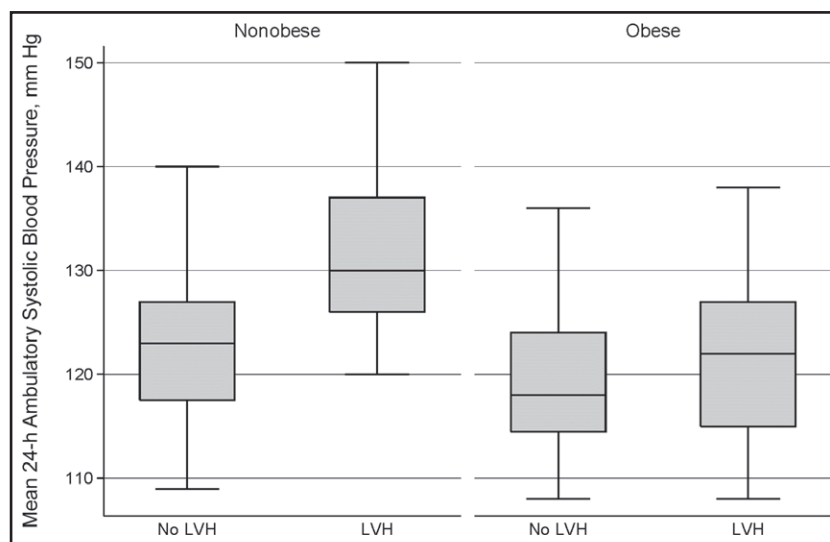


FIGURE 2. Box plots showing the association of systolic blood pressure with distribution of body mass index (BMI) z scores in obese and nonobese hypertensive children with and without left ventricular hypertrophy (LVH).

STUDY LIMITATIONS

Our study was limited by the small sample size and lack of longitudinal data. Furthermore, our findings may not be generalizable as a result of its single-center design. We recommend a larger, multicenter study with longitudinal data to confirm our findings.

CONCLUSIONS

In our multiethnic study of hypertensive children, we identified that obesity and systolic BP were both independently associated with LVH. Hence, to achieve reversal of end-organ damage in children with EH, clinicians should take into account both BP control and weight management.

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