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Aortic Dilatation in Children with Systemic Hypertension

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Abstract

Background—The aim of the study was to determine presence of aortic dilatation in hypertensive children, the prevalence of which is 4–10% in hypertensive adults.

Methods—Prospectively enrolled multiethnic children untreated for their hypertension, underwent an echocardiogram to exclude congenital heart disease and evaluate for end-organ damage and aortic size. The aorta was measured in the parasternal long-axis view at 3 levels: the sinus of Valsalva, supra-tubular junction and the ascending aorta. Aortic dilatation was determined by z-score > 2 at any 1 of the levels measured. Hypertension was defined as blood pressure above the 95th percentile based on the Fourth Working Group criteria confirmed by 24-hour ambulatory blood pressure monitoring.

Results—Among 142 consecutive hypertensive children (median age 14 years, 45% females) aortic dilatation was detected in 2.8% (95% CI 1% to 7%, median age 16 years, 100% females). Children with aortic dilatation, when compared to those without, had significantly more aortic valve insufficiency (p = 0.005) and left ventricular hypertrophy (p = 0.018).

Conclusions—Prevalence of aortic dilatation was 2.8% and was associated with significantly more aortic insufficiency and left ventricular hypertrophy in comparison to those without aortic dilatation.

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Keywords

Echocardiogram; essential hypertension; aortic insufficiency; left ventricular hypertrophy

Introduction

Aortopathy, beginning with dilatation of the aorta and leading to aneurysm formation, is one of the serious complications of systemic hypertension and has been described in 4–10% of adults with hypertension(1–5). Aneurysms can occur anywhere in the aorta and are multifactorial in origin but hemodynamic factors, especially systemic hypertension, may contribute to the progression of aortic aneurysmal dilatation and aortic valve regurgitation in the absence of aortic valve pathology. Hypertensive adults have been found to have higher aortic diameters in comparison to normotensive adults(6) and hypertension is a known risk factor for aortic dilatation in adults, particularly of the ascending aorta, and contributes to aortic dissection(3, 7, 8) in adults.

In adults with untreated, uncomplicated, mild to moderate essential hypertension, the prevalence of dilatation at sinus of Valsalva has been reported at 3.7%, (9). Furthermore, several independent predictors of sinus of Valsalva size in hypertensive adults have been found, including nocturnal diastolic blood pressure, anthropometric variables, male gender, left ventricular hypertrophy, and carotid atherosclerosis (9). Several of the cardiovascular end-organ damage manifestations seen in hypertensive adults have also been reported in hypertensive children, including left ventricular hypertrophy (10, 11) and increased carotid intimal thickness(11, 12). To our knowledge, aortic dilatation in the absence of aortic valve disease has not previously been described in children with hypertension. We postulated that dilatation of aorta in children, in comparison to adults, may have a lower contribution from aging and degenerative changes due smoking, atherosclerosis and so on and have a higher degree of contribution from hypertension. The aim of the study was to determine the prevalence of aortic dilatation in children with untreated systemic hypertension.

Methods

Institutional approval

The protocol was approved by the institutional Committee for the Protection of Human Subjects or the Institutional Review Board. All subjects and parents gave informed assent and consent, respectively for this study. We were careful in maintaining full patient confidentiality, safeguarding the rights and welfare of human subjects, and informing subjects in a confidential manner of the results of the study.

Patient Population

This was a prospective study of subjects aged 1–19 years who were confirmed to have hypertension. Children with history of hypertension consisted of: (1) *Referral Study Population:* patients referred to the hypertension program after detection of elevated blood pressure by a primary care provider on several preceding occasions, and (2) *Recruited Study Population*: patients identified by systematic school-based screening for hypertension in

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students aged 11–18 years in Houston area public schools. Parents are notified in advance by letter sent from each school regarding the screening program. Forms were provided for parents to sign and return if they did not wish their child to participate. At each screening, three seated blood pressure measurements were made at least one-minute apart using oscillometric monitors. Students found to have an average blood pressure above the gender, age and height-percentile specific 95th percentile blood pressure (13) value underwent a second set of blood pressure measurements 1–2 weeks later. Students found to have blood pressure above the 95th percentile at the 2nd screening underwent a 3rd set of blood pressure measurements an additional 1–2 weeks later. Students with elevated blood pressure on all 3 occasions were considered to be hypertensive. Families of hypertensive children are informed of the persistent blood pressure elevation and invited to participate in a clinic-based study of hypertensive end-organ injury in children. Patients recruited by these 2 methods i.e., school screening and referral, as described above have been shown to be similar(14).

Inclusion criteria—Criteria for inclusion in further analysis were: 1) clinic blood pressure elevation above the 95th percentile on 3 previous occasions, and 2) no concurrent medication with the potential to raise blood pressure (e.g., prednisone or methylphenidate).

All children were evaluated in the pediatric hypertension clinic for any secondary causes of hypertension; this was done by history, a physical examination and further testing. Demographic and anthropometric data were collected on all subjects at study entry, including age, gender, height, weight, and ethnicity. Once hypertension was confirmed, all subjects underwent further evaluation for end-organ damage including a transthoracic echocardiogram prior to therapy. An echocardiogram was repeated approximately one year after initiating therapy.

Blood Pressure Protocol

All subjects underwent blood pressure evaluation in the pediatric hypertension clinic by a rigorous protocol. Blood pressure was measured as follows.

Clinic Blood Pressure—Clinic hypertensive status was confirmed in all subjects at the first visit to the hypertension clinic by averaging the last 3 of 4 blood pressure measurements performed by manual auscultation with a mercury sphygmomanometer by trained personnel using methodology recommended by the Fourth Working Group (13).

Ambulatory Blood Pressure Monitoring—All subjects above age 5 years age underwent ambulatory blood pressure monitoring (ABPM) using Spacelabs oscillometric monitors (Spacelabs, Inc., Redmond, WA). Blood pressure was measured every 20 minutes for 24 hours. Subjects with 24-hour systolic blood pressure or diastolic blood pressure greater than the pediatric 95th percentile or blood pressure load (% of blood pressure values exceeding the ^{95th} percentile for the 24-hour period) greater than 25% were considered to have ambulatory hypertension. Subjects with clinic hypertension and 24-hour systolic blood pressure and diastolic blood pressure less than the pediatric 95th percentile and blood pressure load less than 25% were considered to have white coat hypertension and were

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excluded. Subjects with systolic or diastolic hypertension during the night on ABPM were considered to have nocturnal hypertension.

Echocardiography Protocol

Transthoracic echocardiograms were performed on all patients diagnosed with hypertension and repeated after one year. The heart was imaged by trained pediatric sonographers via 2-D, Doppler and M-mode transthoracic echocardiogram (Acuson Sequoia C256, Siemens, PA, USA), using a standard protocol to rule out congenital heart disease, with emphasis on evaluation of the aorta, including 2-D imaging in the parasternal long axis views to image the ascending aorta (1). Measurements were obtained by 2-D echocardiogram at the level of the aortic annulus, sinuses of Valsalva, sinotubular junction, and proximal ascending aorta (15). The measurements were made in systole, at the moment of maximum expansion from inside edge-to-inside edge perpendicular to the long axis of the vessel. Averages of 3 measurements were used for each patient. The studies were acquired and recorded digitally and on a super VHS videocassette for later review. All studies were evaluated for the presence of congenital heart disease, including bicuspid aortic valve and coarctation of the aorta. Those with congenital cardiac disease including bicuspid valves were excluded from this study. Dilatation was based on the normative data for sinus of Valsalva and sinotubular junction available in children for the given body surface area with measurements that were at or above the upper limit of normal (95% confidence interval) (15) at any one level of measurement, i.e., sinus of Valsalva or the sinotubular junction. In addition to normative data mentioned above, any measurement with z-score > 2 at any one level of measurement, i.e., sinus of Valsalva or sinotubular junction or the ascending aorta, was labeled with aortic dilatation (16).

Further, M-mode measurements obtained during diastole via transthoracic echocardiography included intraventricular septal thickness, left ventricular end-diastolic dimension, and posterior wall thickness. Left ventricular mass (LVM) was calculated per Working Group recommendations using the equation of Devereux et al. with measurements obtained by criteria of the American Society of Echocardiography (17). Left ventricular mass index was calculated by dividing LVM by height$^{2.7}$ to minimize effects of age, gender, ethnicity, and overweight status (18–20).

Statistics

Prevalence estimates of aortic dilatation were calculated with the 142 consecutive children with untreated hypertension in the prospective study. After the prospective study, 3 additional children with aortic dilatation were identified but were not included in prevalence calculation. Continuous outcome measures were compared using Wilcoxon Rank-Sum tests and reported as median and interquartile ratio. Categorical variables were tested using two-tailed Fisher’s Exact tests and reported as count (%). Type I Error rate was set at 0.05 and all tests were two-sided.

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Results

To determine the prevalence of aortic dilatation, we evaluated a total of 142 consecutive children (45% females, median age 14 years, range 2 to 18 years) with primary and secondary hypertension in our tertiary pediatric hypertension clinic. The ethnicities of the 142 children were as follows: African American 40%, Caucasian 36%, Hispanic 22%, and Asian 2%. Each underwent an echocardiogram prior to onset of therapy to evaluate for congenital heart disease, left ventricular hypertrophy and aortic dilatation. Aortic dilatation was detected in 4 (95% CI 1% to 7%; 100% females; median age 16 years, range 12 to 18 years) of the 142 children with systemic hypertension giving a prevalence of 2.8%. The etiology of systemic hypertension in those with aortic dilatation was determined to be essential hypertension in all but one child with Turner syndrome without coarctation of aorta who had a normal aortic valve and a single functional kidney without evidence of renal artery stenosis.

To determine the difference in the end-organ damage associated with dilated aorta we performed a case-control study after completion of enrollment of the study population (n = 142). We found 3 additional hypertensive children in our clinic population (one male) with dilated aortas and their data was included for case-control comparison without factoring them in the prevalence calculation (Table 1). All children with aortic dilatation had a normal aortic valve apparatus without any bicuspid valve or stenosis as determined by an echocardiogram, a negative examination for any syndrome (except one for Turner syndrome), and a negative family history of Marfan syndrome, aneurysm, aortic dissection, or sudden death. In the case-control study, comparing those with aortic dilatation (n = 7) against those without aortic dilatation (n =138), left ventricular hypertrophy (86% vs. 38%, $p = 0.018$) and aortic regurgitation, generally mild (43% vs. 4%, $p = 0.005$) was significantly more prevalent in those with aortic dilatation.

Since normative data on blood pressure in children are based on height, age and gender (13), it becomes imperative to compare the blood pressure in these children based on these variables. Hence, in order to evaluate the blood pressure parameters between those with (n=7) and those without aortic dilatation (n = 142), we matched them (1:1) based on height, age and gender (Table 2). We found that hypertensive children with aortic dilatation when compared to their matched hypertensive controls without aortic dilatation had significantly larger aorta at all 3 levels (unlike certain other diseases such as Marfan syndrome where the dilatation is mostly at the sinus of Valsalva), while there were no significant differences in their blood pressure levels (table 2, figure 1). Of the children with dilated aortas, presence of nocturnal hypertension was significantly higher than matched controls (Table 2). The echocardiogram and measurements of aorta were repeated after one year. We found that children who had their blood pressure controlled showed either a decrease in size or no further increase in size of their aorta after one year (Table 3).

Discussion

Aortic dilatation per definition which is based on z-scores would be seen in 2.3% of normotensive children, and we found a prevalence of 2.8% in our prospective study of well

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characterized, multiethnic, untreated hypertensive children; the prevalence of which is reported at 3.7% in untreated hypertensive adults.(9) Despite the modest prevalence of aortic dilatation in children, the presence of aortic insufficiency and left ventricular hypertrophy were significantly higher in those with aortic dilatation than those without. We had confirmed the presence and severity of hypertension in our patients by repeat blood pressure evaluations and by 24-hour ambulatory blood pressure monitoring. Similar to adults (9), nocturnal hypertension was associated with aortic dilatation but unlike adults, children with aortic dilatation were all females. These children with aortic dilatation had a mild abnormality of their aorta which may not be clinically significant but may place them at a higher risk for developing an aneurysm at an older age. Hence, evaluation of aorta does identify an at-risk phenotype at a younger age. Further, defining and identifying aortic dilatation in childhood may help in preventive strategies and for recommendations such as strenuous activities.

All children except for one in our study had childhood-onset essential hypertension without an identifiable etiology for aortic dilatation. (21–28) These findings are similar to adults, where most of hypertensive adults with aortic aneurysms and dissections do not have an identifiable syndrome. (29) Similar to adults, not a large number of hypertensive children were found to have aortic dilatation. Since only a small number of children with hypertension had dilated aortas, there may possibly be an underlying genetic cause, such as intrinsic connective tissue defect, which is brought forth by mechanical factors such as hypertension in this population. Similar to adults, controlling the blood pressure was seen to be beneficial in our study, possibly by preventing further mean circumferential stress on the dilated aortas (30). Studies have determined that a genetic predisposition in some families to aortic aneurysms and dissections is inherited in an autosomal dominant manner with decreased penetrance and variable expression; hence the importance of surveillance for this phenotype as early as possible. (31, 32) Other than the child with Turner syndrome in our study, none of the children with dilated aortas in our study had an identifiable syndrome such as Marfan syndrome or Loeys-Dietz syndrome by physical examination or history. Aortic dilatation has been reported in patients with Turner syndrome, both with and without the presence of hypertension or bicuspid aortic valve (28, 33).

Aortopathy in hypertension may differ from that seen with other diseases. Unlike Marfan syndrome and other syndrome-related aortic dilatation that tends to occur mostly at the sinus of Valsalva and sinotubular junction, the hypertensive children in our study demonstrated significant dilatation from controls at any of the 3 levels including sinus of Valsalva, sinotubular junction and the ascending aorta. This may be related to the mean circumferential stress seen by entire ascending aorta from intra-arterial pressure in chronic uncontrolled hypertension leading to diffuse dilatation in a susceptible aorta. Currently, the protocol for assessment for aortic dilatation by transthoracic echocardiography is variable among centers and in studies reported in the literature. Besides the measurement of aortic valve annulus diameter in the hypertensive adults, the aorta is routinely measured at sinus of Valsalva only (3) whereas for Marfan syndrome, the aorta is measured at 3 levels: sinuses of Valsalva, sinotubular junction and the ascending aorta (15). The current thoracic aortic disease treatment guidelines recommend additional measurements of the ascending and descending aorta on patients with thoracic aortic disease (34) and also in children(35). The

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aorta should be measured at multiple sites in children as the pattern of dilatation can vary(35) and the children may benefit in identifying those who should be monitored closely and who are at- risk for various types of dissections such as type A and type B dissections as adults (34, 36).

Limitations of the study include the small sample size and lack of longitudinal follow up of duration longer than one year. Besides, we did not determine the familial nature of hypertension in this study. Furthermore, we did not use any additional imaging modality such as a cardiac magnetic resonance imaging.

In conclusion, aortic dilatation was seen in 2.8% of hypertensive children in significant association with childhood-onset essential hypertension, female gender and nocturnal hypertension. The presence of aortic insufficiency and left ventricular hypertrophy were significantly higher among those with aortic dilatation than those without, thus identifying them as having greater target organ damage. Thus, hypertensive children may benefit from careful measurements of their aortas by echocardiography to determine this phenotype.

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Table 1

Demographics and echocardiogram findings in hypertensive children with aortic dilatation

Age, Years	Gender	Ethnicity	SBP, mmHg	DBP, mmHg	BSA, m2	Height, cm	SOV, mm (z-score)	STR, mm (z-score)	AAO, mm (z-score)	Aortic valve insufficiency	LVH
16	F	Caucasian	154	105	1.48	155	33 (3)	28 (3.1)	35 (5.4)	Yes	Yes
15	F	Caucasian	128	81	1.69	163	30 (1.5)	26 (1.9)	30 (3.1)	No	Yes
16*	F	Caucasian	148	92	1.7	152	31 (1.7)	27 (2.2)	30 (3.1)	Yes	Yes
17	F	Caucasian	126	80	1.68	165	35 (3)	26 (2)	27 (2)	No	No
15	M	AA	137	80	1.64	165	36 (3.4)	27 (2.4)	29 (2.9)	No	Yes
18	F	AA	147	99	2.36	169	32 (0.8)	28 (1.4)	31 (2.1)	No	Yes
12	F	AA	155	98	1.62	161	30 (1.7)	26 (2.2)	30 (3.4)	Yes	Yes

AA, African American; Wt, weight; Kg, kilograms; cm, centimeters; F, female; M, male; SBP, average of 3 casual systolic blood pressures; DBP, average of 3 casual diastolic BP; NA, not available; LVH, left ventricular hypertrophy;

*Turner syndrome

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Table 2

Comparison of blood pressure and echocardiogram measurements in hypertensive children with aortic dilatation to matched hypertensive controls without aortic dilatation

	Aortic Dilatation	Control	p value
Age, years	16 (15, 17)	16 (15, 17)	1
Gender (% female)	6 (86%)	6 (86%)	1
BSA, m^2	1.69 (1.64, 1.7)	1.77 (1.6, 2)	0.848
Weight, kg	59 (55, 70)	67 (56, 82)	0.406
Height, cm	163 (155, 165)	165 (154, 170)	0.521
Systolic BP, mmHg	147 (128–154)	133 (132–150)	0.848
Diastolic BP, mmHg	92 (80–99)	83 (77–86)	0.249
Nocturnal hypertension	6 (100%)*	1 (20%)	0.015
Sinus of Valsalva, mm	32 (30, 35)	25 (22, 29)	0.005
Sinotubular Junction, mm	27 (26, 28)	23 (19, 26)	0.005
Ascending Aorta, mm	30 (29, 31)	23 (21, 24)	0.003

Values expressed as median (interquartile ranges); BP, blood pressure; BSA, body surface area;

* measurement missing in one child

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Table 3

Change in aortic measurements on repeat echocardiogram in approximately one year after treatment*

Age, years	Gender	Medication	SOV1, mm	SOV2, mm	STR1, mm	STR2, mm	AAO1, mm	AAO2, mm
16	F	Metoprolol, Amlodipine Hydrochlorothiazide	33	33	28	28	35	33
15	F	Amirolide, Metoprolol	30	28	26	27	30	27
16	F	Atenolol	31	29	27	27	30	27
18	F	Lisinopril	32	28	28	26	31	27
12	F	Ramipril, Metoprolol	30	29	26	24	30	28

F, female; M, male; 1, initial measurement prior to therapy; 2, measurement from average of one year follow up after therapy; SOV, sinus of Valsalva; STR, sinotubular junction; AAO, ascending aorta; (*2 patients were lost to follow-up and hence data not included)