Stiffness of the Aortic Wall in Hypercholesterolemic Children

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Arterial stiffness may be an indicator of early vascular changes signaling the development of vascular disease, while hypercholesterolemia is a well-recognized promoter of atherogenesis. It has been shown that hypercholesterolemic children have a thicker intima-media in the carotid artery than children with normal cholesterol. The aim of this study was to assess the stiffness of the abdominal aorta in children with hypercholesterolemia. Noninvasive imaging evaluation of the aorta was performed in 85 outpatient children (age, 3 to 14 years) with and without high cholesterol levels (and) 247 mg/dL [6.4 mmol/L], respectively). Ultrasound imaging of the abdominal aorta that allowed diameter measurements was available in 67 children. Using an image-processing workstation, the maximum and minimum internal diameter of the aorta was measured, and the following indices of elastic properties of the abdominal aorta were derived: arterial strain, pressure-strain elastic modulus, and stiffness. No statistical difference for aortic strain, stiffness, and elastic modulus was found in normocholesterolemic compared with hypercholesterolemic children. The effect of age on the elastic modulus was different in the two groups: in normal children, the elastic modulus increased linearly with age ($y = -0.020 + 0.003 \times$ age [months], $P < .001$), while the high-cholesterol group had a weak increase in this parameter with age ($y = 0.118 + 0.0009 \times$ age, $P = .051$). The slope of the regression equations (elastic modulus *v* age) was significantly different in the two groups ($t = 2.45$, $P = .017$). The behavior of arterial stiffness with respect to age was similar, $y = 0.677 + 0.018 \times$ age ($P = .002$) in normocholesterolemic children and $y = 2.06 + 0.00198 \times$ age ($P = .66$) in hypercholesterolemic children. The slope of the regression equations (stiffness *v* age) was significantly different in the two groups ($t = 2.37$, $P = .021$). The present study demonstrates an influence of hypercholesterolemia on age-related modification in the elastic properties of the aorta. A remodeling of the aortic wall in hypercholesterolemic children (cholesterolemia > 247 mg/dL) could explain the different age-dependent increase in aortic elastic modulus and stiffness.

CHILDREN REPRESENT a segment of the whole population, with distinctive features; however, the study of hypercholesterolemia in the pediatric age group could explain some of the clinically relevant characteristics present in adults. Morphologic studies of the aorta have demonstrated fatty streaks in children as young as 3 years old.[1] There is evidence that at least some of the fatty streaks present in children are likely to proceed to more advanced lesions.[2] The location in the aorta in which fatty streaks first develop into advanced lesions has been identified between the orifice of the inferior mesenteric artery and the bifurcation of the common iliac arteries.[2] Aortic fatty streaks in subjects aged from a few months to 30 years were strongly correlated with low-density lipoprotein cholesterol levels determined before death.[3] A recent ultrasonographic study[4] has demonstrated that hypercholesterolemic children have a higher carotid intima-media thickness than control children.

Follow-up studies are expected to clarify if this thicker carotid wall in hypercholesterolemic children is a predictor of cardiovascular morbidity and mortality in adulthood. In general, carotid intima-media thickness is a well-established and reliable index of generalized atherosclerosis,[5] and extends to other arteries such as the coronary arteries, aorta, and renal and lower-limb arteries. Since early atherosclerotic changes may affect the passive mechanical properties of arteries, there is good reason to assess the atherosclerotic involvement of accessible arteries by noninvasive determination of their mechanical properties (ie, compliance, stiffness, and elastic modulus). Aortic compliance is reduced in adults at increased risk of premature vascular disease.[6] In this instance, another proposed noninvasive indicator of atherosclerosis is aortic compliance measurement.[7] In fact, compliance is an important parameter to characterize the arterial wall and to study possible links between the composition and structure of the aortic wall and cardiovascular risk.

Several different techniques have been used to determine aortic elastic properties: magnetic resonance imaging,[8] Doppler ultrasound examination,[6] echocardiography,[9] echo-tracking,[10] M-mode echography,[11] and B-mode echography.[12] Recently, M-mode transesophageal echocardiography has been used to study the stiffness of the descending thoracic aorta and B-mode echography to measure the carotid diameter and stiffness.[13]

Several parameters have been proposed as indices of the elastic properties of arteries. Arterial strain (S) represents the systolic expansion in diameter normalized for the minimum diastolic diameter, independent of arterial pressure. Elastic modulus (Ep), used with in vitro studies to express the magnitude of the stress required to produce a given strain (ie, stress/strain), can be used in vivo to describe the elastic arterial properties when the arterial thickness to radius ratio is very small (as in children's aortas) and when there is a linearity of the stress-strain relationship during blood pressure variations. Stiffness (β) is based on the assumption that an exponential relation exists between relative pressure, systolic pressure (Ps)/diastolic pressure (Pd), and strain. Since the β values are influenced less by changes in Ps, this index seems better than Ep not only theoretically but also experimentally.

The aim of this study was to evaluate the elastic properties of the abdominal aorta in hypercholesterolemic children and to

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clarify if any cholesterol-related abnormality could be demonstrated in the behavior of aortic elasticity parameters even in the early stages of life.

SUBJECTS AND METHODS

Subjects

One hundred consecutive outpatient children (age, 3 to 14 years) were recruited from the Pediatric Lipid Clinic (Federico II University, Naples, Italy). Some children were not hypercholesterolemic but were siblings of hypercholesterolemic children; other children reported to the Lipid Clinic only for an evaluation of possible hypercholesterolemia. All females were prepubertal but two: one normocholesterolemic and another hypercholesterolemic.

All children underwent a serum determination of cholesterolemia, triglyceridemia, and high-density lipoprotein (HDL) cholesterolemia and a noninvasive B-mode ultrasound evaluation to determine the systolic and diastolic diameter of the abdominal aorta.

Fifteen parents did not give consent for their children to undergo ultrasound examination. The remaining 85 children underwent ultrasound examination, and 67 of these had sufficient echographic images of the abdominal aorta to reliably evaluate the aortic diameter. In 18 cases, echographic images did not allow a reliable measurement of aortic diameter and were discarded.

Methods

Echographic evaluation of the abdominal aorta was performed by a certified sonographer (A.I.) at the Department of Clinical and Experimental Medicine, Federico II University (Naples, Italy) using a Duplex-Scanner Mark IV (Advanced Technology Laboratories, Bothell, WA) with a 7.5-MHz transducer. All subjects were studied after resting supine for at least 10 minutes in a room at a constant temperature of approximately 24°C. The sonographer was unaware of the child's cholesterol levels. The abdominal aorta was examined from the branching site of the superior mesenteric artery to the iliac bifurcation using longitudinal and cross-sectional views to verify the absence of atherosclerotic plaques or other anatomical abnormalities. The pulsatile wall motion of the abdominal aorta was determined at 3 to 5 cm distal to the branching site of the superior mesenteric artery, taking care to avoid exaggerated force during the abdominal scanning. A 5-minute SVHS video-recorded examination was performed, paying attention to ensure vertical alignment of the artery and to avoid drifting of the probe to obtain optimal images clearly showing aortic pulsatility. A single measurement of brachial artery pressure (systolic pressure, Ps; and diastolic pressure, Pd) was made by an independent observer during the ultrasound examination using a sphygmomanometer and cuff of appropriate size for the subject's age and body mass index (BMI).

Quantitative readings of abdominal aorta ultrasound scans were performed centrally at the Division of Vascular Ultrasound Research, Bowman Gray School of Medicine (Winston-Salem, NC). Briefly, the recorded tapes were reviewed by an expert ultrasound reader, and the five consecutive cardiac cycles showing the best images of aortic arterial wall motion were selected. The sequences selected were then imaged on the monitor frame by frame, and the five maximum systolic expansions (systolic diameters, Ds) were frozen and measured with the aid of a dedicated software program designed for diameter measurements, in which the visual placement of edge points was made using a mouse. The same procedure was used to visualize and measure the minimum diastolic arterial diameter (Dd). The five measurements of Ds and Dd were averaged. The relative aortic strain (S) was calculated as the systolic expansion in diameter normalized for the minimum diastolic diameter ([Ds − Dd]/Dd). Further indices were determined by relating this systolic expansion in diameter to the systolic increase in pressure. The elastic modulus, $133.3 \times (Ps - Pd)/S$, and stiffness, $(LnPs - LnPd)/S$, of the abdominal aorta were calculated for each patient. The elastic modulus, Ep, has the dimension of pressure (newtons per square meter, ie, force per unit area), and the factor for converting millimeters of mercury to newtons per square meter is 133.3. Stiffness, referred to as the β index, is dimensionless.

To assess the repeatability of these measurements, 20 scans were measured twice 2 weeks apart by the same reader in a blinded fashion. The coefficient of variation was 3.9% for diastolic diameter, 3.8% for systolic diameter, and 12.1% for elastic modulus and stiffness.

Statistical Analysis

ANOVA was used to test differences between normocholesterolemic and hypercholesterolemic children and sex differences.[14] A linear regression test was used to find a possible relation between cholesterol values and aortic parameters of elasticity, ie, elastic modulus and stiffness. The same test was performed to test the influence of age on distensibility parameters.[15] A *t* test comparing the slopes of regression equations (age *v* elastic modulus and age *v* stiffness) was used to test differences between the two groups of children, normocholesterolemics and hypercholesterolemics. A *P* value less than .05 (two-sided) was considered statistically significant.

RESULTS

In 67 children in whom aortic stiffness and elastic modulus were calculated, the mean cholesterolemia was 249 mg/dL.

There were no differences in age, height, weight, lipids, brachial pressure, aortic diameter, and elastic properties of the aorta in boys and girls. A significant sex difference existed for both systolic and diastolic aortic diameters, with values in boys higher than in girls. No sex difference was found for aortic strain, stiffness, and elastic modulus.

Normocholesterolemic and hypercholesterolemic children did not differ in age, height, weight, BMI, or systolic and diastolic pressure. There was a small but significant difference in triglyceride and HDL cholesterol levels. In grouping by sex, normocholesterolemic and hypercholesterolemic boys differed in triglyceridemia, whereas the girls showed a statistically significant difference in HDL cholesterolemia (Table 1).

Aortic diameter, elastic modulus, and stiffness were not statistically different between hypercholesterolemic children or controls even after adjustment for sex.

In the regression analysis, there was no relationship between total serum cholesterol and elastic modulus or stiffness for the two groups combined (67 children). Elastic modulus showed an age-dependent increase ($y = 0.052 + 0.0017 \times$ age [months], $r = .52, P < .001$), as did stiffness ($y = 1.388 + 0.0097 \times$ age, $r = .32, P < .01$).

To test the possibility of a different relationship between stiffness and age in hypercholesterolemic versus normocholesterolemic children, we performed a regression equation in the two groups. In the normocholesterolemic group, there was a clear direct correlation between age and elastic modulus ($y = -0.020 + 0.003 \times$ age, $R^2 = .49$, $P < .001$), as well as between age and stiffness ($y = 0.677 + 0.018 \times$ age, $R^2 = .30$, $P = .002$); in hypercholesterolemic children, there was a nonsignificant positive relationship between age and elastic modulus ($y = 0.118 + 0.0009 \times$ age, $R^2 = .10$, $P = .051$) and between age and stiffness ($y = 2.06 + 0.00198 \times$ age, $R^2 = .005$, $P = .66$). The slope of the regression equations for age versus

Table 1. Anthropometric Data, Lipids, Brachial Pressure, and Aortic Elastic Properties in Normocholesterolemic (<247 mg/dL) and Hypercholesterolemic (>247 mg/dL) Children

	Boys			Girls			Entire Group		
Parameter	NC (n = 15)	HC (n = 16)	*P*	NC (n = 15)	HC (n = 21)	*P*	NC (n = 30)	HC (n = 37)	*P*
Age (mo)	97.0 ± 35.4	99.7 ± 34.8	.71	88.8 ± 32.1	93.9 ± 30.4	.61	92.9 ± 33.4	96.4 ± 32.0	.60
CHOL (mg/dL)	182.8 ± 35.4	303.8 ± 55.1	<.001*	200.7 ± 29.0	288.6 ± 36.0	<.001*	191.8 ± 33.1	295.2 ± 45.2	<.001*
TG (mg/dL)	62.5 ± 21.8	83.1 ± 27.2	.036*	65.9 ± 22.6	83.2 ± 27.0	.07	64.4 ± 21.8	83.2 ± 27.0	.005*
HDL (mg/dL)	49.6 ± 9.5	48.7 ± 14.8	.68	58.3 ± 10.2	47.2 ± 8.7	.001*	54.9 ± 10.6	47.8 ± 11.7	.006*
Height (cm)	128.8 ± 16.0	131.3 ± 19.6	.82	125.4 ± 16.1	127.1 ± 14.6	.80	127.2 ± 15.7	128.6 ± 16.4	.75
Weight (kg)	31.1 ± 10.3	32.6 ± 15.6	>.999	28.9 ± 9.2	28.9 ± 8.9	.93	30.1 ± 10.0	30.3 ± 11.7	.88
BMI (kg/m²)	18.2 ± 3.2	17.9 ± 4.4	.60	17.9 ± 2.4	17.9 ± 4.5	.52	18.1 ± 2.8	17.9 ± 4.4	.55
Ps (mm Hg)	88.4 ± 15.7	86.2 ± 16.7	.59	85.1 ± 20.0	89.5 ± 18.1	.40	86.7 ± 17.7	88.1 ± 17.3	.71
Pd (mm Hg)	53.2 ± 10.0	51.2 ± 11.0	.80	51.9 ± 0.1	53.1 ± 11.8	.72	52.5 ± 9.4	52.3 ± 11.3	.96
Ds (mm)	10.0 ± 1.93	9.54 ± 1.56	.68	8.54 ± 2.00	8.88 ± 1.37	.35	9.27 ± 2.07	9.17 ± 1.47	.90
Dd (mm)	8.21 ± 1.93	7.68 ± 1.49	.49	6.95 ± 1.83	7.16 ± 1.15	.35	7.58 ± 1.96	7.38 ± 1.31	.99
Strain (%)	23.0 ± 9.6	25.2 ± 7.7	.57	23.7 ± 6.4	24.2 ± 4.2	.80	23.4 ± 8.0	24.6 ± 5.9	.26
STIF	2.52 ± 1.15	2.23 ± 0.88	.53	2.23 ± 1.09	2.26 ± 0.84	.57	2.37 ± 1.11	2.25 ± 0.85	.94
EM (10^5 · N/m²)	0.240 ± 0.14	0.205 ± 0.11	.61	0.206 ± 0.12	0.210 ± 0.08	.55	0.223 ± 0.12	0.207 ± 0.09	.96

NOTE. Results are the mean ± SD with statistics by Mann-Whitney test.

Abbreviations: CHOL, cholesterolemia; TG, triglyceridemia; Ps, systolic pressure; Pd, diastolic pressure; Ds, systolic diameter; Dd, diastolic diameter; STIF, stiffness (dimensionless); EM, elastic modulus.

elastic modulus was significantly different in the two groups ($t = 2.45$, $P = .017$, Fig 1). Similarly, the slope of the regression equations for age versus stiffness was significantly different in hypercholesterolemic children versus controls ($t = 2.37$, $P = .021$; Fig 2).

DISCUSSION

There is conflicting evidence as to the influence of cholesterolemia on aortic mechanical properties. Some investigators have demonstrated an inverse correlation between cholesterolemia and arterial compliance measured by pulse-wave velocity in the aorta and iliac arteries,[16] while others could not confirm any statistical correlation between cholesterolemia and arterial distensibility.[17,18] Giannattasio et al[19] have demonstrated a decreased radial artery compliance measured by an echo-tracking method, in patients with severe hypercholesterolemia. In the Bogalusa Heart Study, an increased elastic modulus of the carotid arteries was associated with increased systolic blood pressure and total cholesterol in 10- to 17-year-old adolescents; furthermore, a parental history of myocardial infarction was related to increased elastic modulus.[20]

Only a few data on arterial compliance are available in the

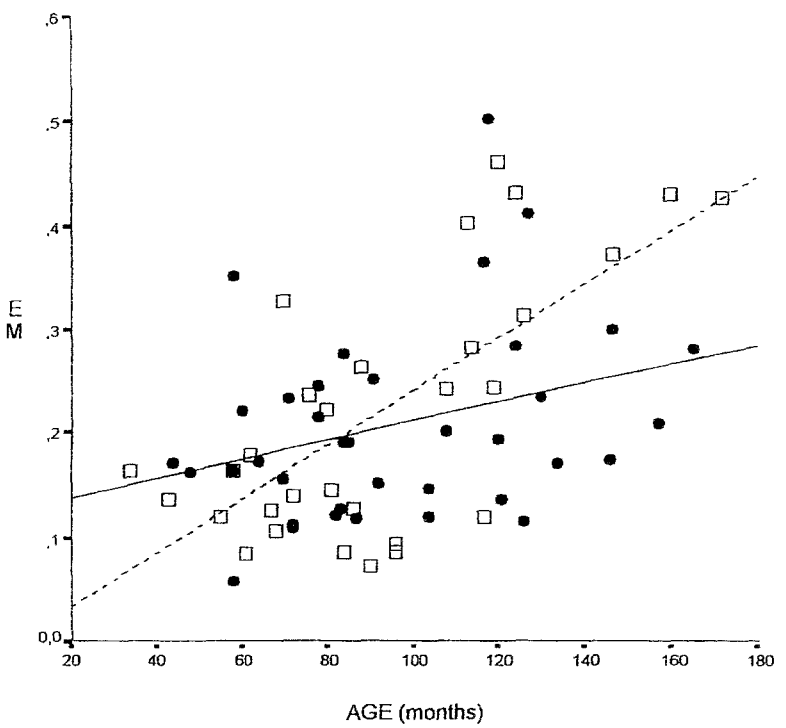

Fig 1. Linear regression between aortic elastic modulus (EM) after adjustment for sex (10^5 N/m²) and age (mo) in (□) normocholesterolemic (<247 mg/dL; $R^2 = .4878$) and (●) hypercholesterolemic (>247 mg/dL; $R^2 = .1004$) children.

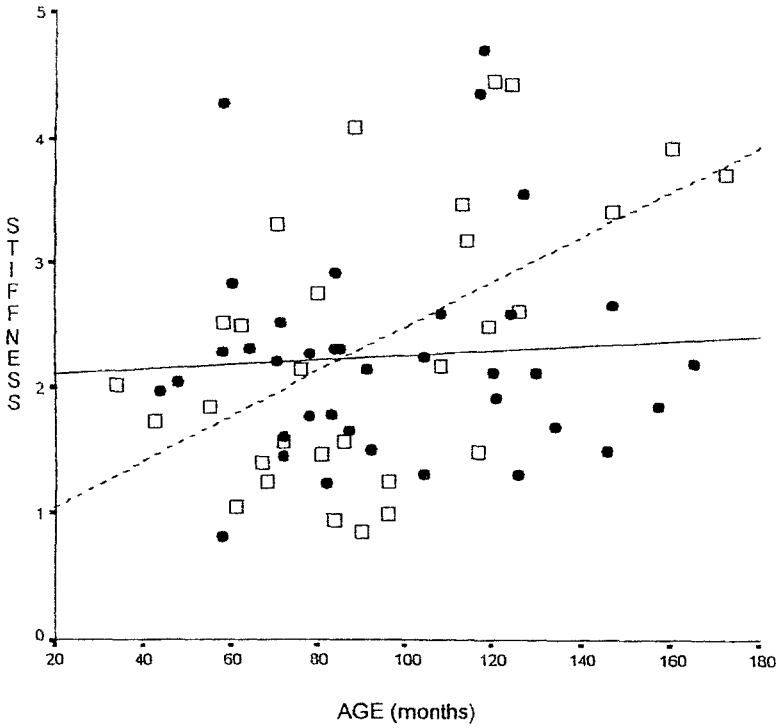

Fig 2. Linear regression between aortic stiffness after adjustment for sex (dimensionless) and age (mo) in (□) normocholesterolemic (<247 mg/dL; R^2 = .3027) and (●) hypercholesterolemic (>247 mg/dL; R^2 = .0053) children.

pediatric population. Van Merode et al[21] have analyzed the vessel wall properties of the common carotid artery in 53 normal boys (aged 4 to 19 years) with a multigate pulsed Doppler system. They found that the carotid artery wall was less distensible in adolescents (15 to 19 years) than in younger children (4 to 14 years), although no statistical difference was found for compliance in children aged 4 to 9 years versus 10 to 14 years. A subgroup analysis of large population data that include children could provide further information. Stiffness and elastic modulus were determined in 76 subjects, including 17 children under age 15. In these children, there was a direct relation between age and stiffness and/or elastic modulus.[22] Similar findings were reported by Kawasaki et al[23] for the abdominal aorta and common carotid artery and by Sonesson et al[24] for the distal abdominal aorta of girls aged 5 to 15 years. In contrast to previous investigators, Laogun and Gosling[25] have reported that aortic compliance increases until the age of 10.

The present study is the first to analyze aortic stiffness and elastic modulus in hypercholesterolemic children. The 95th percentile for the serum cholesterol concentration in a pediatric population in Naples, Italy (age, 2 to 15 years) is between 232 and 247 mg/dL (6.0 and 6.4 mmol/L).[26] Since the benefit derived from the reduction of moderately elevated serum cholesterol levels has not been clearly established in childhood, the highest value, 247 mg/dL, was chosen as a cutoff point for the control group of children. Testing this hypothesis in children forced us to use brachial artery blood pressure as a surrogate for intraaortic pressure. Although this may have some limitations, Imura et al[27] have demonstrated that aortic elastic modulus calculations using brachial or aortic pressure are highly correlated (r = .93, P < .001). A methodological limitation in our study is that only one blood pressure measurement was taken.

The systolic and diastolic diameter of the abdominal aorta was greater in boys versus girls, whereas there was no statistical difference in strain, stiffness, and elastic modulus between the sexes.

There was no statistical difference in aortic elastic modulus or stiffness between normocholesterolemic and hypercholesterolemic children. Both normocholesterolemic and hypercholesterolemic children showed an age-dependent increase in aortic elastic modulus and stiffness. It has been suggested that this age dependency is related to changes in the arterial wall content of elastin and collagen.[9,23] However, the slopes of regression equations in normocholesterolemia and hypercholesterolemia were statistically different (Figs 1 and 2). These findings in a pediatric population are in agreement with observations by Dart et al.[9] Using a similar technique, they reported a significant influence of age on aortic stiffness in hypercholesterolemic adult patients, but a weaker relationship when cholesterol was greater than 5.5 mmol/L. In particular, the slope of the regression line was less steep with a reduced increase in age-dependent stiffness in hypercholesterolemic patients, as in the present study.

There is no unequivocal explanation for this observation. Studies in animals have demonstrated that in the early stages of experimentally induced atherosclerosis, an increased compliance, indicative of greater distensibility, can be found, whereas in the later stages of the disease when focal lesions are present, a lower compliance, indicative of stiffer arteries, can be demonstrated.[28] Vonesh et al,[29] in a postmortem three-dimensional intravascular ultrasound study using human peripheral arterial specimens, found a higher elastic modulus for nondiseased tissue regions versus atherosclerotic regions. Arteries have the capacity to adjust their radius, wall thickness, and composition

in response to different wall tensile stresses and wall shear stresses.[30]

It is possible that hypercholesterolemia induces a remodeling of the arterial wall in the early years of exposure and may thus be responsible for the observed reduced effect of age on elastic modulus and stiffness. Arterial remodeling functions as a compensatory mechanism through which the aortic vasculature functionally maintains distensibility while intima-media thickness increases.[31] Other possible explanations include an influence of differences in physical exercise[8,32] or in dietary habits on aortic compliance.

In conclusion, the present study demonstrates that hypercholesterolemia in children reduces the effect of aging on the elastic properties of the aorta. A remodeling of the aortic wall in hypercholesterolemic children could explain the different age-dependent increase in aortic elastic modulus and stiffness.

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