Increased Intima-Media Thickness of the Common Carotid Artery in Hypercholesterolemic Children

Paolo Pauciullo, Arcangelo Iannuzzi, Renata Sartorio, Concetta Irace, Giuseppe Covetti, Anna Di Costanzo, Paolo Rubba

Abstract Common carotid intima-media thickness was measured by B-mode ultrasound imaging in 46 children (mean age, 7.4 years) with serum cholesterol ≥6.4 mmol/L (mean, 8.25 mmol/L) and in 48 children (mean age, 6.4 years) with serum cholesterol <6.4 mmol/L (mean, 4.60 mmol/L). Maximum thickness was significantly higher in hypercholesterolemic children than in control children (0.50 versus 0.47 mm, P=.007). Subgroup analysis showed that only in children >6.2 years old (the median of all the children's ages) was maximum thickness significantly higher in hypercholesterolemic children than in control children (0.51 versus 0.48 mm, P=.014). The odds ratio (OR) of common carotid intima-media thickening (maximum thickness of the far wall higher than the 95th percentile of the control group, 0.51 mm) between patients and control subjects was statistically significant both in univariate analysis (OR, 6.39; 95% confidence interval, 1.19 to 32.3; P=.025) and after age (OR, 5.96; 95% confidence interval, 1.09 to 32.4; P=.039) and sex (OR, 7.54; 95% confidence interval, 1.38 to 41.2; P=.020) were controlled for. Children >6 years old with serum cholesterol ≥6.4 mmol/L show increased thickness of the common carotid intima-media. (***Arterioscler Thromb*. 1994;14:1075-1079.**)

Key Words • children • atherosclerosis • carotid arteries • hypercholesterolemia

The relationship between hypercholesterolemia and coronary artery diseases (CAD) has been proved in adult CAD patients.[1-3] The significance of this relationship is more controversial in healthy subjects, particularly if their serum cholesterol is <6.4 mmol/L.[4-6] Children form a special subgroup of healthy individuals.

Population-based or "high-risk"–based screenings for serum cholesterol are usually recommended,[7-10] although others oppose this view on the basis of potential harm and of nonproven efficacy in the prevention of adult CAD.[11,12]

Autopsy studies on arterial specimens of human subjects have shown that fatty streaks (nonraised lesions) can be found in the aortas even of 3-year-olds[13] and appear in the coronary arteries during the second decade of life.[14] More advanced coronary atherosclerosis was seen in a majority of young adults in whom autopsies were performed during the Korean and Vietnam wars.[15,16] Aortic fatty streaks detected in subjects who had died between full-term birth and age 29 years appeared to be strongly related to antemortem levels of both total and low-density lipoprotein (LDL) cholesterol.[17] Raised lesions, like fibrous plaques, are related to clinical CAD,[18] but the progression of fatty streaks to fibrous plaques is uncertain. Arterial fibrous plaques have been found in autopsy specimens from children, but no data are available on noninvasive evaluation of the arterial wall in children, which could allow an anatomically based screening of children with early signs of atherosclerosis. B-mode ultrasound imaging of the extracranial carotid arteries offers a valid and repeatable noninvasive method for quantifying the early signs of atherosclerosis.[19-21] Its findings have been shown to be related to the presence and extent of CAD.[22,23] Increased thickness of the intima-media of common carotid arteries has been found in adult hypercholesterolemic individuals compared with control groups.[24,25] The aim of the present study is to evaluate whether hypercholesterolemic children have a thicker intima-media in the common carotid artery compared with that of a control group comparable for sex and age distribution.

Methods

Patients

Data published in Italy suggest that the 95th percentile of serum cholesterol concentration in the age range of 2 to 15 years lies between 6.0 and 6.4 mmol/L.[26,27] Therefore, 46 normotriglyceridemic (<2 mmol/L) children (>2 and <14 years old) with serum total cholesterol ≥6.4 mmol/L on at least two consecutive tests performed 3 months apart, who had been consecutively admitted to the Pediatric Outpatient Lipid Clinic of the Medical School of Federico II University of Naples in the period from January 1990 to December 1991, were included in the present study (Table 1). A complete physical examination and blood tests were performed to exclude secondary forms of hyperlipidemia. All children had first-degree relatives or grandparents with hypercholesterolemia and/or history of CAD before age 55 years. On the basis of the above-mentioned criteria, hypercholesterolemic children qualified for the clinical diagnosis of familial hypercho-

Received October 5, 1993; revision accepted March 25, 1994.

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TABLE 1. Anthropometric Parameters, Serum Cholesterol and Triglycerides, and Blood Pressure of Patients and Control Subjects

	Patients	Control Subjects
N (M, F)	46 (22, 24)	48 (27, 21)
Age, y	7.4±3.39	6.4±2.77
Weight/height, centiles	71±24.4	72±24.2
Serum cholesterol, mmol/L	8.25±1.56*	4.62±0.83
Serum triglycerides, mmol/L	1.03±0.60	0.83±0.27
Systolic blood pressure, mm Hg	102±10.4	99.7±11.1
Diastolic blood pressure, mm Hg	63.4±7.22	60.0±8.96

Values are mean±SD.
*$P<.001$ by analysis of variance.

lesterolemia (FH).[10] Only one child had tendon xanthomata. Homozygous FH children were not included.

Serum cholesterol values presented in the study refer to blood samplings performed before any lipid-lowering intervention was begun. By the time of ultrasonographic examination (on average, 6 months after the baseline blood sampling), 23 children were on a lipid-lowering diet; the others were on diet plus cholestyramine 8 g/d.

Forty-eight clinically healthy normotriglyceridemic children, comparable to the patient group for age ($P=.133$, t test for difference) and sex distribution, with serum total cholesterol <6.4 mmol/L on at least two consecutive determinations made 3 months apart and attending the Pediatric Outpatient Clinic in the same period for a general checkup (which is provided at no cost by the National Health Service), were recruited as a control group (Table 1). All parents were offered a free serum lipid measurement and a noninvasive vascular examination of their children according to the same protocol adopted for hypercholesterolemic children. All parents took advantage of this opportunity. None of the control children received any prescription after the visit. None of the children included in this study (patient or control) had any acute illness, metabolic disease, or malabsorption syndrome.

Procedures

Biochemical Analysis

Venous blood was drawn after a 12-hour fast. Serum cholesterol and triglycerides were measured by the enzymatic colorimetric method (Trinder, Boehringer). Coefficients of variation were <3% for cholesterol and <5% for triglycerides. All analyses were performed under World Health Organization quality control procedures.[28]

Carotid Ultrasonography

Real-time B-mode imaging of distal common carotid arteries (common carotid arteries below the bulb, 1 cm proximal to the bifurcation) was performed with a Biosound 2000 II Sa real-time imager with an 8-MHz annular array probe. Theoretical axial resolution was 0.3 mm. Theoretical lateral resolution was 0.7 mm.

Scans were performed by one sonographer, who was unaware of the children's serum cholesterol levels. Subjects were examined in the supine position. The near and far walls of the common carotid arteries were visualized on a longitudinal plane with a circumferential examination procedure. The probe was moved from a lateral to an anterior projection with the subject's head parallel to the axis of the neck and then moved back to the lateral projection. After examination in the lateral projection, the subject's head was turned by 45° contralateral to the carotid artery under examination, and the probe was moved backward to achieve a posterior projection.

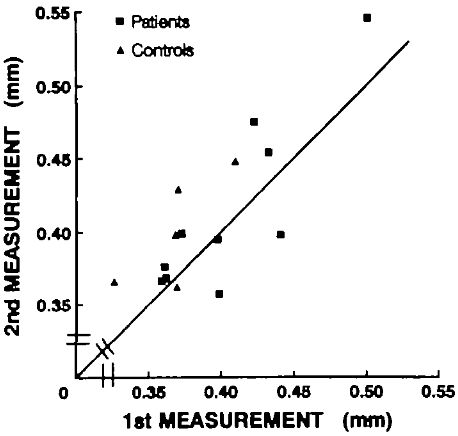

FIG 1. Scatterplot showing reproducibility of measurement of common carotid intima-media maximum thickness (far wall) in 15 children (10 patients and 5 control subjects). The line is the identity line.

In each projection, the gains were adjusted to obtain the best image of the near and the far walls.[21]

Images for intimal plus medial thickness measurement were obtained from videotape recordings of the ultrasonographic scanning. Tapes were displayed on a computer screen (Macintosh II) by use of a scanner (Epson G 2000) and analyzed by software (IMAGE 1.31) that allows quantitative evaluation of vessel intima-media areas. Only images recorded during cardiac systole (corresponding to the maximum diameter of the vessel under examination) were used. The two best images for the near wall (the carotid wall closest to the probe) and the two best images for the far wall (the carotid wall farthest from the probe) on both sides were quantitatively analyzed for a total of eight estimates of intima-media thickness per subject.

The four estimates of near-wall intima-media thickness available in each subject were averaged for calculation of mean intima-media thickness of the near wall. The four estimates of far-wall intima-media thickness available in each subject were averaged for calculation of mean intima-media thickness of the far wall. All eight estimates of intima-media thickness, available for each subject, were averaged to obtain mean intima-media thickness of both walls.

Maximum intima-media thickness for the near wall was the maximum value among the four estimates of near-wall intima-media thickness recorded in each subject. Maximum intima-media thickness for the far wall was the maximum value among the four estimates of far-wall intima-media thickness available in each subject. Maximum intima-media thickness for both walls was the maximum value among the eight estimates of intima-media thickness available in each subject.

Results are presented as mean thickness (per patient average of thicknesses) and as maximum thickness (maximum thickness value recorded in each patient). Separate analyses were performed for the near-wall, far-wall, and both-wall parameters.

The reader was unaware of serum lipid levels and clinical conditions of the children.

Whole-Procedure Reproducibility

The carotid arteries of 15 children (10 patients, 5 control subjects) were scanned twice by the same sonographer 24 hours apart. Mean intima-media thickness of the far wall (first measurement) in these 15 children was 0.34±0.04 mm (range, 0.28 to 0.43 mm). Maximum intima-media thickness of the far wall (first measurement) was 0.39±0.04 mm (range, 0.33 to 0.50 mm). Fig 1 shows the reproducibility of the measurement of far-wall maximum intima-media thickness in these 15 children. The line shown in the figure is the identity line. The correlation coefficient was .81 ($P<.001$). The tapes of these 15 children underwent a totally blinded reading procedure.

The coefficient of variation for each pair of intima-media thickness measurements performed in each of these children was calculated according to the following formula: (standard deviation/mean)×100.[29] The average coefficient of variation for each intima-media thickness parameter is the mean of the 15 coefficients of variation available.

The average coefficients of variation were for mean thickness, near wall, 3.3%; far wall, 3.3%; and both walls, 2.5%; for maximum thickness, near wall, 5.2%; far wall, 5.0%; and both walls, 5.1%.

Reading-Procedure Reproducibility

A second reading procedure was carried out on the tapes of 10 children by the same reader 4 months after the first reading. Average coefficients of variation, calculated as previously described, were for mean thickness, near wall, 2.9%; far wall, 3.0%; and both walls, 2.4%; for maximum thickness, near wall, 4.2%; far wall, 2.7%; and both walls, 3.5%.

Statistical Analysis

Two-sided analysis of variance was used for comparisons between groups after testing for equality of variances and degree of skewness in the distribution. Because of the significant direct relationship (Pearson correlation coefficients) existing between age and carotid intima-media thickness parameters (for maximum thickness, near wall, $r=.26$, $P<.05$; far wall, $r=.24$, $P<.05$; both walls, $r=.28$, $P<.01$), comparisons were controlled for age by covariance analysis. Covariance analysis was also used to correct for the confounding effect of sex. Odds ratios with 95% confidence limits were calculated from two-sided χ^2 tests. Two-sided Mantel-Haenszel χ^2 test was used to test categorical frequencies after age and sex were controlled for.[29]

Results

In the whole group of children (patients+control subjects, n=94), it was found that boys (n=49) had significantly higher intima-media thickness of the carotid artery than girls (n=45): 0.41±0.03 versus 0.39±0.03 mm ($P=.007$) for mean thickness of the far wall and 0.41±0.03 versus 0.40±0.02 mm ($P=.007$) for mean thickness of both walls; 0.47±0.05 versus 0.45±0.04 mm ($P=.031$) for maximum thickness of the far wall and 0.50±0.04 versus 0.47±0.04 mm ($P=.007$) for maximum thickness of both walls. Children of the two sexes did not significantly differ for other parameters. No significant difference was found in the distribution of the two sexes in the two groups of patients and control subjects.

No significant correlation was found in the whole group of children between intima-media thickness parameters and serum cholesterol values.

Table 2 shows mean values for measurements of common carotid intima-media mean and maximum thickness in patients and control subjects. Maximum thicknesses of far walls and both walls were higher in patients than in control subjects ($P=.012$ and $P=.007$, respectively). Statistical significance in the comparisons of these two parameters of maximum thickness remained also after age ($P=.025$ and $P=.017$, respectively) and both age and sex ($P=.012$ and $P=.006$, respectively) were controlled for. No significant difference was found for the other parameters.

Fig 2 and Table 3 present subgroup distribution and analysis of common carotid intima-media maximum thickness in patients and in control subjects divided according to the median of age in the whole population of children included in the study (6.2 years). Mean ages of children ≤6.2 years old were 4.3±1.4 years in patients versus 4.1±1.1 years in control subjects ($P=.706$, t test for difference). Mean ages of children >6.2 years old were 10.1±2.2 years in patients versus 9.4±1.9 years in control subjects ($P=.235$, t test for difference). A significantly higher common carotid intima-media maximum thickness of hypercholesterolemic patients versus control subjects was detectable only in children >6.2 years old ($P=.025$ for far wall and $P=.014$ for both walls). Table 4 shows odds ratios and 95% confidence intervals for common carotid intima-media thickening (maximum thickness >95th percentile in the control group, ie, >0.51 mm) between patients and control subjects. Univariate, age-controlled, and sex-controlled

Table 2. Mean and Maximum Thickness of Common Carotid Intima-Media in Patients and Control Subjects

	Patients (n=46)	Control Subjects (n=48)	*P*
Mean thickness, mm			
Near wall	0.41±0.03	0.40±0.03	.146
Far wall	0.40±0.03	0.39±0.03	.148
Both walls	0.41±0.03	0.40±0.03	.096
Maximum thickness, mm			
Near wall	0.48±0.05	0.46±0.04	.118
Far wall	0.48±0.05	0.45±0.04	.012
Both walls	0.50±0.05	0.47±0.03	.007

Values are mean±SD.

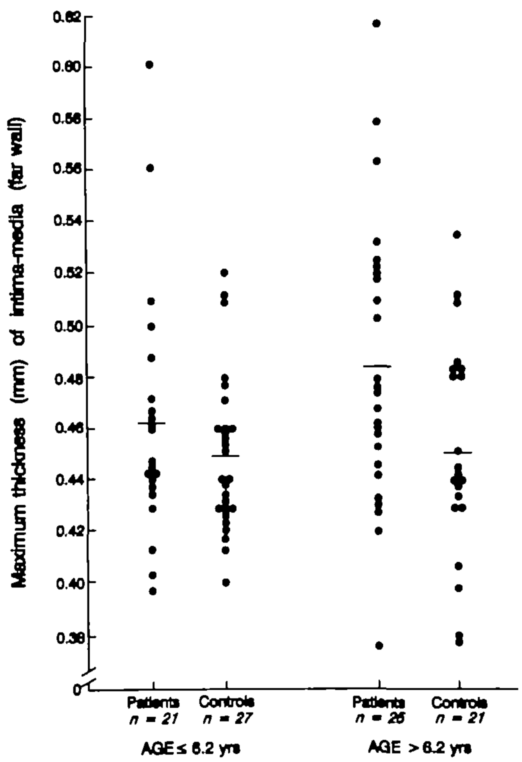

Fig 2. Plot showing distribution and mean of maximum thickness of common carotid intima-media (far wall) in patients and control subjects divided according to median age of all children.

Table 3. Maximum Thickness of Common Carotid Intima-Media in Patients and Control Subjects Divided According to Median Age of All Children

	Patients (n=46)	Control Subjects (n=48)	P
	n=21	n=27	
Age ≤6.2 yr			
Near wall	0.47±0.05	0.46±0.03	.662
Far wall	0.46±0.05	0.45±0.03	.303
Both walls	0.48±0.06	0.47±0.03	.284
	n=25	n=21	
Age >6.2 yr			
Near wall	0.49±0.05	0.47±0.04	.131
Far wall	0.48±0.06	0.45±0.04	.025
Both walls	0.51±0.05	0.48±0.04	.014

Values are in millimeters, mean±SD.

analyses showed that the likelihood of having a common carotid intima-media maximum thickness >0.51 mm was significantly higher in patients than in control subjects.

Discussion

This article addresses the following question: are there differences in the intima-media thickness of the common carotid arteries in hypercholesterolemic children compared with a control group with a similar age and sex distribution? A noninvasive evaluation by B-mode ultrasound imaging indicates that hypercholesterolemic children >6 years old show increased carotid intima-media maximum thickness.

The definition of hypercholesterolemia in children may vary among different populations[30] and cannot refer, as in adulthood, to a measurable increased risk of cardiovascular morbidity. It can only reflect deviations from statistical normality, there being no objective cutoff point available. Data published in Italy suggest that the 95th percentile of serum cholesterol concentration in the age range of 2 to 15 years lies between 6.0 and 6.4 mmol/L.[26,27] Since concern has been expressed about the effectiveness and safety of lipid-lowering treatments in children[12] and since the benefit derived from reduction of moderately raised serum cholesterol levels has not been clearly established even in adulthood, the highest value, that is, 6.4 mmol/L, was chosen as a cutoff point for the control group of children.

In addition to serum cholesterol levels ≥6.4 mmol/L, all our patients also had a positive family history for hypercholesterolemia (≥6.4 mmol/L) and/or premature CAD. According to the statements of the American Expert Panel on Blood Cholesterol Levels in Children and Adolescents,[10] our young patients must be considered as heterozygotes for FH, a condition usually associated with increased CAD risk in adulthood. This was the rationale for their admission to the Outpatient Lipid Clinic and their inclusion as "patients" in the present study.

A major objection against an early screening and lipid-lowering treatment of hypercholesterolemic children was that there is no evidence that their arteries are different from those of their normocholesterolemic peers. To test the null hypothesis, two echographic parameters were chosen in the present study to evaluate the status of the carotid intima-media: mean thickness, ie, the average of all measurements in each subject, and maximum thickness, ie, the highest value of thickness found in each subject. A separate analysis of near-wall, far-wall, and both-wall parameters was carried out, since concern has been expressed about the validity of near-wall measurements.[19,25,31,32] In the present article, far-wall data accounted for most of the differences between groups.

Maximum thickness was found to be increased in hypercholesterolemic children. This is the first demonstration by noninvasive methodology of arterial intima-media abnormalities in hypercholesterolemic children. Functional (but not anatomic) abnormalities have recently been demonstrated in the arteries of boys heterozygous for FH.[33] A relationship between common carotid artery intima-media thickness and age has already been described[25] in adults. Our data indicate that an increased common carotid intima-media maximum thickness in hypercholesterolemic children is already detectable after the age of 6 years. The same is not true for mean thickness (data not shown). This might suggest that thickening is focal rather than diffuse. The measurement of common carotid intima-media thickening, expressed by the parameter of maximum thickness, was able to discriminate between normocholesterolemic and hypercholesterolemic children after age 6 years, while no significant difference was present before that age, irrespective of serum cholesterol levels. No significant correlation was found in the two groups of children between common carotid intima-media thickness parameters and serum cholesterol levels (data not shown), a relationship that has been observed in adults.[25] The lack of this correlation and the presence of significant sex-related differences in intima-media thickness pa-

Table 4. Odds Ratios and 95% Confidence Intervals of Common Carotid Intima-Media Thickening* Between Patients and Control Subjects

	Odds Ratio	95% Confidence Interval	P
Univariate			
Near wall	4.71	1.09-19.8	.034
Far wall	6.39	1.19-32.3	.025
Both walls	5.87	1.61-23.2	.004
Controlled for age			
Near wall	4.42	0.99-19.8	.052
Far wall	5.96	1.09-32.4	.039
Both walls	5.53	1.60-19.1	.007
Controlled for sex			
Near wall	5.06	1.19-21.5	.028
Far wall	7.54	1.38-41.2	.020
Both walls	6.94	2.01-24.0	.002

*Maximum thickness higher than 95th percentile of control subjects=0.512 mm.

rameters indicate that other factors besides serum cholesterol are involved in the process of wall thickening.

Our finding of increased thickness parameters in boys compared with girls is in agreement with the results of the Pathobiological Determinants of Atherosclerosis in Young Adults (PDAY) Study, which demonstrated that young male subjects have a higher prevalence of raised lesions in coronary arteries than young girls do.[34]

An increased common carotid intima-media thickness does not per se mean early atherosclerosis. Stary's[18] autopsy observations in coronary arteries of children and young adults suggest that arterial wall diffuse intimal thickening, probably occurring as part of the intima-media thickening measured by the parameter of mean thickness, is rarely associated with the development of atherosclerotic lesions. Conversely, focal areas of eccentric thickening in the intima were often found to be associated with frankly atherosclerotic lesions such as fibrous plaques. The parameter of maximum thickness, which was found to be increased in hypercholesterolemic children compared with control subjects, is more likely to reflect eccentric than diffuse thickening. In conclusion, the present study indicates that, in children >6 years old, hypercholesterolemia is associated with detectable modifications of common carotid intima-media. Ongoing prospective studies in adults[35] will demonstrate whether or not this increased carotid intima-media thickness implies an increased risk of cardiovascular events.

Acknowledgment

We are grateful to Rosanna Scala for reviewing the manuscript.

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Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Arterioscler Thromb Vasc Biol. 1994;14:1075-1079
doi: 10.1161/01.ATV.14.7.1075
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1079-5642. Online ISSN: 1524-4636