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Original Citation:

Carotid intimal-medial thickness and stiffness are not affected by hypercholesterolemia in uncomplicated essential hypertension / P.S. SABA; M.J. ROMAN; C. LONGHINI; D. SCORZONI; R. PINI; R.B. DEVEREUX; A. GANAU. - In: ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY. - ISSN 1079-5642. - STAMPA. - 19:(1999), pp. 2788-2794.

Availability:

This version is available at: 2158/219234 since:

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12 October 2024

Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Arterioscler Thromb Vasc Biol. 1999;19:2788-2794
doi: 10.1161/01.ATV.19.11.2788
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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Carotid Intimal-Medial Thickness and Stiffness Are Not Affected by Hypercholesterolemia in Uncomplicated Essential Hypertension

Pier Sergio Saba, Mary J. Roman, Carlo Longhini, Daniela Scorzoni, Riccardo Pini, Richard B. Devereux, Antonello Ganau

Abstract—The combined effects of hypertension and hypercholesterolemia on carotid anatomy and stiffness were studied in 62 normotensives, 141 uncomplicated essential hypertensives with a total cholesterol level <240 mg/dL, and 60 essential hypertensives with a total cholesterol level ≥240 mg/dL. Carotid ultrasonography was performed to evaluate intimal-medial thickness (IMT), relative wall thickness, and the presence of plaque. Carotid pressure waveforms were recorded by applanation tonometry to measure carotid stiffness (β) and pressure wave reflection (ie, augmentation index). After adjusting for age, body mass index, and smoking habit by analysis of covariance, no significant differences were found between normocholesterolemic hypertensives and hypercholesterolemic hypertensives in terms of IMT (0.79±0.19 versus 0.81±0.19 mm), relative wall thickness (0.27±0.07 versus 0.28±0.07), carotid stiffness (6.1±3.2 versus 5.6±2.7), augmentation index (18.7±12.9% versus 17.3±12.8%), and prevalence of plaque (30.8% versus 30.7%). In the whole population, carotid IMT was significantly related to age (r=0.43), systolic (r=0.35) and diastolic (r=0.35) blood pressures, body surface area (r=0.22), and cholesterol levels (r=0.22) (all P<0.05). Carotid stiffness was significantly related to age, blood pressure, body mass index, and body surface area but not to cholesterol levels. In multivariate analyses, age, body surface area, and systolic blood pressure, but not cholesterol, smoking habit, or sex, were independent correlates of IMT (multiple R=0.54, P<0.0001), whereas carotid stiffness was independently associated with age, body surface area, and sex (R=0.38, P<0.0001). In conclusion, hypertension is a potent stimulus of vascular hypertrophy. The superimposition of hypercholesterolemia does not substantially augment these changes or further increase arterial stiffness in uncomplicated hypertensive subjects. **(*Arterioscler Thromb Vasc Biol*. 1999;19:2788-2794.)**

Key Words: hypertension ■ hypercholesterolemia ■ carotid arteries ■ atherosclerosis ■ arterial tonometry

Hypertension and hypercholesterolemia are major risk factors for cardiovascular morbidity and mortality in Western countries.[1,2] Both conditions are common in the general population and are frequently associated, thereby steeply increasing the risk of overall and coronary heart disease mortality.[1] Identification of patients at high risk by detection of preclinical disease, when target-organ damage may be in an early and potentially reversible stage, has been emphasized in recent years as a key step in the prevention of major clinical events.[3] Previous reports have shown a close relationship between carotid atherosclerosis and both cerebrovascular and coronary artery disease,[4,5] suggesting that carotid artery evaluation may help to identify high-risk subjects. However, carotid plaque may represent a late stage in the evolution of atherosclerotic disease in several vascular beds.[6–8]

The recent availability of high-resolution ultrasound techniques allows the detection of early arterial modifications, such as intimal-medial thickening, which may precede the development of atherosclerotic plaques. Previous reports have indicated that carotid intimal-medial thickening is associated with coronary artery disease[9,10] and cardiovascular morbidity and mortality.[11–15] Moreover, carotid intimal-medial thickening has been described in association with hypertension[16,17] and hypercholesterolemia.[18,19] Studies of hypercholesterolemia have, however, included subjects with mild hypertension and/or symptomatic cardiovascular disease, and thus, they could not assess the independent contributions of uncomplicated hypertension and hypercholesterolemia to intimal-medial thickening.

Although arterial stiffening has been described in animals with diet-induced hypercholesterolemia in association with structural arterial modifications,[20,21] few data are presently available on the effect of hypercholesterolemia on arterial viscoelastic properties in humans. Because an increased pulse

Received December 15, 1998; revision accepted April 19, 1999.

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wave velocity has been described in hypercholesterolemic monkeys,[21] an earlier return of reflected pressure waves to the central aorta in hypercholesterolemia may augment central systolic blood pressure[22] and thereby ventricular afterload. This study evaluated a population of uncomplicated hypertensive patients with normal and high cholesterol levels to assess the relative contribution of hypercholesterolemia to carotid structural and functional modifications associated with hypertension.

Methods

Study Population

The study is a retrospective evaluation of a population of 395 normotensive and uncomplicated hypertensive subjects enrolled in a cooperative study of preclinical cardiovascular disease in hypertension conducted at Cornell University Medical Center, New York, NY; the Institute of Clinical Medicine, University of Sassari, Sassari, Italy; and the Institute of Internal Medicine, University of Ferrara, Ferrara, Italy. Exclusion criteria were a history or clinical signs of coronary artery disease, heart failure, or valvular heart disease; secondary hypertension; diabetes mellitus; and renal insufficiency. Hypertension was defined as a cuff blood pressure ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic on repeated measurements taken by mercury sphygmomanometry. Sixty-two normotensive, normocholesterolemic subjects and 201 uncomplicated essential hypertensives were selected from this population, based on the availability of cholesterol data. All antihypertensive drug therapy was stopped at least 3 weeks before the study in the 116 (58%) patients who had been on antihypertensive treatment. None of the patients were on lipid-lowering therapy.

The effect of hypercholesterolemia in association with hypertension on carotid structure and stiffness was evaluated by dividing the study population into 3 groups: normal-cholesterol normotensives, normal-cholesterol hypertensives, and high-cholesterol hypertensives, on the basis of a normal to borderline-high (<6.22 mmol/L, or 240 mg/dL) or a high (≥6.22 mmol/L) fasting total serum cholesterol level obtained within 1 month of the vascular examination.[23] Body habitus was evaluated by body mass index (BMI, weight in kilograms per square of height in meters squared) and body surface area (BSA, obtained from height and weight measurements by standard nomograms). The study protocol was approved by the Committee on Human Rights in Research of Cornell University Medical College in 1989 and at intervals thereafter and by the Ethics Committees of the Universities of Sassari and Ferrara.

Carotid Ultrasonography

Carotid ultrasonography was performed in subjects recruited in New York (n=199) by using a Biosound Genesis II system (OTE Biomedica) equipped with a 7.5-MHz probe; subjects recruited in Sassari (n=43) and Ferrara (n=21) were examined with a Toshiba 270 HG system equipped with a 7.5-MHz probe. With the subject in the supine position and the neck in slight hyperextension, the common carotid artery, carotid bulb, and the extracranial portions of internal and external carotid arteries were identified. Two-dimensionally guided M-mode tracings of the distal common carotid artery (≈1 cm proximal to the carotid bulb) were obtained with simultaneous ECG and contralateral carotid pressure waveform tracings (see below) and recorded on ½-in. Super VHS videotape. After the videotape was reviewed, suitable frames for measurement of M-mode images were obtained by using a frame grabber (Imaging Technology Inc) interfaced with a high-resolution (640×480 pixels) video monitor and stored on diskette.

Carotid measurements were performed on the stored images by using mouse-driven software written by 1 of the investigators (R.P.), after calibration for depth and time. The simultaneous carotid pressure tracing (see below) was used to time the carotid artery measurement at end diastole (minimum arterial pressure) and at the time of peak systolic pressure. Measurements included the combined intimal-medial thickness (IMT) of the far wall at end diastole, as have been validated in anatomic correlation studies,[24] and end-diastolic and peak systolic internal dimensions obtained by continuous tracing of the intima-lumen interface of the near and far walls. All measurements were performed on several cycles and averaged.

Relative wall thickness (RWT) of the artery was calculated according to the formula 2×far-wall diastolic thickness/end-diastolic diameter. Because increased distending pressure, as occurs in hypertensive patients, could decrease the IMT due to vessel wall stretching, carotid intimal-medial cross-sectional area was also calculated as $\{[(\text{diastolic diameter}/2)+\text{far-wall diastolic thickness}]^2\times\pi\}-[(\text{diastolic diameter}/2)^2\times\pi]$ as an estimate of circumferential intimal-medial tissue mass.[17,25] Both carotid arteries were scanned to identify the presence and size of atherosclerotic plaques, defined as focal increases in IMT >50% of the surrounding wall; standard wall thickness measurements were never obtained at the level of a discrete plaque.

To minimize operator variability, ultrasonography and tonometry were always performed in each center under the guidance of the same operator (M.J.R., P.S.S., D.S.), and measurements of carotid anatomy were carried out by 2 investigators (M.J.R. for the New York data and P.S.S. for the Sassari and Ferrara data). As previously reported, intraobserver (r=0.98, SEE=0.04 mm for both) and interobserver (r=0.97, SEE= 0.05 mm) reproducibility of blinded wall thickness measurements between the 2 readers was high.[16]

Carotid Stiffness

In association with carotid ultrasonography, carotid pressure waveforms were obtained as described elsewhere[26–28] by using a high-fidelity external pressure transducer (Millar Instruments, Inc) applied to the skin overlying the pulse of the contralateral common carotid artery.

The transducer is internally calibrated (0.2 V/100 mm Hg) and registers absolute changes in applied pressure over a range of 300 mm Hg. To obtain actual carotid blood pressure values, the waveforms require additional external calibration. Based on the observation that mean arterial pressure is nearly identical in all capacitance vessels,[29–31] brachial artery pressure was measured by the cuff and mercury sphygmomanometer method with the patient in the supine position, and mean pressure was calculated as diastolic blood pressure+(⅓×pulse pressure). The resultant value was assigned to the planimetrically computer-derived mean blood pressure of the carotid waveforms with software written by 1 of the investigators (R.P.). Carotid artery stiffness was estimated by Young's modulus and the stiffness index. Young's modulus (E; wall tension per centimeter of thickness for a 100% diameter increase) was calculated according to the formula $E=[(P_s-P_d)/(D_s-D_d)]\times(D/h)$, where P_s and P_d are systolic and diastolic pressures, respectively; D_s and D_d are systolic and diastolic carotid dimensions, respectively; and D and h are carotid mean diameter and wall thickness, respectively.[32] Carotid stiffness was also calculated by the pressure-independent stiffness index β according to the formula[33,34] $\beta=[\ln(P_s/P_d)]/[(D_s-D_d)/D_d]$. This index takes into account the logarithmic relation between arterial pressure and diameter.

Pressure Wave Reflection

The systolic portion of the carotid waveform was analyzed to calculate the augmentation index,[35,36] a means of quantifying the contribution of reflected pressure waves to the central pulse pressure. After identification of the early and late systolic peaks and the inflection that separates them, pressures were determined at peak systolic pressure (P_{pk}) and at the inflection point (P_i) by using the previously described calibrated computer system. The augmentation index was calculated as $(P_{pk}-P_i)$/pulse pressure (when P_{pk} occurred in late systole) or as (P_i-P_{pk})/pulse pressure (when P_{pk} occurred in early systole).[36] Pulse wave analysis was performed by a single investigator (P.S.S.); measurements were repeated on several cycles and averaged.

Plasma Lipid Determinations

Total cholesterol and triglycerides were determined by standard enzymatic methods; the HDL cholesterol fraction was determined after precipitation of apolipoprotein B–containing lipoproteins, and LDL cholesterol was calculated as described by Friedewald et al.[37]

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TABLE 1. Characteristics of Normotensive Subjects and of Normal- and High-Cholesterol Hypertensive Patients

	Normotensive Subjects (Chol<6.22 mmol/L)	Hypertensive Patients	
		Chol<6.22 mmol/L	Chol≥6.22 mmol/L
n	62	141	60
Age, y	49±19	53±11	58±12*†
Sex, % male	61.3	61.7	55.0
Body weight, kg	69.2±17.9	77.1±16.3*	75.0±17.1‡
Body height, m	1.69±0.10	1.70±0.10	1.67±0.10
BMI, kg/m^2	24.0±4.4	26.4±4.0*	26.5±3.7*
BSA, m^2	1.79±0.25	1.88±0.23‡	1.84±0.25
Systolic BP, mm Hg	126±16	156±19*	160±20*
Diastolic BP, mm Hg	76±9	95±12*	92±12*
Total chol, mmol/L	5.10±0.75	5.15±0.67	7.12±0.80*†
HDL chol, mmol/L	1.42±0.41	1.35±0.41	1.45±0.41
LDL chol, mmol/L	3.13±0.83	3.21±0.67	4.79±0.73*†
Total HDL ratio	4.2±1.1	4.2±1.4	5.3±1.5*†
Former or current smokers, %	29.5	40.0	56.7*†

Chol indicates cholesterol; BP, blood pressure.
*$P<0.01$ vs normotensive subjects.
†$P<0.01$ vs hypertensive subjects with cholesterol<6.22 mmol/L.
‡$P<0.05$ vs normotensive subjects.

Hypercholesterolemia was defined as total cholesterol ≥6.22 mmol/L (≥240 mg/dL).[23]

Statistical Analysis

Data were stored and analyzed by using the Crunch[4] Statistical Package (Crunch Software Corp). Relationships between continuous variables were evaluated by linear regression analyses. Comparisons between normotensive and hypertensive subjects were performed by Student's *t* test. Carotid anatomy and stiffness were compared among normal-cholesterol normotensives and normal- and high-cholesterol hypertensives by ANOVA. ANCOVA was also performed to compare groups after controlling for differences in age, BSA, and smoking habit. Both analyses were followed by the Ryan, Einot, Gabriel, and Welsch F test multiple-comparison procedure. Power analysis was performed to assess the minimal difference in IMT detectable in our study. Based on the size of our groups and within-group SDs, differences as small as 0.07 mm for the IMT were detectable between normal and high-cholesterol hypertensives with an α error of 0.05 and a statistical power of 0.90; this detectable difference is lower than the absolute between-group difference in IMT associated with a significantly higher risk of cardiovascular and/or cerebrovascular events.[38,39] Multiple regression analyses were performed to assess independent determinants of carotid intimal-medial cross sectional area and the stiffness index in normotensive and hypertensive subjects. Data are expressed as mean±SD. A 2-tailed *P* value <0.05 was considered significant.

Results

Characteristics of Normotensive and Hypertensive Subjects

Among the 201 hypertensive patients, 141 had total cholesterol levels <6.22 mmol/L (240 mg/dL), while 60 had a total cholesterol level ≥6.22 mmol/L (Table 1). Hypertensive patients with higher cholesterol levels were significantly older than normocholesterolemic hypertensive and normotensive subjects. Both hypertensive groups had significantly greater body weights and BMIs than did normotensives, while the distribution of sex and height was similar among the groups. BSA was significantly greater in normocholesterolemic hypertensives than in normotensive subjects. Both hypertensive groups had similar blood pressure levels, and the normocholesterolemic groups did not differ in total and LDL cholesterol. The total-HDL ratio was significantly increased in hypercholesterolemic hypertensives. Hypercholesterolemic hypertensives were more likely to be current or former smokers.

Carotid Anatomy and Stiffness in Normal- and High-Cholesterol Hypertensive Patients

Carotid wall thickness, RWT, cross-sectional area, and prevalence of plaque were significantly greater in both hypertensive groups than in the normotensive subjects, while normal- and high-cholesterol hypertensives did not differ in these parameters (Table 2). Neither the stiffness index nor Young's elastic modulus differed significantly among the 3 groups, whereas the augmentation index was similarly higher in both hypertensive groups than in normotensive subjects. ANCOVA, after controlling for differences in age, BSA, and smoking habit, yielded similar results (Table 2, values in parentheses). To avoid a potentially inadequate adjustment for age in ANCOVA, each hypertensive group was also stratified by age into 2 subsets (<50 and ≥50 years); carotid parameters were then analyzed in relation to the cholesterol levels. There were no significant differences between the 2 subgroups comparable by age but different in cholesterol level. For example, mean carotid IMT was 0.75±0.17 and 0.71±0.16 mm in hypercholesterolemic and normocholesterolemic patients <50 years old and 0.88±0.19 and 0.85±0.19 mm in older hypercholesterolemic and normocholesterolemic patients ($P=0.38$ and 0.40, respectively).

Univariate Correlates of Carotid Anatomy and Stiffness Parameters in Normotensive and Hypertensive Subjects

In the entire population (upper portion of Table 3), carotid wall thickness and cross-sectional area were directly and

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TABLE 2. Carotid Anatomy and Stiffness in Normal- and High-Cholesterol Hypertensive Subjects

	Normotensive Subjects	Hypertensive Patients	
		Chol<6.22 mmol/L	Chol≥6.22 mmol/L
IMT, mm	0.66±0.17 (0.70)	0.80±0.19* (0.79)*	0.84±0.19* (0.81)*
Internal diameter, mm	5.7±0.7 (5.8)	5.9±0.8 (5.9)	5.9±0.7 (5.8)
RWT	0.24±0.06 (0.25)	0.27±0.07* (0.27)*	0.29±0.07* (0.28)*
Cross-sectional area, mm^2	13.3±4.4 (14.5)	16.9±5.6* (17.0)*	17.5±4.8* (16.6)*
Cross-sectional area/BSA, mm^2/m^2	7.5±2.3 (7.8)	9.0±2.8* (9.1)*	9.7±2.9* (9.3)*
Plaques, %	16.1 (24.3)	27.7* (30.8)*	28.3* (30.7)*
Stiffness index, β	6.2±2.3 (6.5)	6.1±3.2 (6.1)	6.0±2.7 (5.6)
Young's elastic modulus, $dynes/cm^2 \times mm \times 10^{-6}$	0.94±0.46 (0.96)	0.96±0.45 (0.97)	0.93±0.48 (0.89)
Augmentation index, %	8.8±15.1 (10.5)	18.2±12.9* (18.7)*	19.7±12.8* (17.3)*

Chol indicates cholesterol. Values in parentheses are means corrected for age, BMI, and smoking history by ANCOVA.
*$P<0.01$ vs normotensive subjects.

significantly related to total and LDL cholesterol, age, BMI, BSA, and systolic and diastolic blood pressures. Similarly, RWT was directly related to cholesterol levels, age, BMI, and systolic pressure but not to BSA or diastolic blood pressure (Table 3). Carotid lumen diameter was most closely related to older age and higher blood pressure. Young's modulus was significantly related to age and systolic blood pressures and negatively to BMI and BSA. The stiffness index was directly related to age and negatively to BSA; no stiffness index showed a significant relationship with cholesterol levels. Similar results were obtained after repeating the analysis in the hypertensive population only (lower portion of Table 3).

Independent Predictors of Carotid IMT and Stiffness Index

Multiple regression analyses were performed to assess independent predictors of carotid IMT and stiffness (Table 4). Age, BSA, and systolic blood pressure were independent predictors of carotid IMT (multiple $R=0.54$, $P<0.0001$), while total cholesterol, smoking history, and sex did not enter the model. Age, BSA, and male sex, but not cholesterol level, smoking history, and systolic blood pressure, were independent predictors of arterial stiffness (multiple $R=0.38$, $P<0.0001$).

In the subset of hypertensive patients, age and BSA were independent predictors of carotid IMT (multiple $R=0.42$, $P<0.01$), and no residual correlation was found with cholesterol levels (Figure 1). Similarly, Young's elastic modulus of the carotid was independently predicted by systolic blood pressure and BSA, while the stiffness index was independently positively correlated with age and smoking history and negatively with cholesterol levels (Figure 2).

Discussion

The present study indicates that mild to moderate hypercholesterolemia does not play a primary role in increasing common carotid artery IMT in otherwise-healthy hypertensive patients. In fact, although significant, positive, multivariate relationships were found between carotid structure and

TABLE 3. Univariate Correlates of Carotid Anatomy and Stiffness Measures With Cholesterol Levels and Demographic Characteristics

	Total Chol	LDL Chol	Age	BMI	BSA	Systolic BP	Diastolic BP
Total population							
IMT	0.22*	0.21*	0.43*	0.25*	0.22†	0.35*	0.18*
Internal diameter	0.01	0.05	0.24*	0.14†	0.23*	0.29*	0.24*
Cross-sectional area	0.16*	0.16†	0.45*	0.26*	0.26*	0.40*	0.22*
RWT	0.18*	0.15†	0.33*	0.20*	0.11	0.20*	0.04
Young's modulus	−0.03	0.02	0.19*	−0.13†	−0.21*	0.21*	0.19*
Stiffness index β	0.01	0.03	0.33*	−0.07	−0.17*	0.12	0.03
Hypertensive patients							
IMT	0.15†	0.14	0.36*	0.13	0.15†	0.16†	−0.08
Internal diameter	−0.04	−0.03	0.24*	0.07	0.15†	0.29*	0.20*
Cross-sectional area	0.09	0.07	0.40*	0.14	0.19*	0.26*	−0.01
RWT	0.12	0.12	0.23*	0.10	0.06	−0.01	−0.22*
Young's modulus	−0.06	−0.03	0.19*	−0.15†	−0.22*	0.28*	0.22*
Stiffness index β	−0.04	−0.03	0.31*	−0.09	−0.18†	0.17†	0.02

Chol indicates cholesterol; BP, blood pressure.
*$P<0.01$.
†$P<0.05$.

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TABLE 4. Independent Predictors of Carotid IMT and Stiffness Index β

	Multiple R	R^2	Partial Correlation Coefficient*	F	P
Dependent variable: IMT					
Age	0.44	0.19	0.39	69.2	0.0001
BSA	0.52	0.27	0.27	27.5	0.0001
Systolic BP	0.54	0.29	0.19	10.6	0.0013
Total cholesterol	Not entered		...	1.3	0.24
Smoking history†	Not entered		...	0.2	0.69
Sex‡	Not entered		...	0.03	0.86
Dependent variable: stiffness index β					
Age	0.33	0.11	0.32	30.3	0.0001
BSA	0.36	0.13	−0.25	5.5	0.02
Sex‡	0.38	0.15	−0.18	5.4	0.02
Total cholesterol	Not entered		...	2.4	0.12
Smoking history†	Not entered		...	2.1	0.14
Systolic BP	Not entered		...	0.05	0.83

BP indicates blood pressure.
*After the last step.
†Smoking history: never=1; former or current=2.
‡Sex: male=1, female=2.

cholesterol levels after controlling for age and other potentially confounding parameters, hypertensive patients with normal and high cholesterol levels did not differ in carotid wall thickness, RWT, and cross-sectional area. In contrast, the association of hypertension with increased IMT was evident in both groups. Accordingly, independent predictors of carotid cross-sectional area included older age and higher BSA and systolic blood pressure but not total serum cholesterol (Table 4).

These data are partially in contrast with previous reports that indicated a role of hypercholesterolemia in inducing carotid intimal-medial thickening.[12,19,40–44] However, 2 of these studies[19,42] included hypercholesterolemic patients with mild or moderate hypertension; moreover, diabetic patients and/or subjects with signs or symptoms of cardiovascular disease were not excluded. Nevertheless, although Poli et al[42] detected a significant increase in IMT in their hypercholesterolemic group, there was no significant correlation between carotid IMT and plasma cholesterol levels. In contrast, in the population described by Wendelhag et al,[19] the distribution of IMT in hypercholesterolemic patients appeared to be similar to that in normocholesterolemic subjects except for a few subjects in whom IMT values suggested the inclusion of plaques in the calculation. In addition, studies conducted in normotensive children with familial hypercholesterolemia and very high cholesterol levels showed only modest associations between carotid IMT and cholesterol levels.[43,44]

Although it is unclear whether it is more clinically and prognostically meaningful to exclude from the calculation of IMT all discrete areas of wall thickening, measurements performed in arterial segments including discrete plaques could overemphasize the association between risk factors for atherosclerotic disease and the IMT of representative segments of the arterial tree. Data from our study suggest that when IMT is measured in areas free of discrete atherosclerotic lesions, common carotid wall thickness in hypertensive patients is not strongly affected by mild to moderate hypercholesterolemia. Moreover, our results are in accordance with experimental studies[45] that suggest that intimal-medial thick-

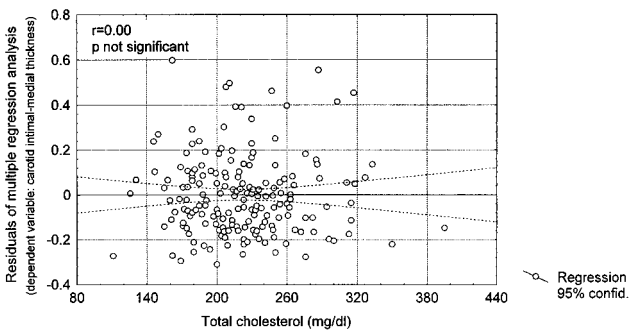

Figure 1. Residual correlation between carotid IMT and cholesterol levels in hypertensive patients after controlling for age and BSA in a multiple regression analysis (multiple R=0.42). Variables introduced in the model were age, sex, systolic blood pressure, and smoking history.

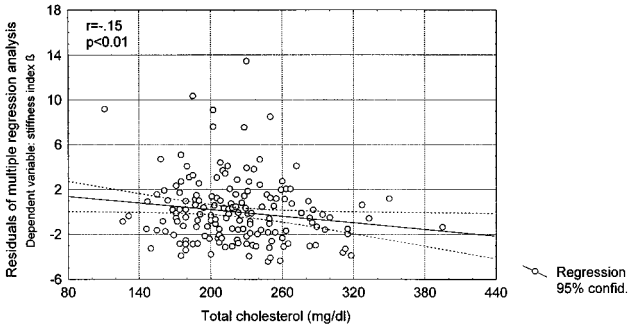

Figure 2. An inverse, significant, residual correlation was present between carotid stiffness index and cholesterol levels in hypertensive patients after controlling for age and smoking history in a multiple regression analysis (multiple R=0.34). Variables introduced in the model were age, sex, systolic blood pressure, and BSA.

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ening is mainly related to increased deformational arterial stresses due to blood pressure elevation, whereas hypercholesterolemia may be more influential in the genesis of discrete atherosclerotic plaques by focal deposition of lipids in the subintimal layers of the arterial wall. This concept is in agreement with observations that normotensive hypercholesterolemic children had mean wall thicknesses similar to those of normocholesterolemic controls, whereas the maximum IMT was significantly higher in the hypercholesterolemic group.[43]

A potential limitation of ultrasonographic evaluation of the arterial intimal-medial complex is that it does not allow separation of increased medial mass due to hypertrophy from increased intimal mass due to atherosclerosis and arteriosclerosis. Therefore, early atherosclerotic lesions involving only the intimal layer may cause only small increases in the composite wall thickness measured by vascular ultrasonography that might be confused with medial hypertrophy in the presence of hypertension. Although this could be a major limitation of ultrasonographic studies of preclinical atherosclerosis, the consistent ability of increased IMT to predict cardiovascular events in multiple populations[11–15] suggests that the different processes that increase overall carotid wall thickness are all prognostically adverse. Furthermore, since the atherosclerotic process typically involves the arterial wall in a focal fashion, whereas hypertension induces diffuse thickening of the intimal-medial complex,[46] ultrasonographic identification of focal intimal-medial thickening can be considered a reliable indicator of atherosclerosis per se.

Surprisingly, carotid stiffness, which is commonly considered an early indicator of vascular damage, was not increased by hypercholesterolemia. In fact, the stiffness index, which takes into account the nonlinearity of the pressure-diameter relation, and Young's elastic modulus, which considers adaptive wall thickening, were not elevated in either hypertensive group, and in particular, were not increased in the hypercholesterolemic patients. Multiple regression analysis conducted in the whole population indicated that age, BSA, and sex, but not cholesterol levels, were independent predictors of the stiffness index. However, in a subanalysis of the hypertensive population, an unexpected modest but significant independent inverse relationship was found between stiffness index and cholesterol level. This surprising finding, which needs verification by other studies, confirms the lack of positive correlations between carotid stiffness and cholesterol levels after controlling for age and smoking history. Moreover, the augmentation index, which is related to aortic pulse wave velocity, was equally elevated in normocholesterolemic and hypercholesterolemic hypertensives, suggesting that neither carotid nor aortic compliance was substantially modified by mild-to-moderate hypercholesterolemia. The evidence for altered arterial stiffness in hypertensive patients when the pressure-sensitive augmentation index was used but not with the pressure-insensitive stiffness index is in accordance with previous reports that did not detect an impact of hypertension on arterial stiffness evaluated at a standardized pressure level.[47,48] Although studies in hypercholesterolemic animals indicated increased arterial stiffness,[20,21] results may have been affected by use of the pressure-dependent pulse wave velocity as the index of vascular stiffness. Other human observations did not detect reduced arterial compliance in nonfamilial hypercholesterolemia[49] or an effect of high cholesterol levels on age-related increases in arterial stiffness.[50,51] Moreover, a recent study reported a lack of association between aortic stiffening and extracoronary atherosclerotic disease, after controlling for the affect of age.[52]

Although ultrasonographic evaluation of uncomplicated hypertensive subjects allows the assessment of vascular damage in a preclinical phase of atherosclerotic disease, the lack of cholesterol-induced arterial modifications in our study may be due to selection of hypertensive subjects at relatively low risk. In fact, the prevalence of carotid plaques, although significantly higher than in normocholesterolemic subjects, was relatively low in the high-cholesterol hypertensive group (31%).

In conclusion, this study indicates that in patients with relatively mild, uncomplicated essential hypertension, sporadic hypercholesterolemia does not substantially affect carotid wall thickness or stiffness. However, although the relatively small sample size of this study had adequate power to detect a moderate intimal-medial thickening induced by high cholesterol levels, lesser changes might have gone undetected in our moderately sized population. Additionally, in the present study, the impact of hypercholesterolemia may have been overwhelmed by hypertension-induced arterial modifications. Further larger studies are needed to assess the independent effect of high cholesterol levels on arterial anatomy and stiffness in normotensive subjects.

Acknowledgments

This study was supported in part by grants HL-18323 and HL-47540 from the National Heart, Lung, and Blood Institute, Bethesda, Md; the Michael Wolk Heart Foundation; and grant 97.04129.CT04 from Consiglio Nazionale delle Ricerche and grant ex-40% 1997 from MURST, Italy (to A.G.). P.S.S. has been the recipient of a research grant from Regione Autonoma della Sardegna, Italy.

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