Carotid Artery Intima-Media Thickness Measured by Ultrasonography in Normal Clinical Practice Correlates Well With Atherosclerosis Risk Factors

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Background and Purpose—The intima-media thickness (IMT) of extracranial carotid arteries determined by B-mode ultrasound is a measurable index of the presence of atherosclerosis. The ultrasonographic scan protocol and the scan reading techniques used until now to measure IMT are, however, time consuming and require the participation of specialized research centers. In this study we present a cross-sectional study of 963 patients attending the Enrica Grossi Paoletti Center in Milan, Italy, with the aim of assessing whether ultrasonographic measurements of carotid artery in routine clinical practice can yield the same results as those obtained with quantitative methods used until now in clinical trials.

Methods—Maximum and mean maximum IMT of carotid arteries were assessed by B-mode ultrasound with the use of the electronic caliper of the machine in real time.

Results—The intraobserver and interobserver variability of IMT of carotid arteries performed with the electronic caliper in real time was similar to that of quantitative processing of frozen images (coefficients of variation of intraobserver and interobserver mean maximum IMT measurements were 4.2% and 7.3%, respectively). Carotid artery IMT thus measured correlated with most of the known atherosclerosis risk factors and discriminated between patients with and without previous history of cardiovascular events. IMT was linearly related to the total number of vascular risk factors both in the whole group and after stratification of patients into 3 age classes.

Conclusions——These observations establish a strong correlation between B-mode imaging of carotid atherosclerosis evaluated in normal clinical practice and data provided by clinical trials and validate this simple reading technique as a means of identifying IMT as another possible risk factor in patients at high risk of vascular disease. **(*Stroke*. 2000;31:2426-2430.)**

Key Words: intima-media thickness ■ risk factors ■ ultrasonics

The intima-media thickness (IMT) of extracranial carotid arteries provides an index of atherosclerosis in other vascular regions[1–5] and has been shown to be associated with most risk factors for atherosclerosis.[6–8] Recently, an increased thickness of carotid IMT determined by B-mode ultrasound has been shown to be directly associated with an increased risk of myocardial infarction and stroke in older adults without a previous history of cardiovascular disease.[9] Thus, carotid artery IMT has been proposed as a risk factor that may be included in the algorithms for cardiovascular risk assessment.[9] However, the ultrasonographic scan protocol and the scan reading techniques used until now are time consuming and require the participation of highly specialized research centers. Large-scale epidemiological studies testing the connection between conventional or unconventional risk factors and carotid atherosclerosis would become more feasible if simpler methods were available to measure carotid IMT, possibly during normal clinical practice. Some authors, to shorten the time for image processing, have limited the number of carotid segments to a single sector, eg, the first centimeter of the common carotid. This approach, however, may result in a loss of information and patient misclassification.

We have investigated whether carotid IMT, measured with an electronic caliper, a method feasible in routine clinical practice, provides suitable information to associate carotid IMT with a patient's risk profile.

Subjects and Methods

Nine hundred sixty-three consecutive patients (487 men and 476 women) attending for the first time the Ultrasound Laboratory of the E. Grossi Paoletti Center for metabolic studies (Niguarda Hospital,

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Milan, Italy) were analyzed by carotid B-mode ultrasound imaging. The carotid IMT[10] was determined manually in real time. Clinical and laboratory parameters were simultaneously assessed. Oral informed consent was obtained from all patients; the study was approved by the Institutional Review Board.

Patients were on a low-fat diet (26% lipids, 22% proteins, 52% carbohydrates; polyunsaturated/saturated fat ratio 0.43) for at least 3 months. Six hundred sixty-eight patients were hyperlipidemic (443 type IIa, 164 type IIb, 2 type III, 55 type IV, and 4 type V) according to World Health Organization criteria[11]; 245 were borderline hyperlipidemic (plasma LDL cholesterol, 4.14 to 4.92 mmol/L; triglycerides, 1.70 to 2.05 mmol/L), and 50 had normal lipid levels. Three hundred three patients (31.5%) were hypertensive (systolic or diastolic blood pressure >160 mm Hg and >90 mm Hg, respectively, or under treatment with hypotensive drugs). Fifty-eight patients (6%) were diabetic and on oral hypoglycemic therapy. One hundred thirty-nine patients (14.4%) had a previous history of coronary heart disease (CHD), 93 (9.7%) of cerebrovascular disease (CVD), and 150 (15.6%) of peripheral arterial disease (PAD). Eighty-two patients had xanthomas, 48 xanthelasmas, and 146 a corneal arcus. Most of the patients had a family history of ischemic vascular disease: 43.6% for CHD, 27.6% for CVD, and 6.4% for PAD. More than a third of the patients were being treated with hypolipidemic drugs (statins, resins, probucol, or fibrates); 25% with hypotensive drugs (β-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, or diuretics); 20% with antiplatelet drugs; 5.7% with oral anticoagulants; 6% with hypoglycemic drugs (insulin or metformin); and <2% with uricosuric drugs or with hormonal replacement therapy. Two hundred seventeen patients were current smokers (186 hypercholesterolemic, 31 normocholesterolemic), and 274 were previous smokers (at least 1 year after smoking cessation).

To investigate the relationship between the number of vascular risk factors and carotid atherosclerosis, we classified each patient according to the presence of single or multiple vascular risk factors, arbitrarily assigning to each risk factor an equal weight. Patients were considered to be exposed to a risk factor when 1 of the following criteria was satisfied: male sex or at least 5 years after menopause for women; age >55 years; LDL cholesterol >4.14 mmol/L; triglycerides >2.28 mmol/L; HDL cholesterol <0.91 or <1.04 mmol/L in men and women, respectively; hypertension; diabetes; smoking habit; or family history of cardiovascular disease. In addition, patients with diabetes (cases; n=58) were compared with 116 patients (controls) matched for age, sex, and total cholesterol levels. The same case-control protocol was applied to patients with hypertension, CHD (angina, myocardial infarction), CVD (stroke, transient ischemic attack), or PAD.

Lipids

Blood samples were collected from the antecubital vein after overnight fasting. Total and HDL cholesterol and triglyceride levels were determined in fresh serum by enzymatic methods[12,13]; HDL levels were obtained by selective precipitation with dextran-$MgCl_2$.[14] Serum LDL cholesterol levels were calculated by Friedewald's formula.[15]

Ultrasound Protocol

Ultrasound examination was performed with the use of an 8-MHz annular array ultrasound imaging system (2000 II s.a., Biosound) by a single trained sonographer. With this technique, 2 parallel echogenic lines separated by an anechoic space can be visualized at levels of the artery wall. It was previously shown that these lines were generated by the blood-intima and media-adventitia interfaces.[10] The distance between the 2 lines gives a reliable index of the thickness of the intimal-medial complex.[10] Subjects were examined in the supine position. Ultrasound scans of the right and left last distal centimeter of common carotid arteries and bifurcation and of the first proximal centimeter of internal carotid arteries in 3 different projections (anterior, lateral, and posterior) were performed. All measurements were made at the time of scanning on unfrozen images of longitudinal scans by using the machine's electronic caliper. Six carotid segments for each projection (near and far walls of bulb and internal and common carotid arteries) were examined. The maximal IMT value of each segment was measured. The complete procedure is generally performed in approximately 30 to 35 minutes. IMT values for the 3 different projections and for right and left carotid arteries were averaged to obtain the mean maximum IMT (MM-IMT). A total of 11 566 carotid segments were imaged, and there were 544 instances of missing data (4.7%). The analysis presented in this report provides substantially identical results when patients with missing data are either considered or excluded. In addition, a pilot study was performed in a random sample of 100 patients of the overall study group. The mean MM-IMT of these subjects did not significantly differ from that calculated after a random deletion of the 5% of observations. Thus, in the MM-IMT assessment, values are presented that include patients with missing data. The highest IMT value found among the 36 segments was defined as the maximal IMT (Max-IMT). For the assessment of interobserver and intraobserver variability of carotid measurements, 20 patients of the study group underwent 2 carotid ultrasound investigations 2 weeks apart. Ultrasound investigation was performed twice at each visit by 2 trained sonographers.

TABLE 1. Intraobserver and Interobserver Variability of IMT Determined With the Electronic Caliper (n=20)

	Mean±SD Difference, mm*	CV, %	*r*
Intraobserver			
MM-IMT	0.04±0.02	4.2	0.95
Max-IMT	0.18±0.22	12.9	0.94
Interobserver			
MM-IMT	0.07±0.05	7.3	0.96
Max-IMT	0.17±0.18	8.5	0.78

CV indicates coefficient of variation.
*Differences between replicate scans.

Statistical Analysis

Mean±SD values were used as descriptive measures of normally distributed variables. Because of the highly skewed distribution of triglycerides, these values were log transformed, which yielded an almost gaussian distribution. Groups were compared by ANCOVA. Differences in categorical variables were analyzed by the χ^2 test. Correlation was analyzed by the nonparametric Spearman method.

Results

Table 1 shows the intraobserver and interobserver variability of IMT of carotid arteries performed with the electronic caliper in real time. The reproducibility was similar to that of quantitative processing of frozen images.[16] In particular, coefficients of variation of intraobserver and interobserver MM-IMT measurements were 4.2% and 7.3%, respectively.

Table 2 shows the characteristics of the population studied. Men in the group were younger than women, had the greatest body mass index (BMI), and presented the greatest percentage of smokers. They had, however, lower values of total, LDL, and HDL cholesterol and higher values of triglycerides and blood glucose than the women. MM-IMT and Max-IMT values were greater in men than in women. Carotid IMT values correlated highly with age in the total population (r=0.43 and r=0.46 for Max-IMT and MM-IMT, respectively; P<0.0001).

The relationship of carotid IMT to the different variables was then evaluated after adjustment for age. Carotid IMT significantly and positively correlated with systolic blood

TABLE 2. Characteristics of Patients in the Overall Group and After Stratification by Sex

	Total Group (n=963)	Women (n=476)	Men (n=487)
Age, y	54.6±11.7	56.2±11.8	53.0±11.3†
Smokers, %	22.5	14.3	30.6†
BMI, kg/m^2	24.0±3.1	23.4±3.3	24.6±2.8†
SBP, mm Hg	135.1±18.0	135.1±18.9	135.1±17.1
DBP, mm Hg	82.9±9.6	82.7±9.5	83.2±9.6
Total cholesterol, mmol/L	6.85±1.47	7.06±1.38	6.64±1.54*
LDL cholesterol, mmol/L	4.80±1.43	4.98±1.40	4.60±1.43†
HDL cholesterol, mmol/L	1.34±0.36	1.47±0.34	1.21±0.32†
Triglycerides, mmol/L	1.85±2.51	1.52±0.82	2.18±3.43†
Blood glucose, mmol/L	5.23±0.77	5.13±0.77	5.34±0.76†
MM-IMT (age adjusted), mm	0.85±0.33	0.77±0.29	0.92±0.36†
Max-IMT (age adjusted), mm	1.69±0.91	1.48±0.80	1.90±0.97*

Data, with the exception of smoking habit, are mean±SD. SBP and DBP indicate systolic and diastolic blood pressure, respectively.

*$P<0.001$, †$P<0.0001$ vs women. Differences in IMT have been assessed by ANCOVA after adjustment of data for age, smoking, BMI, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and blood glucose.

pressure, total cholesterol, LDL cholesterol, triglycerides, and blood glucose and negatively with HDL cholesterol (Table 3).

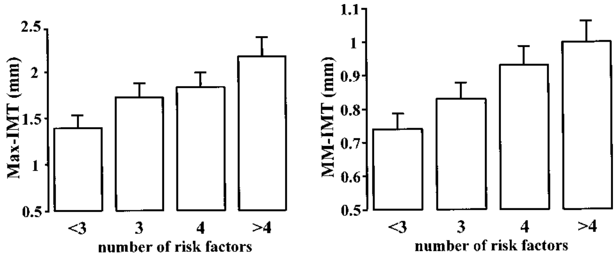
The Figure shows that MM-IMT and Max-IMT values increased with the number of risk factors, with the greatest IMT occurring in patients with >4 risk factors ($P<0.003$ and $P<0.015$ for MM-IMT and Max-IMT, respectively). The relationship between carotid IMT and the number of risk factors was also observed after stratification of patients into 3 age groups (data not shown).

Case-control analysis (Table 4) showed that hypertensive patients had greater IMT. They also differed from the corresponding controls in BMI, triglycerides, and blood glucose. In diabetic patients, by contrast, no significant difference in carotid parameters was found, despite the presence of higher BMI, higher serum triglycerides, and lower levels of HDL cholesterol.

TABLE 3. Spearman Correlation Coefficients Among Age-Adjusted MM-IMT, Max-IMT, and Clinical and Laboratory Variables

	MM-IMT (Age Adjusted)	Max-IMT (Age Adjusted)
BMI	NS	NS
SBP	0.14§	0.19§
DBP	NS	NS
Total cholesterol	NS	0.10†
LDL cholesterol	0.10†	0.13‡
HDL cholesterol	−0.22§	−0.22§
Triglycerides	0.08*	0.07*
Blood glucose	NS	0.09*

*$P<0.05$; †$P<0.01$; ‡$P<0.001$; §$P<0.0001$.



Max-IMT (left) and MM-IMT (right) in relation to number of vascular risk factors.

Table 5 shows that patients with CHD and patients with PAD had greater values of MM-IMT and Max-IMT than corresponding controls, whereas no difference in MM-IMT and Max-IMT was found between patients with CVD and controls.

Discussion

These data demonstrate that IMT measured by a simple method for image processing, which can be performed directly during scanning of the carotid arteries, can provide a reliable index of carotid atherosclerosis. In a population of 963 patients attending a lipid clinic, IMT values of carotid arteries determined in real time with the electronic caliper (1) correlated with most atherosclerosis risk factors, (2) were associated with the number of atherosclerosis risk factors, and (3) discriminated between patients with and without previous history of cardiovascular events. The precision of the method (approximately 0.1 mm) is lower than that of more sophisticated quantitative methods (0.02 to 0.06 mm),[16] but our data suggest that this does not represent a real limitation when an adequate patient sample is used.

In agreement with previous reports, we found statistically significant differences between men and women in carotid IMT.[4,8,17] The correlation coefficients between Max-IMT or MM-IMT and age ($r=0.43$ and $r=0.46$, respectively) were similar to the mean value of correlation coefficients reported by 5 studies ($r=0.48$).[18–22]

Direct and significant correlations between carotid IMT and systolic blood pressure, total cholesterol (age-adjusted Max-IMT only), LDL cholesterol, triglycerides, blood glucose (age-adjusted Max-IMT only), and HDL cholesterol (inversely) were found, all in accordance with previously reported findings.[20,23,24] Again in accordance with previous findings,[20,24–26] IMT was greater in hypertensive patients. On the contrary, no difference was found between diabetic and nondiabetic patients; the high prevalence of these patients with hypercholesterolemia may have masked the effect of diabetes on carotid IMT.[27,28]

Results of the British Regional Heart Study[6] suggest that the presence of plaque, but not IMT, is associated with high risk of disease. In our study Max-IMT but also MM-IMT allowed us to identify groups of patients with previous cardiovascular events, ie, CHD or PAD. We suggest that MM-IMT and/or Max-IMT may represent comprehensive indices of atherosclerosis and that, when a normogram in different types of patients has been defined, they will help clinicians to identify groups of patients likely to benefit from aggressive preventive measures.

TABLE 4. Characteristics of Subjects With (Cases) and Without (Controls) Hypertension and Diabetes

	Hypertension		Diabetes	
	Controls	Cases	Controls	Cases
n	458	229	116	58
Men, %*	51.9	51.9	63.7	63.7
Age, y*	57.3±8.5	57.3±8.5	59.4±8.7	59.4±8.8
Smokers, %	22.1	21.8	13.8	34.5
BMI, kg/m^2	23.8±3.0	24.8±3.2§	24.4±2.7	25.4±3.7†
SBP, mm Hg	130.4±14.6	145.9±18.3¶	138.2±15.5	141.4±19.5
DBP, mm Hg	81.3±8.3	87.5±9.5¶	83.0±8.2	84.9±8.5
Total cholesterol, mmol/L*	6.74±1.39	6.91±1.32	6.64±1.57	6.45±1.06
LDL cholesterol, mmol/L	4.64±1.26	4.78±1.3	4.60±1.63	4.36±0.73
HDL cholesterol, mmol/L	1.36±0.37	1.32±0.35	1.33±0.34	1.12±0.37†
Triglycerides, mmol/L	1.80±2.84	2.29±3.19§	1.56±0.92	3.18±2.40§
Blood glucose, mmol/L	5.22±0.72	5.46±1.03‡	5.42±0.57	7.60±1.85¶
MM-IMT, mm	0.82±0.35	0.94±0.40§	1.00±0.48	1.04±0.41
Max-IMT, mm	1.63±0.95	2.02±1.08§	1.88±1.06	2.16±1.11

Data are mean±SD.
*Matched variable.
†P<0.05, ‡P<0.01, §P<0.0001 vs controls. For hypertension, IMT differences have been assessed after adjustment of data for matching variables and for BMI, triglycerides, and blood glucose. For diabetes, differences in IMT values have been assessed after adjustment of data for matching variables and for BMI, HDL cholesterol, and triglycerides.
¶Differences result from selection of the studied group.

Carotid IMT increased with the number of concurrent risk factors, even after stratification of patients for age, a further indication that MM-IMT and Max-IMT may represent comprehensive indices of carotid and even more widespread atherosclerosis.

The data discussed in this report strongly suggest that measurement of IMT with the electronic caliper is a method feasible in routine clinical practice and provides suitable information to associate carotid IMT with the risk profile of different groups of patients. By the use of this simple methodology, as a result of the

TABLE 5. Characteristics of Subjects With (Cases) and Without (Controls) CHD, CVD, and PAD

	CHD		CVD		PAD	
	Controls	Cases	Controls	Cases	Controls	Cases
n	266	133	186	93	244	122
Men, %*	76.0	76.0	60.2	60.2	69.7	69.7
Age, y*	57.5±9.3	57.5±9.3	59.8±7.8	59.8±7.8	59.0±7.6	59.0±7.6
Smokers, %	29.7	22.6	23.7	26.9	33.5	41.2
BMI, kg/m^2	24.4±3.0	24.6±3.0	24.8±3.0	24.5±3.5	24.5±2.8	24.8±3.1
SBP, mm Hg	138.8±19.2	138.9±19.4	142.2±17.0	144.0±21.5	137.9±17.9	143.6±16.1‡
DBP, mm Hg	84.1±9.7	82.8±9.6	85.1±8.1	84.4±8.7	84.4±9.3	84.0±7.7
Total cholesterol, mmol/L*	6.71±1.37	6.70±1.64	6.58±1.20	6.80±1.42	6.65±1.14	6.59±1.33
LDL cholesterol, mmol/L	4.65±1.34	4.57±1.35	4.57±1.11	4.72±1.30	4.58±1.12	4.46±1.12
HDL cholesterol, mmol/L	1.28±0.33	1.23±0.35	1.28±0.35	1.22±0.36	1.33±0.33	1.19±0.34‡
Triglycerides, mmol/L	2.03±2.63	1.98±1.45	1.98±1.45	1.91±1.08	1.74±0.84	2.71±4.55‡
Blood glucose, mmol/L	5.29±0.72	5.40±0.98	5.50±0.97	5.19±0.62	5.34±0.77	5.39±0.80
MM-IMT, mm	0.94±0.38	1.08±0.49†	1.02±0.40	1.10±0.50	0.86±0.33	1.16±0.42§
Max-IMT, mm	1.94±1.03	2.36±1.19†	2.12±1.08	2.34±1.10	1.75±0.97	2.47±1.09§

Data are mean±SD.
*Matched variable.
†P<0.05, ‡P<0.01, §P<0.0001 vs controls. IMT differences have been observed after adjustment of data for matching factors. For PAD, IMT differences have been observed after adjustment of data for matching factors and for SBP, HDL cholesterol, and triglycerides.

reduction in time and costs, it is possible to extend the analysis of arterial wall thickness to the whole carotid tree, instead of selecting a single segment. However, to perform such studies properly, the following aspects should be carefully taken into account. First, the training of sonographers/readers for each study should be considered, and changes over time in sonographer/reader behavior should also be taken into account. Moreover, in studies involving different sonographers, interobserver variability should be carefully determined. Finally, in longitudinal and/or pharmacological studies, the use of this technique should not be allowed until appropriate validation is performed.

In conclusion, we have shown that measurement of the IMT of carotid arteries with an electronic caliper is a rapid, low-cost method that provides information similar to that obtained by more precise methods. This approach should prove useful in large clinical and/or epidemiological trials in which the evaluation of arterial wall morphological targets using more sophisticated methods for IMT measurement is not practical because of cost and time constraints.

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