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Increased intima-media thickness (IMT) in the common carotid artery (CCA) correlates with conventional risk factors for cardiovascular disease and is an independent predictor of cardiac events. However, correlation between IMT and degree of ischemic heart disease evaluated by coronary angiogram is weak. The purpose of this study was to investigate the relationship between measures of carotid atherosclerosis and the extent and severity of coronary artery disease (CAD) in 111 consecutive patients (60 men and 51 women, mean age 60 years) with known or suspected CAD who were investigated with adenosine-stress myocardial perfusion scintigraphy. Common carotid artery lumen diameter (LD) and IMT of the carotid bulb and distal CCA were measured with ultrasound, and CCA cross-sectional intima-media area (CIMA) was calculated. Seventy-two of 110 patients (65%) had significant perfusion defects. Increasing carotid plaque occurrence (absence, unilateral or bilateral occurrence) correlated with more advanced CAD ($p < 0.01$). The extent and severity of myocardial hypoperfusion correlated significantly with presence of carotid plaque ($r = 0.23$ and 0.24 respectively, $p < 0.05$), CIMA ($r = 0.23$ and 0.22, $p < 0.05$), and LD ($r = 0.26$ and 0.25, $p < 0.01$) but not with IMT. In contrast to CIMA, LD failed to show an independent relation to extent of CAD after adjustment for age, sex, and body mass index. In conclusion, in subjects with intermediate to high risk of ischemic heart disease, occurrence of carotid plaques and increased cross-sectional intima-media area in the common carotid artery are the best parameters for predicting CAD expressed as myocardial hypoperfusion.

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Introduction

Common carotid intima-media thickness (IMT) has gained acceptance as a marker of the atherosclerotic process, related to both local[1,2] and more distant atherosclerosis.[3-5] A relationship to conventional risk factors for coronary artery disease (CAD) has been shown,[6] and an increased common carotid IMT is associated with, and can predict, cardiovascular events.[7] For these reasons, IMT has been suggested for use in clinical trials as

a surrogate measure/marker for coronary atherosclerosis.[8] Nevertheless, the correlation between angiographic extent and severity of CAD and common carotid IMT is weak,[9] and in 1 study was obtained only between angiographically defined CAD and IMT of the carotid bulb.[10] However, there are some indications that calculation of the cross-sectional intima-media area (CIMA) gives a more reliable measurement than IMT,[11] and calculating CIMA in combination with carotid plaque identification has been suggested as a useful diagnostic method, comparable to exercise test and variance ECG, for detecting CAD.[12] One important aspect might be that CIMA also takes account of lumen diameter (LD) and the effect of arterial enlargement on IMT, since LD is influenced by risk factors for cardiovascular disease.[13]

The relationship between coronary angiography and myocardial perfusion scintigraphy has been shown to be rather weak.[14] The latter method is noninvasive and visualizes areas of myocardial hypoperfusion. It is also in possession of prognostic information.[15] A common opinion is that perfusion defects during stress reflect hemodynamically significant stenoses and thus more advanced atherosclerosis. However, a recent study shows that scintigraphy may be used also to detect angiographically unrecognized occult coronary atherosclerosis.[16]

The importance of choice of method and way of calculating the IM complex in comparing the degree of atherosclerotic change in the carotid and coronary arteries needs further evaluation. The aim of the present study was to investigate the relationship between measures of carotid atherosclerosis and the extent and severity of CAD assessed with myocardial perfusion scintigraphy.

Materials and Methods

Subjects

We studied 111 consecutive patients with known or suspected coronary artery disease referred to our department for adenosine-stress myocardial perfusion scintigraphy. The patients, 51 women and 60 men, had a mean age of 60 years (range 29–86 years). There was no difference in body mass index (BMI) between the sexes ($p = 0.38$). Informed consent was obtained from all patients and the study was approved by the local ethics committee.

The day following the adenosine-stress scintigraphy, all patients were investigated with ultrasonography of the carotid arteries, and blood samples were taken for lipid analysis, including total and low-density lipoprotein/high-density lipoprotein (LDL/HDL) cholesterol, and triglycerides.

All patients answered a standardized questionnaire concerning risk factors for atherosclerosis, manifest cardiovascular disease, and current medical therapy. Manifest cardiovascular disease was defined as a previous medical history of myocardial infarction, stroke, or intermittent claudication. Hypercholesterolemia was defined as total plasma cholesterol > 6 mmol/L or documented hypercholesterolemia requiring lipid-lowering drug therapy. Hypertension was defined as documented elevation of blood pressure requiring drug therapy. Smoking status was recorded as never smoked or current or former cigarette smoking, and the lifetime number of pack-years smoked was estimated from the patient's history. Diabetes mellitus was defined as present if previously diagnosed by a physician.

Ultrasound Imaging and Analysis

B-mode ultrasound examinations were performed with an Acuson 128XP with a 7-MHz linear array transducer. The same operator, who was not involved in image analyses, performed all scans. The carotid arteries were scanned, and vessel wall and blood flow velocities were tape-recorded. A blood flow velocity > 1.2 m/s was used to define a stenosis with > 50% lumen diameter reduction.[17]

Magnified pictures were frozen incidentally with the R wave on the ECG. The far wall of the common carotid artery (CCA) and the carotid bulb 5–10 mm proximal and distal to the boundary line of these 2 vessel segments were used for measurements of intima-media thickness (IMT). The distal part of the CCA was used for lumen diameter (LD) measurements.

The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo in the far wall. LD was defined as the distance between the leading edge of the intima-lumen echo of the near wall and the leading edge of the lumen-intima echo of the far wall.[18] The cross-sectional intima-media area (CIMA) was calculated bilaterally by using the formula: $([\text{lumen diameter} + 2 \times \text{IM thickness}]/2)^2 \times 3.14 - (\text{lumen diameter}/2)^2 \times 3.14$.[11] A plaque was defined as > 1 mm in diameter and at least 100% increase

compared with the thickness of the adjacent wall segment.[19] Measurements of IMT did not include plaque.

All measurements were performed by 1 operator, blinded to all other data, using an automated computerized analyzing system.[20] The computer program calculated the average IM thickness of the analyzed section. IMT and LD were calculated separately for each side and as IMT_{mean} and LD_{mean}, respectively (right side + left side / 2).

The reproducibility of the analyzing system was evaluated by remeasuring 30 randomly selected carotid arteries, by a second operator blinded to all previous analyses. The coefficient of variation for interoperator variability regarding IMT_{mean} of the CCA was 7%.

Myocardial Perfusion Scintigraphy

All the patients underwent adenosine-stress, single-photon-emission computed tomography (SPECT) after approximately 12 hours of fasting. Adenosine (Item Development AB) was infused over 5 minutes, and depending on weight, 260–500 MBq Tc-99m-tetrofosmin (Nycomed, Amersham) was injected intravenously at the end of the third minute. Patients performed low-level bicycle exercise (50 watt or 30 watt for men and women, respectively) during the adenosine infusion, except patients with left bundle branch block on ECG (n = 10). SPECT imaging was initiated 30 minutes after the adenosine infusion. Data were acquired by means of a 2-detector (Vertex, ADAC) camera, and transaxial images were constructed as described earlier.[21]

One experienced reader blinded to all data except ECG at rest interpreted the SPECT images. A 16-segment model and a 4-point perfusion score were used for each segment: 0 point = normal perfusion, 1 point = mildly reduced, 2 points = moderately reduced, and 3 points = severely reduced or absent.[21] The 16 scores were added to give a summed stress score (SSS) used as a measure of CAD severity. The number of segments with reduced perfusion (score > 0) was used as a measure of extent of CAD.

A second experienced reader, who blindly scored all segments for the first 50 patients in exactly the same way as reader number 1, assessed interobserver variability for the scintigraphic classification. Exact agreement regarding score of each segment was obtained in 84% of the segments. Agreement regarding normal or abnormal perfusion in each segment was obtained in 89% of the segments and agreement regarding normal or abnormal perfusion for each patient in 94%, ie, in 47 of 50 patients.

Statistical Analysis

Results are given as mean ±1 SD or 95% confidence interval. Student's t tests were used for comparison of means. When more than 2 groups were compared, this was done with analyses of variance. If the F-test demonstrated a significant difference, each pair of means was compared by use of the Duncan test. The Chi-square test was used for comparison of proportions. Univariate or multiple linear regression analyses were used to characterize relationships between variables (or, when appropriate, corresponding nonparametric tests). Statistical significance was set at $p < 0.05$.

Results

The demographics of the study population are summarized in Table I. A history of previous myocardial infarction was more frequent in men (21 of 60 men vs 8 of 51 women, $p < 0.001$); otherwise there was no significant difference between sexes. In total, 38 (34%) subjects gave a history of manifest cardiovascular disease.

Carotid Ultrasound

About 1% of intima-media thickness (IMT) measurements in the common carotid artery (3 of 222) and 9% of those in the carotid bulb (20 of 222) were excluded owing to suboptimal ultrasonographic recording quality.

Twenty-four percent (54/222) of the examined carotid arteries had plaques, distributed among 13 women and 24 men (NS). Five patients had significant stenoses, all of moderate degree (maximal blood flow velocity between 1.2–3.0 m/s).

IMT_{mean} in the common carotid artery (CCA) was 0.76 ±0.15 mm and in the carotid bulb 0.84 ±0.16 mm. There was no significant side difference regarding IMT in the CCA or in the carotid bulb; neither were there any significant differences between the sexes. IMT increased significantly with age, both in the CCA and in the carotid bulb (Table II).

Table I. Results from questionnaire regarding risk factors for atherosclerosis, manifest cardiovascular disease and current medical therapy.

	Patients (n = 111)
Age (mean and range)	60 (29–86)
BMI (mean and 1 SD)	26.9 ±4.1
Hypertension, no. (%)	43 (39%)
Hypercholesterolemia, no. (%)	68 (61%)
Diabetes mellitus, no. (%)	13 (12%)
Previous myocardial infarction, no. (%)	29 (26%)
Stroke/TIA, no. (%)	11 (10%)
Intermittent claudication, no. (%)	8 (7%)
Current smoking, no. (%)	18 (16%)
Current medical treatment, no. (%)	86 (77%)

LD_{mean} was 6.43 ±0.83 mm, larger in men than in women ($p < 0.01$). The CCA diameter was significantly larger on the right side than on the left in both sexes (women $p < 0.05$, men $p < 0.01$). LD_{mean} increased significantly with age (Table II) and with increasing IMT_{mean} ($r = 0.44$, $p < 0.001$).

$CIMA_{mean}$ was 17.4 ±5.1 mm^2. CIMA did not differ significantly between right and left CCA. Furthermore there was no significant difference between sexes regarding $CIMA_{mean}$ or for each side separately, although CIMA in the left CCA tended to be larger in men than in women ($p = 0.08$).

Myocardial Perfusion Scintigraphy

One of 111 examinations was excluded owing to poor image quality. Thirty-eight of the 110 examinations (34.5%) had no signs of reduced perfusion (summed stress score; SSS = 0). Fifty-seven percent (29/51) of the examinations in women and 73% (43/59) of those in men showed perfusion defects (NS). Mean number of segments with reduced perfusion among those 72 patients with SSS > 0 was 4.7 ±2.7. SSS in those with defects was 9.3 ±7.7. Among patients with SSS > 0, men

Table II. Relationship between carotid markers of atherosclerosis and scintigraphic signs of CAD and general risk factors for atherosclerosis.

Duplex Ultrasonography	Plaque	LD	IMT cca	CIMA	IMT bulb
Myocardial scintigraphy					
Number of segments	0.23*	0.26†	0.14	0.23*	0.11
Summed stress score	0.24*	0.25†	0.12	0.22*	0.11
Questionnaire/risk factors					
Previous infarction	0.15	0.24*	0.12	0.23*	0.13
Hypertension	0.30†	0.20*	0.30†	0.30†	0.12
Age	0.32†	0.44†	0.45†	0.50†	0.47†
Gender	0.15	0.31†	0.08	0.18	0.01

Univariate regression, *r* values. (*$p < 0.05$; †$p < 0.01$). When 2 dichotomous variables were tested, nonparametric statistics were used (Spearman). LD = lumen diameter in the common carotid artery (CCA), CIMA = cross-sectional intima-media area in the CCA, IMT = intima-media thickness in the CCA and in the carotid bulb, Number of segments = number of segments with hypoperfusion. IMT, LD, and CIMA were calculated as right side + left side/2.

had significantly more segments with reduced perfusion than women (5.4 ±3.0, vs 3.6 ±1.8, $p < 0.01$), and significantly higher SSS (men 11.5 ±8.8, women 6.2 ±4.2, $p < 0.01$).

Relationship Between Risk Factors, Carotid Atherosclerosis, and Coronary Artery Disease

The main part of the relationships is shown in Table II. The lifetime number of pack-years smoked correlated with both carotid and coronary measures/markers of atherosclerosis as follows: CCA IMT_{mean} ($r = 0.28$, $p < 0.05$); $CIMA_{mean}$ ($r = 0.36$, $p < 0.01$); and LD_{mean} ($r = 0.33$, $p < 0.01$); number of segments with reduced perfusion ($r = 0.41$, $p < 0.001$); and SSS ($r = 0.42$, $p < 0.001$). A history of previous myocardial infarction correlated strongly with number of segments involved and SSS ($r = 0.40$ for both, $p < 0.001$), LD_{mean}, and $CIMA_{mean}$ (Table II). Regarding IMT, only IMT on the left side correlated significantly with previous myocardial infarction (CCA, $r = 0.25$ and carotid bulb, $r = 0.21$, $p < 0.05$ for both). Presence of diabetes mellitus correlated with extent ($r = 0.28$, $p < 0.01$) and severity of CAD ($r = 0.29$, $p < 0.01$), LD_{mean} ($r = 0.27$, $p = < 0.01$), and cross-sectional intima-media area (CIMA) on the left side ($r = 0.23$, $p < 0.05$).

There was a significant association between presence of carotid plaques and extent and severity of CAD measured with perfusion scintigraphy (Table II). In patients with perfusion defects, we further categorized the occurrence of carotid plaques into 3 groups according to the extent of carotid plaque (0 = absence of carotid plaque, 1 = unilateral occurrence of carotid plaques, 2 = bilateral occurrence of carotid plaques). There was a clear relationship between extent of carotid plaque and more advanced CAD (Figure 1).

In univariate analyses, CIMA and LD, but not IMT in the CCA or in the carotid bulb, correlated significantly with both extent and severity of myocardial perfusion defects (Table II). This is shown more in detail in Table III, where the patients are subdivided into 3 groups according to the extent of the perfusion abnormalities. Patients with large perfusion defects had higher LD and greater CIMA than patients with no defects ($p < 0.01$), and significantly greater CIMA than those with small-to-moderate defects ($p < 0.05$). There was no significant difference between patients with no defects and those with small-to-moderate defects.

When the subjects were subdivided between those with and those without perfusion defects on scintigraphy, there was a significant difference between the groups regarding IMT only in the left CCA (without defects 0.72 ±0.14, with defects 0.78 ±0.17 mm, $p < 0.05$).

The possible contributing factors regarding the relationship between carotid atherosclerosis

Figure 1. The relationship between extent of carotid plaque defined as 0 = absence of carotid plaque (n = 46), 1 = unilateral occurrence of carotid plaques (n = 16), 2 = bilateral occurrence of carotid plaques (n = 10), and; *above* the extent of CAD expressed as number of segments with hypoperfusion; *below* the severity of CAD expressed as summed stress score (= SSS), in patients with perfusion defects on myocardial scintigraphy. By ANOVA; *above* F = 4.9, $p < 0.01$; below F = 5.0, $p < 0.01$.

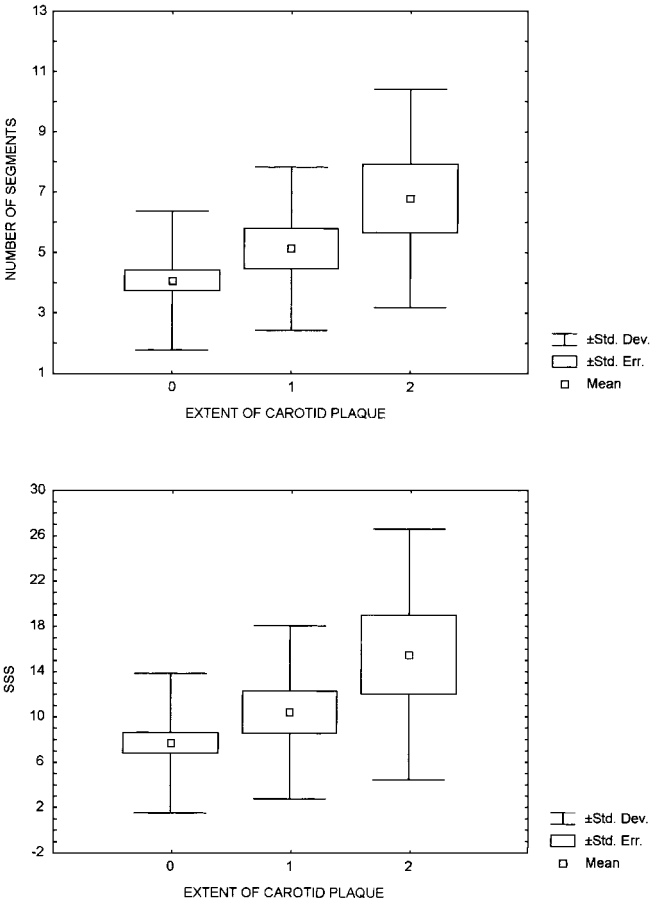

Table III. Ultrasound measurements and their relation to the extent of CAD expressed as number of segments with hypoperfusion on myocardial scintigraphy (mean and 95% confidence interval).

	No Defects (n = 38)	Small-to-Moderate (n = 62)	Large Defects (n = 9)	ANOVA F-Value
CCA				
LD, mm	6.18 5.92–6.44	6.48 6.30–6.67	6.89 6.02–7.76	3.5 (p = 0.03)
IMT, mm	0.73 0.68–0.77	0.76 0.73–0.80	0.85 0.69–0.99	2.5 (p = 0.09)
CIMA, mm^2	16.0 14.6–17.5	17.5 16.3–18.7	21.0 15.0–27.0	3.9 (p = 0.02)
Bulb*				
IMT, mm	0.83 0.77–0.89	0.84 0.80–0.88	0.92 0.74–1.09	0.9 (p = 0.39)

No Defects = 0 segments involved on myocardial perfusion scintigraphy, Small-to-Moderate = 1–7, and Large Defects are > 7 segments involved.

*In the carotid bulb measurements there were 37 subjects with no defects, 51 with small-to-moderate, and 8 with large defects. For abbreviations, see Table II.

and myocardial perfusion defects were assessed with multiple regression analyses. CIMA was independently related to extent of CAD even after adjustment for age, BMI, or gender. LD was independently related to extent of CAD after adjustment for age and BMI, but not after adjustment for gender. When these relationships were analyzed exclusively for men, CIMA in the left CCA, but not CIMA on the right side, $CIMA_{mean}$, or LD, was significantly related to extent of CAD.

The best multivariate model for prediction of $CIMA_{mean}$ was obtained when age, hypertension, extent of CAD, and presence of plaques were entered in the model. These factors together explained approximately 40% of the $CIMA_{mean}$ variance (multiple $r = 0.63$, $p < 0.001$). All variables except plaques had independent contributions to the equation. Similar results were obtained when LD_{mean} was analyzed against age, gender, BMI, hypertension, presence of plaques, and extent of CAD (multiple $r = 0.66$, $p < 0.001$). Age, gender, and BMI contributed independently to the equation.

Discussion

Our material shows moderate-to-high prevalence of CAD with 34% manifest cardiovascular disease and 65% presenting myocardial hypoperfusion. The study demonstrates a relationship between increased IM complex and presence of plaque in the carotid artery, and signs of CAD. The stronger correlation found between the cross-sectional IM area (CIMA) and CAD compared with intima-media thickness (IMT) and CAD stresses the importance of considering lumen diameter (LD) in measuring IMT. Increasing LD will lead to stretching of the arterial wall and narrowing of the IM layer and result in an underestimation of IMT. Since varying artery width influences the detectable degree of IMT, but not IM area,[11] it is obvious that the latter should be calculated in a population with increased likelihood of compensatory arterial enlargement.[22] The result of not considering variations in LD could, at least partly, explain the discrepancy in correlation between IMT and coronary artery disease in populations with

heterogeneous risk of CAD.[3,9,10,23] Another aspect that might be of importance is that increased IMT most likely represents a more diffuse vascular disease and is possibly of less discriminating capacity in the more advanced, obstructive atherosclerosis often seen in high-risk populations. According to our findings, carotid plaque identification then seems to be more relevant, and in combination with calculated CIMA the diagnostic value certainly increases.[12]

The role of carotid plaque identification has been emphasized by the fact that carotid plaque has prognostic implications for cardiovascular death and nonfatal myocardial infarction.[24] Yet we also found a fairly large proportion of patients with signs of CAD that did not present any carotid plaque (64%, 46/72). In other words, the absence of carotid plaques in no way seems to reflect the absence of CAD. This finding fits well with autopsy studies.[25,26]

IMT in the left carotid bulb was associated with a history of previous myocardial infarction, but otherwise we demonstrated no relationship between bulb IMT measurements and CAD, in contrast to findings by Hulthe et al.[10] Apart from their small study sample (n = 32), some difference in CAD risk between our study population and theirs, and another method of detecting CAD (coronary angiography), could be factors explaining the somewhat different results. They selected patients with obstructive coronary atherosclerosis, and as we also found, there was a significant correlation between presence of carotid plaques and severity of CAD.

Indications that atherosclerosis develops earlier and more in the left carotid artery than in the right have been reported.[2,12,19] In our study population, somewhat less numerous, there was no significant side difference. However, CIMA in the left CCA tended to be larger in men than in women ($p = 0.08$) and there were several associations between left carotid artery measurements, but not with right, and risk factors for/history of/scintigraphic signs of CAD. It has been suggested that the difference in anatomy between right and left carotid artery leads to different flow pattern and shear stress in the left carotid artery more similar to those in the major coronary arteries and therefore shows a more obvious relationship.[12] Irrespective of the mechanism/s for this side difference, these findings underline the importance of not focusing only on IMT_{mean}, but also on left side separately, in investigating the relationship between IMT and CAD.

The importance of LD measurement concerning the IM complex has been discussed above. In the univariate analyses, we also found a significant relationship between increased LD and a history of previous myocardial infarction and extent and severity of CAD. These findings were not entirely unexpected since LD correlates with risk factors for cardiovascular disease, and vessel enlargement is a common pathobiological response in early atherosclerosis.[13,22] Further, in univariate analyses, associations have also been reported between carotid enlargement and higher incidence of cardiovascular death and myocardial infarction.[24] The importance of age, gender, and BMI in discussing LD is clear. In fact, LD failed to show an independent relationship to CAD in multiple regression analyses with adjustment for these factors. This makes the interpretation more complex and limits the possibility for a more final conclusion concerning these relationships.

A limitation of this study is an uncertainty regarding the degree of atherosclerosis detected by myocardial perfusion scintigraphy. It is possible that subjects with mild diffuse CAD have normal-appearing scintigrams, which would indeed affect the possibility of measuring the true relationship between atherosclerosis in the coronary and carotid arteries. However, the use of coronary angiography for comparing the relationship will not overcome this problem.[27] On the contrary, results from a recent study using intracoronary sonography suggest that perfusion scintigraphy is better than angiography in detecting lower degrees of coronary atherosclerosis.[16]

Conclusion

In a population with intermediate-to-high risk of ischemic heart disease, calculated CIMA is more closely related to CAD expressed as myocardial hypoperfusion than IMT is. Together with carotid plaque occurrence, CIMA can form a predictor of CAD. Lumen diameter (LD) correlates with risk factors and to some extent also with CAD, but to consider LD as a predictor of CAD cannot be emphasized by the present study.

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