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The Presence of a Calcific Plaque in the Common Carotid Artery as a Predictor of Coronary Atherosclerosis

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Many contradictory reports have been published investigating the relationship between coronary artery disease (CAD) and the increased intima-media thickness (IMT) in the common carotid artery (CCA). However, only a limited number of studies evaluate the relationship between CAD and CCA disease as reflected by both the plaque morphology (fibrous and calcific plaques) and IMT. We have studied the associations between CAD and the wall morphology of CCA by B-mode ultrasound (US). One hundred and forty-four subjects, whose angiography was planned on the basis of suspected CAD, were included into the study. The patients were divided into 4 groups on the basis of B-mode US findings; Group I: normal, Group II: increased IMT (IMT $\geq$ 0.8 mm and plaque absent), Group III: fibrous plaque, Group IV: calcific plaque. Coronary artery disease was diagnosed in 63 patients. A statistically significant correlation was found between CAD and CCA wall morphology ($r = 0.42$, CI (95%) = 0.30–0.51, $p < 0.001$). Positive predictive values were 45.0%, 48.4%, and 75.0% in patients with increased IMT, fibrous plaque, and calcific plaque, respectively. None of the women with normal CCA wall morphology had significant coronary artery lesion. With respect to the normal group, the risk for CAD increased by 4.3 fold with the existence of fibrous plaque ($p = 0.02$) and by 9.9 fold with the existence of calcific plaque ($p < 0.001$). It has been shown that the CCA wall morphology determined by B-mode US is correlated with CAD in patients with chest pain, and the presence of calcific plaque is a better predictor for CAD than that of fibrous plaque and increased IMT. Women with chest pain and normal CCA wall morphology may not need coronary angiography.

Introduction

It is well known that atherosclerosis is a generalized disease and atherosclerotic changes in the arteries commence in the early decades of life.[1] Carotid and coronary arteries are the 2 most common sites of involvement of atherosclerosis within the arterial bed as a whole.[2-4] Epidemiologic studies have confirmed the relationship between carotid and coronary atherosclerosis.[2-4]

Smooth muscle cell proliferation has been shown to be primarily responsible for the intima-

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media thickness (IMT) alterations as an early manifestation of carotid atherosclerosis. In the early stages of atherosclerosis, macrophages migrate to the subendothelial region of the artery wall and transform into foam cells.[5] With continuing lipid deposition in the lesion, the smooth muscle cells, on the other hand, transform into fibroblasts, which in turn synthesize elastin, collagen, and glycosaminoglycans. As a consequence of these changes, the lesion becomes fibrotic. In the final stage of development of atherosclerotic lesions, enhanced calcium deposition alters the fibrotic lesion into a calcific plaque. Carotid atherosclerosis appears to be a dynamic process, as a result of which early and late morphologic changes can be manifest within the same lesion at a given instant of time.[5,6]

Many studies have shown that carotid B-mode ultrasound is a useful noninvasive method to determine the lumen diameter, IMT, and structure of plaques.[3,4,7-11] Whereas some investigators have used the existence of a plaque[3] or the degree of stenosis[12,13] as an assessment of carotid atherosclerosis, still others have used the IMT for this purpose.[7-11,14] There are conflicting reports regarding the existence of a relationship between coronary artery disease (CAD) and the increased IMT in carotid arteries as an early manifestation of carotid atherosclerosis.[3,4,7-14] So far, only a limited number of studies have investigated the relationship between CAD and carotid artery plaque morphology as a late manifestation of carotid atherosclerosis, and the number of patients included in these studies is limited.[15-17]

The aim of the present study was to investigate the relationship between CAD based on coronary angiography and the morphology of the common carotid artery (CCA) wall (increased IMT, fibrous plaque, and calcific plaque) by employing high-resolution B-mode ultrasound.

Methods and Subjects

One hundred and forty-four consecutive patients (87 men, 57 women, mean age: 53.2 ±10.8 years) with chest pain referred for elective coronary angiography were prospectively included into the study. They underwent a routine physical examination. A medical history, electrocardiography, and blood samples to evaluate cardiovascular risk factors (diabetes mellitus, hypercholesterolemia) were obtained from all subjects. Hyperlipidemia was diagnosed for plasma concentrations of low-density lipoprotein (LDL) cholesterol >130 mg/dL or total cholesterol >200 mg/dL.[18] Before coronary angiography, their echocardiography was performed with an Acuson Sequoia C 256 echocardiography device (Acuson Corporation, Mountain View, CA, USA). The patients with valvular heart disease, left ventricular ejection fraction <45%, or a past medical history of stroke or carotid endarterectomy were excluded from the study. Faculty ethical committee approval and written informed consent were obtained from each patient.

Carotid Ultrasound

Before coronary angiography, both CCAs of patients were evaluated with B-mode high-resolution ultrasound (Acuson Aspen, Acuson Corporation, Mountain View, CA, USA) by a radiologist. Maximum IMT (IMT_{max}) was measured over a 1 cm length of the posterior wall proximal to the bulbus of the CCA. The IMT was considered to be increased if its value was greater than or equal to 0.8 mm in any CCA.[19] The lesions with an increased IMT value of more than 50% with respect to the adjacent artery wall were regarded as plaques.[3] The smooth-surfaced, homogeneous, or heterogeneous lesions with a high or intermediate degree of echogenicity without posterior acoustic shadowing were considered as fibrous plaques, while the hyperechogenous lesions with posterior acoustic shadowing were classified as calcified.[6] The subjects with IMT values <0.8 mm and no carotid plaque were classed as normal in the context of carotid atherosclerosis. According to their arterial wall morphology, the patients were subsequently divided into 4 groups;

Group I: Normal (IMT <0.8 mm and plaque absent)

Group II: Increased IMT (IMT >0.8 mm and plaque absent)

Group III: Fibrous plaque (IMT value is not important and calcification absent)

Group IV: Calcific plaque (the presence of fibrous plaque and IMT value is not important)

Coronary Angiography

Following evaluation of CCA with B-mode ultrasound, coronary angiography was performed by a cardiologist who was blinded to the study. After appropriate preparations, a 6 French vascular

sheath was placed into the right femoral artery by using Seldinger technique. Subsequently, using 6 French Judkins right and left catheter, selective coronary angiography was performed, which was followed by ventriculography by using a pigtail catheter. Significant coronary artery disease was defined as either ≥70% reduction of internal diameter of the left anterior descending, circumflex, or right coronary artery or ≥50% reduction of the internal diameter of the left main coronary artery.[20]

Statistical Analysis

All data were recorded on a 9.05 SPSS for Windows data sheet and defined as mean ± standard deviation. Student's t test was used to compare the mean age and plasma lipid profile among groups. Chi-square test was used to analyze other CAD risk factors and the arterial wall morphology for the groups. The relationship between carotid and coronary atherosclerosis was determined by Spearmen rank correlation analysis. Multivariate analysis was used to assess the effect of the traditional risk factors and the wall morphology of CCA on CAD by using a linear logistic regression model, for which all traditional risk factors were entered simultaneously. A p value <0.05 was considered statistically significant.

Results

Coronary artery disease was determined in 63 patients. The mean age of patients with CAD was significantly higher than that of patients who did not have CAD ($p<0.001$). The proportions of male gender ($p<0.0001$) and smokers ($p<0.001$) were significantly higher in patients with CAD, but the plasma lipid profiles were similar for both groups (Table I).

The mean IMT in the right CCA and left CCA were measured as 0.74 ±0.30 mm and 0.76 ±0.29 mm, respectively ($p>0.05$). The mean IMTs of both right and left CCAs were slightly higher in patients with CAD than in patients without CAD, but these differences were not statistically significant (Table II). The distributions

Table I. The patients' risk factors for coronary artery disease and their plasma lipid profile.

	CAD (–) (n=81)	CAD (+) (n=63)
Age, years	50.7 ±10.2	56.5 ±10.8*
Male/female	38/43	49/14†
Hypertension, n (%)	30 (37.0%)	23 (36.5%)
Diabetes mellitus, n (%)	14 (17.3%)	12 (19.0%)
Family history of CAD, n (%)	31 (38.3%)	28 (44.4%)
Smoking, n (%)	29 (35.8%)	40 (63.5%)*
Hyperlipidemia, n (%)	40 (49.4%)	36 (57.1%)
Total cholesterol, mg/dL	199.1 ±38.7	212.2 ±58.2
LDL-cholesterol, mg/dL	123.3 ±34.9	131.9 ±40.6
HDL-cholesterol, mg/dL	40.5 ±6.9	41.4 ±10.1
Triglyceride, mg/dL	176.0 ±97.0	185.1 ±102.7

CAD = coronary artery disease. *$p=0.001$, †$p<0.0001$.

Table II. The mean intima-media thickness of right and left common carotid artery in patients with and without coronary artery disease.

	CAD (–) (n=81)	CAD (+) (n=63)
Right IMT, mm	0.81 ±0.25	0.83 ±0.28
Left IMT, mm	0.78 ±0.29	0.81 ±0.29

CAD = coronary artery disease, IMT = intima-media thickness.

of patients according to CCA wall morphology are presented in Table III. The differences of wall morphology between the groups were statistically significant ($p < 0.001$) (Table III). There was a significant correlation between CCA wall morphology and CAD ($r = 0.42$, CI (95%) = 0.30–0.51, $p < 0.001$).

The wall morphology was used as a covariant in multivariate regression analysis, together with traditional CAD risk factors. With respect to the normal group, the risk for CAD increased by 1.7 fold with an increased IMT, but this increase was not found to be statistically significant ($p = 0.30$). However, the risk for CAD increased by 4.3 fold with the existence of fibrous plaque ($p = 0.02$) and by 9.9 fold with the existence of calcific plaque ($p < 0.001$) (Table IV). We have shown that the existence of calcific plaque was a better predictor of CAD when compared to the existence of fibrous plaque and the increased IMT. Male gender increased the risk for CAD 2.9 fold ($p = 0.001$), while other traditional risk factors were inadequate in predicting the risk for CAD (Table IV). Positive predictive values were 45.0%, 48.4%, and 75.0% in patients with increased IMT, fibrous plaque, and calcific plaque, respectively (Table V, Figure 1). None of the women with normal CCA wall morphology had a significant coronary artery lesion. However, 37.5% of men with normal CCA wall morphology had significant CAD. Furthermore, CAD was diagnosed in 87.0% of men with calcific plaque.

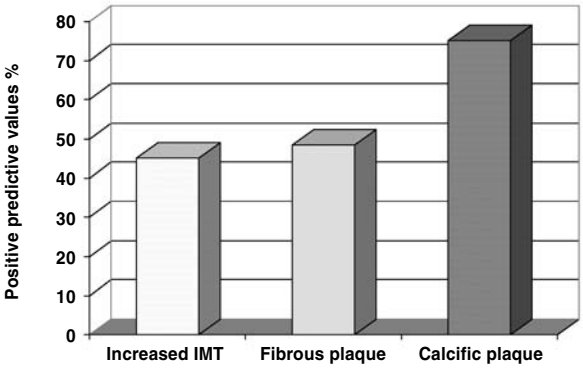

Figure 1. Positive predictive values of the common carotid artery wall morphology subgroups.

Table III. The wall morphology of common carotid artery in patients with and without coronary artery disease.

Wall Morphology	CAD (–)	CAD (+)	Total
Group I, n (%)	45 (55.6%)	12 (19.0%)	57 (39.6%)
Group II, n (%)	11 (13.6%)	9 (14.3%)	20 (13.9%)
Group III, n (%)	16 (19.8%)	15 (23.8%)	31 (21.5%)
Group IV, n (%)	9 (11.0%)	27 (42.9%)	36 (25.0%)
Total, n (%)	81 (100.0%)	63 (100.0%)	144 (100.0%)

CAD = coronary artery disease.

Table IV. The wall morphology of common carotid artery and the determination of the relationship between the risk factors for coronary artery disease and the prevalence of coronary artery disease by multivariable regression analysis.

Risk Factors	Odd's Ratio	CI (95%)	p Value
Wall morphology			
Group I	1.0	Reference	Reference
Group II	1.7	0.5–6.0	0.30
Group III	4.3	1.3–14.1	0.02
Group IV	9.9	2.9–27.6	<0.001
Age	1.1	0.9–1.1	0.08
Sex	2.9	2.0–6.9	0.001
Hypertension	1.6	0.6–4.5	0.33
Diabetes mellitus	1.1	0.6–2.1	0.50
Family history of CAD	2.2	0.9–5.4	0.08
Hyperlipidemia	1.8	0.7–4.3	0.25
Smoking	2.0	0.8–5.0	0.14

CAD = coronary artery disease.

Table V. Sensitivity, specificity, and positive (+) and negative (–) predictive value of increased intima-media thickness, fibrous plaque, and calcific plaque in patients with coronary artery disease.

	Sensitivity (%)	Specificity (%)	(+) PV (%)	(–) PV (%)	Accuracy (%)
Increased IMT	14.3	86.4	45.0	56.5	54.9
Fibrous plaque	23.8	80.3	48.4	57.5	55.6
Calcific plaque	42.9	88.9	75.0	66.7	68.8

IMT = intima-media thickness, PV = predictive value.

Discussion

Many studies have shown that a relationship exists between carotid and coronary atherosclerosis.[2-4,10] Grotta et al[12] found a strong correlation between the extent of coronary atherosclerosis and the progression of carotid atherosclerosis. They also reported that the patients with severe coronary atherosclerosis had a much faster progression of carotid atherosclerosis.[12] While some investigators used the existence of a plaque[3] or the degree of stenosis[12,13] as a measure of carotid atherosclerosis, still others used increased IMT for this purpose.[7-11,14] The increased IMT is an adaptive response to the changes in the shear and tensile stresses on the arterial wall and the blood flow.[11] It represents an early-phase finding of atherosclerotic disease.[5,11] Many studies have shown that a local IMT increase in CCA indicates a significantly increased risk for coronary atherosclerosis.[10,11,21-23] However, these studies did not investigate other manifestations of atherosclerosis such as existence of plaques and plaque morphology.

In our study, we found that the increased IMT values in CCA on its own did not predict coronary atherosclerosis. Several studies in the past decade have found a weak relationship between increased IMT in CCA and CAD[8,14,17] while other studies found that there was no such relationship.[3,4] In The Cholesterol Lowering Atherosclerosis Study (CLAS),[4] 188 patients with a history of coronary artery bypass graft operation were followed up for 2 years. Lipid-lowering therapy was given to a subgroup of these patients while placebo was given to the remainder. No relationship was found between the baseline IMT and coronary artery disease. In a subgroup of The Multicenter Anti-Atheroma Study (MAAS),[3] it was found that there was no correlation between the IMT values of CCA and CAD but that increased IMT values at the level of the carotid artery bulb were related to coronary atherosclerosis. Recently, Takashi et al[17] reported that increased IMT was related to atherosclerosis in middle-aged (40–59 year) persons, but not in older patients. However, in older (60–79 year) subjects, the presence of plaque and calcification did correlate well with CAD. Although the method used by Takashi et al is similar to ours, our results support the latter, not the former. This difference is probably due to the differences in study population and race. We think that the limited number of patients in their middle-aged (n = 13) and elderly (n = 27) subgroups affected their results.

In this study, we found that patients with calcific or fibrous plaques in CCA have more frequently significant coronary artery disease. We also found that the existence of calcific plaques in CCA carries a higher risk for CAD than the presence of fibrous plaque or increased IMT. There was a significant relationship between plaque morphology and CAD. We calculated that the positive predictive values were 45.0%, 48.4%, and 75.0% in patients with increased IMT, fibrous plaque, and calcific plaque, respectively. In patients who had a calcific plaque the risk of CAD increased by 9.9 fold, while this risk was increased by 4.3 fold in those with a fibrous plaque. Ebrahim et al[24] reported that the existence of plaque, rather than increased IMT values, is a major criterion for predicting the risk of CAD. Although they merely considered the existence of a plaque, regardless of whether they were fibrous or calcific, the results of their study showed similarities with our findings. Only a limited number of studies have used plaque morphology as an assessment of carotid atherosclerosis.[6,25] Sterpetti et al[6] followed up patients who had carotid endarterectomy for 39 months with B-mode US and specified 3 different plaque morphologies on the basis of ultrasound images; these were designated as homogeneous-soft (increased IMT), homogeneous-hard (fibrous), and heterogeneous (calcific) plaques. It was postulated that the progression of atherosclerosis was initially represented by an increase in IMT, which was followed by the development of fibrous plaque and finally by calcific plaque.[6] Plaque calcification is an important long-term sequel of atherosclerosis.[25,26] It was shown that symptoms of cerebral ischemia are more extensive in patients with calcific plaque, signifying severe atherosclerosis.[6]

We also detected a significant coronary lesion in 37.5% of men patients with normal carotid morphology, whereas no significant coronary lesions were found in women subjects with normal CCA morphology. In addition, significant CAD was diagnosed in 87% of men patients with calcific plaque. In an angiographic study, Giral et al[27] did not find significant CAD in women patients with positive exercise test and normal carotid morphology. As a result of these findings, it can be argued that it may be unnecessary to perform coronary angiography in many female patients with chest pain but normal carotid morphology.

Although our study was a prospective study, only the relationship between carotid and coronary atherosclerosis was investigated, and no attempt was made to determine the risk of early

and late events in the follow-up. The data from the CAFES-CAVE study[28] demonstrated that carotid and femoral artery morphology obtained by B-mode ultrasound can be used to predict cardiovascular events in a 10-year follow-up. Those authors have shown that cardiovascular events are more extensive in subjects with carotid or femoral artery plaque or stenosis. These long-term findings in a large population confirm the results of our short-term prospective study.

Study Limitations

There are several limitations of the present study. First, our study included a group of patients in a selected population who had chest pain and were suspected of having CAD. Therefore, the results obtained in this study may not apply to a more general population of persons of the same age. Second, we did not compare CCA morphology to noninvasive stress testing like exercise ECG or myocardial perfusion scintigraphy as screening strategies. However, various results have been reported about positive predictive value of exercise ECG in patients with low-medium coronary risk profile and the positive predictive value has been found to increase in patients with high coronary risk profile.[29] A review of 7 studies evaluating the angiographic results of 5,889 asymptomatic men showed that the positive predictive value of a positive exercise test was only 21%. Those authors reported a high incidence of false-positive tests in a population with low coronary risk factors.[30] Although it has long been known that there is a relationship between carotid atherosclerosis and CAD, there are conflicting reports about which carotid wall morphologic changes are better predictors for coronary atherosclerosis. The aim of the present study was to investigate which morphologic changes are better predictors for CAD, not to compare CCA morphology to noninvasive screening tests.

Conclusions

It was found that the wall morphology of CCA as determined by B-mode ultrasound is well correlated with CAD and that the presence of calcific plaques is a better predictor for coronary artery disease, compared to the presence of fibrous plaques or increased IMT. Owing to the high risk of significant coronary artery disease, it is appropriate to investigate CAD in patients with chest pain and calcific plaque in the CCA. Women with chest pain and normal CCA wall morphology may not need coronary angiography.

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