Carotid Artery Disease as a Marker for the Presence of Severe Coronary Artery Disease in Patients Evaluated for Chest Pain

Ioannis Kallikazaros, MD, FESC; Costas Tsioufis, MD; Skevos Sideris, MD; Christodoulos Stefanadis, MD, FAAC; Pavlos Toutouzas, MD, FAAC

Background and Purpose—We sought in this study to elucidate whether carotid artery disease detected by ultrasonography can be a clinically useful marker for the presence of severe coronary artery disease (CAD) in patients evaluated for chest pain.

Methods—Duplex ultrasonography and quantitative coronary angiography were used to assess carotid and coronary artery atherosclerosis in 225 consecutive patients (mean age, 58 ± 9 years) with chest pain referred for cardiac catheterization.

Results—CAD was present in 197 patients (88%). Fifty-seven patients (25%) had 1-vessel disease, 52 (23%) had 2-vessel disease, 53 (24%) had 3-vessel disease, and 35 (16%) had left main stem CAD (LMS-CAD). The incidence of severe CAD (3-vessel disease or LMS-CAD) was 24% and 63% in the normal and impaired ejection fraction (EF) subgroups, respectively (P < 0.005). Carotid disease (lumen diameter stenosis of ≥50%) was present in 5.3%, 13.5%, 24.5%, and 40% of patients with 1-, 2-, and 3-vessel disease and LMS-CAD, respectively. Moreover, the incidence of carotid disease in patients with severe CAD was 31% in the entire study population and 46% and 5% in the subgroups with impaired and normal EF, respectively (P < 0.005). In the entire study population, the presence of severe CAD was determined by age, male sex, and carotid disease; in the impaired EF group by age and carotid disease; and in the normal EF group only by age. Carotid disease has a high negative (92%) and a high positive (91%) predictive value for the presence of severe CAD in the subgroup with normal and impaired EF, respectively.

Conclusions—In patients evaluated for chest pain, carotid disease is significantly correlated with severe CAD. Furthermore, in patients with impaired left ventricular systolic performance the presence of carotid disease reflects the presence of severe CAD, while in patients with normal EF the absence of carotid disease reflects the absence of severe CAD. (Stroke. 1999;30:1002-1007.)

Key Words: angiography • carotid artery diseases • coronary artery disease • ultrasonography, Doppler, duplex

Because atherosclerosis is considered a generalized disease, mainly manifested in the entire vasculature, an association between coronary and peripheral vascular disease has been well established.1–4 The important relationship between carotid artery disease and coronary artery disease (CAD) is best expressed by the high incidence of myocardial infarction following carotid endarterectomy and the devastating effects of neurological injury occurring occasionally after routine coronary artery bypass.5–8 Furthermore, patients with severe CAD, such as left main stem CAD (LMS-CAD) or 3-vessel disease, comprise a heterogenous population with a wide spectrum of disease severity; for optimum perioperative management, they should be screened for carotid artery disease before bypass surgery.7,8

In the evaluation of patients with suspected CAD, carotid artery intima-media wall thickness has been reported to be a useful marker for the presence of CAD.9,10 However, the precise relationship between the extent of carotid artery atherosclerosis and the severity of CAD has not been well evaluated. For this purpose, we studied by carotid artery ultrasonography the potential role of carotid disease in identifying the presence of severe CAD in patients who had been referred for chest pain evaluation by coronary angiography. In addition, we investigated the accuracy of carotid disease in predicting the presence of severe CAD in the subgroups of patients with normal or impaired left ventricular systolic performance.

Subjects and Methods

Study Population
The study population consisted of 225 consecutive patients aged 58 ± 9 years (range, 35 to 77 years) who had been referred to our hospital for chest pain evaluation suggestive of ischemic heart disease.
Patients with a history of previous myocardial infarction, angiographically documented CAD, cerebrovascular disease, congenital heart disease, cardiomyopathy, valvular heart disease, and any systemic disease were excluded. We also excluded patients with coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or carotid endarterectomy, because the interpretation of the coronary angiogram or the carotid duplex ultrasonogram may be obscured in these cases.

After a careful history was taken, the patients underwent a physical examination, chest x-ray, ECG, and ultrasound examination of the heart. Blood was drawn from fasting patients on the morning of catheterization for assay of glucose and lipid concentrations by standard laboratory methods. The study protocol included an evaluation of risk factors for cardiovascular disease, carotid artery ultrasonography, and coronary artery angiography–left ventriculography.

The study protocol was approved by the institutional ethics committee of our hospital. Written informed consent was obtained from all patients after a detailed description of the procedure was given.

Evaluation of Risk Factors Variables
The risk factor variables evaluated in this study included age, sex, hypercholesterolemia, hypertension, diabetes mellitus, family history of CAD, and smoking status. The latter was assessed with smokers defined as those patients consuming at least 1 cigarette daily.

Hypercholesterolemia was defined as total plasma cholesterol of >200 mg/dL in the previous 12 months or documented hypercholesterolemia requiring lipid-lowering drug therapy. Hypertension was coded as present if there was any history of high blood pressure or if the blood pressure measured twice in the hospital exceeded 140 mm Hg systolic or 90 mm Hg diastolic. Diabetes mellitus was defined if the patient had a history of diabetes or if the fasting plasma glucose exceeded 126 mg/dL or 200 mg/dL 2 hours after the meal. Family history was coded as positive if a first-degree relative had had a significant coronary event before the age of 60 years.

Assessment of Carotid Atherosclerosis
Atherosclerosis of both left and right carotid arteries was assessed by duplex ultrasound scanning with a Hewlett Packard Sonos 2.500 commercially available machine with a 7.5/5.5-MHz imaging transducer. The technique for carotid artery ultrasound scanning has been previously described in detail.12,14 In brief, the severity of carotid atherosclerosis was evaluated by using the maximum percentage diameter stenosis recorded by B-mode ultrasonography in the case of mild stenoses and by using parameters of the flow velocity pattern measured by Doppler ultrasonography in the case of severe stenoses. The maximum stenosis was defined as the greatest stenosis observed on the right or left side. Accordingly, our patients were classified into 1 of the following 5 categories: (1) carotid arteries with no signs of atherosclerotic lesions, (2) 2% to 15% diameter stenosis, (3) 16% to 49% diameter stenosis, (4) 50% to 79% diameter stenosis, and (5) 80% to 100% diameter stenosis.

We defined as carotid disease the carotid atherosclerosis with a lumen diameter stenosis of ≥50% (the latter 2 categories). All measurements were performed over 5 cycles and averaged. Each scanning period averaged 25 minutes and was recorded on Super VHS videotape for later offline analysis by 2 independent readers. The interobserver variability for the percentage of carotid artery stenosis was low (4.5±3%).

Coronary Angiography–Left Ventriculography
Coronary angiography and left ventriculography were performed by the Judkins technique. The percentage of diameter stenosis was calculated by quantitative coronary angiography with a commercially available automated coronary analysis system (DCI-S, Phillips Medical System).15 CAD was defined as diameter lumen stenosis of >50% in at least 1 major coronary artery. According to the number of diseased vessels, our patients were classified into 1 of the following 5 patient groups: group 1, patients with no vessel disease; group 2, patients with 1-vessel disease; group 3, patients with 2-vessel disease; group 4, patients with 3-vessel disease; and group 5, patients with LMS-CAD and or without other vessel disease. Groups 4 and 5 were defined as severe CAD.

Also, according to the left ventricular systolic performance level, our patients were classified into 2 groups with normal ejection fraction (EF) (>50%) or with impaired EF (≤50%).

Statistical Analysis
χ² tests were used to detect statistically significant relationships between categorical variables. A value of P<0.05 was considered statistically significant.

Stepwise multiple logistic regression was used to detect statistically significant associations between a dichotomous dependent variable and a number of independent ones. Sensitivity, specificity, and predictive values were calculated by use of a standard method.

Results
We studied 225 consecutive patients (198 men; mean age, 58±9 years; range, 35 to 77 years). The demographic and clinical characteristics of the entire study population, as well as of the subgroups according to the EF value, are presented in Table 1.

In the group with impaired left ventricular EF, the number of older patients, smokers, hypertensive patients, and hypercholesterolemic patients was higher than in the group with normal EF.

Carotid Artery Duplex Ultrasonography Data
Carotid artery atherosclerosis was present in 164 patients (73%); 61 patients (27%) had normal left and right normal arteries. The classification of the entire study population as well as subgroups is listed, according to the severity of carotid atherosclerosis, in Table 2. The group with impaired EF had significantly fewer patients without atherosclerotic signs than the group with normal EF (P<0.05).

Carotid artery disease was found in 38 patients (18%): the subgroup with impaired EF had a significantly greater number of patients with carotid artery disease (28 patients, 33%) compared with the group with normal EF (10 patients, 7%) (P<0.005).

Regarding the location of atherosclerotic plaques in the carotid tree, the bulb was the most common site (in 127 lesions), followed by the internal carotid artery (in 88 lesions) and the common carotid artery (in 80 lesions). Carotid artery...
stenoses were found to be equally distributed between the right and left carotid arteries.

Coronary Angiography Findings

CAD was found in 197 patients (88%), whereas 28 patients (12%) had coronary arteries without critical stenosis. The classification, by diseased vessel, of the study population is presented in Table 3.

The group with impaired EF had significantly fewer patients without CAD, as well as patients with 1- and 2-vessel disease, compared with the group with normal EF (4%, 15%, and 18% versus 18%, 31%, and 26%, respectively; P<0.005). In addition, the latter group had a significantly smaller number of patients with 3-vessel disease, LMS, and severe CAD (16%, 9%, and 24% versus 36%, 27%, and 63%, respectively; P<0.005) compared with the group with impaired EF.

Correlation Between Carotid and Coronary Atherosclerosis

The distribution of carotid disease in the groups with different degrees of CAD is shown in Figure 1. There was a stepwise increase in the number of patients with carotid disease among the patients with increasing severity of CAD, because carotid disease was present in 5.3%, 13.5%, 24.5%, and 40% of patients with 1-, 2-, and 3-vessel disease and LMS-CAD, respectively. In addition, the incidence of carotid disease in patients with severe CAD was 31% (27 of 88 patients) in the entire study population.

Furthermore, the incidence of carotid disease in the subgroup of patients with severe CAD and impaired EF was greater (25 of 54 patients, 46.3%) compared with patients with severe CAD and normal EF (2 of 34 patients, 5.8%; P<0.005) (Figure 2).

Forward stepwise logistic regression analysis was applied to identify factors that were independently associated with the presence of severe CAD. Severe CAD as a dependent variable was entered in a regression model with 8 independent variables.

This analysis revealed that age, male sex, and carotid disease were independently related to the presence of severe CAD in the entire study population (Table 4). Furthermore, using the same regression model, in the group with impaired EF it was revealed that age and carotid disease were independently associated with severe CAD, while in the group with normal EF only age was independently associated with severe CAD (P<0.005 for both cases). In the entire study population, carotid disease has a high negative predictive value (92%), an acceptable sensitivity (71%) and specificity (68%), and a low positive predictive value for the presence of severe CAD. In the subgroup of patients with impaired EF, carotid disease has a high positive predictive value (91%), a high sensitivity (90%), an acceptable specificity (50%), and a low negative predictive value for the presence of severe CAD. In the patients with normal EF, carotid disease has a high negative predictive value (92%) and an acceptable specificity (75%) for the presence of severe CAD.

TABLE 2. Classification of Patients According to Degree of Carotid Atherosclerosis

<table>
<thead>
<tr>
<th>Degree of Carotid Atherosclerosis</th>
<th>Entire Study Population (n=225)</th>
<th>Patient Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>No signs of atherosclerotic lesions</td>
<td>61 (27%)</td>
<td>14 (16%)</td>
</tr>
<tr>
<td>2%–15% diameter stenosis</td>
<td>43 (19%)</td>
<td>14 (16%)</td>
</tr>
<tr>
<td>16%–49% diameter stenosis</td>
<td>83 (36%)</td>
<td>29 (35%)</td>
</tr>
<tr>
<td>50%–79% diameter stenosis</td>
<td>28 (13%)</td>
<td>19 (22%)</td>
</tr>
<tr>
<td>80%–100% diameter stenosis</td>
<td>10 (5%)</td>
<td>9 (11%)</td>
</tr>
</tbody>
</table>

TABLE 3. Classification of Patients According to CAD

<table>
<thead>
<tr>
<th>Vessel Disease</th>
<th>Entire Study Population (n=225)</th>
<th>Patient Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-vessel disease</td>
<td>28 (12%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>57 (25%)</td>
<td>13 (15%)</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>52 (23%)</td>
<td>15 (18%)</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>53 (24%)</td>
<td>31 (36%)</td>
</tr>
<tr>
<td>LMS-CAD</td>
<td>35 (16%)</td>
<td>23 (27%)</td>
</tr>
<tr>
<td>Severe CAD</td>
<td>88 (39%)</td>
<td>54 (63%)</td>
</tr>
</tbody>
</table>

Forward stepwise logistic regression analysis was applied to identify factors that were independently associated with the presence of severe CAD. Severe CAD as a dependent variable was entered in a regression model with 8 independent variables.

This analysis revealed that age, male sex, and carotid disease were independently related to the presence of severe CAD in the entire study population (Table 4). Furthermore, using the same regression model, in the group with impaired EF it was revealed that age and carotid disease were independently associated with severe CAD, while in the group with normal EF only age was independently associated with severe CAD (P<0.005 for both cases). In the entire study population, carotid disease has a high negative predictive value (92%), an acceptable sensitivity (71%) and specificity (68%), and a low positive predictive value for the presence of severe CAD. In the subgroup of patients with impaired EF, carotid disease has a high positive predictive value (91%), a high sensitivity (90%), an acceptable specificity (50%), and a low negative predictive value for the presence of severe CAD. In the patients with normal EF, carotid disease has a high negative predictive value (92%) and an acceptable specificity (75%) for the presence of severe CAD.

Figure 1. Distribution of carotid disease according to the extent of CAD in the entire study population. VD indicates vessel disease.
the severity of coronary atherosclerosis have been sought for clinical screening of patients with chest pain syndromes.1,9,10,21,22 Thus, carotid intima-media thickness has been suggested as a surrogate marker for coronary atherosclerosis for use in clinical trials.

Craven et al1 have suggested that B-mode score is strongly and independently associated with CAD in patients aged >50 years and is at least as useful as well-known risk factors for identifying patients with CAD. Furthermore, it is reported21 that carotid intima-media thickness is significantly correlated with the extent and severity of CAD, but this relationship is weak. Salonen and Salonen22 reported that greater common carotid intima media thickness values in middle-aged men may be independently associated with higher subsequent risk of acute coronary events. Recently, the Atherosclerosis Risk in Communities study10 reported that mean carotid intima-media thickness is a noninvasive predictor of future cardiovascular events.

However, possible additional associations between carotid disease and the severity of CAD have not been well addressed. To investigate this issue further, we extended our attention to the exact relationship between carotid disease and CAD. We found that carotid disease could indicate the presence of severe CAD in patients undergoing coronary angiography for chest pain. Moreover, the combination of carotid disease with impaired left ventricular systolic performance could predict the presence of severe CAD. Also, the absence of carotid disease in a patient with normal left ventricular systolic performance may reflect the absence of severe CAD.

In concordance with the above, Hertzer et al2 studied patients with asymptomatic carotid bruits or transient ischemic attacks and revealed severe operable CAD in 37% of patients clinically suspected of having CAD and in 16% of patients without suspected CAD.

Furthermore, it has been demonstrated23 that nearly one half of patients with either symptomatic or asymptomatic cerebrovascular disease had an abnormal 201Tl test; consequently, these patients may be screened for cardiac disease. Similarly, the presence of increases in wall thickness beyond those predicted by age and sex may identify individuals at higher risk for coronary disease and stroke, and internal carotid artery stenosis correlates more strongly with CAD than wall thickness.4 In this study, the prevalence of coronary disease increased from 17% in patients without stenosis in the carotid arteries to 46% in those with stenosis of >75%. Seino et al24 reported the coexistence of carotid artery disease and CAD in 33% of Japanese patients in their study, as assessed by supraorbital Doppler flow analysis.

Several studies have reported a high incidence of LMS-CAD in candidates for carotid endarterectomy and coronary artery bypass. Vigneswaran et al25 reported that postoperative cerebrovascular complications were more common in patients who had coronary artery revascularization for stenosis for LMS-CAD and, consequently, for optimum perioperative management patients with LMS stenosis should be screened for carotid artery disease before bypass surgery. In previously published studies12,25 we found a significant relationship

In this study we evaluated the relationship between carotid disease and the presence of severe CAD in patients with chest pain who were referred for evaluation.

Our main finding was that carotid disease was significantly related to the presence of severe CAD, defined as LMS-CAD or 3-vessel disease. Furthermore, in patients with impaired left ventricular systolic performance, the presence of carotid disease reflects the presence of severe CAD, whereas in patients with normal EF the absence of carotid disease reflects the absence of severe CAD.

Carotid atherosclerosis is important in view of its relationship to cerebrovascular ischemic disease and coronary atherosclerosis.16,17 This relationship is best expressed by the knowledge that the annual mortality rate after transient ischemic attacks is mainly caused by myocardial infarction and is similar to the annual cardiac mortality rate in patients with stable angina pectoris.18

Autopsy studies have demonstrated a strong correlation between the extent of extracranial carotid and coronary atherosclerosis.19,20 Noninvasive measurements that relate to the severity of coronary atherosclerosis have been sought for clinical screening of patients with chest pain syndromes.1,9,10,21,22 Thus, carotid intima-media thickness has been suggested as a surrogate marker for coronary atherosclerosis for use in clinical trials.

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The entire study population

for the relationship between 8 variables and severe CAD in the entire study population as well as in the subgroups with impaired and normal EF.

**TABLE 4. Stepwise Multiple Logistic Regression Coefficients for the Relationship Between 8 Variables and Severe CAD in the Entire Study Population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient b</th>
<th>Wald</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0774</td>
<td>15.71</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>1.175</td>
<td>5.435</td>
<td>0.0197</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>1.167</td>
<td>8.403</td>
<td>0.0037</td>
</tr>
<tr>
<td>Constant</td>
<td>-6.2264</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The variables smoking, hypercholesterolemia, hypertension, diabetes mellitus, and positive family history did not enter the equation, according to the selection criteria (probability for entry, <0.05; probability of removal, >0.01).
between carotid artery disease and LMS disease in patients undergoing coronary angiography.

In a similar way, the absence of thoracic plaque detected by multipeptide transesophageal echocardiography was found to be a powerful predictor for absence of significant CAD in elderly patients, even in the elderly. However, it has been reported that atherosclerotic aortic plaque detected by transesophageal echocardiography is useful in predicting significant CAD only in a relatively young population and not in elderly patients.

Coronary arteriography is still the “gold standard” for the diagnosis of CAD, although nowadays there are several very useful noninvasive tests (eg, the exercise test and the stress echo test). However, patients frequently demonstrate repolarization abnormalities on the resting or the exercise ECG, thus making it difficult to interpret ischemic changes during stress or in the case of chest pain, when performance of a stress test on a patient is not recommended. Also, at times the patient’s current treatment did not allow clear results.

Ultrasound, a valid, simple, safe, noninvasive bedside technique for the assessment of extracoronary atherosclerosis, has been widely used to study carotid atherosclerosis. In the management of patients with chest pain, carotid duplex scan obviously cannot replace the already-existing, noninvasive tests for evaluation of CAD. Our classification of patients as to low or normal EF was based on ventriculography. However, it is known that equally good information can be acquired through the ultrasonographic, noninvasive evaluation of the patient.

Based on the findings of our study, the knowledge of the EF of a patient referred for chest pain, along with the information about the atherosclerotic state of the carotid arteries, provides significant information about the presence or absence of severe CAD.

Several factors may have limited the apparent strength of the relationship we found between carotid disease and severe CAD. First, we studied a group of consecutive patients who were referred for coronary angiography for suspected ischemic heart disease. This selection bias means that our findings regarding the relationship of carotid disease with severe CAD are relevant only to this special group of patients and may not be applicable to the general population. Second, regardless of the method of analysis, coronary angiography frequently underestimated the severity of atherosclerotic disease, although it is a reasonable method for measuring the extent and severity of CAD.

Also, classification of the extent of CAD based on the number of diseased vessels may not be as precise as other specific indexes. However, this classification is very common in everyday clinical practice, and consequently the relationship of carotid disease to the diseased vessels is of practical value. Finally, for the evaluation of carotid disease, carotid duplex ultrasonography is considered a reliable and acceptable test, and angiography is required only in special cases.

Conclusions

In patients being evaluated for chest pain, the presence of carotid disease is significantly related to the presence of severe CAD. In particular, in patients with impaired left ventricular systolic performance, the presence of carotid disease reflects the presence of severe CAD, whereas in patients with normal EF the absence of carotid disease reflects the absence of severe CAD.

References


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