Association of Subclinical Wall Changes of Carotid, Femoral, and Popliteal Arteries With Obstructive Coronary Artery Disease in Patients Undergoing Coronary Angiography*

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Study objectives: To examine the association of occult atherosclerosis of carotid, femoral, and popliteal arteries with the presence and severity of obstructive coronary artery disease (CAD) in patients without a history or presence of cerebrovascular or peripheral arterial disease using ultrasound examination of peripheral arteries.

Patients/methods: One hundred eighty-four such individuals underwent routine coronary angiography. Obstructive CAD was found in 103 cases, which comprised the patient group. The remaining 81 individuals comprised the control group. All were blindly examined by duplex ultrasonography in order to assess occult atherosclerosis, as indicated by the estimation of intima-media thickness of the carotid artery (IMTC), intima-media thickness of the femoral artery (IMTF), intima-media thickness of the popliteal artery (IMTP), and ultrasonic biopsy (UB) of the carotid and femoral arteries. For the individuals with positive coronary angiography findings, the severity of CAD was estimated by the number of the diseased vessels.

Results: IMTC, IMTF, IMTP, and UB showed significant correlation with the presence of obstructive CAD, but only IMTC and IMTF were independent predictive factors, with specificity of 74% and 60% and sensitivity of 76% and 70%, respectively. Additionally, our analysis yielded a regression model that, for a given value of IMTC and IMTF, may estimate the probability of CAD: \[ p \text{ (CAD)} = e^{(-4.765 + 3.36 \text{ IMTC} + 1.91 \text{ IMTF})/1} + e^{(-4.765 + 13.36 \text{ IMTC} + 1.91 \text{ IMTF})}. \] Patients with one-vessel disease had significantly lower IMTC (p < 0.001) and UB (p = 0.011) and lower IMTF (p = 0.057) than those with three-vessel disease.

Conclusions: The assessment of occult atherosclerosis by duplex ultrasonography in both the carotid and the femoral arteries is significantly associated with the presence and severity of CAD. (CHEST 2005; 128:2538–2543)

Key words: coronary artery disease; intima-media thickness; occult atherosclerosis; peripheral arterial disease; ultrasonic biopsy

Abbreviations: CAD = coronary artery disease; IMT = intima-media thickness; IMTC = intima-media thickness of carotid artery; IMTF = intima-media thickness of femoral artery; IMTP = intima-media thickness of popliteal artery; ROC = receiver operator characteristic; UB = ultrasonic biopsy

A correlation of coronary artery disease (CAD) with atherosclerosis of peripheral arteries and the determination of noninvasive indexes for its existence and extent have been sought by many researchers. Some studies1–4 report that the intima-media thickness (IMT) of peripheral arteries obtained by B-mode ultrasound could play this role, even though more reliable indexes exist only for the carotid artery. Other studies5,6 have claimed that a morphologic classification of carotid and femoral arterial wall changes detected by high-resolution...
ultrasound may be an early and accurate indicator of global atherosclerotic disease. However, the majority of the above studies are fragmentary and involve different patient populations, most of them having clinically manifested peripheral arterial disease. Additionally, the precise relationship between the extent of subclinical atherosclerotic disease of peripheral arteries and the existence and severity of CAD has not been well evaluated. For this purpose, we studied the potential role of subclinical atherosclerotic disease, concurrently detected by ultrasound on three different arterial beds, in identifying the presence and severity of obstructive CAD in a single population of patients at risk for ischemic heart disease with totally asymptomatic peripheral arterial disease.

MATERIALS AND METHODS

Study Group

One hundred eighty-four consecutive patients (mean age, 61.7 ± 8.3 years [± SD]) undergoing coronary angiography at the University Hospital of Heraklion for suspected CAD were included in this study. The inclusion criteria were as follows: absence of history or presence of peripheral arterial disease, as indicated by an ankle brachial pressure index > 0.9, carotid artery surgery, or cerebrovascular event and absence of history of previous angiographically documented CAD, congenital heart disease, cardiomyopathy, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty. Written informed consent was obtained from all patients after they were given a detailed description of the procedure.

Coronary Angiography

Coronary angiography was performed using a standard Judkins technique. Obstructive CAD was defined as the existence of a stenosis > 50% of the lumen diameter of at least one major coronary vessel. Patients with such a stenosis comprised the patient group (n = 103), and the remaining individuals (with stenosis < 50%) were assigned to the control group (n = 81). The severity of the disease referred to the number of identified stenosed vessels (lumen diameter < 50%) [one-, two- or three-vessel disease] and was evaluated by two experienced cardiologists, blind to the ultrasound evaluation of the carotid, femoral, and popliteal arteries.

Ultrasound Evaluation

IMT Measurement: All scans were performed by one observer following the method described by Geroulakos et al., using a color duplex scanner (Sequoia TM 512; Acuson Corporation; Mountain View, CA) with an 8-MHz linear array scan head. Scan settings (power output, 50%; dynamic range, 60 decibels; gain; gray scale; filters; ramp) were preset at machine startup and remained constant during examination. All subjects were initially examined in a supine position with a slight extension of the neck. The anterior and lateral projections were used in order to image the common carotid and common femoral arteries longitudinally. The popliteal arteries were evaluated in a decubitus position.

The IMT of the carotid artery (IMTC), the IMT of the femoral artery (IMTF), and the IMT of the popliteal artery (IMTP) were measured by ultrasound. The popliteal arteries were evaluated at one-, two-, or three-vessel bifurcations. The images were zoomed to standard size. The IMTC was calculated as the mean value of six individual measurements at different points within the region of interest (three for the right and three for the left carotid). The IMTF and IMTP were estimated using the same technique.

Ultrasonic Biopsy Estimation

Ultrasonic biopsy (UB) assessment was performed using the method originally described by Belcaro et al.8 The carotid and femoral bifurcations were localized by a transverse scan. The probe was rotated 90° to obtain and record the longitudinal image of both the anterior and posterior wall, with the latter being used for evaluation. Both arteries were evaluated for a length of 3 cm (1.5 cm proximally and distally to the flow divider). The initial classification included five classes corresponding to five scores, ranging from 0 to 8 for each artery (Table 1). The subject’s ultrasound score was obtained by dividing the sum of the scores of the four arteries by four.

Ultrasound evaluation, including IMT measurement and UB, was performed blind to coronary angiography. We did not perform an assessment of interobserver and intraobserver variability, since our experience in using the ultrasound technique in estimating peripheral vessels is well documented.9–12

Statistical Analysis

All descriptive statistics are presented as mean ± SD. The differences between patients and control subjects in the IMT of each artery and the UB were assessed using the unpaired t test. Stepwise logistic regression analysis was used to identify the independent prognostic factors among the parameters recognized as being statistically significant. The specificity and sensitivity of our results were evaluated by receiver operator characteristic (ROC) analysis. The UB and IMT of each artery in patients with different severities of CAD were compared using analysis of variance and post hoc Bonferroni adjusted pair-wise comparisons. Probability values < 0.05 were considered statistically significant.

RESULTS

Detection of CAD

The mean age of the participants was 61.7 ± 8.3 years. Elective coronary arteriography revealed the presence of obstructive CAD in 103 of 184 individuals (patient group), while the remaining 81 subjects were assigned to the control group (n = 50%)

Table 1—UB Classification

<table>
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<tr>
<th>Class</th>
<th>Description</th>
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<tr>
<td>I (score 0)</td>
<td>Normal arterial wall</td>
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<tr>
<td>II (score 2)</td>
<td>Luminal interface disruption (intervals of &lt; 0.5 cm)</td>
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<tr>
<td>III (score 4)</td>
<td>Intima-media granulation or increased intima-media thickness &gt; 1 mm</td>
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<tr>
<td>IV (score 6)</td>
<td>Plaque without hemodynamic disturbance</td>
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<tr>
<td>V (score 8)</td>
<td>Asymptomatic atherosclerotic plaque with hemodynamic disturbance</td>
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(control group) had no angiographically obstructive lesions. The clinical characteristics were similar in both groups (Table 2).

Univariate analysis showed that IMTC, IMTF, IMTP, and UB had significantly higher values in patients with obstructive CAD than in control subjects (Table 3). ROC analysis showed that all four indexes yielded a significant area under the ROC curve (0.81, 0.73, 0.71, and 0.77 for IMTC, IMTF, IMTP, and UB, respectively). However, as Figure 1 shows, IMTC was superior to others almost uniformly. The sensitivity and specificity of IMTC, IMTF, IMTP, and UB for the prognosis of obstructive CAD are shown in Table 4.

Stepwise binary logistic regression showed that among IMTC, IMTF, IMTP, and UB, only IMTC (odds ratio, 5.3; 95% confidence interval, 2.6 to 10.6) and IMTF (odds ratio, 2.6; 95% confidence interval, 1.3 to 4.9) were independently associated with obstructive CAD. Specifically, IMTC entered first ($\chi^2 = 56.3$, p < 0.001), followed by IMTF ($\chi^2 = 8.4$, p < 0.005).

Finally, based on the model, the estimated probability that a patient has obstructive CAD as a function of IMTC and IMTF is given by the following equation (Fig 2): $p \ (CAD) = e^{-4.765 + 3.36 \ IMTC + 1.91 \ IMTF} / (1 + e^{-4.765 + 13.36 \ IMTC + 1.91 \ IMTF})$. The model fit did not change when variables such as age, sex, smoking, diabetes mellitus, hypertension, or hypercholesterolemia were forced in the model.

Severity of CAD

Table 5 shows the values of all the indexes in patients with obstructive CAD according to the number of affected vessels. Analysis of variance showed significant differences for IMTC (p < 0.001) and UB (p < 0.02), and post hoc Bonferroni-adjusted pairwise comparison revealed that patients with one-vessel disease had significantly lower IMTC (p < 0.001), UB (p = 0.011), and lower IMTF (p = 0.057) than those with three-vessel disease.

Discussion

Atherosclerosis is a generalized, progressive disease that may simultaneously affect several arterial...
trees of the body. Among other efforts in the direction of management of atherosclerosis, early detection of subclinical (asymptomatic) CAD and subsequent prevention of possible future ischemic events is one of our most important tasks. Since the seminal work of Hertzer et al and Martinez et al in the early 1980s, we have accepted that patients with peripheral arterial occlusive disease frequently have concomitant CAD, which remains the leading cause of both early and late mortality following peripheral vascular reconstructive surgery. Along these lines, atherosclerotic changes of peripheral arteries might be considered to mirror the condition of coronary arterial circulation.

In this study, we tried to establish an association between subclinical arterial wall changes, as detected by ultrasonography, in three different peripheral arterial territories, including the carotid, femoral, and popliteal arteries, and the presence and severity of obstructive CAD. To our knowledge, such a study evaluating individuals with no clinical signs of peripheral arterial occlusive disease and incorporating those three peripheral arteries concurrently in the same patient population has not been reported yet in the English-language literature.

According to our results, IMT changes of both the carotid and femoral arteries appeared to be independent predictors of both the existence and the severity of obstructive CAD. In addition, our analysis yielded for the first time a regression model that for a given value of IMTC and IMTF may estimate the probability of obstructive CAD. In contrast, the IMT of the popliteal artery and UB do not seem to play a significant predictive role in detecting CAD.

Our results for IMTC are in line with those of previous isolated clinical reports. In the Rotterdam study, an increased IMTC was found to be associated with future cerebrovascular and cardiovascular events. Similarly, in the Atherosclerosis Risk in Communities study, IMTC was related to clinically manifested cardiovascular disease affecting distant vascular beds. The correlation between carotid and coronary atherosclerosis has also been confirmed when it was assessed by imaging techniques only. In a study by Mack et al, the rate of changes of the IMTC detected by ultrasonography was positively correlated with the changes in coronary artery atherosclerosis determined by angiography. Additionally, Geroulakos et al showed for the first time that the IMTC was associated not only with the presence of atherosclerotic risk factors but also with the presence of angiographic CAD data, and that there was a significant linear trend between increasing IMT and the number of coronary vessels involved.

Other relative studies used the carotid bulb disease or employed more complex systems to evaluate the IMT at different sites of the carotid artery including the carotid bulb. At this point, it should be pointed out that IMT changes observed in the present study were detected in the absence of focal or diffuse plaque formation and therefore in the absence of hemodynamically or clinical significant atherosclerotic disease. The benefits of estimating the IMT of the common carotid artery are that it is typically constant throughout its length, it can be accurately and easily assessed by ultrasound, and plaques are found in the vessel only during the late stages of atherosclerosis. In contrast, the IMT and plaques of the carotid bulb cannot always be visualized adequately.
The available data on the relation of IMTF and CAD are few and conflicting. In this study, we found that IMTF might serve as an indicator and as an independent risk factor for the presence of obstructive CAD. Moreover, we observed that patients with one-vessel disease had relatively, but not significantly, lower IMTF \((p = 0.057)\) than those with three-vessel disease. Megnier et al\(^{21}\) reported that IMTF predicts the existence of coronary calcium as assessed by ultrafast CT and concluded that IMTF could be of clinical value for stratifying CAD risk. Additionally, Held et al\(^{3}\) found later that IMTF is related to the risk of myocardial infarction and revascularization. Furthermore, Lekakis et al\(^{22}\) reported that IMTF is a strong predictor of the extent and severity of coronary atherosclerosis; however, this strong correlation was observed by using the Gensini score, a more general marker for the estimation of the severity of CAD. Moreover, Lekakis et al\(^{22}\) included patients with symptomatic peripheral disease, who were excluded in our study. Patients with already symptomatic peripheral disease can be expected to have more severe arterial disease. However, Hulthe et al\(^{18}\) in a relatively small study, did not find a significant relation between IMTF and the severity of CAD as evaluated by angiography. The discrepancy between the results of our study and those reported by Hulthe et al\(^{18}\) could be explained by the small number of patients included in their study and the different methodology used for evaluating the extent of coronary artery atherosclerosis, since they tried to correlate IMTF with the degree of stenosis and not the number of diseased coronary vessels.

Regarding IMTP, there are few studies\(^{2,3}\) in the literature concerning its association with preexisting CAD; in these studies, CAD was positively associated with increased wall thickness in the popliteal arteries. Our observation that patients with obstructive CAD had generally higher values of IMTP are in line with those findings, even though in our study we found that IMTP was not an independent factor for obstructive CAD.

Apart from IMT, Belcaro et al\(^{5,6}\) found that the UB carotid and femoral classification of subclinical atherosclerotic lesions can separate asymptomatic subjects into groups of different risk for cardiovascular events. They concluded that UB might serve as a simple technique to assess subclinical atherosclerosis and could be useful in selecting subjects prone to have cardiovascular events. In our study, we found that UB does indeed have higher values in patients with obstructive CAD, but it is not an independent diagnostic factor. However, our findings indicate that UB might be useful for determining which CAD patients have significant disease. Certainly, further studies are needed in order to elucidate this matter.

The aim of this study was to evaluate whether subclinical atherosclerotic disease occurring concurrently in multiple peripheral arteries (eg, common carotid, common femoral, and popliteal) can mirror the presence and severity of obstructive CAD in an adult patient population with no history or signs of peripheral arterial disease. The size of our study population may be considered small for such a kind of investigation. However, it was enough to demonstrate the strong relationship between the early arterial wall changes and presence and extent of CAD, at the same time yielding a regression model that for a given value of IMTC and IMTF may estimate the probability of CAD. The importance of our study is that the development of obstructive CAD may be reflected by preceded IMT changes in multiple peripheral arteries, which can be easily and accurately detected by ultrasound. This could contribute to a more effective identification of patients at risk of future ischemic heart disease.

Certainly, some factors may have limited the apparent strength of the suggested regression model or the relationships we found between the arterial wall changes in different peripheral arteries and CAD. Thus, classification of the severity of CAD based on the number of the diseased vessels may not be as accurate as other specific indexes and coronary angiography frequently underestimates the severity of atherosclerotic disease.\(^{23}\) Additionally, our control group of patients were referred for coronary angiography for suspected ischemic heart disease. This selection criterion mean that our results cannot necessarily be applied to the general population or extrapolated to other patient populations selected by other criteria. Regarding the regression model, studies of larger samples will be necessary to confirm our results before this model can be used as a diagnostic tool in this specific group of patients.

References